Office Action Summary	Application No.	Applicant(s)	
	10/502,685	GOVIND ET AL.	
	Examiner	Art Unit	
	Alton N. Pryor	1616	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 August 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,5-9,12-24* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,5-9,12-24* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-3,5-9.12-24 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-3,5-9.12-24 are rejected because of abbreviations (PVP, HFA 227, PEG, etc.). Replace abbreviations with terms.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-3,5-9,12-16 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Claims reciting *2 mg/ml* and *4 mg/ml* budesonide set forth new matter issues.

Declarations

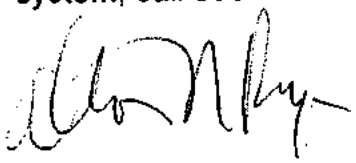
Declarations provide unexpected stability results for compositions 0.001% w/w to 0.01% w/w budesonide.

Telephonic Inquiry

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Alton N. Pryor whose telephone number is 571-272-0621. The examiner can normally be reached on 8:00 a.m. - 4:30 p.m..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Johann Richter can be reached on 571-272-0646. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.



Alton Pryor
Primary Examiner
AU 1616

Index of Claims

Application/Control No.	Applicant(s)/Patent under Reexamination
10/502,685	GOVIND ET AL.
Examiner	**Art Unit**
Alton N. Pryor	1616

√	Rejected	–	(Through numeral) Cancelled	N	Non-Elected	A	Appeal
=	Allowed	÷	Restricted	I	Interference	O	Objected

Claim		Date
Final	Original	11/6/07
	1	√
	2	√
	3	√
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	5	√
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	7	–
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	11	
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Claim	
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Search Notes

Application/Control No.	Applicant(s)/Patent under Reexamination	
10/502,685	GOVIND ET AL.	
Examiner	**Art Unit**	
Alton N. Pryor	1616	

SEARCHED			
Class	Subclass	Date	Examiner
424	45,48, 489	11/6/2007	ANP

INTERFERENCE SEARCHED			
Class	Subclass	Date	Examiner

SEARCH NOTES (INCLUDING SEARCH STRATEGY)		
	DATE	EXMR

Request For Continued Examination (RCE) Transmittal

Address to:
Mail Stop RCE
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Application Number	10/502,685
Filing Date	July 27, 2004
First Named Inventor	Nayna Govind et al.
Group Art Unit	1616
Conf No.	7568
Examiner Name	Alton Pryor
Attorney Docket Number	06275-410US1

This is a Request for Continued Examination (RCE) under 37 C.F.R. §1.114 of the above-identified application.
Request for Continued Examination (RCE) practice under 37 CFR 1.114 does not apply to any utility or plant application filed prior to June 8, 1995, or to any design application. See Instruction Sheet for RCEs (not to be submitted to the USPTO) on page 2.

1. Submission required under 37 C.F.R. §1.114 Note: If the RCE is proper, any previously filed unentered amendments and amendments enclosed with the RCE will be entered in the order in which they were filed unless applicant instructs otherwise. If applicant does not wish to have any previously filed unentered amendment(s) entered, applicant must request non-entry of such amendment(s)

   a. ☐ Previously submitted. If a final Office action is outstanding, any amendment filed after the final Office action may be considered as a submission even if this box is not checked.

      i. ☐ Consider the arguments in the Appeal Brief or Reply Brief previously filed on _____

      ii. ☐ Other _____

   b. ☒ Enclosed

      i. ☒ Amendment/Reply

      ii. ☒ Affidavit(s)/Declaration(s)

      iii. ☐ Information Disclosure Statement (IDS)

      iv. ☒ Other Exhibits A-C and formal Drawings

2. Miscellaneous

   a. ☐ Suspension of action on the above-identified application is requested under 37 C.F.R. §1.103(c) for a period of _____ months. (Period of suspension shall not exceed 3 months; Fee under 37 C.F.R. §1.17(i) required)

   b. ☐ Other _____

3. Fee The RCE fee under 37 C.F.R. §1.17(e) is required by 37 C.F.R. §1.114 when the RCE is filed.

   a. ☒ The Director is hereby authorized to charge the following fees, or credit any overpayments, to Deposit Account No. 06-1050

      i. ☒ RCE fee required under 37 CFR 1.17(e)

      ii. ☐ Extension of time fee (37 CFR 1.136 and 1.17)

      iii. ☒ Other Excess claims fees and any deficiencies

   b. ☐ Check in the amount of $_____ enclosed

   c. ☐ Payment by credit card (Form PTO-2038 enclosed)

SIGNATURE OF APPLICANT, ATTORNEY OR AGENT REQUIRED

Name (Print/Type)	Janis K. Fraser, Ph.D., J.D.	*Registration No. (Attorney/Agent)*	34,819
Signature		*Date*	Aug. 21, 2007

CERTIFICATE OF MAILING OR TRANSMISSION

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to Mail Stop RCE, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450 or facsimile transmitted to the U.S. Patent and Trademark Office on the date shown below.

Name (Print/Type)			
Signature		*Date*	

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants	: Nayna Govind *et al.*	Art Unit	: 1616
Serial No.	: 10/502,685	Examiner	: Alton Pryor
Filed	: July 27, 2004	Conf. No.	: 7568
Title	: COMPOSITION FOR INHALATION		

MAIL STOP RCE
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

SUBMISSION UNDER 37 CFR § 1.114(c)

Please amend the above-identified application as follows:

Amendments to the Claims:

This listing of claims replaces all prior versions and listings of claims in the application:

Listing of Claims:

1. (Currently amended) A pharmaceutical composition comprising formoterol or a salt or solvate thereof, or a solvate of a salt;[[,]] budesonide[[,]]; HFA 227[[,]]; PVP and PEG, wherein the PVP is present at a concentration ~~in an amount~~ of 0.001% w/w to 0.01% w/w and the budesonide is present at a concentration of 4 mg/ml.

2. (Currently amended) A pharmaceutical composition according to claim 1 wherein the PEG is present at a concentration from about 0.05 to about 0.35% w/w.

3. (Previously presented) A pharmaceutical composition according to claim 1 in which the PVP is PVP K25.

4. (Canceled)

5. (Previously presented) A pharmaceutical composition according to claim 1 in which the PEG is PEG 1000.

6. (Currently amended) A pharmaceutical composition according to claim 1 in which the PEG is present at a concentration ~~in an amount~~ of 0.3% w/w.

7. (Previously presented) A pharmaceutical composition according to claim 1 in which formoterol is in the form of its fumarate dihydrate salt.

8. (Currently amended) A pharmaceutical composition according to claim 1 in which the formoterol or salt or solvate thereof, or solvate of a salt, is in the form of the ~~single~~ R, R-enantiomer.

9. (Currently amended) A pharmaceutical composition according to claim 1 in which the ~~second active ingredient is~~ budesonide is in the form of the 22R-epimer ~~of budesonide~~.

10-11. (Canceled)

12. (Currently amended) A method of treating ~~or preventing~~ the symptoms of a respiratory disorder, comprising administering to a patient a pharmaceutical composition according to claim 1, wherein the respiratory disorder is asthma, rhinitis, or chronic obstructive pulmonary disease (COPD).

13. (Previously presented) The method of claim 12, wherein the respiratory disorder is asthma.

14. (Previously presented) The method of claim 12, wherein the respiratory disorder is rhinitis.

15. (Previously presented) The method of claim 12, wherein the respiratory disorder is COPD.

16. (New) A pharmaceutical composition comprising formoterol, or a salt or solvate thereof, or a solvate of a salt; budesonide; HFA 227; PVP; and PEG, wherein the PVP is present at a concentration of 0.001% w/w and the budesonide is present at a concentration of 2 mg/ml.

17. (New) A pharmaceutical composition comprising formoterol, or a salt or solvate thereof, or a solvate of a salt; budesonide; HFA 227; PVP; and PEG, wherein the PVP is present

at a concentration of 0.001% w/w to 0.01% w/w and the budesonide is present at a concentration of 8 mg/ml.

18. (New) A pharmaceutical composition comprising formoterol, or a salt or solvate thereof, or a solvate of a salt; budesonide; HFA 227; PVP; and PEG, wherein the PVP is present at a concentration of 0.0001% to 0.001% w/w and the budesonide is present at a concentration of 1 mg/ml.

19. (New) The pharmaceutical composition of claim 1, wherein the concentration of PVP is 0.001% or 0.01% w/w.

20. (New) The pharmaceutical composition of claim 1, wherein the concentration of PVP is 0.001% w/w.

21. (New) The pharmaceutical composition of claim 17, wherein the concentration of PVP is 0.001% or 0.01% w/w.

22. (New) The pharmaceutical composition of claim 17, wherein the concentration of PVP is 0.001% w/w.

23. (New) The pharmaceutical composition of claim 18, wherein the concentration of PVP is 0.0001%, 0.0005%, or 0.001% w/w.

24. (New) The pharmaceutical composition of claim 18, wherein the concentration of PVP is 0.001% w/w.

Amendments to the Drawings:

The attached replacement sheets of drawings (including FIGs. 1-16) include changes to FIGs 2 and 3. In FIGs. 2 and 3, the legends were deleted, and the concentration of PVP for each data set is indicated within the graphs themselves.

The attached FIGs. 1-16 are formal drawings that replace the original sheets including FIGs. 1-16.

REMARKS

This submission includes an amendment and remarks responsive to the Final Office Action dated January 29, 2007.

Upon entry of the amendment, claims 1-3, 5-9 and 12-24 will be pending in the application. Claims 1, 2, 6, 8, 9, and 12 are amended and new claims 16-24 added. Claims 4, 10, and 11 were canceled by a previous amendment. Support for the amended and new claims can be found in the specification and claims as originally filed. For example, support for amended claim 1 and new claims 19 and 20 can be found at least in FIG. 4 and at paragraphs [0005]-[0009] and [0036] of the published application (US2005/0089478). Support for new claim 16 can be found at least in FIG. 5 and in paragraphs [0005]-[0009] and [0036]. Support for new claims 17, 21, and 22 can be found at least in paragraphs [0005]-[0009] and [0036] and the table at [0056]. Support for new claims 18, 23, and 24 can be found at least in FIG. 6 and in paragraphs [0005]-[0009] and [0036]. (The support for independent claims 1 and 16-18 is further detailed below.) No new matter is added by the amendment.

Applicants also submit herewith formal drawings and a Declaration of inventor Nayna Govind under 37 CFR § 1.132, containing Exhibits A, B, and C, which illustrate suspension stability data of certain formulations with varying concentrations of PVP. Exhibit A is a graph of OSCAR (Optical Suspension Characterization)[1] data for a formulation containing 1 mg/ml budesonide (*i.e.*, 40 µg per dose).[2] Exhibits B and C are graphs of OSCAR and Turbiscan[3] data, respectively, for a formulation containing 8 mg/ml budesonide.

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[1] See paragraphs [0019]-[0023].

[2] The graphs in this declaration and the graphs and tables in the specification characterize various formulations as delivering a specified amount of budesonide per dose (or per actuation), rather than stating the concentration of budesonide *per se* in each formulation. However, one can readily correlate the per-dose amounts, which range from 40 µg to 320 µg, to the corresponding concentration of budesonide in the formulation, based on a description of the formulations in the specification at paragraph [0036]. According to this description, the formulations that were tested in the experiments contained a constant level of formoterol fumarate dihydrate and a concentration of budesonide that varied from 1 mg/ml to 8 mg/ml. Each formulation was loaded into a canister with a valve that delivered a set volume that did not vary. The formulation that contained 1 mg/ml budesonide delivered 40 µg budesonide per actuation (or "dose"). Thus, any data presented as corresponding to a 40 µg dose of budesonide was obtained with a formulation containing 1 mg/ml budesonide. Likewise, the formulation that contained 2 mg/ml budesonide delivered 80 µg budesonide, the formulation that contained 4 mg/ml budesonide delivered 160 µg budesonide, and the formulation that contained 8 mg/ml budesonide delivered 320 µg budesonide.

[3] See paragraphs [0024] to [0033].

Applicants respectfully request that the Examiner consider the references on the Information Disclosure Statement submitted November 3, 2006, and indicate that he has done so by returning an initialed copy of the form PTO-1449.

All of the pending claims were rejected on one or more grounds, as discussed below.

35 U.S.C. § 112, first paragraph

Claims 12-15 are rejected under 35 U.S.C. § 112, first paragraph, for failing to satisfy the enablement requirement, because the claims "recite preventing language." Office Action at page 2, paragraph I. Applicants do not concede that the claims lack enablement for this or any other reason. However, solely in the interest of furthering prosecution, Applicants have amended claim 12 to delete the term "preventing," while reserving the right to pursue such scope in a continuation application. In view of the amendment, Applicants respectfully request that the rejection under 35 USC § 112, 1st paragraph, for lack of enablement be withdrawn.

35 U.S.C. § 103

Claims 1-3, 5-9 and 12-15 are rejected under 35 U.S.C. § 103(a) as being unpatentably obvious over Meade *et al.* (US 20030018019). Office Action at page 2. The Office Action does not say that Meade *et al.* is cited in combination with any other reference, which would suggest that it is cited alone. However, since a second reference, Weers *et al.* (US 6,309,623), was combined with Meade *et al.* in the previous Office Action mailed May 4, 2006, and Weers *et al.* is mentioned a few times in the "Examiner argues" section of page 3 of the present Office Action, Applicants surmise that the Examiner may have intended it to still be part of the rejection. Clarification is requested.

In sections (a) through (d) below, Applicants respond to each of the Examiner's arguments labeled (a) through (d), respectively, at page 3 of the Office Action.

(a) The Examiner states that "[s]ince the prior art does not disclose any particular range of PVP, it is imperative that Applicant show the criticality of the invention comprising 0.001% w/w PVP by testing the invention comprising slightly more and less than 0.001% w/w PVP."

Applicants disagree that they must show experimental evidence to overcome the obviousness rejection, as the Examiner has not met his burden of establishing that it was *prima facie* obvious to use 0.001% w/w PVP (or any other particular concentration of PVP) in the claimed formulations. Nevertheless, Applicants note that such evidence is present in the application as filed, and is further supported by supplemental data presented in the attached Declaration and exhibits.

The specification describes a number of OSCAR and Turbiscan measurements of suspension stability carried out on formulations containing budesonide at concentrations of 1 mg/mL, 2 mg/mL, 4 mg/mL, and 8 mg/mL (equivalent to 40 μg, 80 μg, 160 μg, and 320 μg budesonide per actuation) and various concentrations of PVP ranging from 0.0001% to 0.05% w/w. See the description of these test formulations in the specification at paragraph [0036]. The results of these experiments are shown in FIGs. 2-6 in the application and in Exhibits A, B, and C attached to the enclosed Declaration of Nanya Govind. For the Examiner's convenience, these experiments and results are summarized in the table below.

Budesonide concentration	**Budesonide per actuation**	**OSCAR**	**Turbiscan**	**Preferred PVP concentration**
1 mg/mL	40 μg	Exhibit A	FIG. 6	0.0001%-0.001%
2 mg/mL	80 μg	FIG. 3	FIG. 5	0.001%
4 mg/mL	160 μg	FIG. 2	FIG. 4	0.001%-0.01%
8 mg/mL	320 μg	Exhibit B	Exhibit C	0.001%-0.01%

In addition to the OSCAR and Turbiscan measurements, the specification at paragraphs [0040] to [0055] describes digital photographic analyses of the same formulations, with the data from those analyses set forth in the table at paragraph [0056] of the specification.

Because the data, taken as a whole, indicate that the preferred amount of PVP varies somewhat with the concentration of budesonide in the formulation, Applicants present four independent claims, each limited to a different concentration of budesonide and a corresponding level or range of PVP. For example, claim 1 is now limited to one particular concentration of

budesonide, 4 mg/ml (corresponding to 160 μg budesonide per actuation in the experiments reported in the application, as explained in footnote 2 above), while new independent claims 16-18 are respectively limited to 2, 8 and 1 mg/ml budesonide. The concentration of PVP specified in each of the four independent claims is derived from data in the specification indicating the best concentration or range of concentrations of PVP to use with each particular concentration of budesonide, as explained below. Though not necessary for support, additional data in Exhibits A, B, and C of the Declaration are provided for completeness.

Amended claim 1 now specifies that the concentration of budesonide is 4 mg/ml and the concentration of PVP is 0.001% w/w to 0.01% w/w. These concentrations of PVP are derived from the data in FIG. 4 (obtained using the Turbiscan method) and in the table at [0056] (obtained using a digital photograph analysis such as illustrated in FIGs. 9-11), all regarding a formulation that in the experiments described in the specification contains 4 mg/ml and delivers 160 μg budesonide per actuation. As can be seen both in this table and in FIG. 4, for a formulation containing this particular level of budesonide, a concentration of PVP in the range of 0.001% w/w to 0.01% w/w would be expected to give the best suspension stability over time, better than higher (0.03 and 0.05%) or lower (0.0001%) concentrations of PVP produced with this amount of budesonide.[4] Nothing in the prior art would have led one to expect that this amount of PVP would produce superior results with 4 mg/ml budesonide (or any other concentration of budesonide, for that matter).

New claim 16 is limited to a budesonide concentration of 2 mg/ml (corresponding to a dose of 80-μg per actuation in the experiments described in the specification) and a PVP concentration of 0.001% w/w. The criticality of 0.001% w/w PVP in a formulation containing 2 mg/ml budesonide is illustrated in FIGs. 3 and 5; this concentration of PVP also produced the best results when measured by digital photography as indicated in the table at [0056]. These data show that formulations with higher or lower concentrations of PVP were less able to maintain a good suspension of a 2 mg/ml budesonide formulation over time. Nothing in the prior art would

[4] The data in FIG. 2 (also obtained with 4 mg/ml budesonide, but using the OSCAR method) also support the superiority of 0.001% PVP in particular, and to a lesser extent that of 0.01%; however, it is clear that the range from 0.01% to 0.001% would be better than higher or lower concentrations of PVP.

have led one to expect that 0.001% w/w PVP would provide this benefit in a formulation containing 2 mg/ml budesonide (or any other concentration of budesonide, for that matter).

New claim 17 is limited to a budesonide concentration of 8 mg/ml (corresponding to a dose of 320 μg per actuation in the experiments described in the specification) and a PVP concentration of 0.001% w/w to 0.01% w/w. This PVP concentration range is derived from the digital photographic data summarized in the table at [0056]. It can be seen from the table that, for a formulation containing 8 mg/ml budesonide, 0.01% w/w PVP produced optimal stability results when analyzed by the digital photographic method, with 0.001% also producing good results. Further data regarding formulations containing this concentration of budesonide are shown in Exhibits B and C attached to the enclosed Declaration. Exhibit B shows that, when measured by OSCAR over a 2 minute time period, 0.01% PVP produces the most stable formulations with 8 mg/ml budesonide. When the stability of the 8 mg/ml formulations was measured by the Turbiscan method over a 15 min time period, 0.01% and 0.001% PVP both proved far more stable than higher or lower concentrations of PVP (see Exhibit C).

New claim 18 is limited to a budesonide concentration of 1 mg/ml (corresponding to a dose of 40 μg per actuation in the experiments described in the specification) and a PVP concentration of 0.0001% w/w to 0.001% w/w. This range of PVP concentrations is derived from the FIG. 6 Turbiscan data and the digital photographic data shown in the table at [0056] for 1 mg/ml budesonide formulations. As shown in both FIG. 6 and the table, concentrations of PVP at or below 0.001% produced relatively stable formulations of 1 mg/ml budesonide. This conclusion is buttressed by the OSCAR data provided in Exhibit A attached to the enclosed Declaration.

There is no suggestion in Meade that varying concentrations of PVP would have any effect on suspension stability whatsoever, and there is further no indication which concentrations of PVP are best suited for any composition containing budesonide, much less the particular budesonide concentrations specified in the present claims. It is clear from the data in the specification that the stability of any given budesonide formulation depends on the concentration of PVP utilized. One can derive a few generalizations from these data: (1) higher budesonide concentrations tended to require more PVP to maintain a stable suspension; (2) all of the budesonide concentrations tested (from 1 mg/ml to 8 mg/ml) were more stable if the PVP

concentration was kept below 0.05% w/w; and (3) the best results overall were obtained using 0.001% PVP w/w. None of those results could have been predicted based on the prior art cited by the Examiner, which in fact gave no reason to expect any improvement in stability by adding PVP, much less by keeping the concentration of PVP below 0.05% w/w.

(b) The Examiner states that "[i]t is improper to conclude that amount of phosphatidylcholine used in Weers would equate to the amount of PVP that should be used since structures differ in both chemical and physical properties. In addition it is important to note that Weers is not relied upon for the use of PVP since Meade uses PVP." As explained in the November 3rd reply at page 10, neither Meade nor Weers discloses any particular concentration of PVP, and neither provides any motivation to select the particular concentration or range of concentrations of PVP required by Applicants' claims. As amended, the claims specify the preferred concentration of PVP to be used with specified concentrations of budesonide. There is no teaching or suggestion in Meade or Weers that would lead one to such a preferred concentration.

(c) and (d) The Examiner states that Applicants failed "to provide examples, which show the criticality of 0.001% w/w PVP versus the invention where the PVP concentration is slightly greater or less than 0.001% w/w PVP." Applicants do not understand why the Examiner believes the examples need to concern concentrations that are "slightly greater or less than 0.001% w/w PVP", as ***any*** differences in effect for different concentrations of PVP would appear to be surprising in view of prior art that taught nothing about specific concentrations of PVP and nothing about improved stability of budesonide suspensions or other benefits attributable to PVP. Applicants submit that the examples provided in the specification and discussed above are more than ample to support the nonobviousness of the present claims.

In view of the foregoing, Applicants respectfully request that the rejection under 35 USC § 103(a) be withdrawn.

Please apply the excess claims fee of $400 and any other necessary charges or credits to Deposit Account No. 06-1050, referencing Attorney Docket No. 06275-410US1.

Respectfully submitted,

Date: Aug. 21, 2007

Janis K. Fraser, Ph.D., J.D.
Reg. No. 34,819

Fish & Richardson P.C.
225 Franklin Street
Boston, MA 02110
Telephone: (617) 542-5070
Facsimile: (617) 542-8906

DocNo 21659466

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant	: Nayna Govind *et al.*	Art Unit	: 1616
Serial No.	: 10/502,685	Examiner	: Alton Pryor
Filed	: July 27, 2004	Conf. No.	: 7568
Title	: COMPOSITION FOR INHALATION		

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

DECLARATION OF NAYNA GOVIND UNDER 37 C.F.R. §1.132

I, Nayna Govind, a citizen of the UK residing in Nottingham U.K. hereby declare as follows:

1. I am a Team Manager at AstraZeneca AB, employed at AstraZeneca Charnwood, Loughborough. I received my B. Pharm (Hons) degree in Pharmacy from Bradford University. I have over 12 years experience in the field of pressurized metered dose inhalers. I have published over 6 scientific articles. A copy of my CV is attached as Exhibit D.

2. I have reviewed the above-referenced patent application and the U.S. Patent and Trademark Office Action mailed January 29, 2007. The data presented below and in the attached Exhibits A-C supplement the data provided in the patent application.

3. The present application includes the results of experiments that measured the suspension stability of various metered dose inhaler budesonide formulations. Two of the techniques used to measure suspension stability were Optical Suspension Characterization (OSCAR) and Turbiscan. These techniques are described in the above-referenced application at paragraphs [0019] – [0033] of the published application (US 2005/0089478).

4. The published application at paragraphs [0036] through [0064] describes preparation of several metered dose inhaler suspension formulations containing 0.3% w/w

PEG 1000, 0.09 mg/ml formoterol fumarate dihydrate, and various amounts of budesonide and PVP, in HFA227 propellant. Some data quantifying the relative suspension stability of these formulations are provided in the application as filed. Additional data for some of these formulations are described below.

5. Exhibit A is a graph of OSCAR data obtained with formulations containing 1 mg/mL budesonide (corresponding to 40 µg budesonide per actuation) and various concentrations of PVP. These data indicate that, when measured by OSCAR over a 2 minute time period, 0.0001% to 0.001% PVP produces the most stable formulations of 1 mg/ml. budesonide. This is consistent with the results of the application's FIG. 6 Turbiscan data generated with the same formulation over a 15 minute time period.

6. Exhibit B is a graph of OSCAR data obtained with formulations containing 8 mg/mL budesonide (corresponding to 320 µg budesonide per actuation) and various concentrations of PVP. These data indicate that, when measured by OSCAR over a 2 minute time period, 0.01% PVP produces the most stable formulations of 8 mg/mL budesonide, consistent with the data in the table at paragraph [0056] of the specification.

7. Exhibit C is a graph of Turbiscan data obtained with the same formulations described in the preceding paragraph, *i.e.*, containing 8 mg/mL budesonide. The Exhibit C data show that, when measured by the Turbiscan technique over a 15 minute time period, 8 mg/ml. budesonide formulations containing 0.01% and 0.001% PVP proved more stable than those containing higher or lower concentrations of PVP.

8. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment or both, under Section 1001 of Title 18 of the

United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

DATE: 31 July 2007

Name: Nayna Govind
NAYNA GOVIND

21686569.doc

CURRICULUM VITAE

Name: Nayna Govind

Date of joining AstraZeneca: 17 February 1997

Date of joining Pharmaceutical and Analytical R&D: 17 February 1997

EDUCATION

1991-1994 Doctor of Philosophy, Aston University, Birmingham
PhD Thesis Title: Cyclodextrin complexes of antimicrobial agents

1987-1991 BPharm (Hons) in Pharmacy, Upper Second Class Degree
University of Bradford, West Yorkshire

MEMBERSHIPS/AFFILIATIONS

Royal Pharmaceutical Society of Great Britain
Academy of Pharmaceutical Sciences

WORK EXPERIENCE

07/2006-present *Team Manager, Inhalation Team, AstraZeneca Charnwood*

- Manage, develop and coach staff
- Provide resource, support and technical expertise to ensure Symbicort project milestones are met
- Ensure SHE and GMP standards are upheld

06/02-07/06 *Associate Principal Scientist, AstraZeneca Charnwood*

- PD author for Symbicort pMDI MAA submission
- PD lead for co-ordination of PAI activities
- PD author for Pre-NDA and NDA documentation

02/97-06/02 *Senior Pharmaceutical Scientist, AstraZeneca Charnwood*

- Setting up of pilot creativity & innovation area for site use
- Development of pMDI products for emerging pulmonary projects and pMDI R&T activities (Iressa, SEDS, Nanoparticles)
- Patent support work for pMDI formulations
- Support for Oxis pMDI Tech Transfer
- 3 month temporary position as Team Manager for Oxis pMDI team
- Development of AR-C89855 pMDI
- Drafted regulatory documentation for Viozan pMDI
- Responsible for AR-C68397AA drug substance activities

- Co-ordination of AR-C68397AA Turbuhaler activities
- Development of Symbicort HFA pMDI formulation

10/94-2/97 *Advanced Development Scientist, 3M Health Care Ltd*

- Development of HFA pMDI formulations for external customers.

PUBLICATIONS

Marlow, M, Govind, N, Symbicort formulation patent, WO2003063842

Plumb A P, Carlstoft Å K E, Govind N, Noble A, O'Brien J, Stensland B, Preformulation Salt Selection Studies On AR-C89855, A Compound For Inhalation Administration, in Proceedings for BPC 2002

Govind N, Liljedahl S, Assessment of Pressurised Metered Dose Inhaler Suspension Formulations using the Turbiscan, in Proceedings of Respiratory Drug Delivery VIII, 2002

Wu Z Z, Govind N, Johnson P, US Patent 6315985 C-17/21 OH 20-Ketosteroid solution aerosol products with enhanced chemical stability, Nov 2001

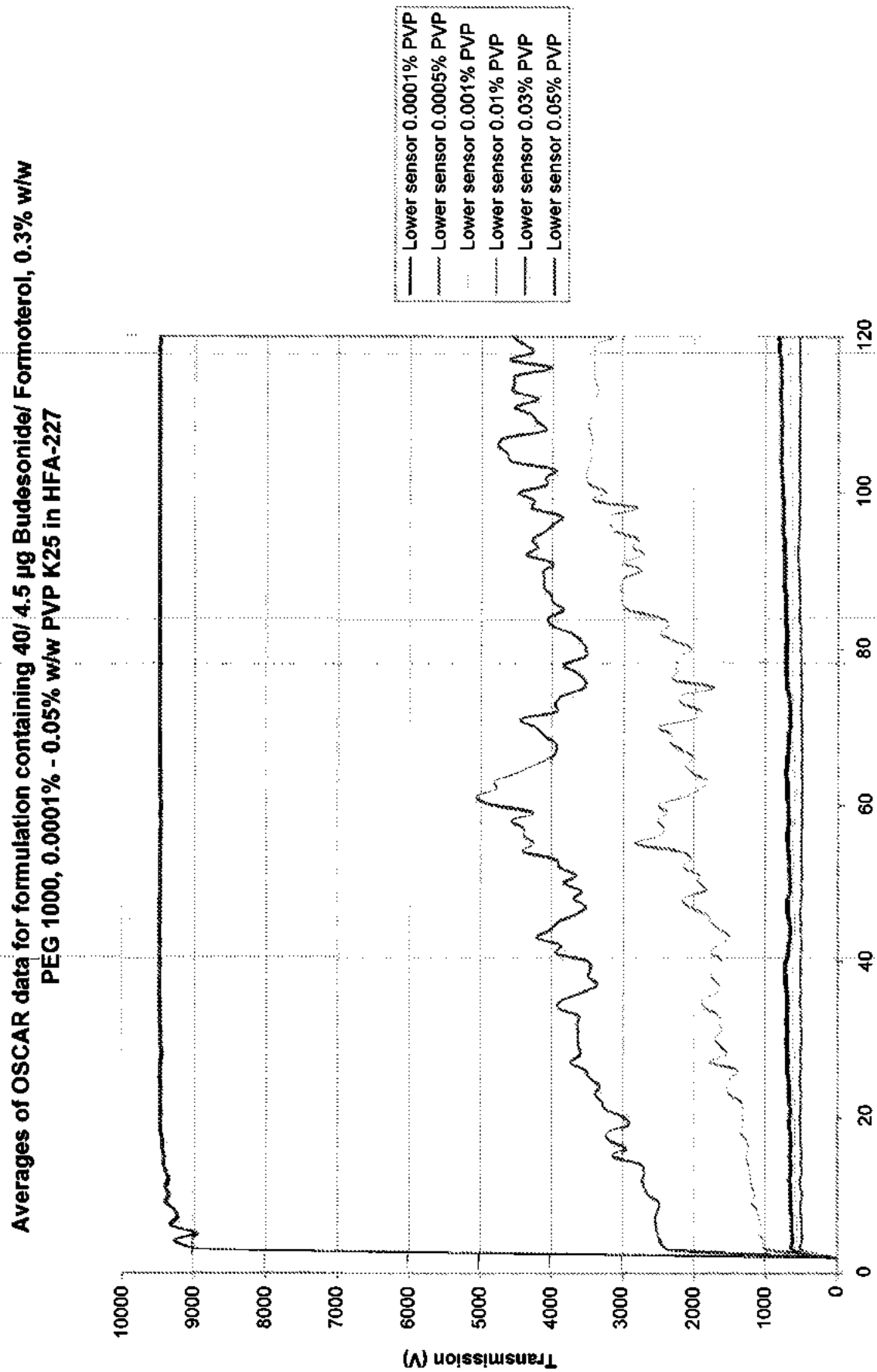
Govind N, Price A, Brindley A, Correlation of Two Methods for Assessing pMDI Suspension Stability, in Proceedings of Respiratory Drug Delivery VII, 2000

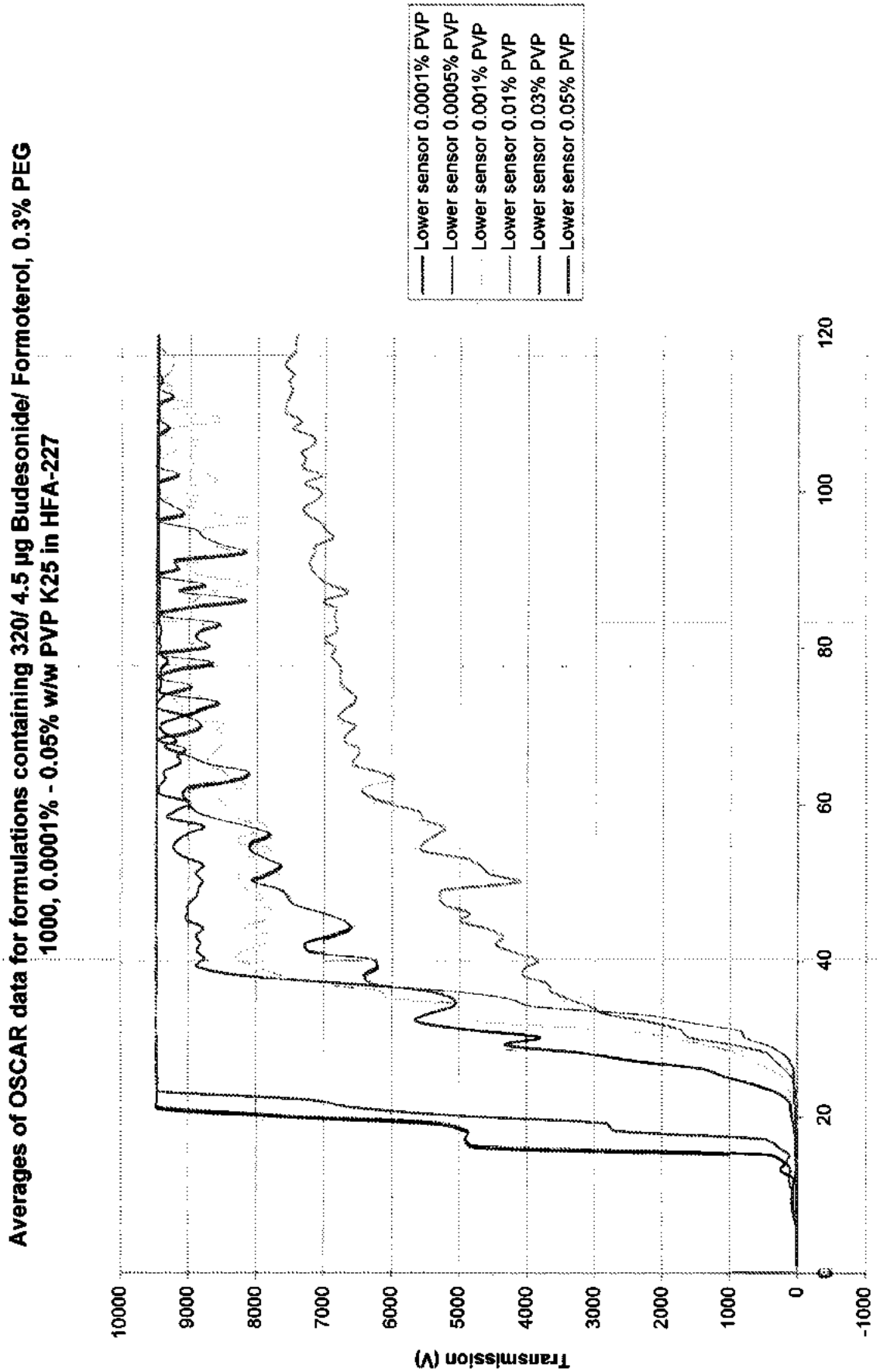
Govind N et al, US Patent 6039932 Medicinal inhalation aerosol formulations containing budesonide, Mar 2000

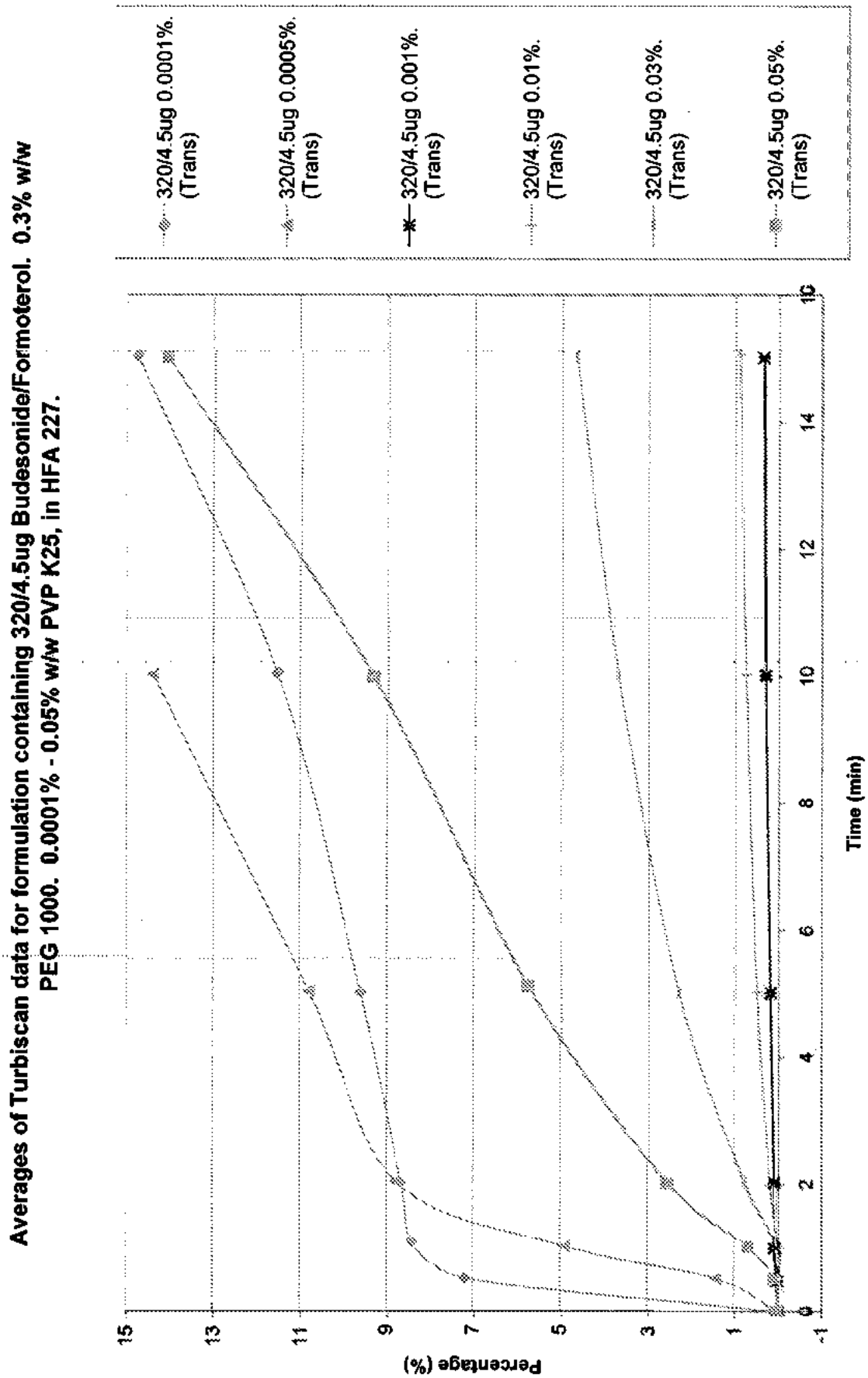
Govind N, Lambert P, Method Development of the OSCAR Technique for the Characterisation of Metered Dose Inhaler Suspension Formulations, in Proceedings of Drug Delivery to the Lungs VI, pp 16-19, 1998

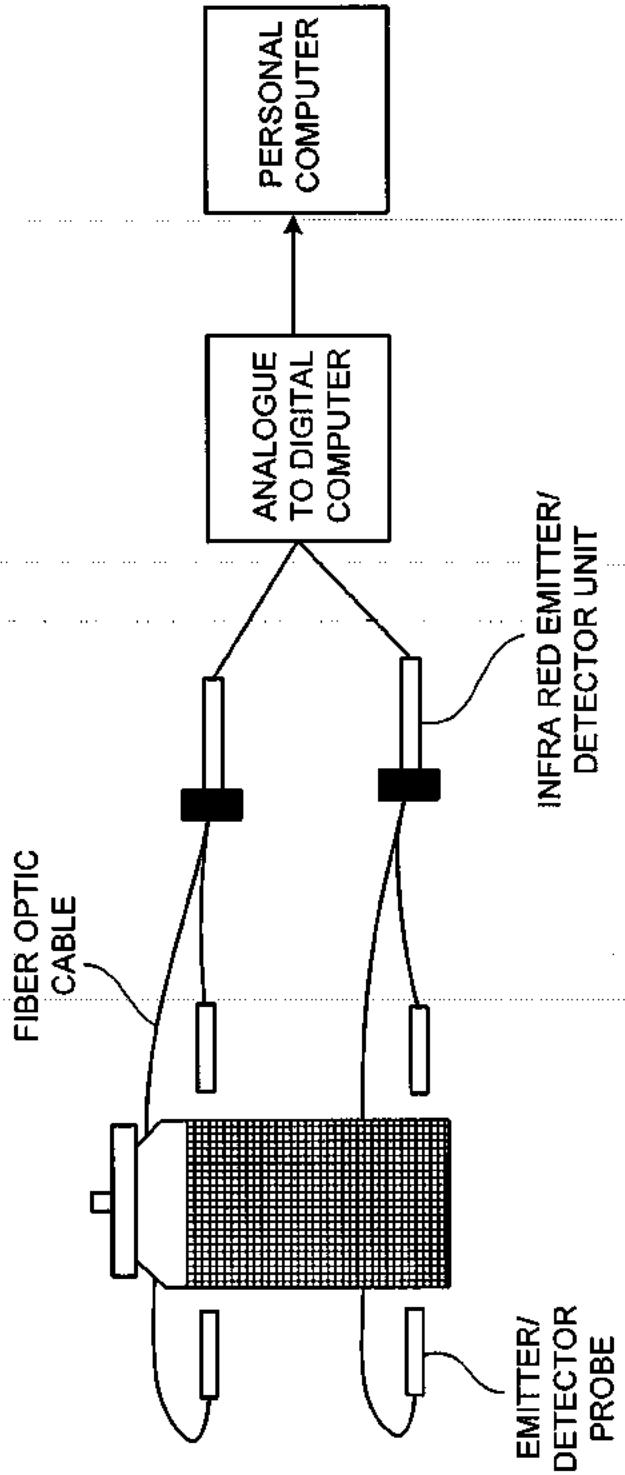
Irwin WJ, Chauhan N, Smith EL, Grattan TJ, The Calculation of Free Drug Concentration in Cyclodextrin-Drug Complexes in the Presence of Competitors. *Pharmaceutical Sciences* 1995, 1:423-427

Signed.....Nfovind..... **Date**...31.July.07....


Averages of OSCAR data for formulation containing 40/ 4.5 µg Budesonide/ Formoterol, 0.3% w/w
PEG 1000, 0.0001% - 0.05% w/w PVP K25 in HFA-227
Lower sensor 0.0001% PVP
Lower sensor 0.0005% PVP
Lower sensor 0.001% PVP
Lower sensor 0.01% PVP
Lower sensor 0.03% PVP
Lower sensor 0.05% PVP
Transmission (V)
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
0
20
40
60
80
100
120
Time (s)


Averages of OSCAR data for formulations containing 320/ 4.5 µg Budesonide/ Formoterol, 0.3% PEG 1000, 0.0001% - 0.05% w/w PVP K25 in HFA-227
Lower sensor 0.0001% PVP
Lower sensor 0.0005% PVP
Lower sensor 0.001% PVP
Lower sensor 0.01% PVP
Lower sensor 0.03% PVP
Lower sensor 0.05% PVP
Transmission (V)
Time (s)
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
-1000
0
20
40
60
80
100
120


Averages of Turbiscan data for formulation containing 320/4.5ug Budesonide/Formoterol. 0.3% w/w PEG 1000. 0.0001% - 0.05% w/w PVP K25, in HFA 227.
320/4.5ug 0.0001%. (Trans)
320/4.5ug 0.0005%. (Trans)
320/4.5ug 0.001%. (Trans)
320/4.5ug 0.01%. (Trans)
320/4.5ug 0.03%. (Trans)
320/4.5ug 0.05%. (Trans)
Percentage (%)
Time (min)
15
13
11
9
7
5
3
1
-1
0
2
4
6
8
10
12
14
16



SCHEMATIC FOR OSCAR SET-UP

FIG. 1

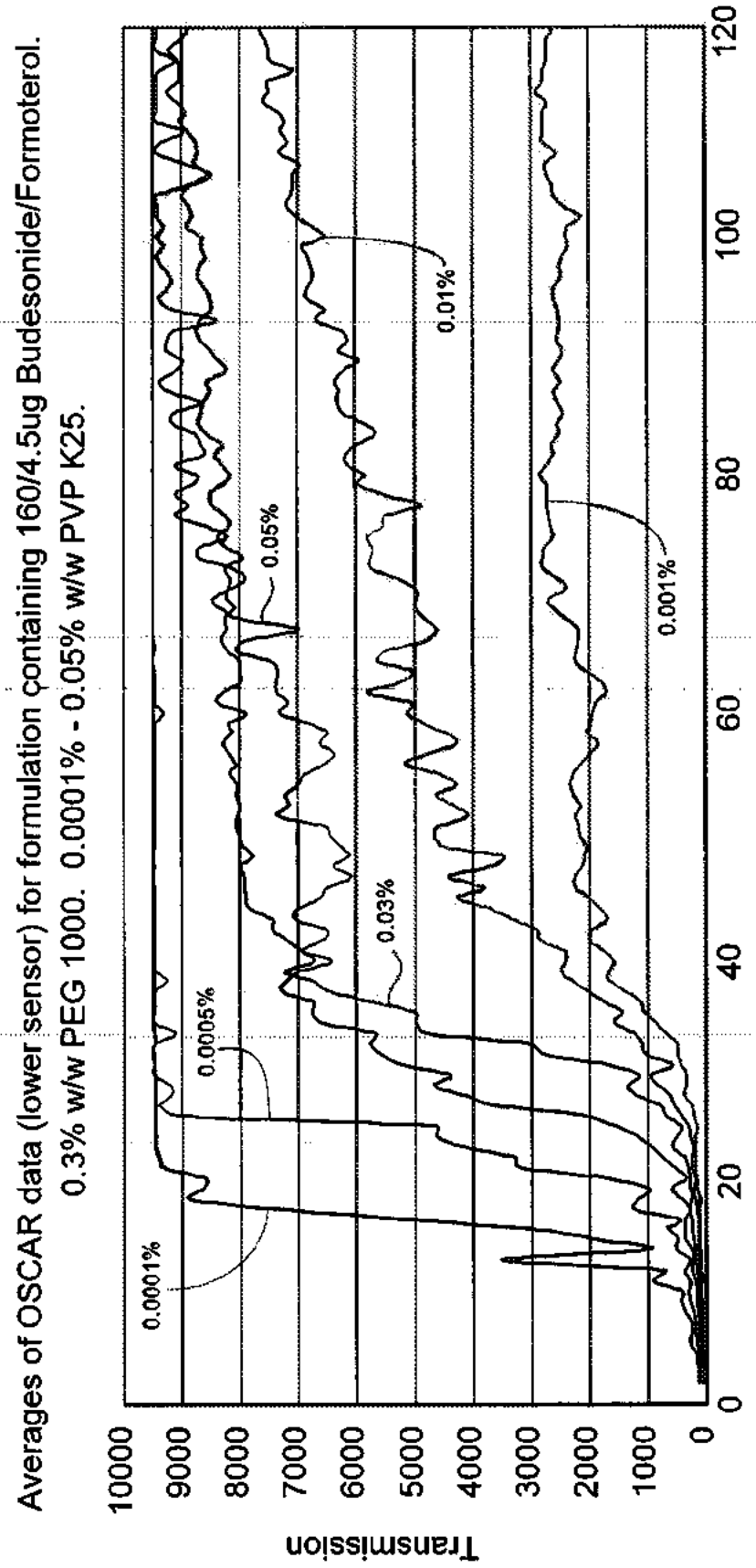

Averages of OSCAR data (lower sensor) for formulation containing 160/4.5ug Budesonide/Formoterol.
0.3% w/w PEG 1000. 0.0001% - 0.05% w/w PVP K25.
Transmission
Time (sec)
0.0001%
0.0005%
0.03%
0.05%
0.01%
0.001%
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
0
20
40
60
80
100
120

FIG. 2

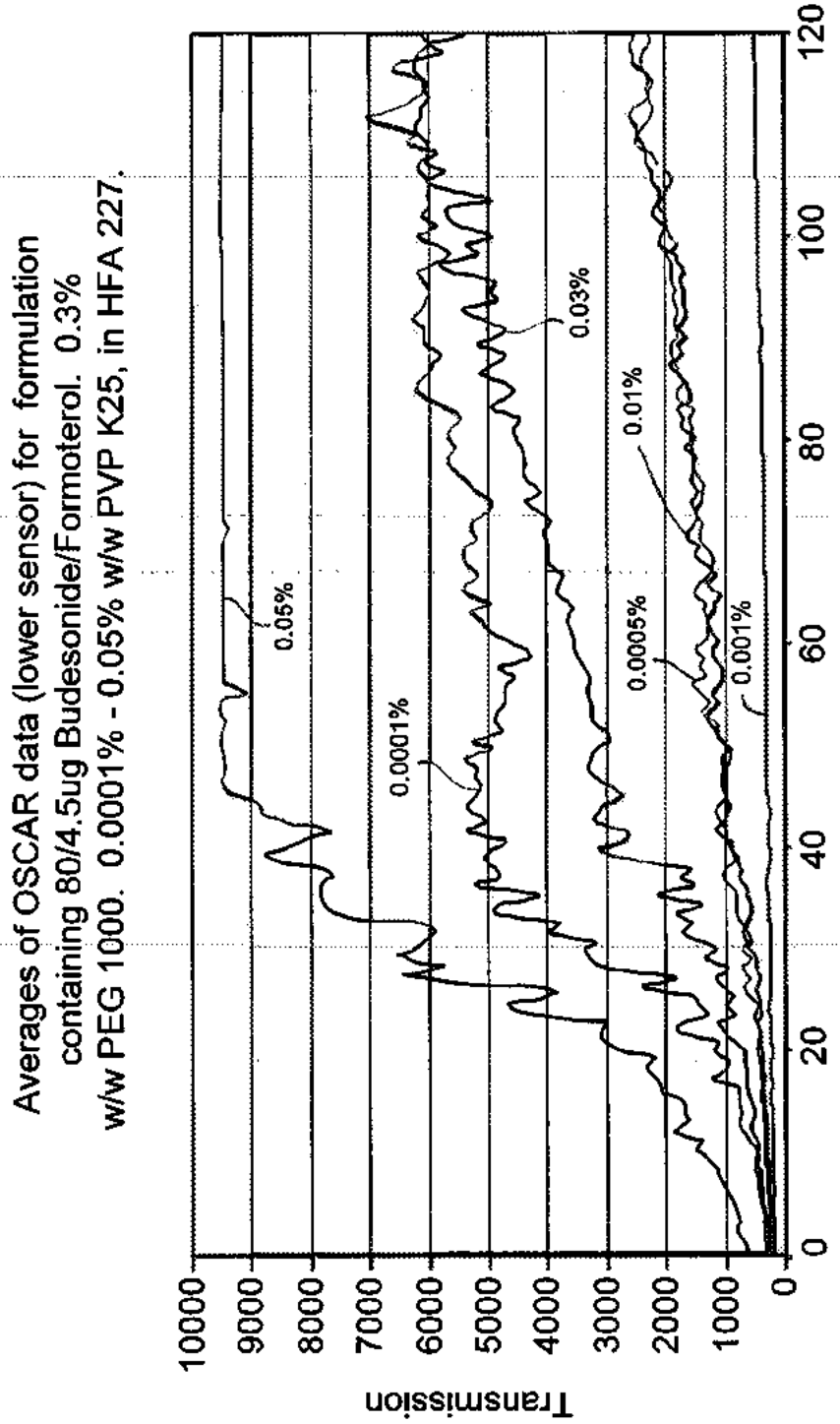

Averages of OSCAR data (lower sensor) for formulation
containing 80/4.5ug Budesonide/Formoterol. 0.3%
w/w PEG 1000. 0.0001% - 0.05% w/w PVP K25, in HFA 227.
Transmission
Time (sec)
0.05%
0.0001%
0.03%
0.01%
0.0005%
0.001%
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
0
20
40
60
80
100
120

FIG. 3

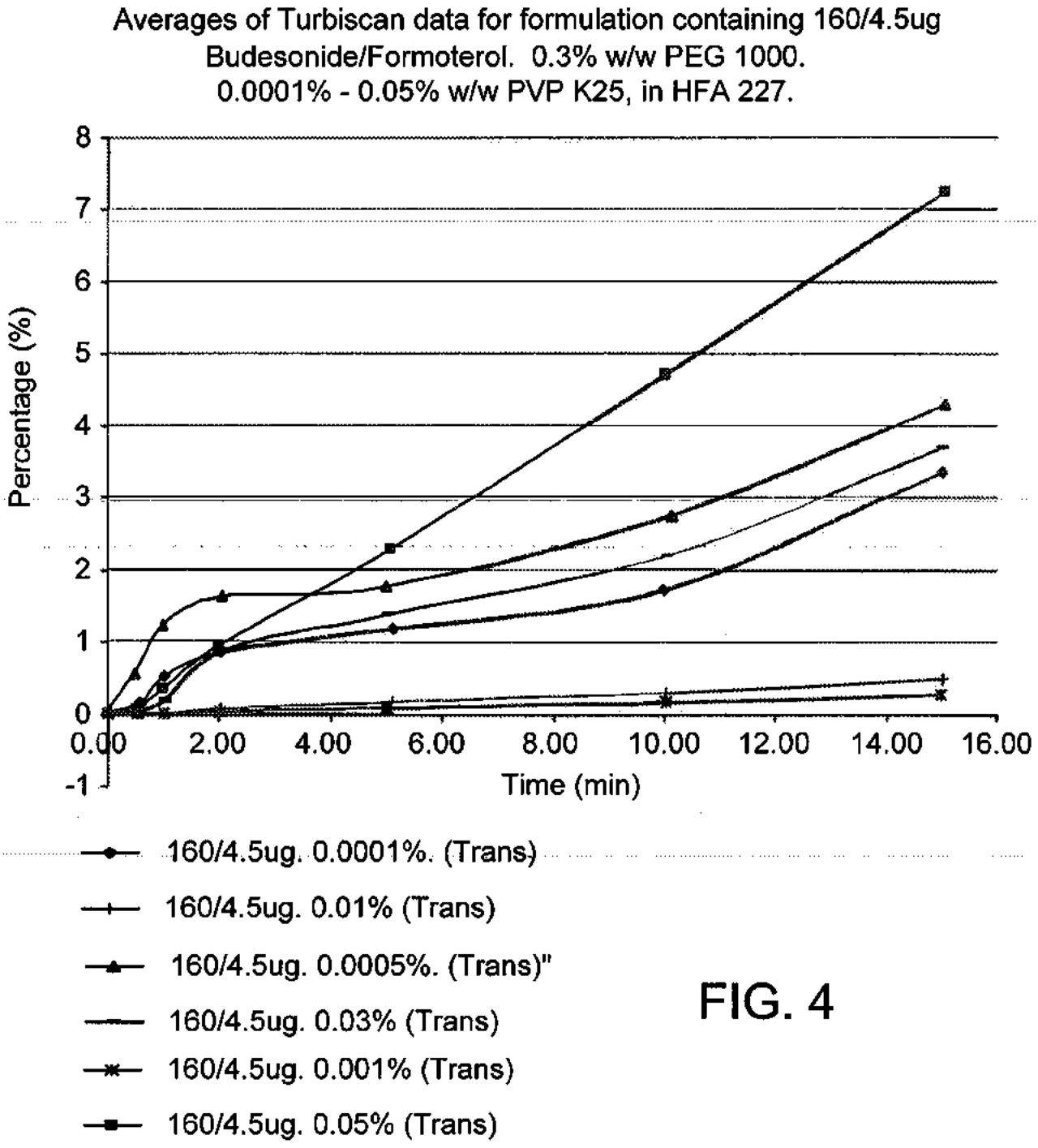

Averages of Turbiscan data for formulation containing 160/4.5ug Budesonide/Formoterol. 0.3% w/w PEG 1000. 0.0001% - 0.05% w/w PVP K25, in HFA 227.
Percentage (%)
8
7
6
5
4
3
2
1
0
-1
0.00
2.00
4.00
6.00
8.00
10.00
12.00
14.00
16.00
Time (min)
160/4.5ug. 0.0001%. (Trans)
160/4.5ug. 0.01% (Trans)
160/4.5ug. 0.0005%. (Trans)"
160/4.5ug. 0.03% (Trans)
160/4.5ug. 0.001% (Trans)
160/4.5ug. 0.05% (Trans)

FIG. 4

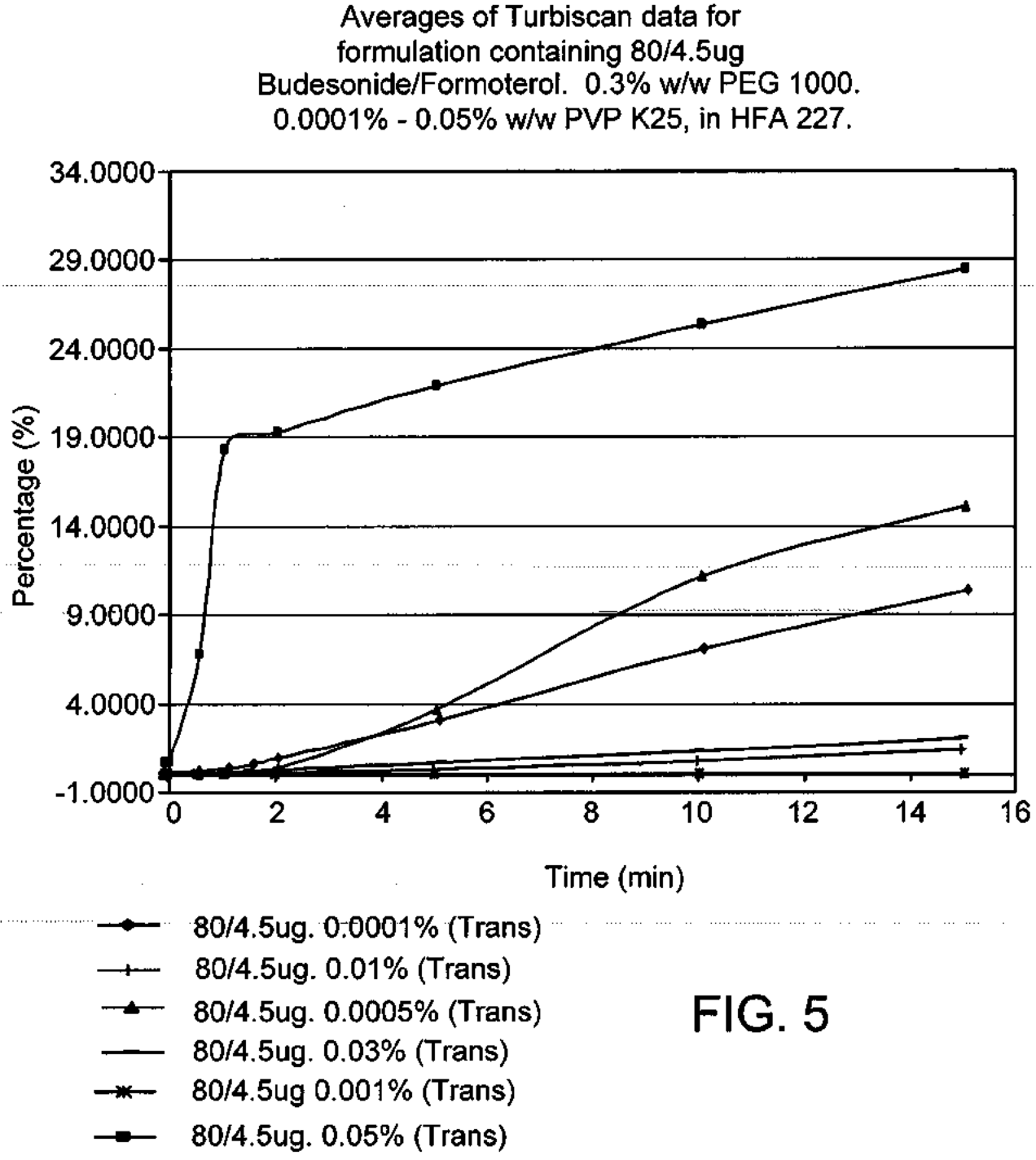

Averages of Turbiscan data for
formulation containing 80/4.5ug
Budesonide/Formoterol. 0.3% w/w PEG 1000.
0.0001% - 0.05% w/w PVP K25, in HFA 227.
34.0000
29.0000
24.0000
19.0000
14.0000
9.0000
4.0000
-1.0000
Percentage (%)
0
2
4
6
8
10
12
14
16
Time (min)
80/4.5ug. 0.0001% (Trans)
80/4.5ug. 0.01% (Trans)
80/4.5ug. 0.0005% (Trans)
80/4.5ug. 0.03% (Trans)
80/4.5ug 0.001% (Trans)
80/4.5ug. 0.05% (Trans)

FIG. 5

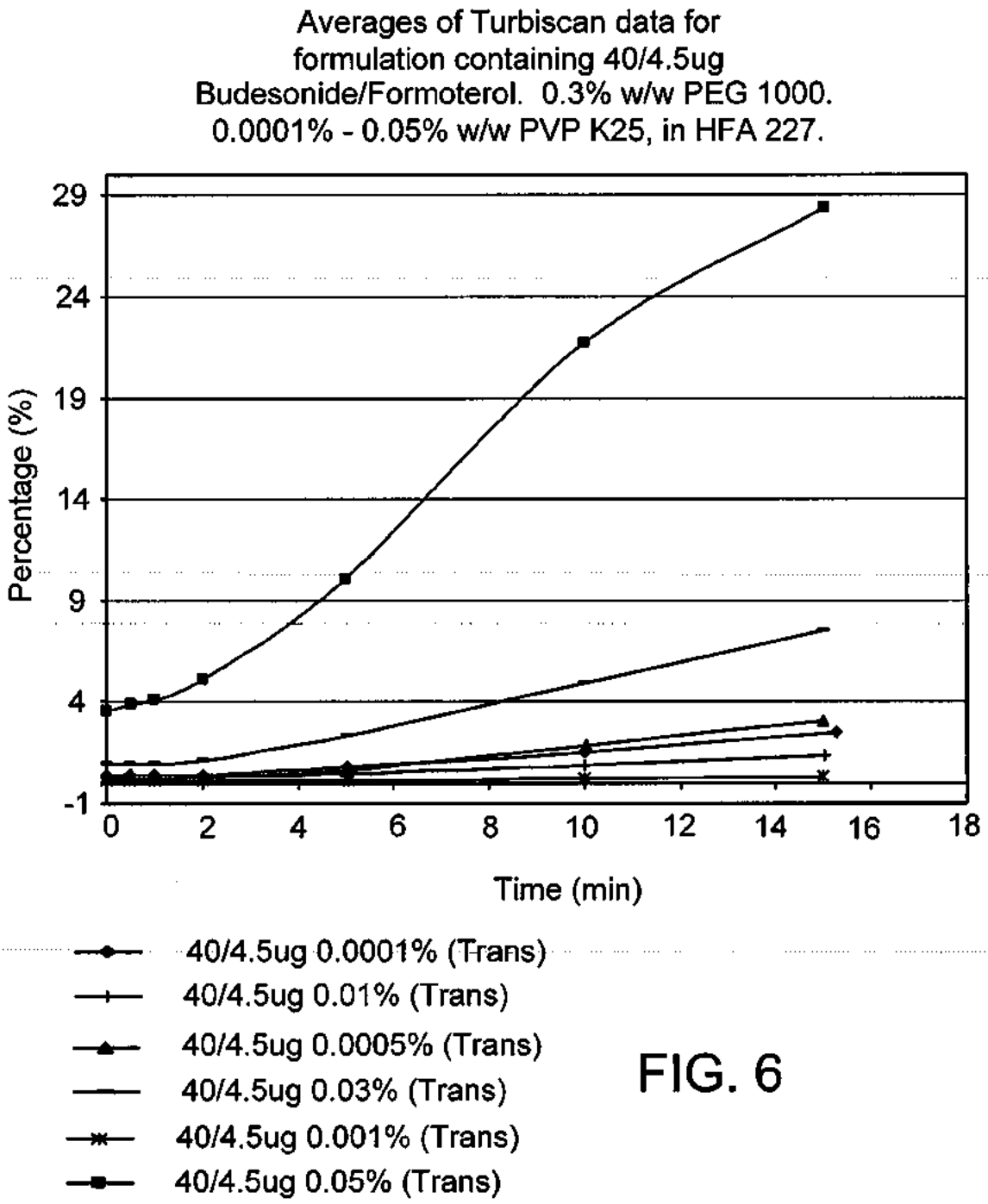

Averages of Turbiscan data for formulation containing 40/4.5ug Budesonide/Formoterol. 0.3% w/w PEG 1000. 0.0001% - 0.05% w/w PVP K25, in HFA 227.
Percentage (%)
29
24
19
14
9
4
-1
0
2
4
6
8
10
12
14
16
18
Time (min)
40/4.5ug 0.0001% (Trans)
40/4.5ug 0.01% (Trans)
40/4.5ug 0.0005% (Trans)
40/4.5ug 0.03% (Trans)
40/4.5ug 0.001% (Trans)
40/4.5ug 0.05% (Trans)

FIG. 6

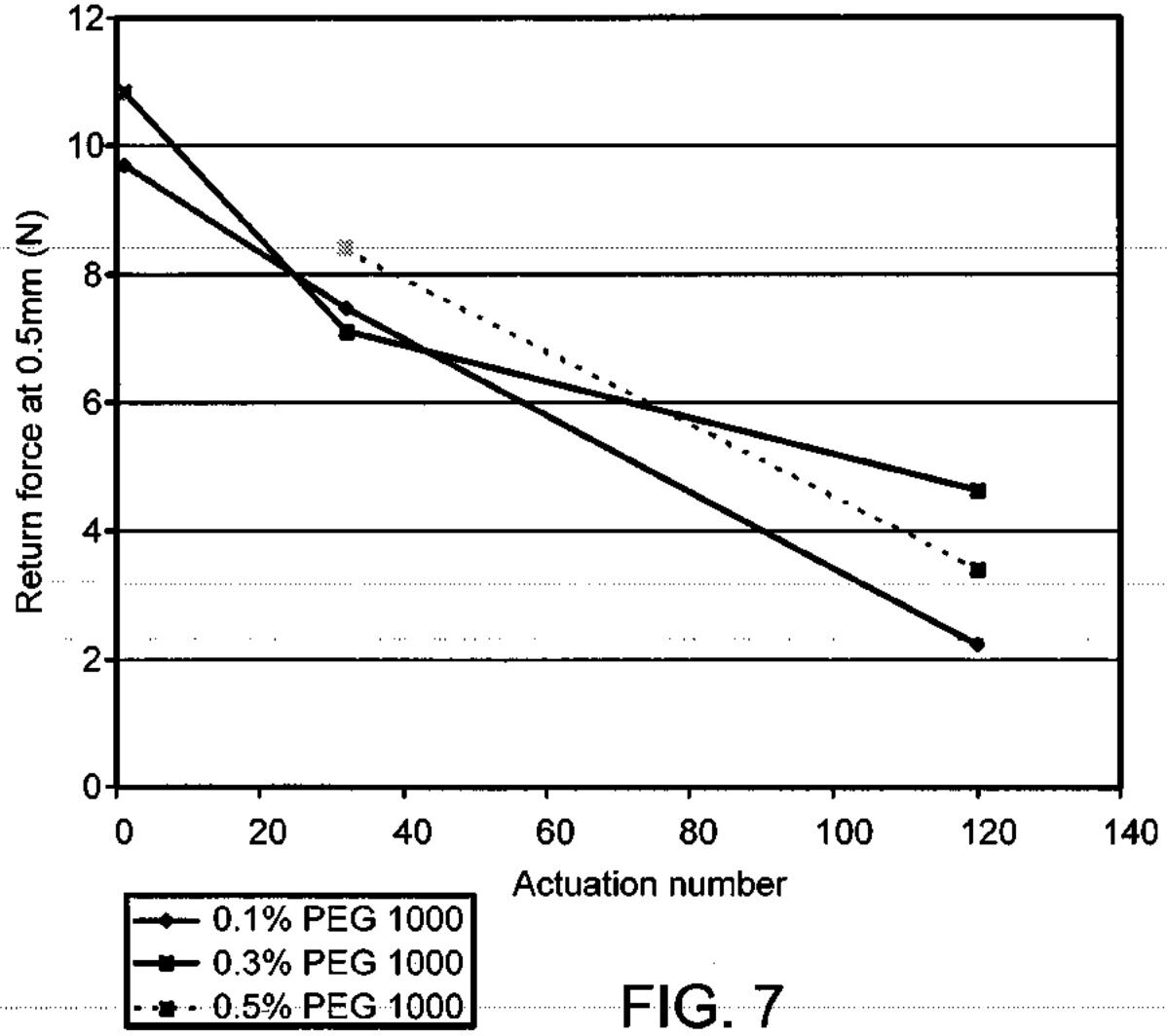

12
10
8
6
4
2
0
Return force at 0.5mm (N)
0
20
40
60
80
100
120
140
Actuation number
0.1% PEG 1000
0.3% PEG 1000
0.5% PEG 1000

FIG. 7

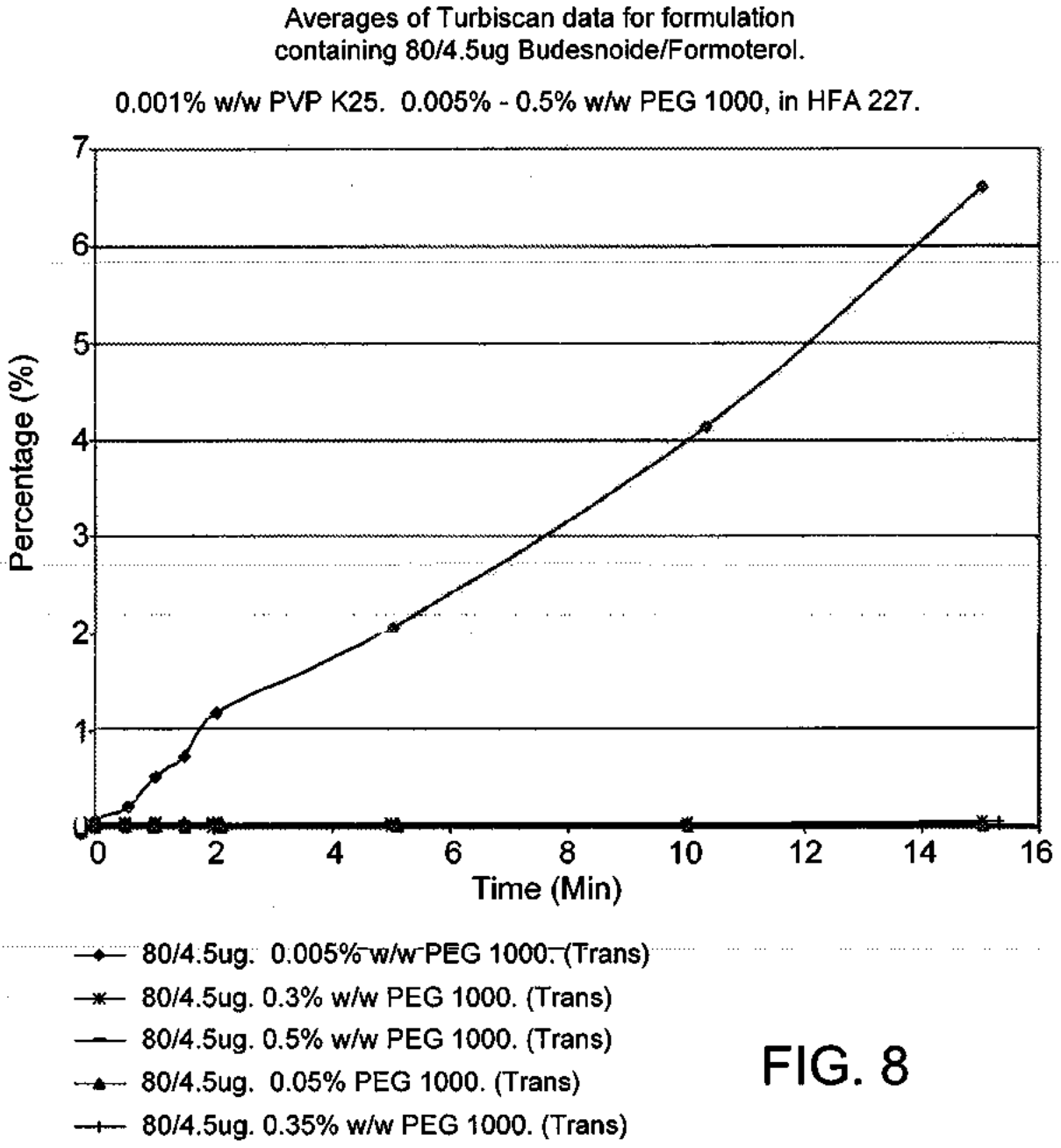

Averages of Turbiscan data for formulation
containing 80/4.5ug Budesnoide/Formoterol.
0.001% w/w PVP K25. 0.005% - 0.5% w/w PEG 1000, in HFA 227.
Percentage (%)
Time (Min)
0
1
2
3
4
5
6
7
0
2
4
6
8
10
12
14
16
80/4.5ug. 0.005% w/w PEG 1000. (Trans)
80/4.5ug. 0.3% w/w PEG 1000. (Trans)
80/4.5ug. 0.5% w/w PEG 1000. (Trans)
80/4.5ug. 0.05% PEG 1000. (Trans)
80/4.5ug. 0.35% w/w PEG 1000. (Trans)

FIG. 8

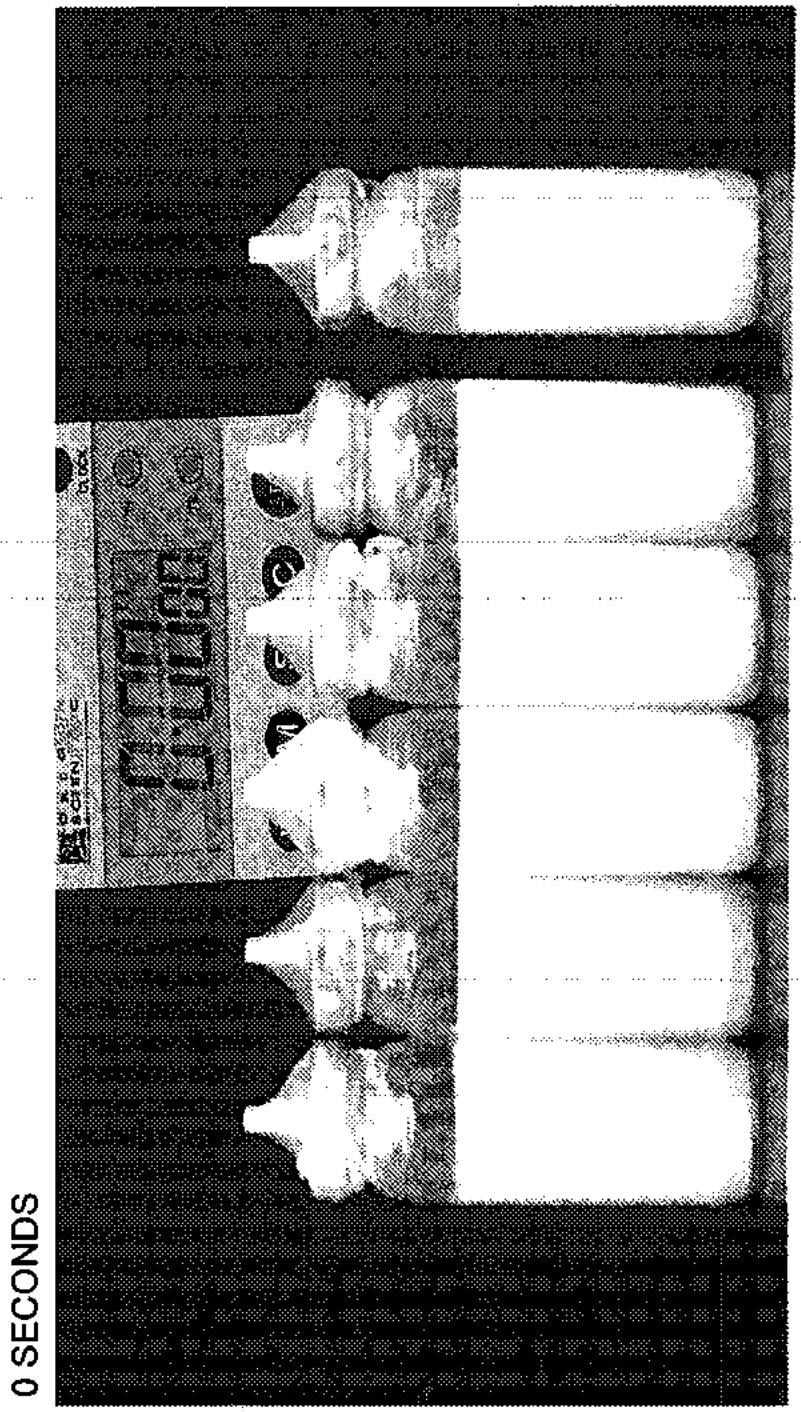


FIG. 9

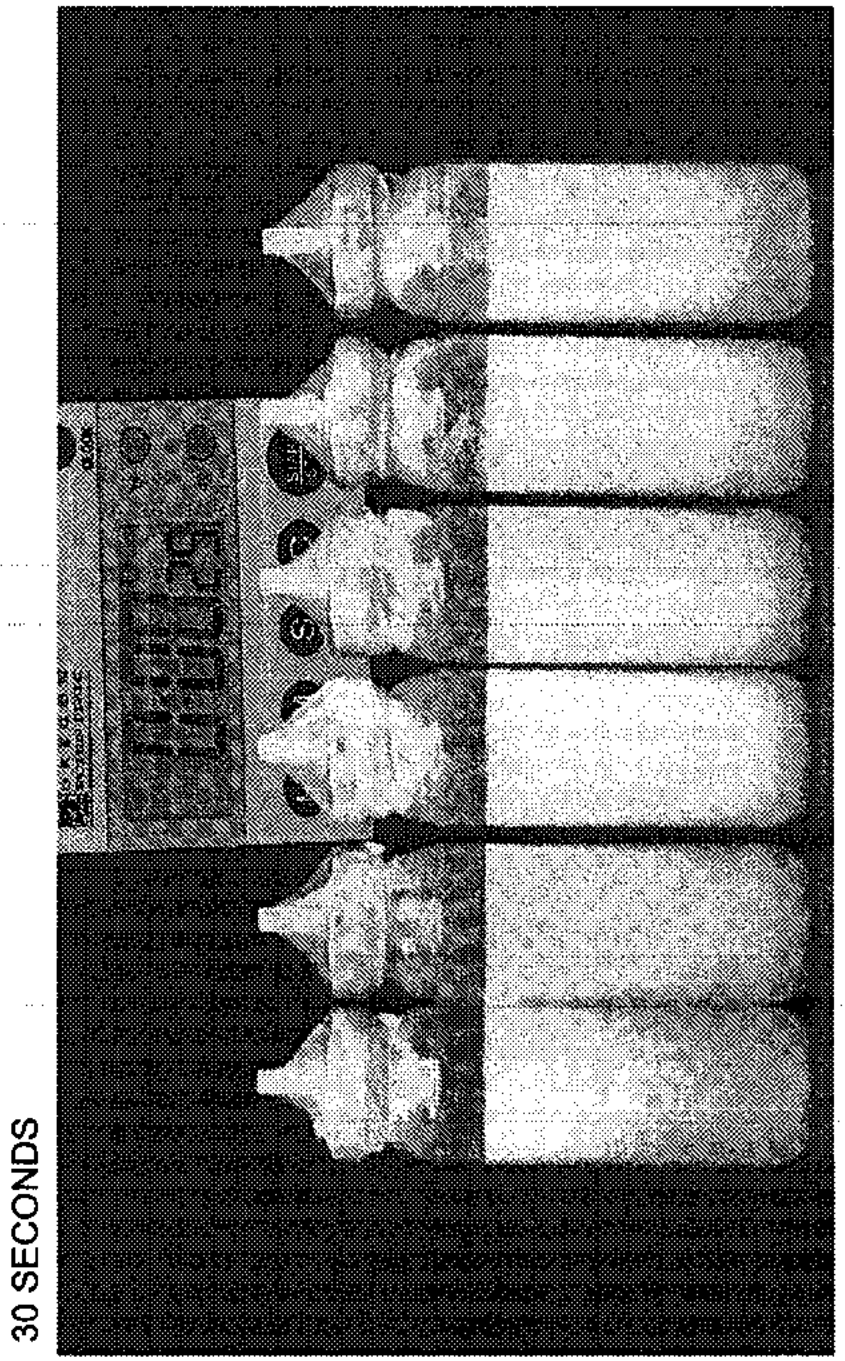


FIG. 10

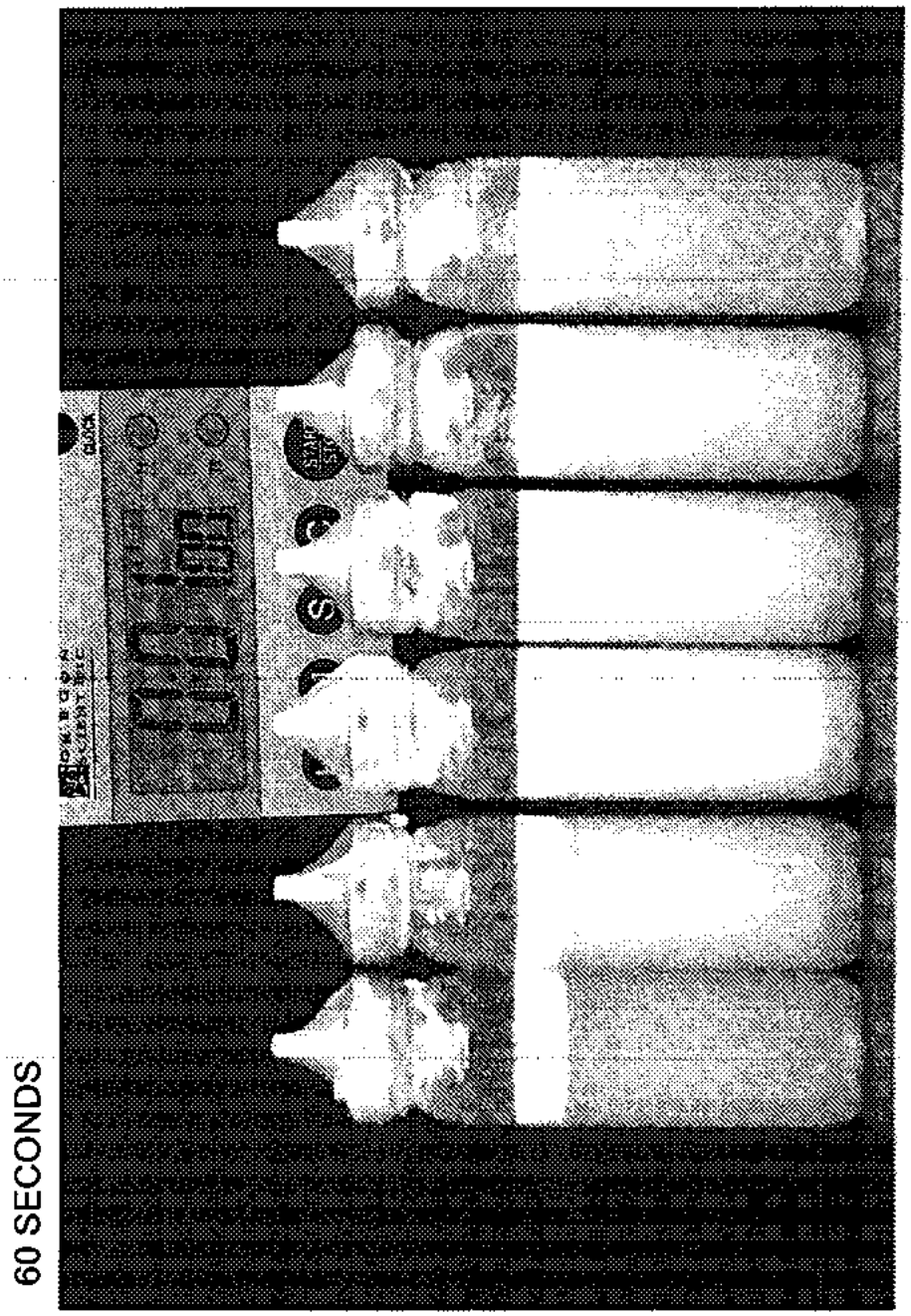


FIG. 11

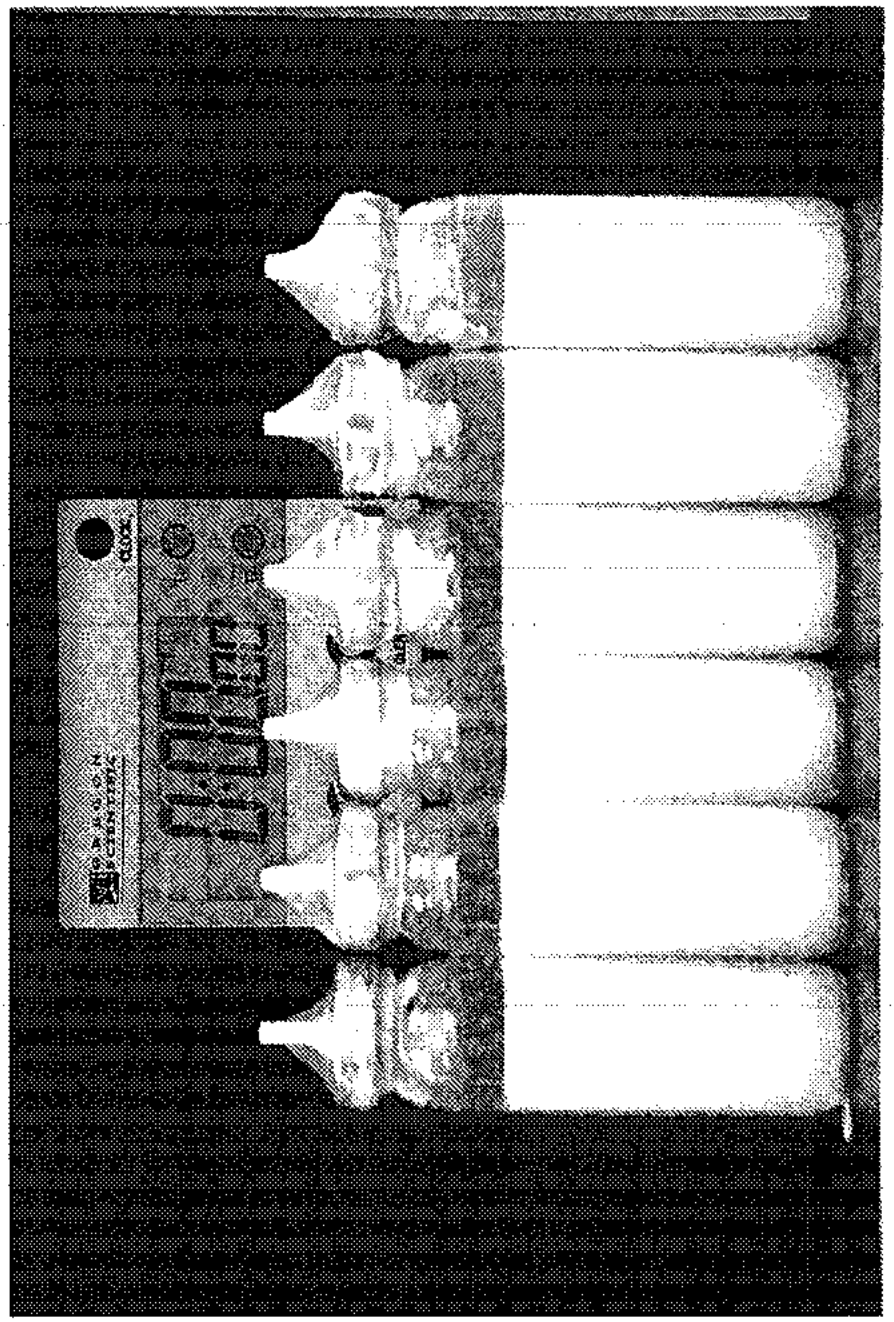


FIG. 12

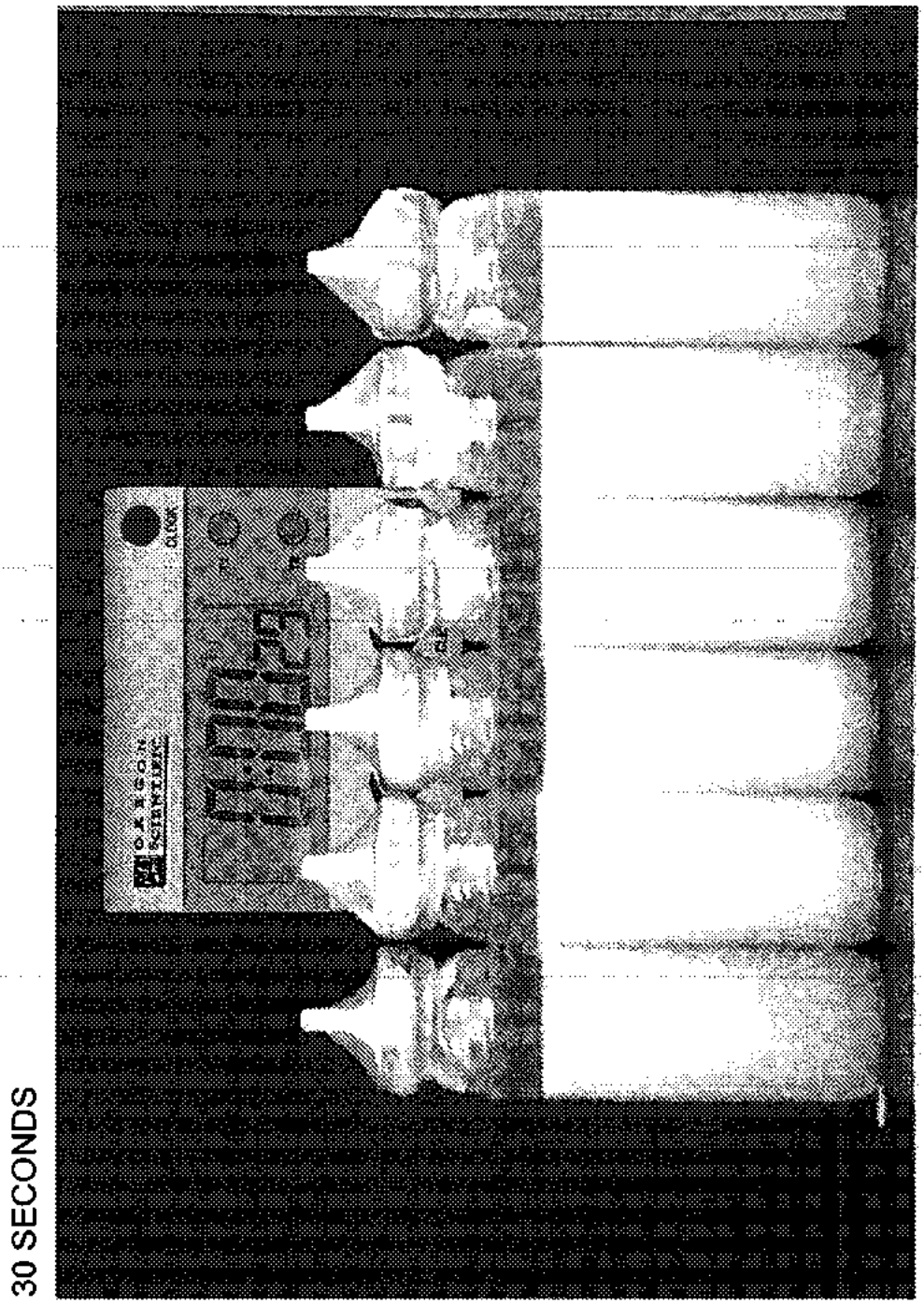


FIG.13

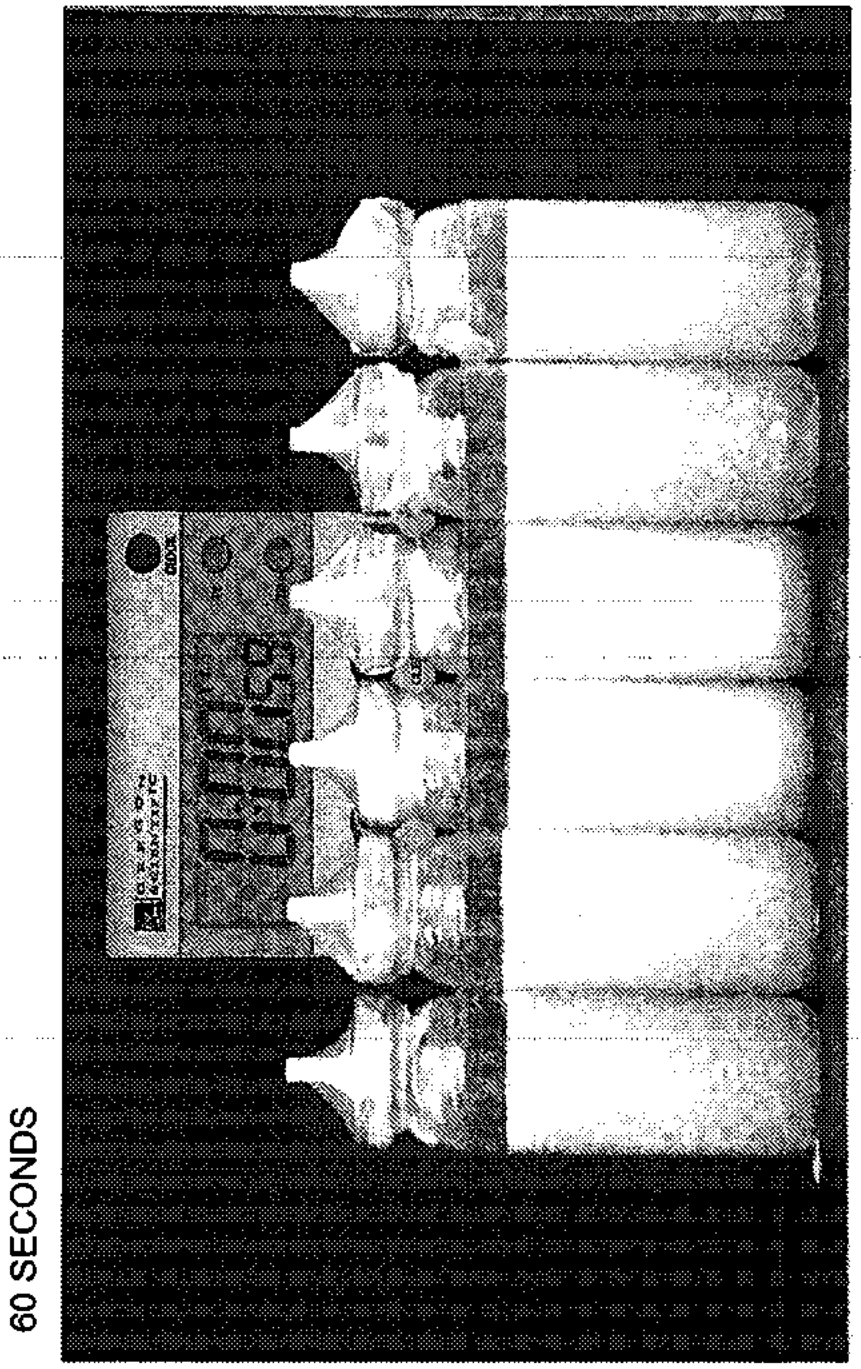
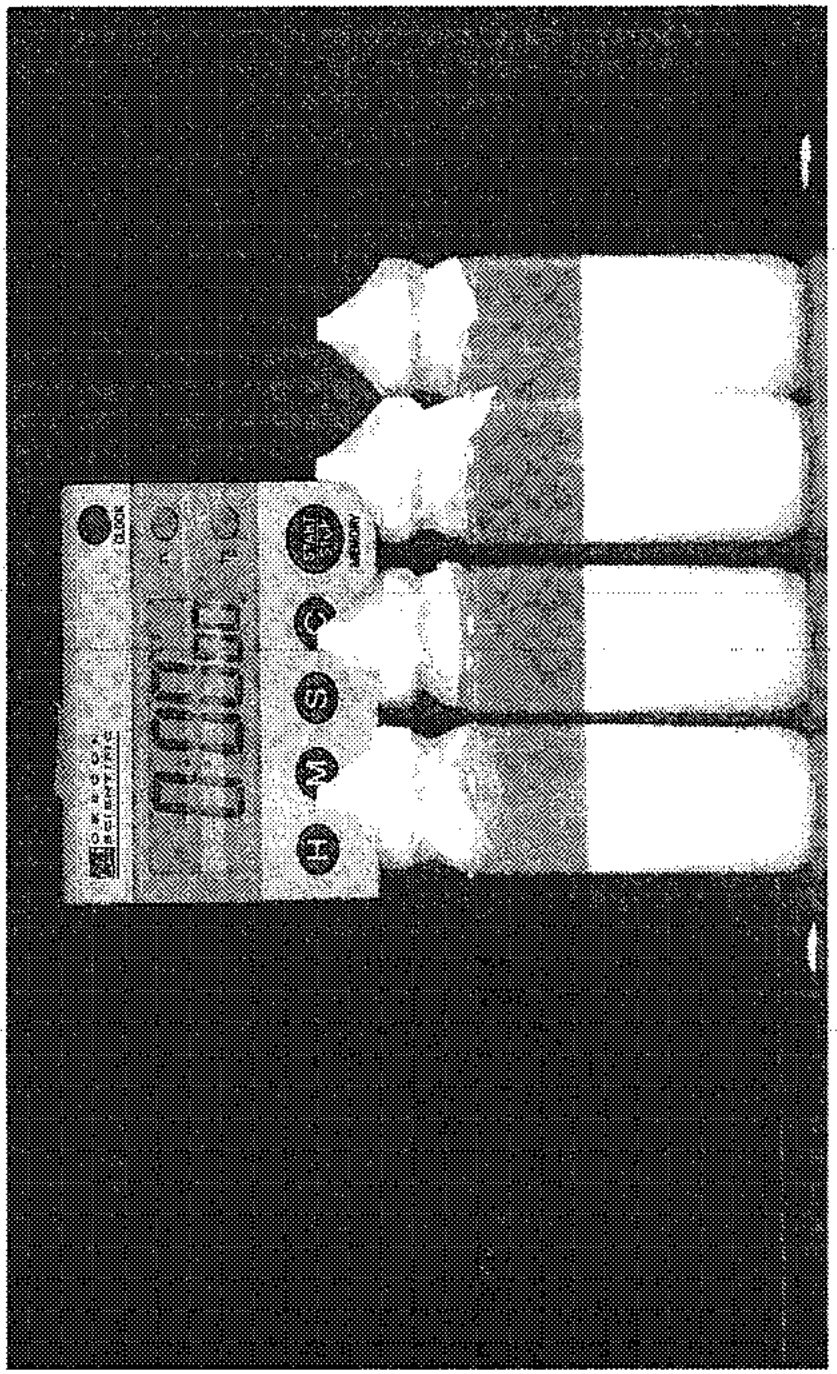


FIG. 14



PEG concn = left – right 0.005, 0.05, 0.35 and 0.5% w/w

FIG. 15

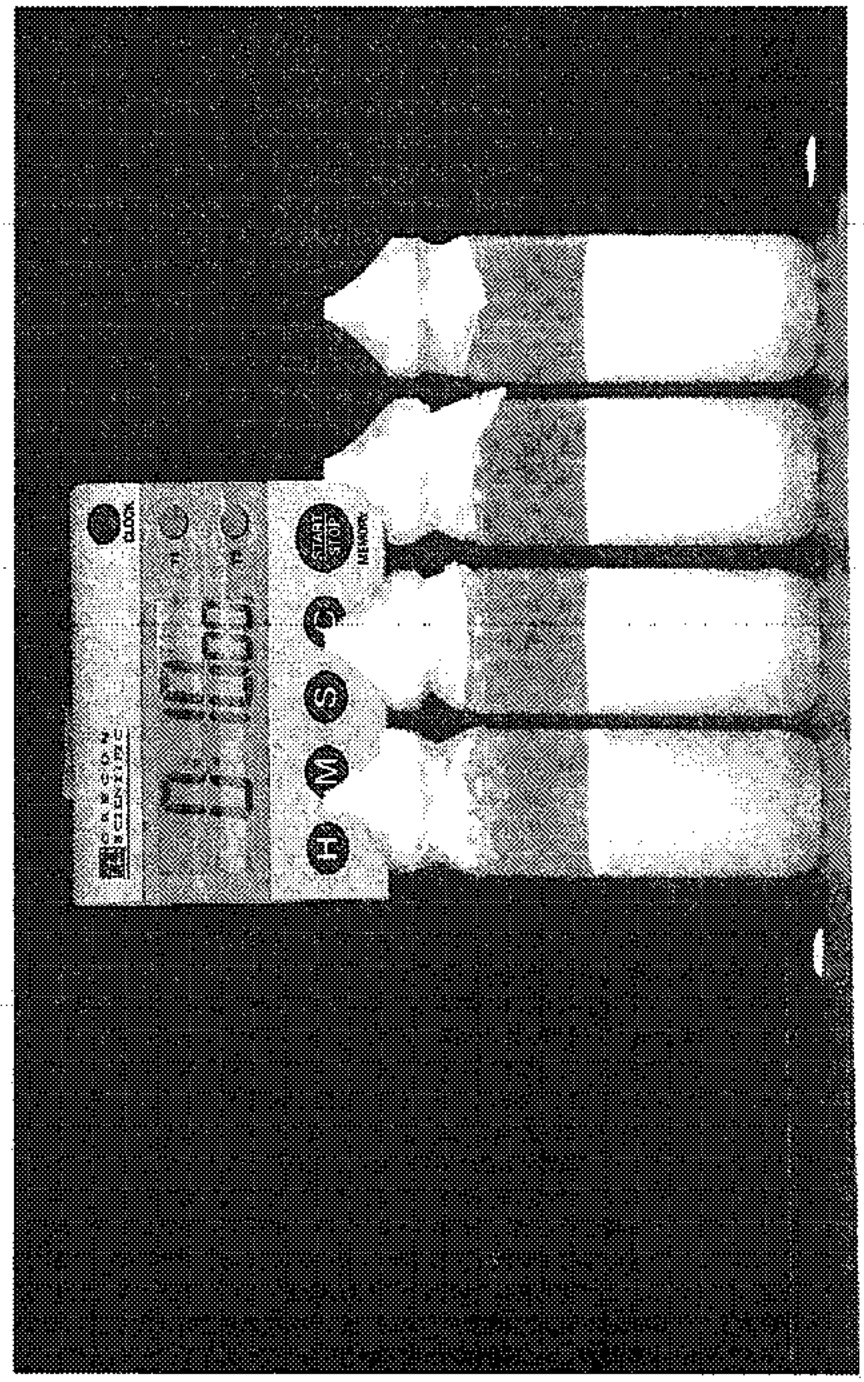


FIG. 16

Electronic Patent Application Fee Transmittal

Application Number:	10502685
Filing Date:	27-Jul-2004
Title of Invention:	Composition for inhalation
First Named Inventor/Applicant Name:	Nayna Govind
Filer:	Allyson Russell Hatton/Kimberly Hutchins
Attorney Docket Number:	06275-410US1

Filed as Large Entity

U.S. National Stage under 35 USC 371 Filing Fees

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Claims in excess of 20	1615	4	50	200
Independent claims in excess of 3	1614	1	200	200
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Extension-of-Time:				
Miscellaneous:				
Request for continued examination	1801	1	790	790
		Total in USD ($)		**1190**

Electronic Acknowledgement Receipt

EFS ID:	2107194
Application Number:	10502685
International Application Number:	
Confirmation Number:	7568
Title of Invention:	Composition for inhalation
First Named Inventor/Applicant Name:	Nayna Govind
Customer Number:	26164
Filer:	Allyson Russell Hatton/Stacey Seidel
Filer Authorized By:	Allyson Russell Hatton
Attorney Docket Number:	06275-410US1
Receipt Date:	21-AUG-2007
Filing Date:	27-JUL-2004
Time Stamp:	16:10:51
Application Type:	U.S. National Stage under 35 USC 371

Payment information:

Submitted with Payment	yes
Payment was successfully received in RAM	$1190
RAM confirmation Number	1236
Deposit Account	061050

File Listing:

Document Number	Document Description	File Name	File Size(Bytes) /Message Digest	Multi Part /.zip	Pages (if appl.)

1		rce.pdf	2224662 8be41efcab305068102e3560f653c59c963b5709	yes	37

	Multipart Description/PDF files in .zip description		
	Document Description	**Start**	**End**
	Request for Continued Examination (RCE)	1	1
	Amendment After Final	2	2
	Claims	3	5
	Amendment After Final	6	6
	Applicant Arguments/Remarks Made in an Amendment	7	13
	Affidavit/Dec/Exhibit after Notice of Appeal	14	18
	Affidavit/Dec/Exhibit after Notice of Appeal	19	21
	Drawings	22	37

Warnings:					
Information:					
2	Fee Worksheet (PTO-06)	fee-info.pdf	8450 95f503dfc2c262e2b19b83cba6e7071bd0936e5b	no	2
Warnings:					
Information:					
			Total Files Size (in bytes):	2233112	

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

PTO/SB/06 (12-04)
Approved for use through 7/31/2006. OMB 0651-0032
U.S. Patent and Trademark Office: U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

PATENT APPLICATION FEE DETERMINATION RECORD
Substitute for Form PTO-875

Application or Docket Number: 10502685

APPLICATION AS FILED – PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA	SMALL ENTITY RATE ($)	SMALL ENTITY FEE ($)	OR	OTHER THAN SMALL ENTITY RATE ($)	OTHER THAN SMALL ENTITY FEE ($)
BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A			N/A	
SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A			N/A	
EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A			N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*	X =		OR	X =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*	X =			X =	
APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $250 ($125 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).						
MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))			N/A			N/A	
			TOTAL			TOTAL	

* If the difference in column 1 is less than zero, enter "0" in column 2.

APPLICATION AS AMENDED – PART II

11.3.06

AMENDMENT A

	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	SMALL ENTITY RATE ($)	SMALL ENTITY ADDITIONAL FEE ($)	OR	OTHER THAN SMALL ENTITY RATE ($)	OTHER THAN SMALL ENTITY ADDITIONAL FEE ($)
Total (37 CFR 1.16(i))	* 12	Minus	** 20	* —	X =		OR	X 50 =	
Independent (37 CFR 1.16(h))	* 1	Minus	*** 3	* —	X =		OR	X 200 =	
Application Size Fee (37 CFR 1.16(s))							OR		
FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))					N/A		OR	N/A	
					TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	✓

08.21.07

AMENDMENT B

	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)	OR	RATE ($)	ADDITIONAL FEE ($)
Total (37 CFR 1.16(i))	* 21	Minus	** 20	= 1	X =		OR	X =	200
Independent (37 CFR 1.16(h))	* 4	Minus	*** 3	= 1	X =		OR	X =	200
Application Size Fee (37 CFR 1.16(s))							OR		
FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))					N/A		OR	N/A	
					TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	400

1, 16, 17, 18

Pd

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".
*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".
The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.

This collection of information is required by 37 CFR 1.16. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant	: Nayna Govind *et al.*	Art Unit	: 1616
Serial No.	: 10/502,685	Examiner	: Alton Pryor
Filed	: July 27, 2004	Conf. No.	: 7568
Title	: COMPOSITION FOR INHALATION		

MAIL STOP AF
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

NOTICE OF APPEAL

Applicants hereby appeal to the Board of Patent Appeals and Interferences from the action dated January 29, 2007, finally rejecting claims 1-3, 5-9, and 12-15.

A petition for an extension of time under 37 CFR § 1.136 to extend the time to respond to the final rejection for three months to and including July 29, 2007, is attached.

Please apply the required fee of $500 for the appeal, and any other necessary charges, or any credits, to Deposit Account No. 06-1050, referencing Attorney Docket No. 06275-410US1.

Respectfully submitted,

Date: July 27, 2007

Janis K. Fraser, Ph.D., J.D.
Reg. No. 34,819

Fish & Richardson P.C.
225 Franklin Street
Boston, MA 02110
Telephone: (617) 542-5070
Facsimile: (617) 542-8906

21698323.doc

Electronic Patent Application Fee Transmittal

Application Number:	10502685
Filing Date:	27-Jul-2004
Title of Invention:	Composition for inhalation
First Named Inventor/Applicant Name:	Nayna Govind
Filer:	Allyson Russell Hatton/Kimberly Hutchins
Attorney Docket Number:	06275-410US1

Filed as Large Entity

U.S. National Stage under 35 USC 371 Filing Fees

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				
Extension - 3 months with $0 paid	1253	1	1020	1020

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Miscellaneous:				
			Total in USD ($)	**1020**

Electronic Acknowledgement Receipt

EFS ID:	2019205
Application Number:	10502685
International Application Number:	
Confirmation Number:	7568
Title of Invention:	Composition for inhalation
First Named Inventor/Applicant Name:	Nayna Govind
Customer Number:	26164
Filer:	Allyson Russell Hatton/Kimberly Hutchins
Filer Authorized By:	Allyson Russell Hatton
Attorney Docket Number:	06275-410US1
Receipt Date:	27-JUL-2007
Filing Date:	27-JUL-2004
Time Stamp:	13:54:59
Application Type:	U.S. National Stage under 35 USC 371

Payment information:

Submitted with Payment	yes
Payment was successfully received in RAM	$1020
RAM confirmation Number	5746
Deposit Account	061050

File Listing:

Document Number	Document Description	File Name	File Size(Bytes) /Message Digest	Multi Part /.zip	Pages (if appl.)

1		410.pdf	268022 a41dbe2d06f0aaf879d331aaa082316b7f121871	yes	2

Multipart Description/PDF files in .zip description		
Document Description	**Start**	**End**
Extension of Time	1	1
Notice of Appeal Filed	2	2

Warnings:

Information:

2	Fee Worksheet (PTO-06)	fee-info.pdf	8158 c8b2207e5721630d91e0185a29a502be7b36e293	no	2

Warnings:

Information:

Total Files Size (in bytes):	276180

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111
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New International Application Filed with the USPTO as a Receiving Office
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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant	: Nayna Govind *et al.*	Art Unit	: 1616
Serial No.	: 10/502,685	Examiner	: Alton Pryor
Filed	: July 27, 2004	Conf. No.	: 7568
Title	: COMPOSITION FOR INHALATION		

MAIL STOP AF
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

PETITION FOR THREE-MONTH EXTENSION OF TIME

Pursuant to 37 CFR § 1.136, Applicants hereby petition that the period for response to the action dated January 29, 2007, be extended for three months to and including July 29, 2007.

Please apply the required fee of $1020, and any other necessary charges, or any credits, to Deposit Account No. 06-1050, referencing Attorney Docket No. 06275-410US1.

Respectfully submitted,

Date: July 23, 2007

Janis K. Fraser, Ph.D., J.D.
Reg. No. 34,819

Fish & Richardson P.C.
225 Franklin Street
Boston, MA 02110
Telephone: (617) 542-5070
Facsimile: (617) 542-8906

21698324.doc

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/502,685	07/27/2004	Nayna Govind	06275-410US1	7568

26164 7590 01/29/2007

FISH & RICHARDSON P.C.
P.O BOX 1022
MINNEAPOLIS, MN 55440-1022

EXAMINER	
PRYOR, ALTON NATHANIEL	
ART UNIT	**PAPER NUMBER**
1616	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	01/29/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/502,685	GOVIND ET AL.	
	Examiner	Art Unit	
	Alton N. Pryor	1616	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *03 November 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) *1-3,5-9 and 12-15* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *1-3,5-9,12-15* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

I. Rejection of claims 12-15 under 35 USC 112, 1st paragraph will be maintained in light of amendment filed 1/3/06 for reason on record and reason as follows. Claims 12-15 recite preventing language.

II. Rejection of claims 1-3,5-9,12 under 35 USC 103(a) as being obvious over Meade will be maintained for reason on record and reason as follows. Claims 13-15 are added to this rejection.

Applicant argues:

a) Neither Meade nor Weers disclose a pharmaceutical composition comprising PVP at a concentration of 0.001 % w/w. In fact, neither reference discloses any particular concentration of PVP. Therefore, it is important for Applicant to show the criticality of the claimed PVP concentration versus concentrations of PVP slightly greater and less than 0.001 %.

b) In examples described in Weers at columns 30-35, the concentration of phosphatidylcholine ranges from 0.03% w/w in Example 1 to 0.11% w/w in Example VIII, which is 30 to 110 times higher than specified in claim 1. No implication in Weers would suggest that when PVP is used, it should be in a far lower concentration than that utilized for phosphatidylcholine.

c) The surprising discovery that 0.001% w/w PVP gave consistently stable formulation over the required dosage, incorporating a wide

range of concentrations of active compounds and at much lower concentration than recited in the prior art.

d) It was demonstrated that 0.001% w/w PVP gave the best suspension stability when compared to a range of PVP concentrations from 0.0001% to 0.05% w/w. This could not have been predicted from Mistry et al. or from the references cited in the Office Action (Meade and Weers).

Examiner argues:

a) Since the prior art does not disclose any particular range of PVP, it is imperative that applicant show the criticality of the invention comprising 0.001 % w/w PVP by testing the invention comprising slightly more and less than 0.001% w/w PVP.

b) It is improper to conclude that amount of phosphatidylcholine used in Weers would equate to the amount of PVP that should be used since structures differ in both chemical and physical properties. In addition it is important to note that Weers is not relied upon for the use of PVP since Meade uses PVP.

c) Applicant fails to provide examples, which show the criticality of 0.001 % w/w PVP versus the invention where the PVP concentration is slightly greater or less than 0.001 % w/w PVP.

d) See argument in Examiner's c).

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Telephonic Inquiry

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Alton N. Pryor whose telephone number is 571-272-0621. The examiner can normally be reached on 8:00 a.m. - 4:30 p.m..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Johann Richter can be reached on 571-272-0646. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Alton Pryor
Primary Examiner
AU 1616

Search Notes

Application/Control No.	Applicant(s)/Patent under Reexamination
10/502,685	GOVIND ET AL.
Examiner	**Art Unit**
Alton N. Pryor	1616

SEARCHED			
Class	Subclass	Date	Examiner
424	45,46 489	1/18/2007	ANP

INTERFERENCE SEARCHED			
Class	Subclass	Date	Examiner

SEARCH NOTES (INCLUDING SEARCH STRATEGY)		
	DATE	EXMR
inventor	1/17/2007	ANP

PTO/SB/06 (12-04)
Approved for use through 7/31/2006. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

PATENT APPLICATION FEE DETERMINATION RECORD

Substitute for Form PTO-875

Application or Docket Number: 10502685

APPLICATION AS FILED – PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA	SMALL ENTITY RATE ($)	SMALL ENTITY FEE ($)	OR	OTHER THAN SMALL ENTITY RATE ($)	OTHER THAN SMALL ENTITY FEE ($)
BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A			N/A	
SEARCH FEE (37 CFR 1.16(k), (l), or (m))	N/A	N/A	N/A			N/A	
EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A			N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*	X =		OR	X =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*	X =			X =	
APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $250 ($125 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).						
MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))			N/A			N/A	
			TOTAL			TOTAL	

* If the difference in column 1 is less than zero, enter "0" in column 2.

APPLICATION AS AMENDED – PART II

11.3.06

AMENDMENT A	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	SMALL ENTITY RATE ($)	SMALL ENTITY ADDITIONAL FEE ($)	OR	OTHER THAN SMALL ENTITY RATE ($)	OTHER THAN SMALL ENTITY ADDITIONAL FEE ($)
Total (37 CFR 1.16(i))	* 12	Minus	** 20	= —	X =		OR	X 50 =	
Independent (37 CFR 1.16(h))	* 1	Minus	*** 3	= —	X =		OR	X 200 =	
Application Size Fee (37 CFR 1.16(s))									
FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))					N/A		OR	N/A	
					TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

AMENDMENT B	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)	OR	RATE ($)	ADDITIONAL FEE ($)
Total (37 CFR 1.16(i))	*	Minus	**	=	X =		OR	X =	
Independent (37 CFR 1.16(h))	*	Minus	***	=	X =		OR	X =	
Application Size Fee (37 CFR 1.16(s))									
FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))					N/A		OR	N/A	
					TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".
*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".
The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.

PTO/SB/07 (08-03)
Approved for use through 7/31/2006. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

MULTIPLE DEPENDENT CLAIM FEE CALCULATION SHEET

Substitute for Form PTO-1360
(For use with Form PTO/SB/06)

Application Number	Filing Date
10/502,635	
Applicant(s)	

11-3-06

Use for additional claims or amendments

CLAIMS	AS FILED 7-27-04		AFTER FIRST AMENDMENT		AFTER SECOND AMENDMENT	
	Indep	Depend	Indep	Depend	Indep	Depend
1	1		1			
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Total Depend	11		11			
Total Claims	12		12			

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant	: Nayna Govind *et al.*	Art Unit	: 1616
Serial No.	: 10/502,685	Examiner	: Alton Nathaniel Pryor
Filed	: July 27, 2004	Conf. No.	: 7568
Title	: COMPOSITION FOR INHALATION		

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

AMENDMENT IN REPLY TO ACTION OF MAY 4, 2006

Please amend the above-identified application as follows:

Amendments to the Claims:

This listing of claims replaces all prior versions and listings of claims in the application:

Listing of Claims:

1. (Currently amended) A pharmaceutical composition comprising formoterol, budesonide, HFA 227, PVP and PEG, wherein PVP is present in an amount of 0.001% w/w.

2. (Currently amended) A ~~formulation~~ pharmaceutical composition according to claim 1 ~~characterised in that the PVP is present from about 0.0005 to about 0.05 %w/w and~~ wherein the PEG is present from about 0.05 to about 0.35% w/w.

3. (Previously presented) A pharmaceutical composition according to claim 1 in which the PVP is PVP K25.

4. (Canceled)

5. (Previously presented) A pharmaceutical composition according to claim 1 in which the PEG is PEG 1000.

6. (Previously presented) A pharmaceutical composition according to claim 1 in which the PEG is present in an amount of 0.3% w/w.

7. (Previously presented) A pharmaceutical composition according to claim 1 in which formoterol is in the form of its fumarate dihydrate salt.

8. (Previously presented) A pharmaceutical composition according to claim 1 in which the formoterol is in the form of the single R, R-enantiomer.

9. (Previously presented) A pharmaceutical composition according to claim 1 in which the second active ingredient is the 22R-epimer of budesonide.

10-11. (Canceled)

12. (Currently amended) A method of treating or preventing the symptoms of a respiratory disorder ~~in a mammal which comprises~~, comprising administering to a patient a pharmaceutical composition according to claim 1, wherein the respiratory disorder is asthma, rhinitis, or chronic obstructive pulmonary disease (COPD).

13. (New) The method of claim 12, wherein the respiratory disorder is asthma.

14. (New) The method of claim 12, wherein the respiratory disorder is rhinitis.

15. (New) The method of claim 12, wherein the respiratory disorder is COPD.

REMARKS

Upon entry of the above amendment, claims 1-3, 5-9, and 12-15 will be pending, claims 4, 10 and 11 having been canceled and new claims 13-15 added. Support for the amendments and the new claims can be found throughout the specification and in the original claims. For example, support for the amendment to claim 1 can be found, *e.g.*, in original claim 4. Support for the amendment to claim 12 and for new claims 13-15 can be found, *e.g.*, in the specification at page 2, lines 18-23. No new matter has been added.

35 U.S.C. § 112, first paragraph

Claims 10-12 are rejected under 35 U.S.C. § 112, first paragraph, for allegedly failing to satisfy the enablement requirement. Claims 10 and 11 have been canceled, so the rejection of these claims is moot. The Examiner discusses several of the Wands factors in his explanation of the enablement rejection. Applicants address the Examiner's views of each of these factors below in the order in which they appear in the Office Action.

1. Nature of the invention. Claims 10 and 11 have been canceled, and claim 12, as amended, is directed to a method of treating a respiratory disorder, wherein the respiratory disorder is asthma, rhinitis, or COPD.

2. State of the prior art and the predictability or lack thereof in the art. The Examiner states that "in the absence of a showing of correlation between all the diseases claimed as capable of being treated by the composition of the instant claims, one of ordinary skill in the art is unable to fully predict possible results from the administration of the composition due to the unpredictability of the role of the respiratory disorder." Office Action at page 3. Applicants do not concede that one of ordinary skill in the art would not be able to predict possible results from the administration of the claimed composition in appropriate respiratory disorders in general.

However, in order to expedite prosecution, claims 10 and 11 have been canceled, and claim 12, as amended, is limited to a method of treating asthma, rhinitis, or COPD.

The Examiner is reminded that regarding the relationship of predictability of the art and the enablement requirement, "[t]he amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability in the art." MPEP 2164.03, citing In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). Further, "[t]he more that is known in the prior art about the nature of the invention, how to make, and how to use the invention, and the more predictable the art is, the less information needs to be explicitly stated in the specification." MPEP 2164.03.

Certainly, methods of treating respiratory diseases such as COPD, asthma, and rhinitis using compositions containing corticosteroids, such as budesonide, and/or beta-2-agonists, such as formoterol, have been described. For example, Zetterström *et al.* ("Improved asthma control with budesonide/formoterol in a single inhaler, compared with budesonide alone" *Eur. Respir. J.* 18:262-268, 2001; reference AK on the enclosed Form 1449) reported that asthma patients benefited from a combination therapy of budesonide and formoterol. Use of budesonide in the treatment of rhinitis is described in Pipkorn *et al.* ("Budesonide—a New Nasal Steroid" *Rhinology* 18:171-175, 1980; reference AI on the enclosed Form 1499). Bauer *et al.* (WO 99/15182, reference AC on the enclosed form 1449) reported a combination of budesonide and formoterol for the treatment of patients with COPD. HFAs, PVPs and PEGs were also known at the priority date of the application to be used in pressurized meter dose inhalers (pMDIs) (see, *e.g.*, WO 93/05765, cited in the information disclosure statement submitted July 27, 2004). In view of the knowledge in the field of treating respiratory disorders including COPD, asthma and rhinitis, and the disclosure of the specification, the claimed method can be reasonably predicted to successfully treat these disorders.

3. Quantity of experimentation needed to make or use the invention based on the content of the disclosure. The Examiner states that the quantity of experimentation is undue because "[o]ne of ordinary skill in the art would first need to determine the type of respiratory disorder to

be treated, and then determine if the composition would be suitable for said treatment and/or prevention." Office Action at page 4. Applicants do not concede that the quantity of experimentation needed to make or practice the originally claimed invention is undue. However, claims 10 and 11 have been canceled, and claim 12, as amended, is limited to a method of treating asthma, rhinitis, or COPD. Thus, there is no need to "determine the type of respiratory disorder to be treated."

The generalized use of aerosolized compositions in pMDIs for the delivery of therapeutics to treat respiratory disorders was well-known at the filing date of the application (see, *e.g.*, WO 93/05765, WO 01/78693, and WO 02/03958, cited in the Information Disclosure Statement submitted July 27, 2004). As discussed above, the use of budesonide and/or formoterol for the treatment of asthma, rhinitis and COPD was also known at the filing date of the application.

In view of the state of the knowledge in the field of treating asthma, rhinitis, and COPD at the priority date of the application, combined with guidance provided in the specification, it certainly would not require undue experimentation to make the formulations described in the specification, and then use them for the treatment of these disorders. The administration of the pharmaceutical compositions from pMDIs, and the subsequent monitoring of the subject for an improvement in symptoms, are routine methods.

(The Examiner skips from point 3 to point 6, as we do here also.)

6. Existence of working examples. The Examiner notes that "Applicant provides no working examples of how instant composition treats or prevents respiratory disorders…[or] how instant composition treats or prevents specific respiratory disorders such as asthma, rhinitis, or COPD." Office Action at page 4. As stated by the U.S. Court of Customs and Patent Appeals, "a specification need not contain a working example if the invention is otherwise disclosed in such a manner that one skilled in the art will be able to practice it without an undue amount of experimentation." In re Borkowski, 422 F.2d 904 (CCPA 1970).

The examples at pages 2 through 12 of the specification describe methods to evaluate physical suspension stability and pMDI valve performance. Thus working examples of the novel compositions are provided. Methods of treating asthma, rhinitis and COPD using budesonide and formoterol formulations are well known, and undue experimentation would not be required to perform the treatment method described in claim 12.

7. Breadth of the claims. The Examiner states that "Claims 10-12 are extremely broad due to the vast number of possible respiratory disorders encompassed by the instant invention." Office Action at page 4. Applicants do not concede that the claims as originally filed were overly broad. However, the breadth of the claims has been narrowed by the cancellation of claims 10 and 11 and the amendment of claim 12 such that it is limited to a method of treating asthma, rhinitis, or COPD. As amended, the claims certainly cannot be said to be overly broad.

8. Level of ordinary skill in the art. The Examiner admits that "the level of ordinary skill in the art is high," but asserts "the specification fails to provide sufficient support of the instant composition of the claims for the treatment of any respiratory disorder." Office Action at page 4. Applicants do not concede that the specification fails to provide sufficient support for the claims as originally presented. However, claims 10 and 11 have been canceled, and claim 12, as amended, is now directed to a method for treating asthma, rhinitis, and COPD. As discussed above, in view of the state of the knowledge in the field of treating these respiratory disorders, and the disclosure provided in the specification, undue experimentation is not required to practice the treatment method of claim 12.

In consideration of the Wands factors as discussed above, one of ordinary skill in the art would be able to practice the subject matter described in claim 12 without undue experimentation.

Prevention (prophylaxis): The Examiner states:

> the specification lacks the critical steps necessary in presenting some type of predictable response in a population of hosts deemed necessary to prevent a respiratory disorder. Reasonable guidance with respect to preventing a respiratory disorder relies on quantitative analysis from defined populations which have been successfully pre-screened and are predisposed to particular types of respiratory disorder…All of this underscores the criticality of providing workable examples which is not disclosed in the specification. Office Action at pages 5-6.

This ground for rejection appears to have been directed at the term "prophylaxis" that appeared in original claims 10 and 11. Those claims have been canceled. Claim 12, as amended, now reads "A method of treating or preventing the symptoms of a respiratory disorder… wherein the respiratory disorder is asthma, rhinitis or chronic obstructive pulmonary disease (COPD)." Insofar as this ground for rejection may be applied to claim 12, as amended, Applicants traverse.

Combination therapies including budesonide and formoterol have been shown to **prevent the symptoms** of at least asthma and COPD. For example, with respect to asthma, Zetterström *et al.* (submitted herewith) showed that a combination of budesonide and formoterol can effectively **prevent asthma symptoms**. Table 2 at page 265 of Zetterström indicates that administration of budesonide and formoterol, in separate inhalers or in a single inhaler, resulted in a significant increase in the number of reliever-use-free days and symptom-free days, and a significant decrease in night-time awakenings due to asthma. As an increase in symptom-free days means that asthma symptoms have been prevented on some days, these observations are evidence that a combination therapy of budesonide and formoterol can **prevent the symptoms of asthma**.

Calverley *et al.* ("Maintenance therapy with Budesonide and Formoterol in Chronic Obstructive Pulmonary Disease" *Eur. Respir. J.* 22:912-919, 2003; reference AE on the enclosed From 1449) reported that **COPD** patients benefited from a maintenance therapy of budesonide and formoterol. These patients exhibited a prolonged time to first exacerbation and had fewer

total exacerbations. In other words, the maintenance therapy **prevented** exacerbations. Calverley *et al.* in the abstract.

Lumry *et al.* ("A review of the preclinical and clinical data of newer intranasal steroids used in the treatment of allergic rhinitis," *J. Allergy Clin. Immunol.* 104:S150-8, 1999; reference AG on the enclosed Form 1449) reported that intranasal steroids including budesonide have been effective in the **prophylactic treatment** of seasonal allergic rhinitis and perennial rhinitis, including use in "preventing rhinitis symptoms." See, *e.g.*, page S155, column 1.

In view of the reported successes of the use of budesonide and formoterol for maintenance therapy of asthma and COPD (*i.e.*, for prevention of symptoms), and for the use of steroids, including budesonide, for prevention of symptoms in patients with allergic rhinitis, it is reasonable to predict that the claimed composition will effectively prevent symptoms of these respiratory disorders. Clearly, those having ordinary skill in the art would understand the meaning of the term "prevention" as it is used in claim 12 and would find such use for the claimed composition to be predictable and possible without undue experimentation.

In view of the foregoing, Applicants request that the rejection under 32 U.S.C. § 112, first paragraph, for failure to satisfy the enablement requirement be withdrawn.

35 U.S.C. §112, second paragraph

The Examiner rejected claim 11 as being indefinite because the abbreviation for COPD was not defined in the specification. Claim 11 has been canceled; the phrase "chronic obstructive pulmonary disease (COPD)" has been added to claim 12. One of ordinary skill in the art of treating respiratory disorders would understand that "COPD" means "chronic obstructive pulmonary disease," a well-known respiratory disorder. See, e.g., page 1, line 9, of WO 99/15182 (reference AC on the enclosed From 1449). In view of the amendment to claim 12, Applicants respectfully request that the rejection under 35 U.S.C. § 112, second paragraph, be withdrawn.

35 U.S.C. § 103

The Examiner rejected claims 1-12 under 35 U.S.C. § 103(a) as being unpatentable over Meade *et al.* (US 20030018019) and Weers *et al.* (US 6,309,623). Claims 2, 4, 10 and 11 have been canceled. While not conceding that the original claims are unpatentably obvious over the cited art, claim 1 has been amended to specify that PVP (polyvinylpyrrolidone) is present in an amount of 0.001% w/w.

The Examiner characterizes Meade *et al.* as teaching a pharmaceutical composition comprising anticholinergics, corticosteroids including budesonide, and betamimetics including formoterol, and as teaching HFA227, PEG and PVP as possible additions to the compositions therein. Office Action at page 7. The Examiner characterizes Weers *et al.* as teaching that drugs such as budesonide and formoterol are administered to patients for the treatment of respiratory disorders, and concludes that it would have been obvious to one having ordinary skill in the art to have modified the invention of Meade to administer the claimed pharmaceutical composition to a patient for the treatment of respiratory disease. Office Action at page 8.

Applicants contend that the present claims are not obvious in view of the teachings of Meade *et al.* and Weers *et al.* Neither Meade nor Weers, alone or in combination, suggest the claimed formulations. For example, neither Meade nor Weers disclose a pharmaceutical composition containing PVP at a concentration of 0.001% w/w. In fact, neither Meade nor Weers disclose any particular concentration of PVP, and certainly give no motivation to select the particular concentrations required by Applicants' claims. Weers lists PVP as an ingredient suitable for use in microspheres, without mentioning how much to use (see col. 16, line 62, and col. 18, lines 16-17). More specifically, Weers includes PVP in a list of agents that would be suitable to form the structural matrix of the microspheres. One of skill in the art would expect that a component that forms the structural matrix of a particle would be present at a concentration greater than the very small concentration required in Applicants' claims (0.001% w/w). Although Weers does not suggest an appropriate concentration for use of PVP in microspheres, Weers does describe the appropriate concentration of phosphatidylcholine, another

exemplary compound described as suitable for the formation of a structural matrix. In the exemplary formulations described in Weers at columns 30-35, the concentration of phosphatidylcholine ranges from 0.03% w/w in Example I to 0.11% w/w in Example VIII, *i.e.*, 30 to 110 x higher than specified in claim 1. There is no teaching in Weers that can be taken to imply that, when PVP is used, it should be in a far lower concentration than that utilized for, *e.g.*, phosphatidylcholine.

Applicants, using PVP in a context other than microspheres, in fact made the surprising discovery that 0.001% w/w PVP gave "consistently stable formulations over the required dose range, incorporating a wide range of concentrations of the active components, and at a much lower concentration than indicated in the prior art." Specification at page 2. Prior to Applicants' invention, when PVP was used in a pharmaceutical composition, it was not used at the very low concentration recited in Applicants' claims. One reference identified by Applicants as teaching the use of PVP in a pharmaceutical composition is Mistry *et al.* (WO93/05765, cited in the IDS submitted July 27, 2004). Mistry *et al.* identified certain polymers as being soluble in hydrofluorocarbons, such as hydrofluoroalkane (HFA), and as being capable of stabilizing medicament suspensions. See Mistry at page 1, lines 18-23. In particular, Mistry identified PVPs as polymers having a wide range of average molecular weights and giving acceptable suspensions. Mistry at page 2, lines 7-8. However, the appropriate amount of PVP required to stabilize a suspension will depend on the physical characteristics of the particular medicament. The specific PVP-containing formulations taught by Mistry *et al.* contain PVP at concentrations ranging from 0.0025% to 0.5% w/w; *i.e.*, 2.5 to 500 x higher than specified in claim 1. See Mistry *et al.* at pages 10-17. Applicants surprisingly demonstrated that 0.001% w/w PVP gave the best suspension stability when compared to a range of PVP concentrations from 0.0001% to 0.05% w/w. See Specification at page 6 in the table and at lines 6-7; and at pages 8-9, *e.g.*, at lines 3, 10, 13, 20, and 22. This could not have been predicted from Mistry *et al.* or from the references cited in the Office Action (Meade and Weers).

A reasonable expectation of success is the standard used to determine obviousness under U.S. law. MPEP 2141(II), citing Hodosh v. Block Drug Co., Inc., 786 F.2d 1136, 1143 n.5, 229

USPQ 182, 187 n.5 (Fed. Cir. 1986). Mistry discloses the concentration of PVP believed to be most suitable for use in pharmaceutical formulations prior to Applicants' discovery. Thus in view of this teaching in Mistry, neither Meade nor Weers (or even Mistry) would lead one having ordinary skill in the art to believe that he or she could prepare the formulation of claim 1 with a reasonable expectation of success. One having ordinary skill in the art would not expect to obtain a formulation with the excellent physical suspension stability as was discovered by Applicants.

In view of (i) the amendment to claim 1 and (ii) Applicants' surprising discovery that the specified low concentration of PVP contributes to superior qualities of suspension stability, claims 1, 3, 5-9 and 12 are not unpatentably obvious over Meade and Weers. Applicants therefore respectfully request that that the rejection under 35 U.S.C. § 103 be withdrawn.

In view of the foregoing, Applicants contend that the present claims are in condition for allowance, which action is requested.

Please apply the $1020 fee for the Petition for a Three Month Extension of Time, and any other necessary charges, or any credits, to Deposit Account No. 06-1050, referencing Attorney Docket No. 06275-410US1.

Respectfully submitted,

Date: May 3, 2006

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Other Documents (Include Author, Title, Date, and Place of Publication)		
Examiner Initial	Desig. ID	Document
	BE	Calverley *et al.*, "Maintenance therapy with budesonide and formoterol in chronic obstructive pulmonary disease" *Eur. Respir. J.* 22:912-919 (2003)
	BF	Cazzola *et al.*, "Effect of salmeterol and formoterol in patients with chronic obstructive pulmonary disease" *Pulm Pharmacol.* 7:103-7 (1994)
	BG	Lumry, "A review of the preclinical and clinical data of newer intranasal steroids used in the treatment of allergic rhinitis," *J. Allergy Clin. Immunol.* 104:S150-8 (1999) (abstract only)
	BH	Milgrom and Taussig, "Keeping Children with Exercise-Induced Asthma Active" *Pediatrics* 104:38-42 (1999)
	BI	Pipkorn *et al.*, "Budesonide- a New Nasal Steroid" *Rhinology* 18:171-175 (1980)
	BJ	Renkema *et al.*, "Effects of long-term treatment with corticosteroids in COPD" *Chest* 109:1156-62 (1996)
	BK	Zetterström *et al.*, "Improved asthma control with budesonide/formoterol in a single inhaler, compared with budesonide alone" *Eur. Respir. J.* 18:262-268 (2001)
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(54) Title: NEW USE FOR BUDESONIDE AND FORMOTEROL

(57) Abstract

The invention provides the use of formoterol and budesonide in the treatment of chronic obstructive pulmonary disease.

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NEW USE FOR BUDESONIDE AND FORMOTEROL

Field of the Invention

The invention provides the use of formoterol and budesonide in the treatment of chronic obstructive pulmonary disease (COPD).

Background to the Invention

Chronic obstructive pulmonary disease (COPD) is a term which refers to a large group of lung diseases which can interfere with normal breathing. It is estimated that 11% of the U.S. population has COPD and the incidence is increasing. The two most important conditions covered by COPD are chronic bronchitis and emphysema.

Chronic bronchitis is a long-standing inflammation of the bronchi which causes increased production of mucous and other changes. The patients' symptoms are cough and expectoration of sputum. Chronic bronchitis can lead to more frequent and severe respiratory infections, narrowing and plugging of the bronchi, difficult breathing and disability.

Emphysema is a chronic lung disease which affects the alveoli and/or the ends of the smallest bronchi. The lung loses its elasticity and therefore these areas of the lungs become enlarged. These enlarged areas trap stale air and do not effectively exchange it with fresh air. This results in difficult breathing and may result in insufficient oxygen being delivered to the blood. The predominant symptom in patients with emphysema is shortness of breath.

At present moderate to severe COPD is treated with a variety of monotherapies including inhaled or orally administered bronchodilators, inhaled anti-cholinergic agents and orally administered steroids, especially corticosteroids. The problem with these treatments is that none of them is especially effective. For example, many patients with COPD have a

reversible component. Accordingly a new treatment is required for decreasing the intensity of exacerbations, thereby improving the lung function of patients suffering from COPD.

Description of the Invention

It has surprisingly been found that the combination of formoterol and budesonide is effective in treating COPD.

The combination of budesonide and formoterol reduces the number of exacerbations of COPD compared to the monotherapies using budesonide or formoterol, thereby improving the lung function of the patients. Thus, the combination of budesonide and formoterol will give greater compliance, greater efficacy, less exacerbations and/or better sleep.

The present invention also gives an increased compliance and efficacy and thereby quality of life.

According to the invention there is provided the use of a composition comprising, in admixture or separately:

(a) a first active ingredient which is formoterol, a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt;

(b) a second active ingredient which is budesonide; and

a molar ratio of the first active ingredient to the second active ingredient of from 1:2500 to 12:1,

in the manufacture of a medicament for use in the treatment of chronic obstructive pulmonary disease.

The composition used in the invention optionally additionally comprises one or more pharmaceutically acceptable additives, diluents and/or carriers. The composition is preferably in the form of a dry powder, wherein the particles of the pharmaceutically active ingredients preferably have a mass median diameter of less than 10 μm.

The invention also includes the use of a kit containing:

(i) a vessel containing the first active ingredient;

(ii) a vessel containing the second active ingredient;

(iii) a molar ratio of the first active ingredient to the second active ingredient of from 1:2500 to 12:1; and

(iv) instructions for the simultaneous, sequential or separate administration of the active ingredients to a patient in need thereof;

in the manufacture of a medicament for use in the treatment of chronic obstructive pulmonary disease.

A patient suffering from COPD can be treated by administering via inhalation a composition as defined above. Alternatively such a patient can be treated by administering via inhalation, simultaneously, sequentially or separately, (i) a dose of the first active ingredient; and (ii) a dose of the second active ingredient. The molar ratio of the first active ingredient to the second active ingredient is from 1:2500 to 12. The doses can be provided to the patient for inhalation in dry powder form.

The invention further provides the use of budesonide and of formoterol in the manufacture of a composition or a kit, as used in the invention, for use in the treatment of chronic obstructive pulmonary disease.

The first and second active ingredients of the kit used in the invention can be administered simultaneously, sequentially or separately to COPD. By sequential is meant that the first and second active ingredients are administered one after the other. They still have the desired effect if they are administered separately but less than about 12 hours apart, preferably less than about 2 hours apart, more preferably less than about 30 minutes apart, and most preferably one immediately after the other.

The molar ratio of the first active ingredient to the second active ingredient is suitably from 1:555 to 2:1 and preferably from 1:150 to 1:1. The molar ratio of the first active ingredient

to the second active ingredient is more preferably from 1:133 to 1:6. The molar ratio of the first active ingredient to the second active ingredient can also be 1:70 to 1:4.

Preferably the amount of the first active ingredient used is preferably from 2 to 120 nmol (more preferably from 7 to 70 nmol). The amount of the second active ingredient used is preferably from 0.1 to 5 μmol (preferably 0.15 to 4 μmol) or from 45 to 2200 μg, more preferably from 65 to 1700 μg.

Throughout the specification, the amount of the first and second active ingredient used relate to unit doses unless explicitly defined differently.

Suitable physiologically acceptable salts of formoterol include acid addition salts derived from inorganic and organic acids, for example the chloride, bromide, sulphate, phosphate, maleate, fumarate, tartrate, citrate, benzoate, 4-methoxybenzoate, 2- or 4-hydroxybenzoate, 4-chlorobenzoate, p-toluenesulphonate, methanesulphonate, ascorbate, acetate, succinate, lactate, glutarate, gluconate, tricarballylate, hydroxynaphthalene-carboxylate or oleate salts or solvates thereof. The first active ingredient is preferably formoterol fumarate, especially the dihydrate thereof.

When the first active ingredient is formoterol fumarate dihydrate, the amount of the first active ingredient used is suitably from 1 to 50 μg, more suitably from 3 to 30 μg.

Preferably the composition or kit used in the invention comprises unit doses of 6 μg of formoterol fumarate dihydrate and 100 μg of budesonide, or 4.5 μg of formoterol fumarate dihydrate and 80 μg of budesonide, either of which is administered up to four times a day. Alternatively the composition or kit of the invention comprises unit doses of 12 μg of formoterol fumarate dihydrate and 200 μg of budesonide, or 9 μg of formoterol fumarate dihydrate and 160 μg of budesonide, either of which is administered once or twice a day.

More preferably the composition or kit used in the invention comprises unit doses of 6 μg of formoterol fumarate dihydrate and 200 μg of budesonide, or 4.5 μg of formoterol fumarate dihydrate and 160 μg of budesonide, either of which is administered up to four times a day. Alternatively the composition or kit of the invention comprises unit doses of 12 μg of formoterol fumarate dihydrate and 400 μg of budesonide, or 9 μg of formoterol fumarate dihydrate and 320 μg of budesonide, either of which is administered once or twice a day.

Most preferably the composition or kit used in the invention comprises unit doses of 6 μg of formoterol fumarate dihydrate and 400 μg of budesonide, or 4.5 μg of formoterol fumarate dihydrate and 320 μg of budesonide, either of which is administered up to four times a day.

Preferably the active ingredient(s) are used in admixture with one or more pharmaceutically acceptable additives, diluents or carriers, preferably in an amount of from 50 μg to 25 mg per dose, more preferably in an amount of from 50 μg to 10 mg, most preferably in an amount of from 100 to 2000 μg per unit dose. Examples of suitable diluents or carriers include lactose, dextran, mannitol or glucose. Preferably lactose is used, especially as the monohydrate.

One or more of the ingredients is preferably in the form of a dry powder, more preferably a finely divided powder, e.g. micronised dry powder, most preferably an agglomerated micronised dry powder. As an alternative to agglomeration, the finely divided active ingredients may be in the form of an ordered mixture with the pharmaceutically acceptable additive, diluent or carrier. An ordered mixture comprises fine particles of an active ingredient in association with coarse particles or a mixture of coarse and finely divided particles of the pharmaceutically acceptable additive, diluent or carrier. The ingredients used in the invention can be obtained in these preferred forms using methods known to those of skill in the art. The particle size of the active ingredients is preferably less than 10 μm.

Administration may be by inhalation orally or intranasally. The active ingredients are preferably adapted to be administered, either together or individually, from dry powder inhaler(s) (DPIs), especially Turbuhaler® (Astra AB), pressurised metered dose inhaler(s) (pMDIs), or nebuliser(s).

When the active ingredients are adapted to be administered, either together or individually, from pressurised inhaler(s), they are preferably in finely divided, and more preferably in micronised form. They may be dissolved or, preferably, suspended in a liquid propellant mixture. The propellants which can be used include chlorofluorocarbons, hydrocarbons or hydrofluoroalkanes. Especially preferred propellants are P134a (tetrafluoroethane) and P227 (heptafluoropropane) each of which may be used alone or in combination. They are optionally used in combination with one or more other propellants and/or one or more surfactants and/or one or more other excipients, for example ethanol, a lubricant, an anti-oxidant and/or a stabilising agent.

When the active ingredients are adapted to be administered, either together or individually, via nebuliser(s) they may be in the form of a nebulised aqueous suspension or solution, with or without a suitable pH or tonicity adjustment, either as a unit dose or multidose device.

The composition or kit used in the invention may optionally be administered as divided doses from 1 to 4, and preferably once or twice a day.

The invention is illustrated by the following Examples which are not intended to limit the scope of the application. In the Examples micronisation is carried out in a conventional manner such that the particle size range for each component is suitable for administration by inhalation. Turbuhaler is a trademark of Astra AB.

Example 1

6 Parts by weight of formoterol fumarate dihydrate was mixed with 794 parts by weight of lactose monohydrate. The blend was micronised using a high pressure air jet mill and then conditioned using the process of EP-A-717 616. 200 Parts by weight of micronised budesonide was added to the conditioned product by mixing and homogenising with a low pressure jet mill. The mixture was then spheronised using the process of EP-A-721 331 and filled into the storage compartment of a Turbuhaler.

Example 2

4.5 Parts by weight of formoterol fumarate dihydrate was mixed with 835 parts by weight of lactose monohydrate. The blend was micronised using a high pressure air jet mill and then conditioned using the process of EP-A-717 616. 160 Parts by weight of micronised budesonide was added to the conditioned product by mixing and homogenising with a low pressure jet mill. The mixture was then spheronised using the process of EP-A-721 331 and filled into the storage compartment of a Turbuhaler.

Example 3

12 Parts by weight of formoterol fumarate dihydrate was mixed with 588 parts by weight of lactose monohydrate. The blend was micronised using a high pressure air jet mill and then conditioned using the process of EP-A-717 616. 400 Parts by weight of micronised budesonide was added to the conditioned product by mixing and homogenising with a low pressure jet mill. The mixture was then spheronised using the process of EP-A-721 331 and filled into the storage compartment of a Turbuhaler.

Example 4

6 Parts by weight of formoterol fumarate dihydrate was mixed with 894 parts by weight of lactose monohydrate. The blend was micronised using a high pressure air jet mill and then conditioned using the process of EP-A-717 616. 100 Parts by weight of micronised budesonide was added to the conditioned product by mixing and homogenising with a low

pressure jet mill. The mixture was then spheronised using the process of EP-A-721 331 and filled into the storage compartment of a Turbuhaler.

Example 5

4.5 Parts by weight of formoterol fumarate dihydrate was mixed with 915 parts by weight of lactose monohydrate. The blend was micronised using a high pressure air jet mill and then conditioned using the process of EP-A-717 616. 80 Parts by weight of micronised budesonide was added to the conditioned product by mixing and homogenising with a low pressure jet mill. The mixture was then spheronised using the process of EP-A-721 331 and filled into the storage compartment of a Turbuhaler.

Example 6

12 Parts by weight of formoterol fumarate dihydrate was mixed with 788 parts by weight of lactose monohydrate. The blend was micronised using a high pressure air jet mill and then conditioned using the process of EP-A-717 616. 200 Parts by weight of micronised budesonide was added to the conditioned product by mixing and homogenising with a low pressure jet mill. The mixture was then spheronised using the process of EP-A-721 331 and filled into the storage compartment of a Turbuhaler.

Example 7

6 Parts by weight of formoterol fumarate dihydrate was mixed with 994 parts by weight of lactose monohydrate. The blend was micronised using a high pressure air jet mill and then conditioned using the process of EP-A-717 616. The mixture was then spheronised using the process of EP-A-721 331 and filled into the storage compartment of a Turbuhaler.

200 Parts by weight of micronised budesonide was mixed with 800 parts by weight of lactose monohydrate. The blend was micronised using a high pressure air jet mill and then conditioned using the process of EP-A-717 616. The mixture was then spheronised using the process of EP-A-721 331 and filled into the storage compartment of a Turbuhaler.

Example 8

4.5 Parts by weight of formoterol fumarate dihydrate was mixed with 995 parts by weight of lactose monohydrate. The blend was micronised using a high pressure air jet mill and then conditioned using the process of EP-A-717 616. The mixture was then spheronised using the process of EP-A-721 331 and filled into the storage compartment of a Turbuhaler.

160 Parts by weight of micronised budesonide was mixed with 840 parts by weight of lactose monohydrate. The blend was micronised using a high pressure air jet mill and then conditioned using the process of EP-A-717 616. The mixture was then spheronised using the process of EP-A-721 331 and filled into the storage compartment of a Turbuhaler.

Example 9

12 Parts by weight of formoterol fumarate dihydrate was mixed with 988 parts by weight of lactose monohydrate. The blend was micronised using a high pressure air jet mill and then conditioned using the process of EP-A-717 616. The mixture was then spheronised using the process of EP-A-721 331 and filled into the storage compartment of a Turbuhaler.

400 Parts by weight of micronised budesonide was mixed with 600 parts by weight of lactose monohydrate. The blend was micronised using a high pressure air jet mill and then conditioned using the process of EP-A-717 616. The mixture was then spheronised using the process of EP-A-721 331 and filled into the storage compartment of a Turbuhaler.

Example 10

6 Parts by weight of formoterol fumarate dihydrate was mixed with 994 parts by weight of lactose monohydrate. The blend was micronised using a high pressure air jet mill and then conditioned using the process of EP-A-717 616. The mixture was then spheronised using the process of EP-A-721 331 and filled into the storage compartment of a Turbuhaler.

100 Parts by weight of micronised budesonide was mixed with 900 parts by weight of lactose monohydrate. The blend was micronised using a high pressure air jet mill and then conditioned using the process of EP-A-717 616. The mixture was then spheronised using the process of EP-A-721 331 and filled into the storage compartment of a Turbuhaler.

Example 11

4.5 Parts by weight of formoterol fumarate dihydrate was mixed with 995 parts by weight of lactose monohydrate. The blend was micronised using a high pressure air jet mill and then conditioned using the process of EP-A-717 616. The mixture was then spheronised using the process of EP-A-721 331 and filled into the storage compartment of a Turbuhaler.

80 Parts by weight of micronised budesonide was mixed with 920 parts by weight of lactose monohydrate. The blend was micronised using a high pressure air jet mill and then conditioned using the process of EP-A-717 616. The mixture was then spheronised using the process of EP-A-721 331 and filled into the storage compartment of a Turbuhaler.

Example 12

12 Parts by weight of formoterol fumarate dihydrate was mixed with 988 parts by weight of lactose monohydrate. The blend was micronised using a high pressure air jet mill and then conditioned using the process of EP-A-717 616. The mixture was then spheronised using the process of EP-A-721 331 and filled into the storage compartment of a Turbuhaler.

200 Parts by weight of micronised budesonide was mixed with 800 parts by weight of lactose monohydrate. The blend was micronised using a high pressure air jet mill and then conditioned using the process of EP-A-717 616. The mixture was then spheronised using the process of EP-A-721 331 and filled into the storage compartment of a Turbuhaler.

Example A

Patients suffering from COPD are first put through a run-in period of 2 weeks and are then split into 4 groups of approximately equal numbers. Each group is then given either budesonide/formoterol, budesonide alone, formoterol alone or placebo for a period of 12 months.

The following parameters for each patient are monitored throughout: mild and severe exacerbations, FEV_1 (forced expiratory volume in one second), vital capacity (VC), peak expiratory flow (PEF), symptom scores and Quality of Life. Of these, mild and severe exacerbations are considered to be primary efficacy variables, whereas the remaining parameters are considered to be secondary efficacy variables.

Claims

1. Use of a composition comprising, in admixture or separately:

(a) a first active ingredient which is formoterol, a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt;

(b) a second active ingredient which is budesonide; and

a molar ratio of the first active ingredient to the second active ingredient of from 1:2500 to 12:1,

in the manufacture of a medicament for use in the treatment of chronic obstructive pulmonary disease.

2. Use according to claim 1, wherein the composition comprises one or more pharmaceutically acceptable additives, diluents and/or carriers.

3. Use of a kit containing:

(i) a vessel containing a first active ingredient which is formoterol, a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt;

(ii) a vessel containing a second active ingredient which is budesonide;

(iii) a molar ratio of the first active ingredient to the second active ingredient of from 1:2500 to 12:1; and

(iv) instructions for the simultaneous, sequential or separate administration of the first and second active ingredients to a patient in need thereof;

in the manufacture of a medicament for use in the treatment of chronic obstructive pulmonary disease.

4. Use according to claim 3, wherein the first and/or second active ingredient is used in admixture with one or more pharmaceutically acceptable additives, diluents and/or carriers.

5. Use according to any one of the preceding claims, wherein the first active ingredient is formoterol fumarate dihydrate.

6. Use according to any one of the preceding claims, wherein the molar ratio of the first active ingredient to the second active ingredient is from 1:555 to 2:1, preferably from 1:70 to 1:4.

7. Use of formoterol, a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt in the manufacture of a composition as defined in claim 1 or 2 or a kit as defined in claim 3 or 4 for use in the treatment of chronic obstructive pulmonary disease.

8. Use of budesonide in the manufacture of a composition as defined in claim 1 or 2 or a kit as defined in claim 3 or 4 for use in the treatment of chronic obstructive pulmonary disease.

9. A method for the treatment of a patient suffering from chronic obstructive pulmonary disease which method comprises administering to the patient via inhalation, simultaneously, sequentially or separately, a therapeutically effective amount of (i) a dose of a first active ingredient which is formoterol, a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt; and (ii) a second active ingredient which is budesonide, and wherein the molar ratio of the first active ingredient to the second active ingredient is from 1:2500 to 12:1.

10. A method for the treatment of a patient suffering from chronic obstructive pulmonary disease which method comprises administering to the patient via inhalation a therapeutically effective amount of a composition as defined in claim 1 or 2.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 98/01599

A. CLASSIFICATION OF SUBJECT MATTER

IPC6: A61K 31/57 // (A61K 31/57, 31:165)
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC6: A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Schweiz Med Wochenschr, Volume 127, 1997, C. Wyser et al, "Neue Aspekte in der Behandlung des Asthma bronchiale und chronisch obstruktiver Lungenkrankheiten" page 885 - page 890 --	1-8
X	WO 9311773 A1 (AKTIEBOLAGET ASTRA), 24 June 1993 (24.06.93) --	1-8

☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" erlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
22 December 1998	07 -01- 1999
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer Eva Johansson Telephone No. +46 8 782 25 00

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 98/01599

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 9-10
because they relate to subject matter not required to be searched by this Authority, namely:

See PCT Rule 39.1(iv): Methods for treatment of the human or animal body by surgery or therapy, as well as diagnostic methods.

2. [ ] Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

01/12/98

International application No.
PCT/SE 98/01599

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9311773 A1	24/06/93	AU 673660 B	21/11/96
		AU 3085892 A	19/07/93
		CA 2123909 A	24/06/93
		CZ 9401434 A	15/12/94
		EP 0613371 A	07/09/94
		HR 921445 A	31/12/94
		HU 75156 A	28/04/97
		HU 9401843 D	00/00/00
		JP 7502036 T	02/03/95
		NO 942116 A	07/06/94
		NZ 246050 A	21/12/95
		SG 48301 A	17/04/98
		SK 73394 A	08/03/95
		US 5674860 A	07/10/97

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant	: Nayna Govind *et al.*	Art Unit	: 1616
Serial No.	: 10/502,685	Examiner	: Alton Pryor
Filed	: July 27, 2004	Conf. No.	: 7568
Title	: COMPOSITION FOR INHALATION		

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

PETITION FOR THREE-MONTH EXTENSION OF TIME

Pursuant to 37 CFR §1.136, applicant hereby petitions that the period for response to the action dated May 4, 2006, be extended for three months to and including November 4, 2006.

Please apply the $1020 fee and any other charges or credits to Deposit Account No. 06-1050, referencing Attorney Docket No. 06275-410US1.

Respectfully submitted,

Date: November 3, 2006

Allyson R. Hatton, Ph.D.
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21470607.doc

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant	: Nayna Govind *et al.*	Art Unit	: 1616
Serial No.	: 10/502,685	Examiner	: Alton Nathaniel Pryor
Filed	: July 27, 2004	Conf. No.	: 7568
Title	: COMPOSITION FOR INHALATION		

MAIL STOP AMENDMENT
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT

Applicants request consideration of the references listed on the attached PTO-1449 form. This statement is being filed after a first Office action on the merits, but before receipt of a final Office action or a Notice of Allowance. Please apply the $180 payment of the late submission fee of 37 CFR § 1.17(p) and any other charges or credits to Deposit Account No. 06-1050, referencing Attorney Docket No. 06275-410US1.

Respectfully submitted,

Date: Nov. 3, 2006

Janis K. Fraser, Ph.D., J.D.
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Facsimile: (617) 542-8906

21469937.doc

Electronic Patent Application Fee Transmittal

Application Number:	10502685
Filing Date:	27-Jul-2004
Title of Invention:	Composition for inhalation
First Named Inventor/Applicant Name:	Nayna Govind
Filer:	Allyson Russell Hatton/Kimberly Hutchins
Attorney Docket Number:	06275-410US1

Filed as Large Entity

U.S. National Stage under 35 USC 371 Filing Fees

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				
Extension - 3 months with $0 paid	1253	1	1020	1020

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Miscellaneous:				
Submission- Information Disclosure Stmt	1806	1	180	180
		Total in USD ($)		**1200**

Electronic Acknowledgement Receipt

EFS ID:	1292419
Application Number:	10502685
International Application Number:	
Confirmation Number:	7568
Title of Invention:	Composition for inhalation
First Named Inventor/Applicant Name:	Nayna Govind
Customer Number:	26164
Filer:	Allyson Russell Hatton/Devon Weide
Filer Authorized By:	Allyson Russell Hatton
Attorney Docket Number:	06275-410US1
Receipt Date:	03-NOV-2006
Filing Date:	27-JUL-2004
Time Stamp:	16:53:49
Application Type:	U.S. National Stage under 35 USC 371

Payment information:

Submitted with Payment	yes
Payment was successfully received in RAM	$1200
RAM confirmation Number	506
Deposit Account	061050

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)	Multi Part /.zip	Pages (if appl.)

1		06275410US1REPLY.pdf	2405357	yes	12
	Multipart Description/PDF files in .zip description				
	Document Description		**Start**	**End**	
	Amendment - After Non-Final Rejection		1	1	
	Claims		2	3	
	Applicant Arguments/Remarks Made in an Amendment		4	12	
Warnings:					
Information:					
2	Information Disclosure Statement (IDS) Filed	06275410USI1449.pdf	252075	no	1
Warnings:					
Information:					
This is not an USPTO supplied IDS fillable form					
3	Foreign Reference	WO1999015182.pdf	686865	no	18
Warnings:					
Information:					
4	NPL Documents	21469914.pdf	347216	no	6
Warnings:					
Information:					
5	NPL Documents	21469912.pdf	389383	no	8
Warnings:					
Information:					
6	NPL Documents	21469911.pdf	319907	no	7
Warnings:					
Information:					
7	NPL Documents	21469910.pdf	94004	no	7
Warnings:					
Information:					

8	NPL Documents	21469909.pdf	1156221	no	9
Warnings:					
Information:					
9	NPL Documents	21464294.pdf	552442	no	5
Warnings:					
Information:					
10	NPL Documents	lum.pdf	3181531	no	10
Warnings:					
Information:					
11	Extension of Time	ext.pdf	29636	no	1
Warnings:					
Information:					
12	Information Disclosure Statement (IDS) Filed	ids.pdf	34903	no	1
Warnings:					
Information:					
This is not an USPTO supplied IDS fillable form					
13	Fee Worksheet (PTO-875)	fee-info.pdf	8320	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	9457860		

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/502,685	07/27/2004	Nayna Govind	06275-410US1	7568

26164 7590 05/04/2006

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MINNEAPOLIS, MN 55440-1022

EXAMINER	
PRYOR, ALTON NATHANIEL	
ART UNIT	**PAPER NUMBER**
1616	

DATE MAILED: 05/04/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/502,685	GOVIND ET AL.	
	Examiner	Art Unit	
	Alton N. Pryor	1616	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *27 July 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) *1-12* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *1-12* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *7/27/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 10-12 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

For rejections under 35 U.S.C. 112, first paragraph, the following factors must be considered (In re Wands, 8 USPQ2d 1400, 1404 (CAFC, 1988)):

1) Nature of invention.

2) State of prior art.

3) Quantity of experimentation needed to make or use the invention based on the content of the disclosure

4) Level of predictability in the art.

5) Amount of direction and guidance provided by the inventor.

6) Existence of working examples.

7) Breadth of claims.

8) Level of ordinary skill in the art.

See below:

1) Nature of the invention.

The nature of the invention is pharmaceutical composition / method for treatment of a respiratory disorder in a patient (claims 10,12) and for treatment of asthma, rhinitis or COPD (claim 11). Note claims 10 and 12 recite broadly the treatment of a respiratory disease.

2) State of the prior art and the predictability or lack thereof in the art.

The state of the prior art is that it involves screening *in vitro* and *in vivo* to determine how effective a composition is in treating specific diseases. There is no absolute predictability even in view of the seemingly high level of skill in the art. The existence of these obstacles establishes that the contemporary knowledge in the art would prevent one of ordinary skill in the art from accepting any therapeutic regimen on its face. The instant claimed invention is highly unpredictable as discussed below:

It is noted that the pharmaceutical art is unpredictable, requiring each embodiment to be individually assessed for physiological activity. *In re Fisher,* 427 F.2d 833, 166 USPQ 18 (CCPA 1970) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statue. Further, their mode of action is often unknown or very unpredictable and administration of the drugs can be accompanied by undesirable side effects.

Thus, in the absence of a showing of correlation between all the diseases claimed as capable of being treated by the composition of the instant claims, one of ordinary skill in the art is unable to fully predict possible results from the administration of the composition due to the unpredictability of the role of respiratory disorder.

3) Quantity of experimentation needed to make or use the invention based on the content of the disclosure.

The quantity of experimentation needed is undue experimentation. One of ordinary skill in the art would first need to determine the type of respiratory disorder to be treated, and then determine if the composition would be suitable for said treatment and/or prevention.

6) Existence of working examples.

Applicant provides no working examples of how instant composition treats or prevents respiratory disorders. In addition, Applicant provides no working examples of how instant composition treats or prevents specific respiratory disorders such as asthma, rhinitis, or COPD.

7) Breadth of claims.

Claims 10-12 are extremely broad due to the vast number of possible respiratory disorders encompassed by the instant invention.

8) Level of ordinary skill in the art.

The level of ordinary skill in the art is high. Due to the unpredictability in the pharmaceutical art, it is noted that each embodiment of the invention is required to be individually assessed for physiological activity by *in vitro* and *in vivo* screening to determine how effective the composition would be in treating or preventing respiratory disorders.

Hence, the specification fails to provide sufficient support of the instant composition of the claims for the treatment of any respiratory disorder. As a result necessitating one of ordinary skill in the art to perform an exhaustive search to determine which diseases can be treated / prevented by the instant composition in order to practice the claimed invention.

Genentec Inc. V. *Novo Nordisk A/S* (CAFC) 42 USPQ 2D 1001, states that:

"a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion" and "[p]atent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable".

Therefore, in view of the Wands factors, and *In re Fisher* (CCPA 1970) discussed above, to practice the claimed invention herein, a person of ordinary skill in the art would have to engage in undue experimentation to test which respiratory disorders can be treated by the composition encompassed in instant claims, with no assurance of success.

The above list is by no means complete, but demonstrates the extraordinary breadth of causes, mechanisms, and treatment (or lack thereof) for respiratory disorder. It establishes that it is not reasonable to any agent to be able to treat respiratory disorder generally.

This rejection can be overcome by providing experimental data for treating specific respiratory disorders using the instant composition.

Lastly, with regards to the prevention (prophylaxis) of respiratory disorder in general and asthma, rhinitis, or COPD specifically), the specification lacks the critical steps necessary in presenting some type of predictable response in a population of hosts deemed necessary to prevent a respiratory disorder. Reasonable guidance with respect to preventing a respiratory disorder relies on quantitative analysis from defined populations which have been successfully pre-screened and are predisposed to particular types of respiratory disorder. This type of data might be derived from

widespread genetic analysis, respiratory disorder clusters, or family histories. The essential element towards the validation of a preventive therapeutic is the ability to test the drug on subjects monitored in advance of clinical respiratory disorder and link those results with subsequent histological confirmation of the presence or absence of disease. This irrefutable link between antecedent drug and subsequent knowledge of the prevention of the disease is the essence of a valid preventive agent. Further, a preventive administration also must assume that the therapeutic will be safe and tolerable for anyone susceptible to the disease. All of this underscores the criticality of providing workable examples which is not disclosed in the specification, particularly in an unpredictable art such as respiratory disorder therapy.

In view of the teachings above, and the lack of guidance and or exemplification in the specification, it would not be predictable that the invention of preventing respiratory disorder would function as contemplated. Thus, it would require undue experimentation by one of skill in the art.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 11 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 11 is rejected for reciting an abbreviation "COPD". The abbreviation is not defined in the specification.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-12 are rejected under 35 U.S.C. 103(a) as being unpatentable over Meade et al (US 20030018019; 1/23/03) and Weers et al (US 6309623; 10/30/01). Meade teaches a pharmaceutical composition comprising anticholinergics, corticosteroids including budesonide, and betamimetics including formoterol. See abstract, paragraphs 3-5,16. Meade teaches that the formoterol can exist in the form of formoterol fumarate and as the enantiomeric salt of R,R stereoisomer. See paragraphs 9-12. Meade teaches that budesonide can be present in the form its enantiomers, mixture of enantiomers, or in the form of racemates. See paragraph 20. Meade teaches that propellant gas such as HFA 227, co-solvent such as polyethylene glycol (PEG), and surfactants such as polyvinylpyrrolidone (PVP) can be added the composition. See paragraphs 14 and 50. Meade teaches that the pharmaceutical composition is used to treat diseases of the respiratory tract such as asthma and chronic obstructive pulmonary disease (COPD). See paragraph 18. Meade does not teach 1) an exemplified a pharmaceutical composition comprising budesonide (also 22R epimer), formoterol, HFA227, PEG, and PVP and administering the composition to a patient having a respiratory disorder; 2) the instant types of PEG such as PEG 1000 and PVP such as PVP K25, 3) the instant amounts of PVP and PEG. Weers teaches that drugs

such as budesonide and formoterol are administered to patients for the treatment of respiratory disorders. See column 19 lines 30-67, claims 72,74,87. It would have been obvious to one having ordinary skill in the art to have modified the invention of Meade to additionally administer the pharmaceutical composition to a patient for the treatment of respiratory disease. One would have been motivated to do this since Weers teaches that drugs such as budesonide and formoterol are administered to said patients for treatment of respiratory disorders. An artisan would have been expected to arrive at the instant composition comprising budesonide, formoterol, HFA227, PEG, and PVP since the composition is suggested by Weers and would have been expected to function effectively in the treatment of respiratory disorders. Also note that it would have been obvious to employ the 22R epimer of budesonide since Meade teaches that budesonide can be present in the form its enantiomers, mixture of enantiomers, or in the form of racemates (which includes the 22R epimer) of budesonide. It would have been obvious to an artisan to employ PEG-1000 and PVP K25 at the time of the prior art invention in place of PEG and PVP. One would have been motivated to do this with an expectation of success because PEG-1000 is structurally similar to PEG and PVP 25K is structurally similar to PVP 25K. Note, in the absence of unexpected results structurally similar compounds belonging to the same family are expected to possess similar chemical and physical properties, and thus yield similar results. With respect to the instant amounts of PEG (0.05 - 0.35 % w/w) and PVP (0.0005 – 0.5% w/w), one would have been expected to determine the optimum amount of PVP and PEG (which may have fallen within the instant range). One would have been motivated to do this because optimum

amounts of excipients (solvents, surfactants, etc.) enhance the effectiveness / delivery of the active ingredients.

Telephonic Inquiry

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Alton N. Pryor whose telephone number is 571-272-0621. The examiner can normally be reached on 8:00 a.m. - 4:30 p.m..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan can be reached on 571-272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Alton Pryor
Primary Examiner
AU 1616

Notice of References Cited	Application/Control No. 10/502,685	Applicant(s)/Patent Under Reexamination GOVIND ET AL.	
	Examiner Alton N. Pryor	Art Unit 1616	Page 1 of 1

U.S. PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Name	Classification
*	A	US-2003/0018019	01-2003	Meade et al.	514/171
*	B	US-6,309,623	10-2001	Weers et al.	424/45
	C	US-			
	D	US-			
	E	US-			
	F	US-			
	G	US-			
	H	US-			
	I	US-			
	J	US-			
	K	US-			
	L	US-			
	M	US-			

FOREIGN PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Country	Name	Classification
	N					
	O					
	P					
	Q					
	R					
	S					
	T					

NON-PATENT DOCUMENTS

*		Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages)
	U	
	V	
	W	
	X	

*A copy of this reference is not being furnished with this Office action. (See MPEP § 707.05(a).)
Dates in MM-YYYY format are publication dates. Classifications may be US or foreign.

Substitute Form PTO-1449 (Modified)	U.S. Department of Commerce Patent and Trademark Office	Attorney's Docket No. 06275-410US1	Application No. 10/502685
Information Disclosure Statement by Applicant (Use several sheets if necessary) (37 CFR §1.98(b))		Applicant Nayna Govind et al.	
		Filing Date Herewith	Group Art Unit

U.S. Patent Documents

Examiner Initial	Desig. ID	Document Number	Publication Date	Patentee	Class	Subclass	Filing Date If Appropriate
AWP	AA	6,004,537	12/21/1999	Blondino et al.			
	AB						
	AC						
	AD						
	AE						
	AF						
	AG						
	AH						
	AI						

Foreign Patent Documents or Published Foreign Patent Applications

Examiner Initial	Desig. ID	Document Number	Publication Date	Country or Patent Office	Class	Subclass	Translation Yes	Translation No
AWP	AJ	EP 0 534 731	03/31/1993	Europe				
	AK	WO 93/05765	04/01/1993	WIPO				
	AL	WO 93/11773	06/24/1993	WIPO				
	AM	WO 98/21175	05/22/1998	WIPO				
	AN	WO 01/78693	10/25/2001	WIPO				
AWP	AO	WO 02/03958	01/17/2002	WIPO				

Other Documents (include Author, Title, Date, and Place of Publication)

Examiner Initial	Desig. ID	Document
	AP	
	AQ	
	AR	
	AS	

Examiner Signature	Date Considered
Alton N. Pryor	9/26/06

EXAMINER: Initials citation considered. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

Substitute Disclosure Form (PTO-1449)

Index of Claims

Application/Control No.	Applicant(s)/Patent under Reexamination
10/502,685	GOVIND ET AL.
Examiner	**Art Unit**
Alton N. Pryor	1616

√	Rejected	–	(Through numeral) Cancelled	N	Non-Elected	A	Appeal
=	Allowed	+	Restricted	I	Interference	O	Objected

Claim		Date
Final	Original	4/25/06
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UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

Bib Data Sheet

CONFIRMATION NO. 7568

SERIAL NUMBER	FILING OR 371(c) DATE	CLASS	GROUP ART UNIT	ATTORNEY DOCKET NO.
10/502,685	07/27/2004 RULE	424	1616	06275-410US1

APPLICANTS

Nayna Govind, Loughborough, UNITED KINGDOM;
Maria Marlow, Loughborough, UNITED KINGDOM;

**** CONTINUING DATA ***************************

This application is a 371 of PCT/SE03/00156 01/29/2003

**** FOREIGN APPLICATIONS *********************

SWEDEN 0200312-7 02/01/2002

Foreign Priority claimed	STATE OR COUNTRY	SHEETS DRAWING	TOTAL CLAIMS	INDEPENDENT CLAIMS
☐ yes ☐ no	UNITED KINGDOM	16	12	1

35 USC 119 (a-d) conditions met ☐ yes ☐ no ☐ Met after Allowance

Verified and Acknowledged _____ Examiner's Signature Initials

ADDRESS

26164

TITLE

Composition for inhalation

FILING FEE RECEIVED	FEES: Authority has been given in Paper No. _____ to charge/credit DEPOSIT ACCOUNT No. _____ for following:
1080	☐ All Fees ☐ 1.16 Fees (Filing) ☐ 1.17 Fees (Processing Ext. of time) ☐ 1.18 Fees (Issue) ☐ Other _____ ☐ Credit

Search Notes	Application/Control No.	Applicant(s)/Patent under Reexamination	
	10/502,685	GOVIND ET AL.	
	Examiner	Art Unit	
	Alton N. Pryor	1616	

SEARCHED			
Class	Subclass	Date	Examiner
424	45,46 489	4/20/2006	ANP

INTERFERENCE SEARCHED			
Class	Subclass	Date	Examiner

SEARCH NOTES (INCLUDING SEARCH STRATEGY)		
	DATE	EXMR
stic	4/20/2006	ANP

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     (FILE 'HOME' ENTERED AT 08:18:12 ON 20 APR 2006)

     FILE 'REGISTRY' ENTERED AT 08:18:51 ON 20 APR 2006
L1             0 S HFA227/CN
L2             1 S HFA 227/CN
L3             1 S PEG/CN
L4             1 S PVP/CN
L5             1 S FORMOTEROL/CN
L6            11 S FORMOTEROL
L7             1 S BUDESONIDE/CN
L8            23 S BUDESONIDE

     FILE 'CAPLUS, USPATFULL' ENTERED AT 08:32:08 ON 20 APR 2006
L9          4685 S HFA227 OR HFA 227 OR HEPTAFLUOROPROPANE OR HYDROPERFLUOROPROP
L10       365942 S PEG OR POLYETHYLENEGLYCOL OR POLYETHYLENE GLYCOL OR L3
L11       124559 S PVP OR POLYVINYLPYRROLIDONE OR POLYVINYL PYRROLIDONE OR L4
L12         4952 S BUDESONIDE OR L7 OR L8
L13         2198 S FORMOTEROL OR L5 OR L6
L14       129376 S L9 AND L10 OR L11 OR L12 OR L13
L15           78 S L9 AND L10 AND L11 AND L12 AND L13
L16        38081 S (TREAT? OR CONTROL? OR PREVENT?) (3A) (ASTHMA? OR RHINIT? OR
L17           56 S L16 AND L15
L18          738 S L12 (P) L13
L19           40 S L18 AND L9 AND L10 AND L11
L20           28 S L19 AND L16
```

UNITED STATES PATENT AND TRADEMARK OFFICE

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U.S. APPLICATION NUMBER NO.	FIRST NAMED APPLICANT	ATTY. DOCKET NO.
10/502,685	Nayna Govind	06275-410US1

INTERNATIONAL APPLICATION NO.	
PCT/SE03/00156	
I.A. FILING DATE	PRIORITY DATE
01/29/2003	02/01/2002

26164
FISH & RICHARDSON P.C.
225 FRANKLIN STREET
BOSTON, MA 02110

CONFIRMATION NO. 7568

371 ACCEPTANCE LETTER

OC000000014797872

Date Mailed: 12/21/2004

NOTICE OF ACCEPTANCE OF APPLICATION UNDER 35 U.S.C 371 AND 37 CFR 1.495

The applicant is hereby advised that the United States Patent and Trademark Office in its capacity as a Designated / Elected Office (37 CFR 1.495), has determined that the above identified international application has met the requirements of 35 U.S.C. 371, and is ACCEPTED for national patentability examination in the United States Patent and Trademark Office.

The United States Application Number assigned to the application is shown above and the relevant dates are:

07/27/2004	07/27/2004
DATE OF RECEIPT OF 35 U.S.C. 371(c)(1), (c)(2) and (c)(4) REQUIREMENTS	DATE OF COMPLETION OF ALL 35 U.S.C. 371 REQUIREMENTS

A Filing Receipt (PTO-103X) will be issued for the present application in due course. **THE DATE APPEARING ON THE FILING RECEIPT AS THE " FILING DATE" IS THE DATE ON WHICH THE LAST OF THE 35 U.S.C. 371 (c)(1), (c)(2) and (c)(4) REQUIREMENTS HAS BEEN RECEIVED IN THE OFFICE. THIS DATE IS SHOWN ABOVE.** *The filing date of the above identified application is the international filing date of the international application (Article 11(3) and 35 U.S.C. 363).* Once the Filing Receipt has been received, send all correspondence to the Group Art Unit designated thereon.

The following items have been received:

- Copy of the International Application filed on 07/27/2004
- Copy of the International Search Report filed on 07/27/2004
- Copy of IPE Report filed on 07/27/2004
- Preliminary Amendments filed on 07/27/2004
- Information Disclosure Statements filed on 07/27/2004
- Oath or Declaration filed on 07/27/2004
- Request for Immediate Examination filed on 07/27/2004
- U.S. Basic National Fees filed on 07/27/2004
- Priority Documents filed on 07/27/2004

Applicant is reminded that any communications to the United States Patent and Trademark Office must be mailed to the address given in the heading and include the U.S. application no. shown above (37 CFR 1.5)

JOHN L ANDERSON
Telephone: (703) 308-9116

PART 3 - OFFICE COPY

FORM PCT/DO/EO/903 (371 Acceptance Notice)

SUBSTITUTE FORM PTO-1390 U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE

TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371

ATTORNEY'S DOCKET NUMBER
06275-410US1

U.S. APPLICATION NO. (If known, see 37 CFR 1.5)
10/502685

INTERNATIONAL APPLICATION NO.	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED
PCT/SE2003/000156	29 January 2003	1 February 2002

TITLE OF INVENTION
COMPOSITION FOR INHALATION

APPLICANT(S) FOR DO/EO/US
Nayna Govind and Maria Marlow

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. ☒ This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
2. ☐ This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.
3. ☒ This is an express request to begin national examination procedures (35 U.S.C. 371(f)). The submission must include items (5), (6), (9) and (21) indicated below.
4. ☒ The US has been elected (Article 31).
5. ☒ A copy of the International Application as filed (35 U.S.C. 371(c)(2))
   a. ☒ is attached hereto (required only if not communicated by the International Bureau).
   b. ☐ has been communicated by the International Bureau.
   c. ☐ is not required, as the application was filed in the United States Receiving Office (RO/US).
6. ☐ An English language translation of the International Application as filed (35 U.S.C. 371(c)(2)).
   a. ☐ is attached hereto.
   b. ☐ has been previously submitted under 35 U.S.C. 154(d)(4).
7. ☒ Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371(c)(3))
   a. ☐ are attached hereto (required only if not communicated by the International Bureau).
   b. ☐ have been communicated by the International Bureau.
   c. ☐ have not been made; however, the time limit for making such amendments has NOT expired.
   d. ☒ have not been made and will not be made.
8. ☐ An English language translation of amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).
9. ☒ An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)).
10. ☐ An English language translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)).

Items 11 to 20 below concern document(s) or information included:

11. ☒ An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
12. ☐ An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
13. ☒ A preliminary amendment.
14. ☐ An Application Data Sheet under 37 CFR 1.76.
15. ☐ A substitute specification.
16. ☐ A power of attorney and/or change of address letter.
17. ☐ A computer-readable form of the sequence listing in accordance with PCT Rule 13*ter*.2 and 37 CFR 1.821 - 1.825.
18. ☐ A second copy of the published international application under 35 U.S.C. 154(d)(4).
19. ☐ A second copy of the English language translation of the international application under 35 U.S.C. 154(d)(4).
20. ☒ Other items or information:
    Copies of intrnational Preliminary Report and Search Report

CERTIFICATE OF MAILING BY EXPRESS MAIL
Express Mail Label No. EV382036625US
Date of Deposit: July 27, 2004

U.S. APPLICATION NO. (if known, see 37 CFR 1.5) 10/502685	INTERNATIONAL APPLICATION NO. PCT/SE2003/000156	ATTORNEY'S DOCKET NUMBER 06275-410US1

21. ☒ The following fees are submitted:	CALCULATIONS PTO USE ONLY	
Basic National Fee (37 CFR 1.492 (a) (1) - (5)):		
Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO and International Search Report not prepared by the EPO or JPO **$1080**		
International preliminary examination fee (37 CFR 1.482) not paid to USPTO but International Search Report prepared by the EPO or JPO..... **$920**		
International preliminary examination fee (37 CFR 1.482) not paid to USPTO but international search fee (37 CFR 1.445(a)(2)) paid to USPTO **$770**		
International preliminary examination fee (37 CFR 1.482) paid to USPTO but all claims did not satisfy provisions of PCT Article 33(1)-(4)..... **$730**		
International preliminary examination fee (37 CFR 1.482) paid to USPTO and all claims satisfied provisions of PCT Article 33(1)-(4)..... **$100**		
ENTER APPROPRIATE BASIC FEE AMOUNT =	$1,080.00	
Surcharge of **$130** for furnishing the oath or declaration later than 30 months from the earliest claimed priority date (37 CFR 1.492(e)).	$0.00	

CLAIMS	NUMBER FILED	NUMBER EXTRA	RATE		
Total Claims	12 - 20 =	0	x **$18**	$0.00	
Independent Claims	1 - 3 =	0	x **$86**	$0.00	
MULTIPLE DEPENDENT CLAIMS(S) (if applicable)			+ **$290**	$0.00	
TOTAL OF ABOVE CALCULATIONS =				$1,080.00	
☐ Applicant claims small entity status. See 37 CFR 1.27. The fees indicated above are reduced by 1/2.				$0.00	
SUBTOTAL =				$1,080.00	
Processing fee of **$130** for furnishing the English Translation later than 30 months from the earliest claimed priority date (37 CFR 1.492(f))				$0.00	
TOTAL NATIONAL FEE =				$1,080.00	
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31). **$40.00** per property +				$0.00	
TOTAL FEES ENCLOSED =				$1,080.00	
				Amount to be refunded:	$
				charged:	$

a. ☒ A check in the amount of $1,080.00 to cover the above fees is enclosed.

b. ☐ Please charge my Deposit Account No. 06-1050 in the amount of $0.00 to cover the above fees. A duplicate copy of this sheet is enclosed.

c. ☒ The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 06-1050. A duplicate copy of this sheet is enclosed.

NOTE: Where an appropriate time limit under 37 CFR 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b) must be filed and granted to restore the application to pending status.

SEND ALL CORRESPONDENCE TO:

PTO Customer No: 26164

SIGNATURE

Janis K. Fraser, Ph.D., J.D.
NAME

34,819
REGISTRATION NUMBER

SUBSTITUTE FORM PTO-1390 U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE

TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371

ATTORNEY'S DOCKET NUMBER
06275-410US1

U.S. APPLICATION NO. (If known, see 37 CFR 1.5)
10/502685

INTERNATIONAL APPLICATION NO.	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED
PCT/SE2003/000156	29 January 2003	1 February 2002

TITLE OF INVENTION
COMPOSITION FOR INHALATION

APPLICANT(S) FOR DO/EO/US
Nayna Govind and Maria Marlow

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. ☒ This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
2. ☐ This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.
3. ☒ This is an express request to begin national examination procedures (35 U.S.C. 371(f)). The submission must include items (5), (6), (9) and (21) indicated below.
4. ☒ The US has been elected (Article 31).
5. ☒ A copy of the International Application as filed (35 U.S.C. 371(c)(2))
   a. ☒ is attached hereto (required only if not communicated by the International Bureau).
   b. ☐ has been communicated by the International Bureau.
   c. ☐ is not required, as the application was filed in the United States Receiving Office (RO/US).
6. ☐ An English language translation of the International Application as filed (35 U.S.C. 371(c)(2)).
   a. ☐ is attached hereto.
   b. ☐ has been previously submitted under 35 U.S.C. 154(d)(4).
7. ☒ Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371(c)(3))
   a. ☐ are attached hereto (required only if not communicated by the International Bureau).
   b. ☐ have been communicated by the International Bureau.
   c. ☐ have not been made; however, the time limit for making such amendments has NOT expired.
   d. ☒ have not been made and will not be made.
8. ☐ An English language translation of amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).
9. ☒ An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)).
10. ☐ An English language translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)).

Items 11 to 20 below concern document(s) or information included:

11. ☒ An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
12. ☐ An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
13. ☒ A preliminary amendment.
14. ☐ An Application Data Sheet under 37 CFR 1.76.
15. ☐ A substitute specification.
16. ☐ A power of attorney and/or change of address letter.
17. ☐ A computer-readable form of the sequence listing in accordance with PCT Rule 13*ter*.2 and 37 CFR 1.821 - 1.825.
18. ☐ A second copy of the published international application under 35 U.S.C. 154(d)(4).
19. ☐ A second copy of the English language translation of the international application under 35 U.S.C. 154(d)(4).
20. ☒ Other items or information:
    Copies of intrnational Preliminary Report and Search Report

CERTIFICATE OF MAILING BY EXPRESS MAIL
Express Mail Label No. EV382036625US
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REGISTRATION NUMBER

Composition for inhalation

Field of the invention

The present invention relates to a formulation comprising formoterol and budesonide for use in the treatment of inflammatory conditions/disorders, especially respiratory diseases such as asthma, COPD and rhinitis.

Background of the invention

Stability is one of the most important factors which determines whether a compound or a mixture of compounds can be developed into a therapeutically useful pharmaceutical product.

Combinations of formoterol and budesonide are known in the art, see for example WO 93/11773 discloses such a combination that is now marketed as Symbicort® in a dry powder inhaler. There are a variety of other inhalers by which a respiratory product can be administered, such as pressurised metered dose inhalers (pMDI's). Formulations for pMDI's may require certain excipients as disclosed in WO 93/05765.

It has now been found that certain HFA formulations comprising formoterol and budesonide together with polyvinylpyrrolidone (PVP) and polyethylene glycol (PEG) exhibit excellent physical suspension stability.

Description of the invention

In accordance with the present invention, there is provided a pharmaceutical composition comprising formoterol, budesonide, HFA 227, PVP and PEG characterised in that the PVP is present from about 0.0005 to about 0.03 %w/w and the PEG is present from about 0.05 to about 0.35% w/w.

Preferably the PVP is present in an amount of 0.001 % w/w. Preferably the PVP is PVP K25.

Preferably the PEG is present in an amount of 0.3 % w/w. Preferably the PEG is PEG 1000.

Preferably the concentrations of formoterol/budesonide are such that the formulation delivers formoterol/budesonide at 4.5/40 mcg, 4.5/80 mcg, 4.5/160 mcg or 4.5/320mcg per actuation.

The formoterol can be in the form of a mixture of enantiomers. Preferably the formoterol is in the form of a single enantiomer, preferably the R, R enantiomer. The formoterol can be in the form of the free base, salt or solvate, or a solvate of a salt, preferably the formoterol is in the form of its fumarate dihydrate salt. Other suitable physiologically salts that can be used include chloride, bromide, sulphate, phosphate, maleate, tartrate, citrate, benzoate, 4-methoxybenzoate, 2- or 4-hydroxybenzoate, 4-chlorobenzoate, p-toluenesulphonate, benzenesulphonate, ascorbate, acetate, succinate, lactate, glutarate, gluconate, tricaballate, hydroxynapaphthalenecarboxylate or oleate.
Preferably the second active ingredient is budesonide, including epimers, esters, salts and solvates thereof. More preferably the second active ingredient is budesonide or an epimer thereof, such as the 22R-epimer of budesonide.

The pharmaceutical compositions according to the invention can be used for the treatment or prophylaxis of a respiratory disorder, in particular the treatment or prophylaxis of asthma, rhinitis or COPD.
In a further aspect the invention provides a method of treating a respiratory disorder, in particular asthma, rhinitis or COPD, in a mammal, which comprises administering to a patient a pharmaceutical composition as herein defined.

The compositions of the invention can be inhaled from any suitable MDI device. Doses will be dependent on the severity of the disease and the type of patient, but are preferably 4.5/80 mcg or 4.5/160 mcg per actuation as defined above.

The concentration of PVP (0.001%w/w) used in this formulation has been found to give consistently stable formulations over the required dose range, incorporating a wide range of concentrations of the active components, and at a much lower concentration than indicated in the prior art.

The invention is illustrated by the following examples.

Experimental section

Two methods can be used to evaluate physical suspension stability: Optical suspension characterisation (OSCAR), and TURBISCAN. Both methods are used to semi-quantify sedimentation/creaming rates. OSCAR measurements are performed using the PET bottles directly. For TURBISCAN analysis, the suspensions are transferred to custom designed pressure cells for measurement of light transmittance and backscattering.

METHODOLOGY

OSCAR

Optical Suspension Characterisation (OSCAR) equipment is custom designed for the rapid and reproducible semi-quantification of metered dose inhaler suspension characteristics.

The OSCAR equipment utilises changes in light transmission with time, to characterise a pre-agitated suspension formulation (a schematic diagram of the equipment is shown in Figure 1). The equipment consists of a twin headed test assembly. The head on the left side of the equipment is used with dilute suspensions and the right for concentrated suspensions. The selector switch mounted between the two test heads is used to alternate concentration choice. The output from the selected test head is directed to the equipment mounted voltage display and to the computer for data logging. The analogue signals from photodetectors are digitised and the values collected in data files, these are then processed using a suitable software package. There are two equipment mounted voltage displays, one each for the upper and lower photodetectors. The upper and lower photodetectors are height adjustable and a position readout display is provided to indicate the set height for each test run.

The Reagecon Turbidity standards (2500-4000 NTU) are used to calibrate the sensitivity of the OSCAR equipment. In this case, the 3000 NTU turbidity calibration standard is used as a standard calibration check. However any of the turbidity standards can be used to adjust the sensitivity of the probes to a specific voltage appropriate to the formulation.

Samples for test on the OSCAR equipment are presented in PET bottles crimped with non-metering valves.

For background information and prior art for this method refer to papers from Drug Delivery to the Lungs IX, 1997, Method Development of the OSCAR technique for the characterization of metered dose inhaler formulations, Authors N. Govind, P. Lambert And Drug delivery to the Lungs VI, 1995, A Rapid Technique for Characterisation of the Suspension Dynamics of metered Dose Inhaler Formulations, Author, PA Jinks (3M Healthcare Ltd)

TURBISCAN

Turbiscan MA 2000 is a concentrated dispersion and emulsion stability and instability analyser, or a vertical scan macroscopic analyser. It consists of a reading head moving along a flat-bottomed, 5ml cylindrical glass cell, which takes readings of transmitted and backscattered light every 40 μm on a maximum sample height of 80mm. The scan can be repeated with a programmable frequency to obtain a macroscopic fingerprint of the sample.

The reading head uses a pulsed near infrared light source (wavelength = 850 nm) and two synchronous detectors:

Transmission detector: Picks up light transmitted through the solution in the tube, at 0°

Backscattering detector: Receives the light back scattered by the product at 135°.

The profile obtained characterises the samples homogenieity, concentration and mean particle diameter. It allows for quantification of the physical processes the sample is undergoing. As well as detecting destabilisation, Turbiscan allows comparison of, for example, the sedimentaion rate of different suspensions.

Turbiscan may be used in several modes, eg transmitted or backscattering modes. Turbiscan has been used here in these examples to measure the transmitted light as a funtion of time

Dispersion instability is the result of two physical processes: a) particle size increases as a result of the formation of aggregates, due to flocculation b) particle migration resulting in creaming or sedimentation. When a product is stable (ie no flocculation, creaming or

sedimentation), the transmitted and backscattered light will remain constant i.e. scans of these will show a constant level profile. If the product undergoes changes in particle size, variations in the transmitted/ backscattered light show as change in the direction of the scan from horizontal or steady state profile.

For pressurised systems a cell capable of handling pressurised samples is required. Such a cell was used for the evaluations of these HFA formulations. The scans were performed in the AUTO mode.

The % transmission averages shown in the figure (see later) were taken from a zone around the middle of the suspension sample.

INITIAL EVALUATION

For the initial evaluation, only OSCAR was used.

Formulations containing formoterol fumarate dihydrate, budesonide, 0.001% w/w PVP K25 and either 0.1 % w/w or 0.3% PEG 1000 in HFA-227 were prepared in polyethylene terephlate (PET) bottles crimped with a continuous valve. For all formulations, the formoterol fumurate dihydrate concentration remained constant at 0.09mg/ml (equivalent to 4.5 mcg formoterol fumurate dihydrate per actuation) and the budesonide concentration varied between approximately 1mg/ml to 8 mg/ml (equivalent to 40 mcg to 320 mcg per actuation).

Early OSCAR data for Symbicort pMDI formulations

Budesonide dose ex-actuator	Formoterol dose ex-actuator	PVP K25 concentration (% w/w)	Time seconds	Transmittance (mV) Lower sensor	
				PEG concn %w/w 0.1	0.3
40 µg	4.5 µg	0.001	30 seconds		257
			60 seconds		264
80 µg	4.5 µg	0.001	30 seconds	202	
			60 seconds	240	
		0.002	30 seconds	184	
			60 seconds	185	
160 µg	4.5 µg	0.001	30 seconds	208	114
			60 seconds	304	191
		0.002	30 seconds	248	
			60 seconds	327	
320 µg	4.5 µg	0.001	30 seconds		475
			60 seconds		570
		0.002	30 seconds		930
			60 seconds		1443

OSCAR analysis of these formulations gave relatively low light transmittance values at the lower sensor, which is indicative of stable suspensions with low flocculation characteristics. Early indications were that the 0.001% w/w PVP with 0.3% PEG 1000 would give the best suspension.

FURTHER EVALUATION: various concentrations of PVP K25 with a constant PEG 1000 concentration of 0.3% w/w.

OSCAR, Turbiscan and photographic methods were used to evaluate the formulations. OSCAR and Turbiscan techniques have been described earlier. Samples with varying concentrations of PVP were analysed to determine suspension stability over time.

PHOTOGRAPHIC ANALYSIS

For the photographic analysis , samples were prepared in PET bottles and photographed digitally over time, using a black background. These photographs (some of which are shown here) show the behaviour of the suspension over time and allow easy comparison of the effectiveness of the various concentrations of PVP. The concentration of PVP varied from 0.0001 to 0.05 % w/w. From left to right on the photographs the concentration of PVP is as follows:

0.0001 far left	0.0005	0.001	0.01	0.03	0.05 far right

DIGITAL PHOTOGRAPHY OF FORMULATIONS SHOWING DEGREE OF DISPERSION OVER TIME

Figures 9, 10 and 11 show Budesonide 160µg/shot, Formoterol 4.5µg/shot with various PVP K25 concentrations and 0.3% PEG 1000 at 0, 15, 30, and 60 seconds standing time.

Figures 12, 13 and 14 shows Budesonide 80µg/shot, Formoterol 4.5µg/shot with various PVP K25 concentrations and 0.3% PEG 1000 at 0, 30, and 60 seconds standing time.

TABLE OF DEGREEE OF DISPERSION OF SUSPENSIONS OVER TIME: (ALL SAMPLES)

Photographs were taken of all doses (320µg/4.5µg to 40µg/4.5µg) at 0, 15, 30, 60, 90 seconds, and 2, 5 and 10 minutes. As this produced too many photographs to reproduce here, a chart has been constructed to give a reprentation of the degree of dispersion over time.

If the sample was fully suspended, the sample was rated 0 e.g. at 0 minutes they were fully dispersed. From there, the samples have been rated in increments of 1-5 at 20% intervals to express the degree of dispersion i.e. 0 was fully suspended and 5 fully creamed. This allows some comparison across the whole dose range and PVP concentration range used. (Note concentration of Formoterol is 4.5µg/shot in all the samples)

(Samples are all fully dispersed at 0 seconds and therefore all have a score of 0)

Fully dispersed – 0

More than 80% dispersed ie less than 20% clear liquid present 1

More than 60% dispersed ie less than 40% clear liquid present 2
Less than 40% dispersed ie more than 60% clear liquid present 3
Less than 20% dispersed ie more than 80% clear liquid present 4
Fully creamed 5

TABLE OF DEGREEE OF DISPERSION OF SUSPENSIONS OVER TIME: ALL SAMPLES

Dose	Time	PVP concentration (% w/w)					
µg/shot Budesonide	Sec/mins	0.0001	0.0005	0.001	0.01	0.03	0.05
320	15	2	1	0-1	0-1	0-1	0-1
	30	3	3	2	1-2	2	2
	60	4	4	3-4	2	3	3-4
	90	4	5	5	3	5	5
	2	5	5	4-5	4-5	5	5
	5	5	5	5	5	5	5
	10	5	5	5	5	5	5
160	15	3	2	0-1	0-1	2	2
	30	3	2	1	1	2	2
	60	5	4	1	2	4	5
	90	5	5	1	2	5	5
	2	5	5	1	2	5	5
	5	5	5	2	4	5	5
	10	5	5	2	4	5	5
80	15	2	1	0	0	1	1
	30	3	2	1	1	2	2
	60	4	2	1	1-2	3	3
	90	5	3	1-2	1-2	4	3
	2	5	3-4	1	1	5	4
	5	5	4	2	2	5	5
	10	5	5	3	3	5	5
40	15	1	1	0	0	1	2
	30	2	1	1	2	2	3
	60	1-2	1	1	2	2	3
	90	1-2	1-2	1-2	2	2-3	4
	2	2	2	2	3	4	5

	5	3	**2**	**2**	3	4	5
	10	4-5	3	2	4	5	5

Suspensions considered excellent are highlighted in bold.
It can be seen that the formulations with 0.001% w/w PVP gave the best suspension stability overall.

OSCAR DATA (Graphs of light transmission versus time)

Figure 2 shows the average OSCAR transmission readings (lower sensor only) for various concentrations of PVP K25. A low transmission reading indicates that the suspension is dispersed preventing light being transmitted. Hence, it can be seen that the lowest line is the most stable formulation. This is the 0.001% PVP sample.

In Figure 3, the bottom line, again with low transmission readings, clearly shows that the formulation containing 0.001% PVP is the most stable.

TURBISCAN DATA(Graphs of percentage (%) light transmission versus time)

Data from the Turbiscan can be intepretated in a similar vein to the OSCAR data in that a low percentage (%) transmission indicates the suspension is dispersed . The % transmission averages quoted here were taken from a zone around the middle of the suspension sample. In Figure 4 the most stable formulation is the lowest line with the lowest % transmission, i.e. the bold black line with 0.001%w/w PVP

Figures 5 and 6 show that the suspension with 0.001% w/w PVP is the most stable (bottom bold line) with the lowest % transmission.

FURTHER EVALUATION: Determination of the optimum PEG 1000 concentration.

For this evaluation, photography, turbiscan and force to fire data (valve performance) was used to determine the optimum PEG concentration.

Line1

METHODOLOGY - Force to fire (return force at 0.5mm stem return)

Force to fire testing was performed using the Lloyd LRX testing machine. The pMDI unit to be tested was placed valve down in a can holder on the lower platform of the unit. The upper crosshead was then moved to just above the base of the can. Can actuations were performed using a standard protocol. During measurement, force data is captured by means of the load cell located at the top of the upper crosshead. This program was designed to output the return force at 0.5mm stem return as this is the point at which the metering chamber is considered to refill.

A low return force is indicative of high friction and potential sticking problems. It also suggests there may be a problem with low actuation weights as the propellant enters the metering chamber more slowly and has time to vaporise. Force to fire testing was performed at preset actuations.

DATA

FORCE TO FIRE DATA

Figure 7 shows the effect of PEG 1000 concentration on stem return force for the 4.5/160 μg formoterol/budesonide formulation

This shows that at 120 actuations, the return force is greater for the 0.3% w/w PEG 1000 concentration than for the other concentrations of 0.5% and 0.1%. In general, the higher the return force the lesser the chance of the valve stem sticking. The above data shows that in this case 0.3% would be preferred.

TURBISCAN DATA

The Turbiscan data (figure 8) shows that there is little difference between the stability of suspensions made with varying levels of PEG 1000 except for the 0.005% w/w level which was unsatisfactory.

PHOTOGRAPHIC ANALYSIS

Digital photographs of suspensions containing Budesonide, Formoterol, HFA 227, 0.001%w/w PVP and varying levels of PEG 1000 show little variation in suspension stability over time (0 seconds to 10 minutes) except for the 0.005% w/w PEG level (in agreement with the Turbiscan data).

Figures 15 and 16 show Budesonide 80µg/shot, Formoterol 4.5µg/shot with 0.001% PVP K25 and various concentrations of PEG 1000 at 0 (1) and 10 minutes (2) standing time

PRODUCT PERFORMANCE DATA

In addition to the above, product performance data for formulations containing formoterol fumurate dihydrate/budesonide at the following strengths, 4.5/80 mcg per actuation and 4.5/160 mcg per actuation, with 0.001% PVP K25 and either 0.1% or 0.3% PEG 1000 were stable for up to 12 months at 25°C/60% RH.

Product performance data for Symbicort formulations containing 0.001% PVP K25 and 0.1% PEG 1000 in HFA-227

Product strength (µg) (FFD/budesonide)	**Fine particle fraction (% cumulative undersize for 4.7 µm cut-off)**			
	Drug	Initial	25°C/60% RH 6 months	25°C/60% RH 12 months
4.5/80	Budesonide	51.3	52.8	62.0
	FFD	55.4	53.5	59.7
4.5/160	Budesonide	50.0	48.8	47.0
	FFD	54.2	52.1	51.3

Product performance data for Symbicort formulations containing 0.001% PVP K25 and 0.3% PEG 1000 in HFA-227

Product strength (µg) (FFD/budesonide)	Fine particle fraction (% cumulative undersize for 4.7 µm cut-off)			
	Drug	Initial	25°C/60% RH 6 months	25°C/60% RH 12 months
4.5/80	Budesonide	55.8	50.6	51.3
	FFD	64.2	57.6	58.7
4.5/160	Budesonide	48.7	50.2	52.3
	FFD	55.6	59.1	61.2

Claims.

1. A pharmaceutical composition comprising formoterol, budesonide, HFA 227, PVP and PEG.

2. A formulation according to claim 1 characterised in that the PVP is present from about 0.0005 to about 0.05 %w/w and the PEG is present from about 0.05 to about 0.35% w/w.

3. A pharmaceutical composition according to claim 1 or 2 in which the PVP is PVP K25.

4. A pharmaceutical composition according to claim 1 to 3 in which the PVP is present in an amount of 0.001% w/w.

5. A pharmaceutical composition according to any one of claims 1 to 4 in which the PEG is PEG 1000.

6. A pharmaceutical composition according to any one of claims 1 to 5 in which the PEG is present in an amount of 0.3% w/w.

7. A pharmaceutical composition according to any one of claims 1 to 6 in which formoterol is in the form of its fumarate dihydrate salt

8. A pharmaceutical composition according to any one of claims 1 to 7 in which the formoterol is in the form of the single R, R-enantiomer.

9. A pharmaceutical composition according to any one of claims 1 to 8 in which the second active ingredient is the 22R-epimer of budesonide.

10. A pharmaceutical composition according to any one of claims 1 to 9 for use for the treatment or prophylaxis of a respiratory disorder.

11. A pharmaceutical composition according to any one of claims 1 to 9 for use for the treatment or prophylaxis of asthma, rhinitis or COPD.

12. A method of treating a respiratory disorder in a mammal which comprises administering to a patient a pharmaceutical composition according to any one of claims 1 to 9.

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

CORRECTED VERSION

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(75) Inventors/Applicants *(for US only)*: **GOVIND, Nayna** [GB/GB]; AstraZeneca R & D Charnwood, Bakewell Road, Loughborough, Leicestershire LE11 5RH (GB). **MARLOW, Maria** [GB/GB]; AstraZeneca R & D Charnwood, Bakewell Road, Loughborough, Leicestershire LE11 5RH (GB).

(74) Agent: **GLOBAL INTELLECTUAL PROPERTY**; AstraZeneca AB, S-151 85 Södertälje (SE).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

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WO 2003/063842 A1

(54) Title: COMPOSITION FOR INHALATION

(57) Abstract: The invention relates to a formulation comprising formoterol and budesonide for use in the treatment of respiratory diseases. The composition further contains HFA 227, PVP and PEG, preferably PVP K25 and PEG 1000.

Fig 1/16

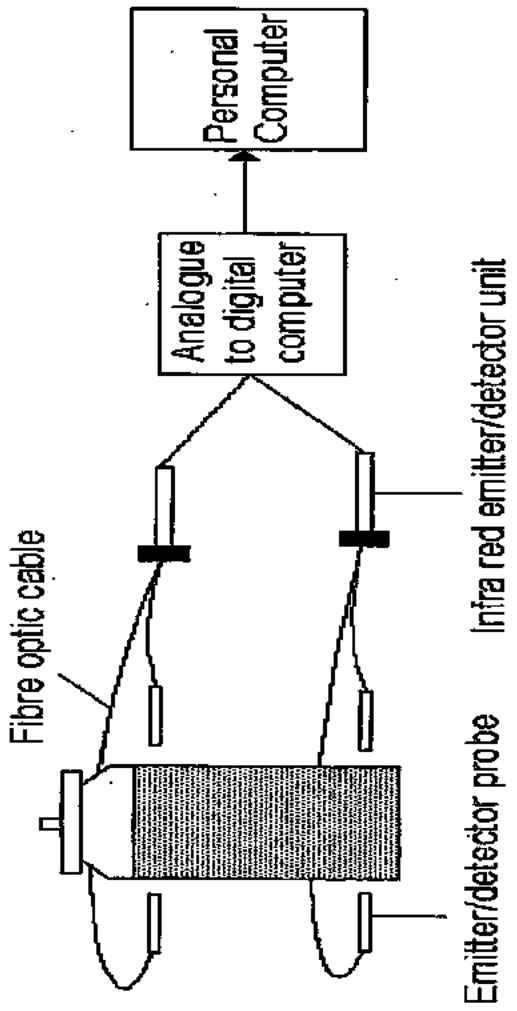


Figure 1: Schematic for OSCAR set-up

Fig 2/16

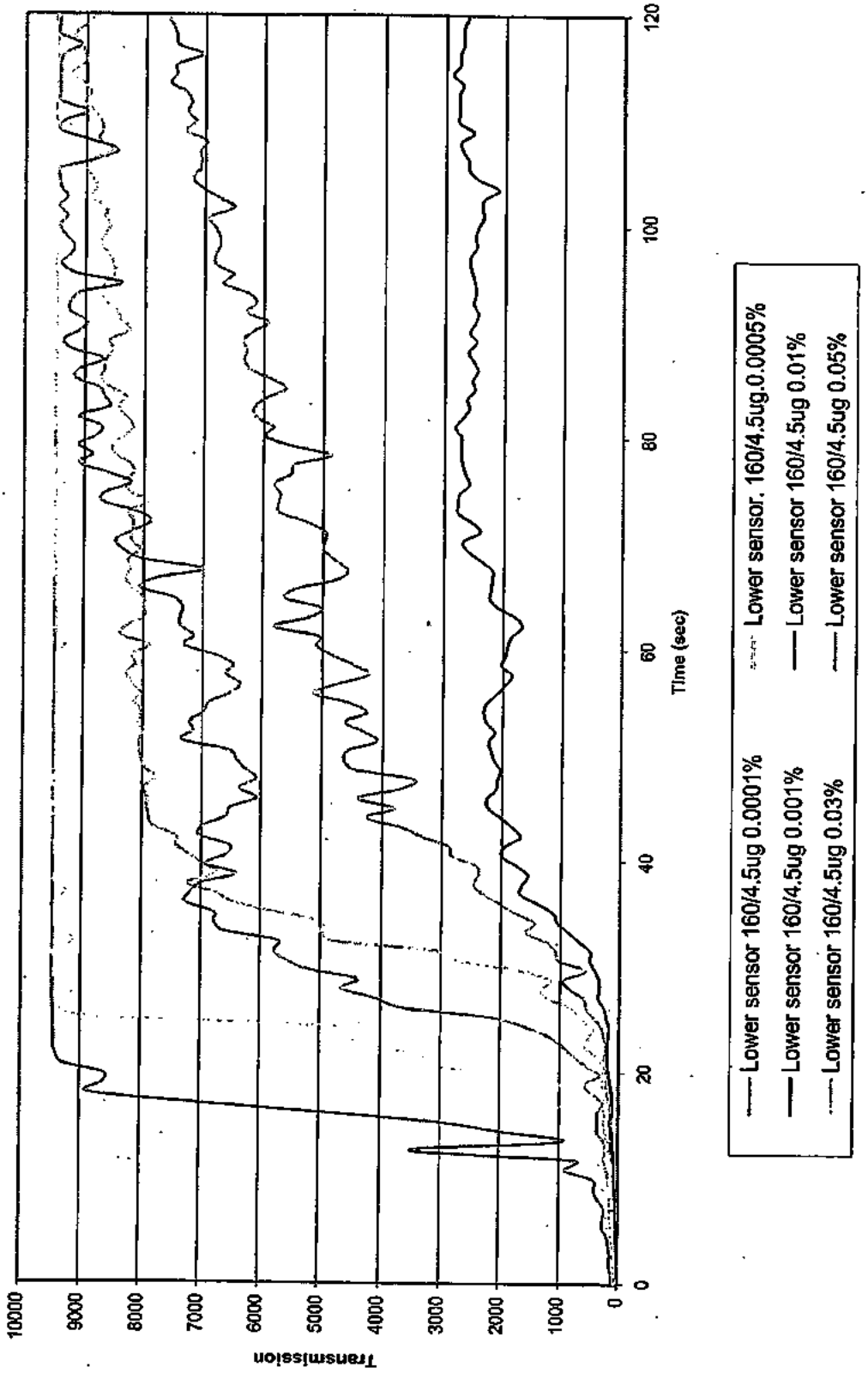


Figure 2: Averages of OSCAR data for formulation containing 160/4.5ug Budesonide/Formoterol. 0.3% w/w PEG 1000. 0.0001% - 0.05% w/w PVP K25.

Fig 3/16

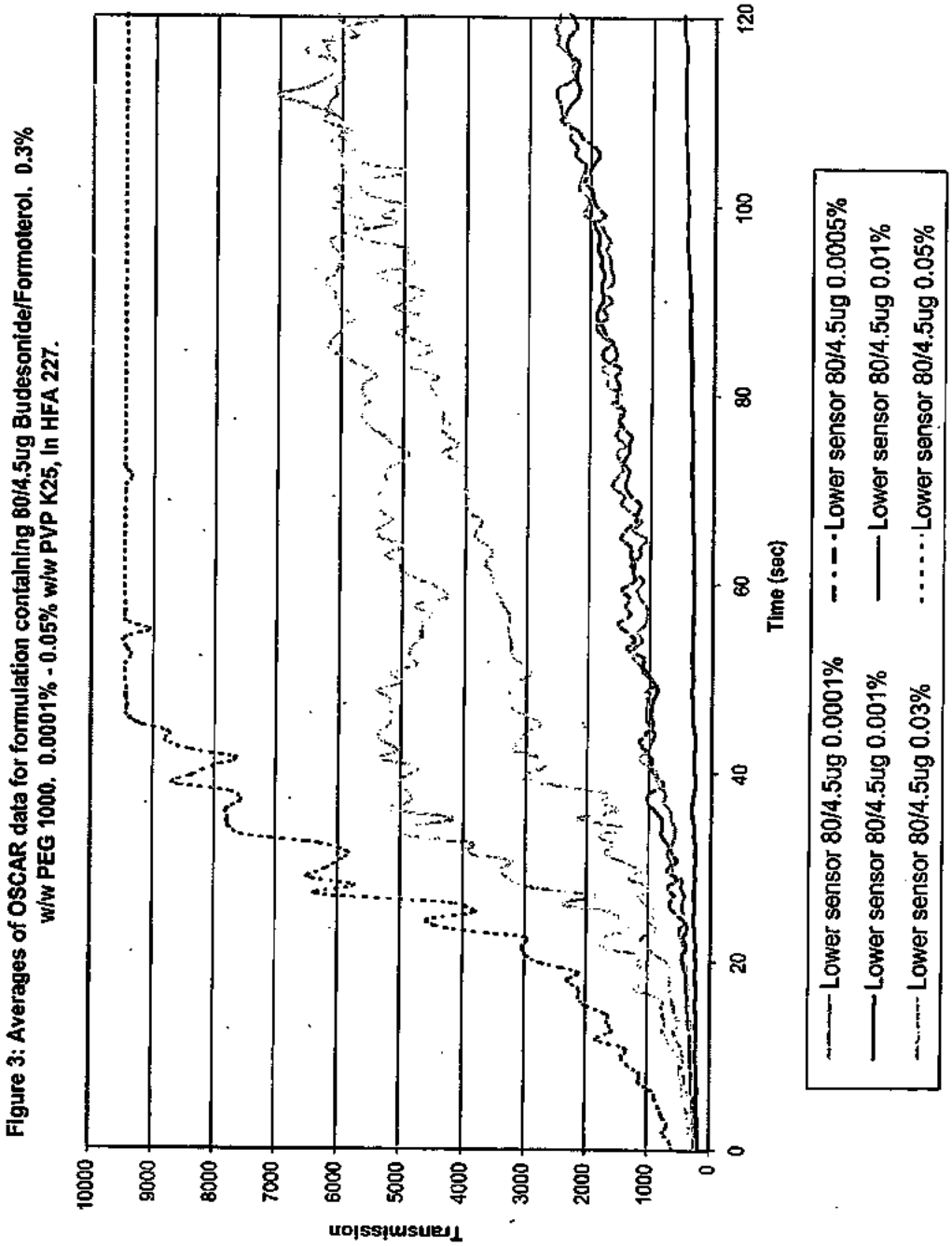


Figure 3: Averages of OSCAR data for formulation containing 80/4.5ug Budesonide/Formoterol. 0.3% w/w PEG 1000. 0.0001% - 0.05% w/w PVP K25, in HFA 227.

Fig 4/16

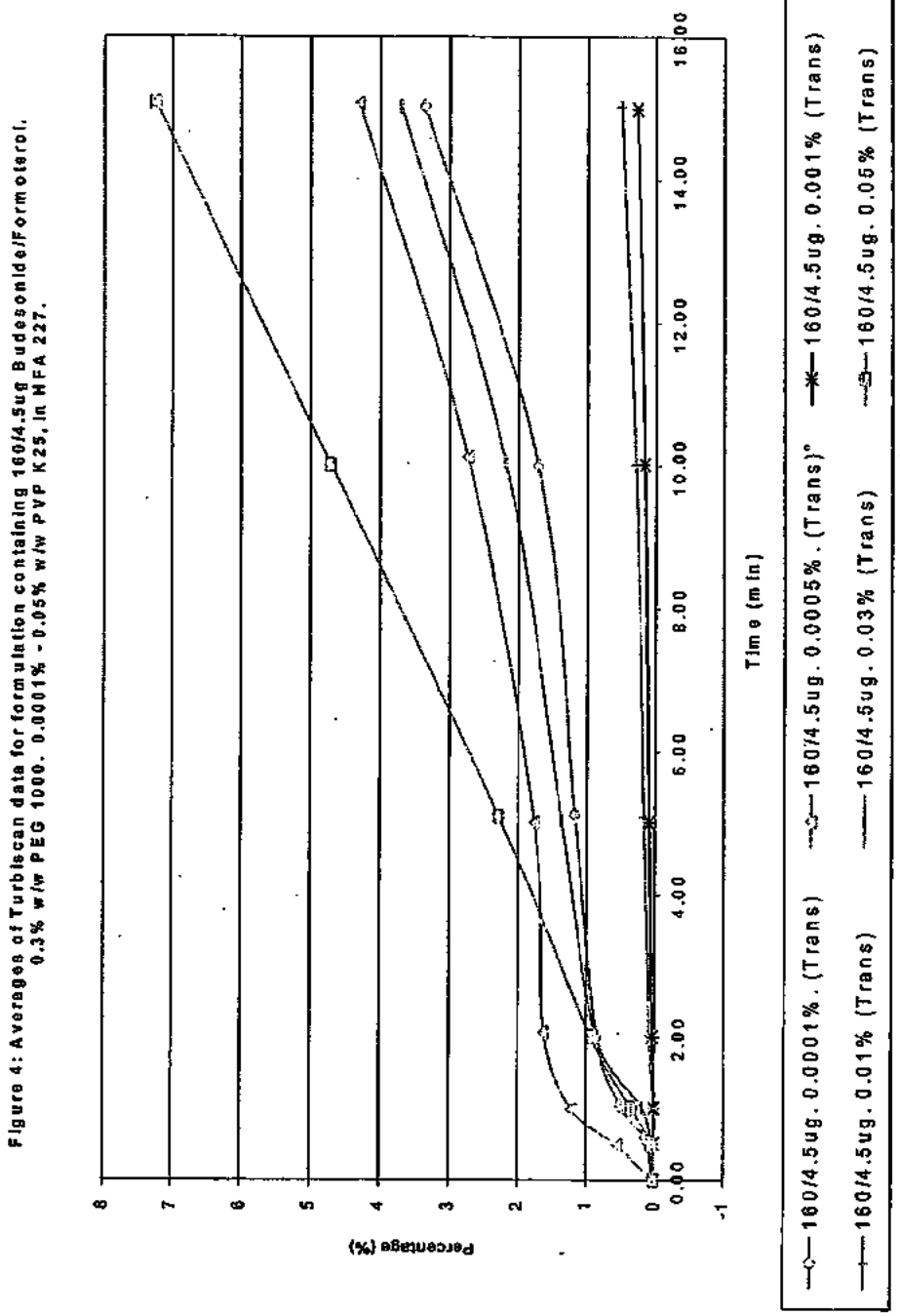


Figure 4: Averages of Turbiscan data for formulation containing 160/4.5ug Budesonide/Formoterol.
0.3% w/w PEG 1000. 0.0001% - 0.05% w/w PVP K25, in HFA 227.
Percentage (%)
Time (min)
160/4.5ug. 0.0001%. (Trans)
160/4.5ug. 0.0005%. (Trans)*
160/4.5ug. 0.001% (Trans)
160/4.5ug. 0.01% (Trans)
160/4.5ug. 0.03% (Trans)
160/4.5ug. 0.05% (Trans)

Fig 5/16

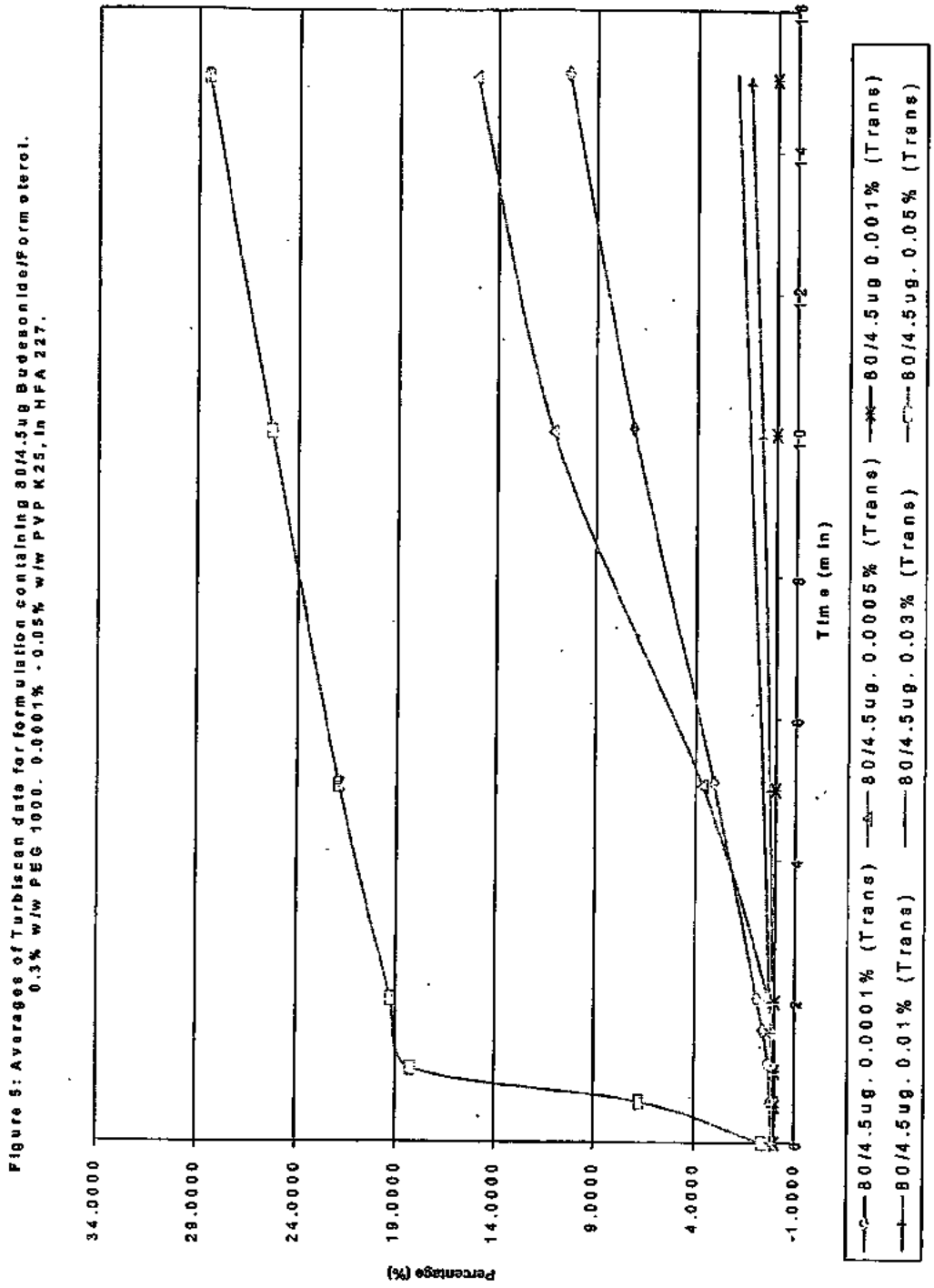


Figure 5: Averages of Turbiscan data for formulation containing 80/4.5ug Budesonide/Formoterol.
0.3% w/w PEG 1000. 0.0001% - 0.05% w/w PVP K25, in HFA 227.
Percentage (%)
34.0000
29.0000
24.0000
19.0000
14.0000
9.0000
4.0000
-1.0000
Time (min)
80/4.5ug. 0.0001% (Trans)
80/4.5ug. 0.0005% (Trans)
80/4.5ug 0.001% (Trans)
80/4.5ug. 0.01% (Trans)
80/4.5ug. 0.03% (Trans)
80/4.5ug. 0.05% (Trans)

Fig 6/16

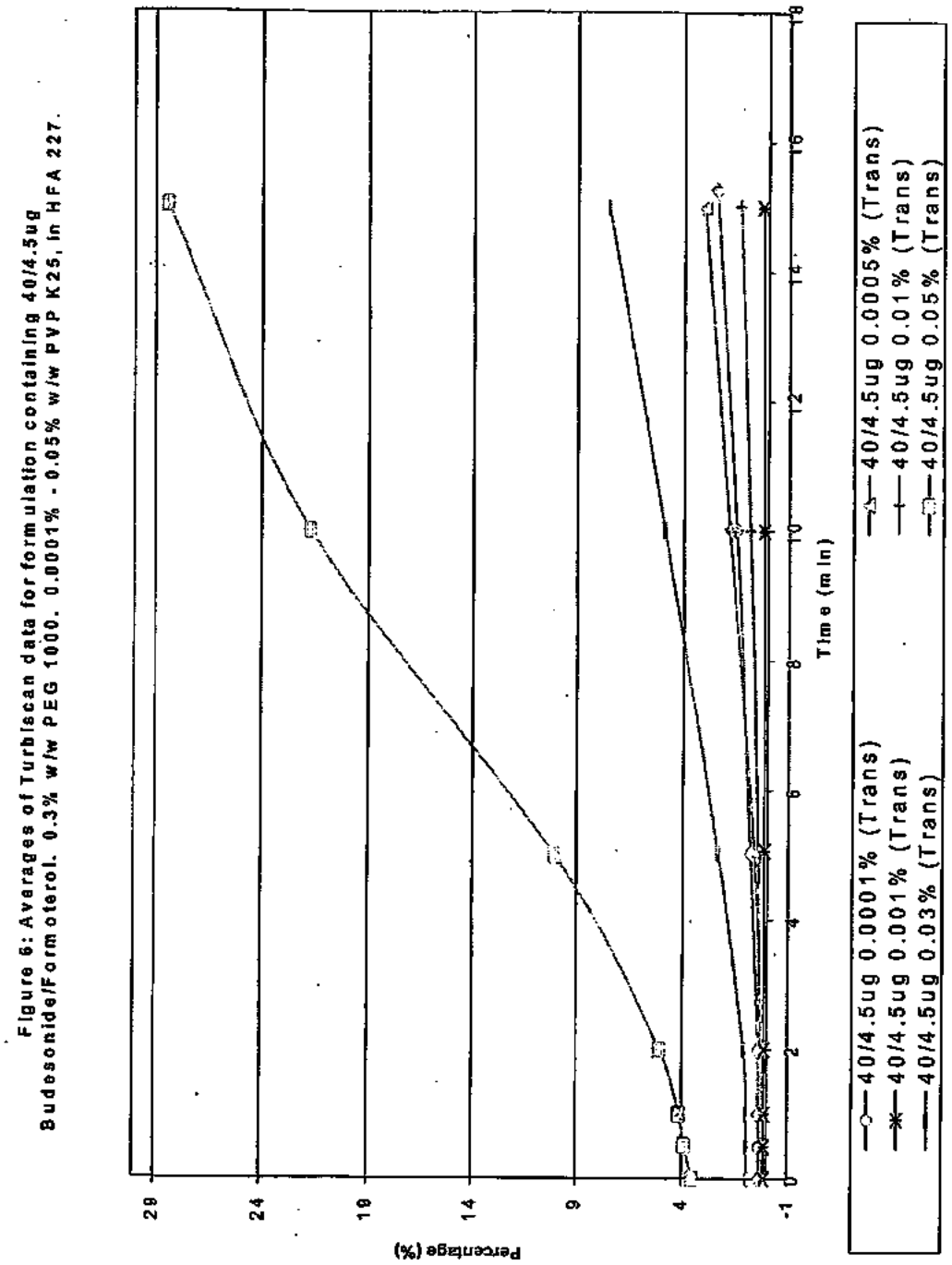


Figure 6: Averages of Turbiscan data for formulation containing 40/4.5ug
Budesonide/Formoterol. 0.3% w/w PEG 1000. 0.0001% - 0.05% w/w PVP K25, in HFA 227.
Percentage (%)
Time (min)
40/4.5ug 0.0001% (Trans)
40/4.5ug 0.001% (Trans)
40/4.5ug 0.03% (Trans)
40/4.5ug 0.0005% (Trans)
40/4.5ug 0.01% (Trans)
40/4.5ug 0.05% (Trans)

Fig 7/16

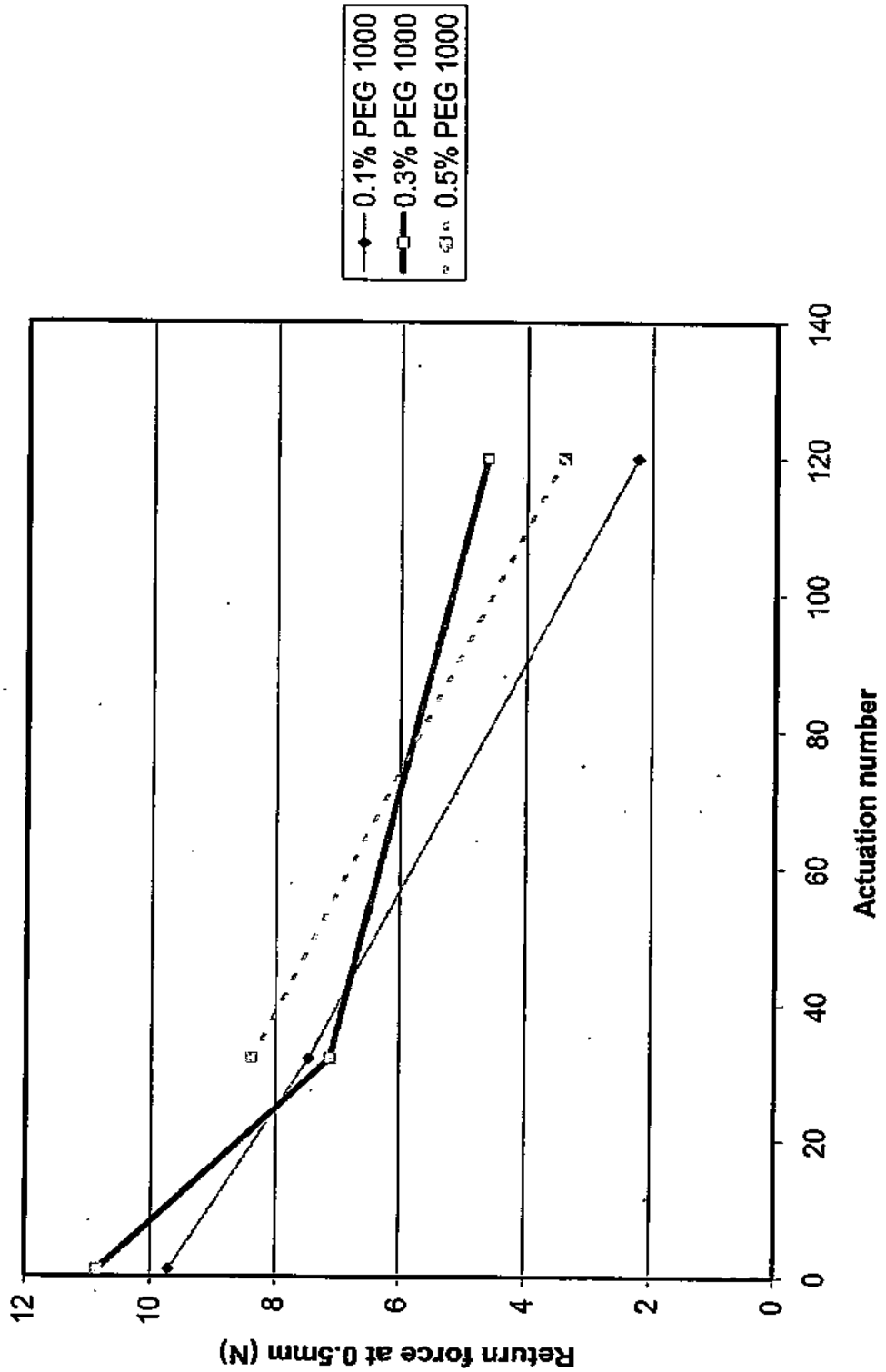

0.1% PEG 1000
0.3% PEG 1000
0.5% PEG 1000
Actuation number
0
20
40
60
80
100
120
140
Return force at 0.5mm (N)
0
2
4
6
8
10
12

Fig. 8/16

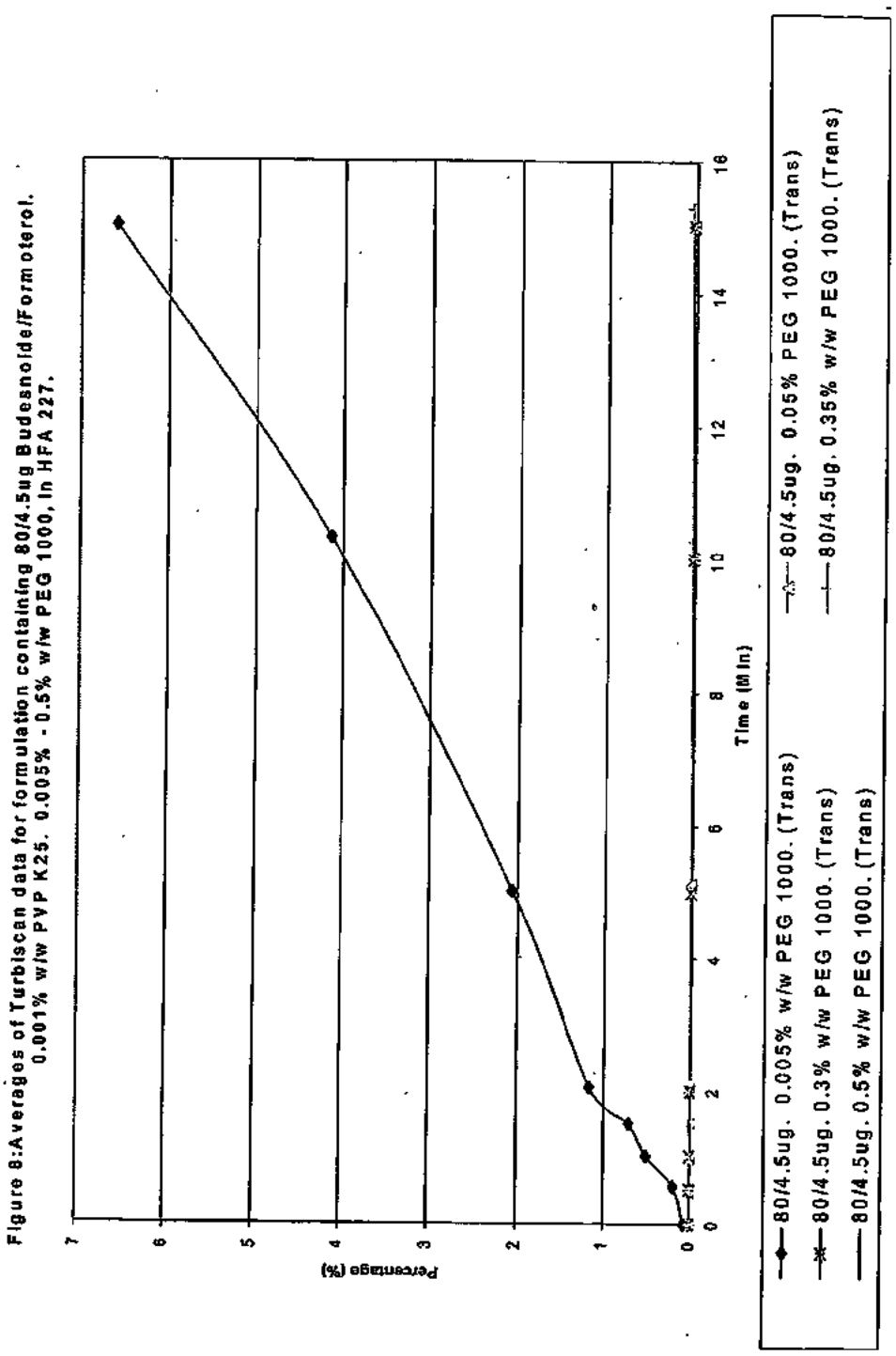


Figure 8:Averages of Turbiscan data for formulation containing 80/4.5ug Budesonide/Formoterol. 0.001% w/w PVP K25. 0.005% - 0.5% w/w PEG 1000, In HFA 227.
Percentage (%)
Time (Min)
80/4.5ug. 0.005% w/w PEG 1000. (Trans)
80/4.5ug. 0.3% w/w PEG 1000. (Trans)
80/4.5ug. 0.5% w/w PEG 1000. (Trans)
80/4.5ug. 0.05% PEG 1000. (Trans)
80/4.5ug. 0.35% w/w PEG 1000. (Trans)

Fig. 9/16

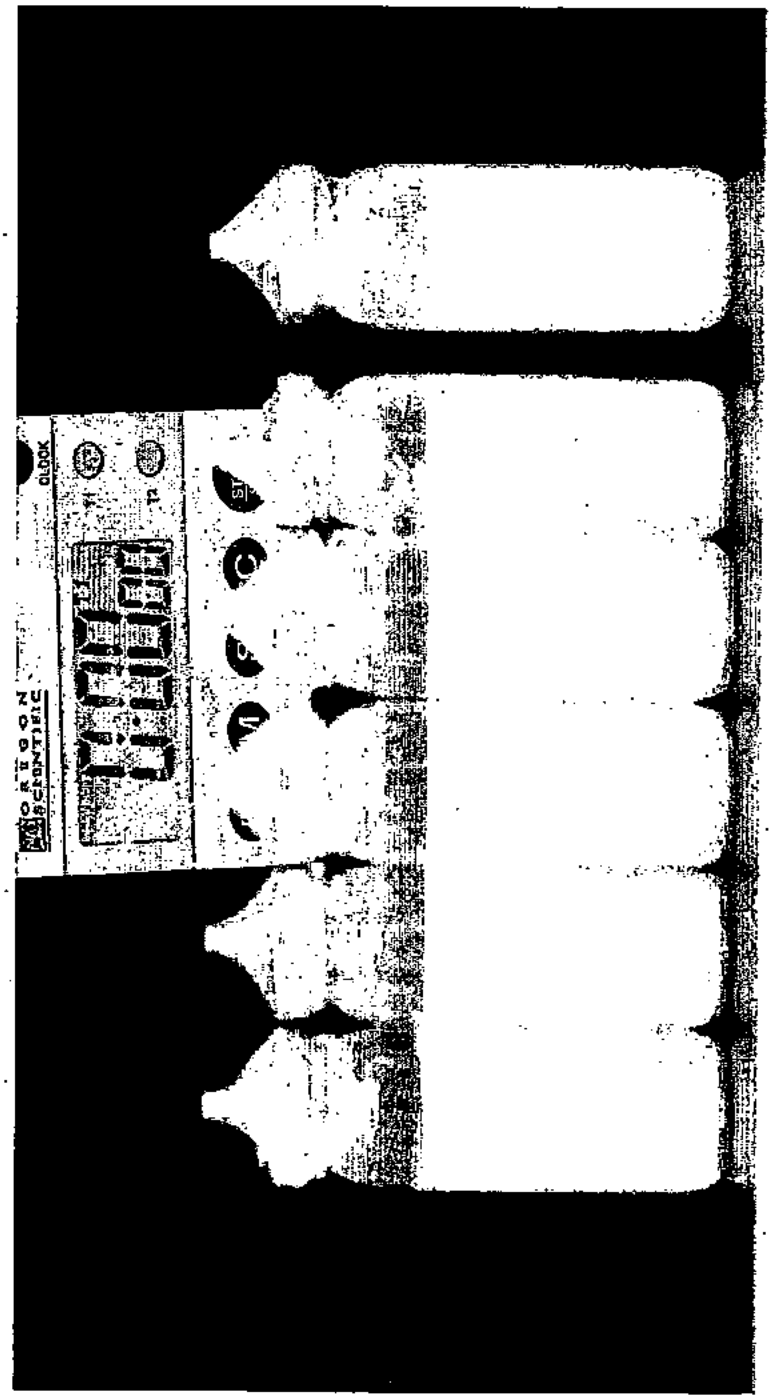


Fig. 10/16

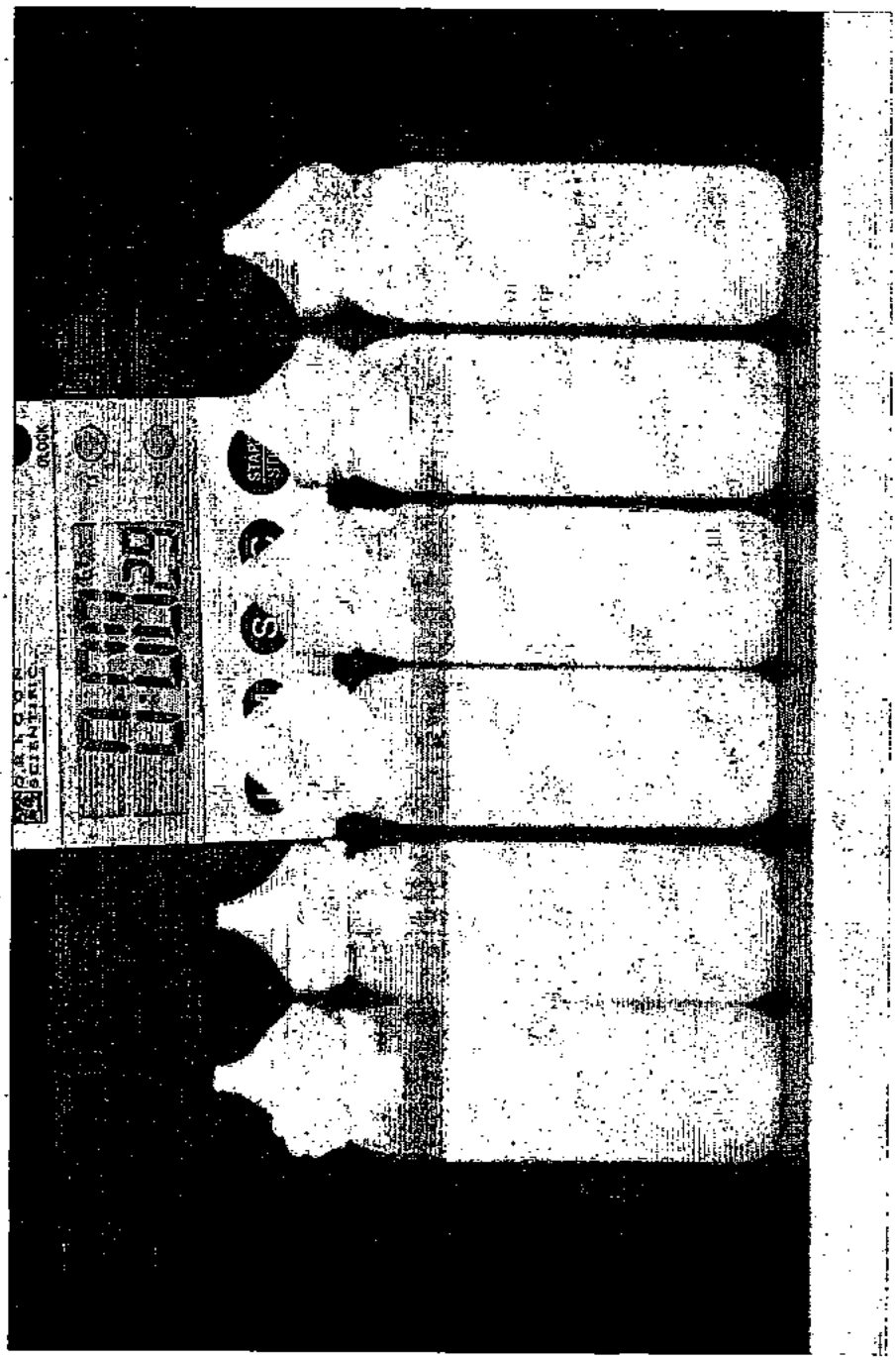


Fig. 11/16

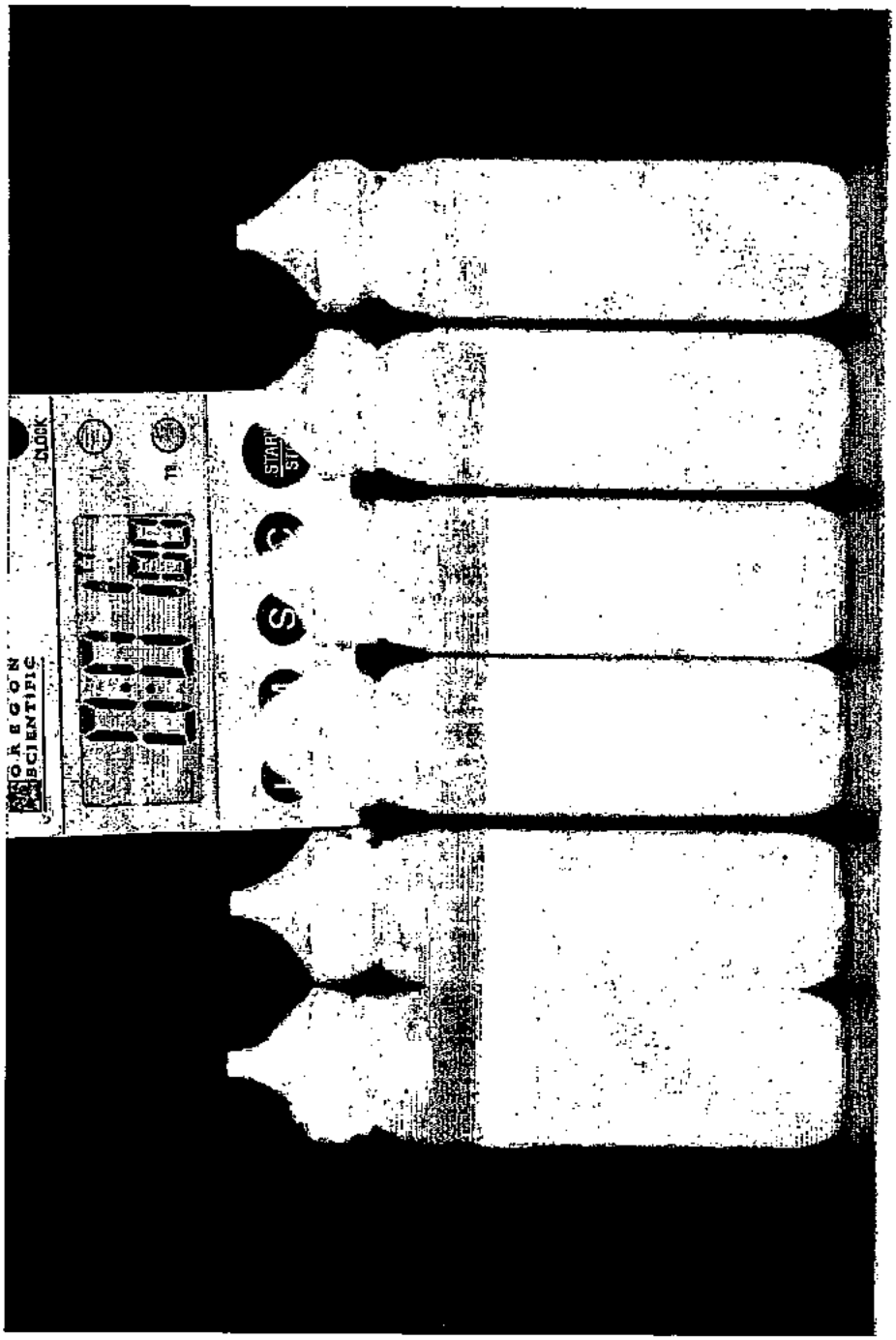


Fig. 12/16

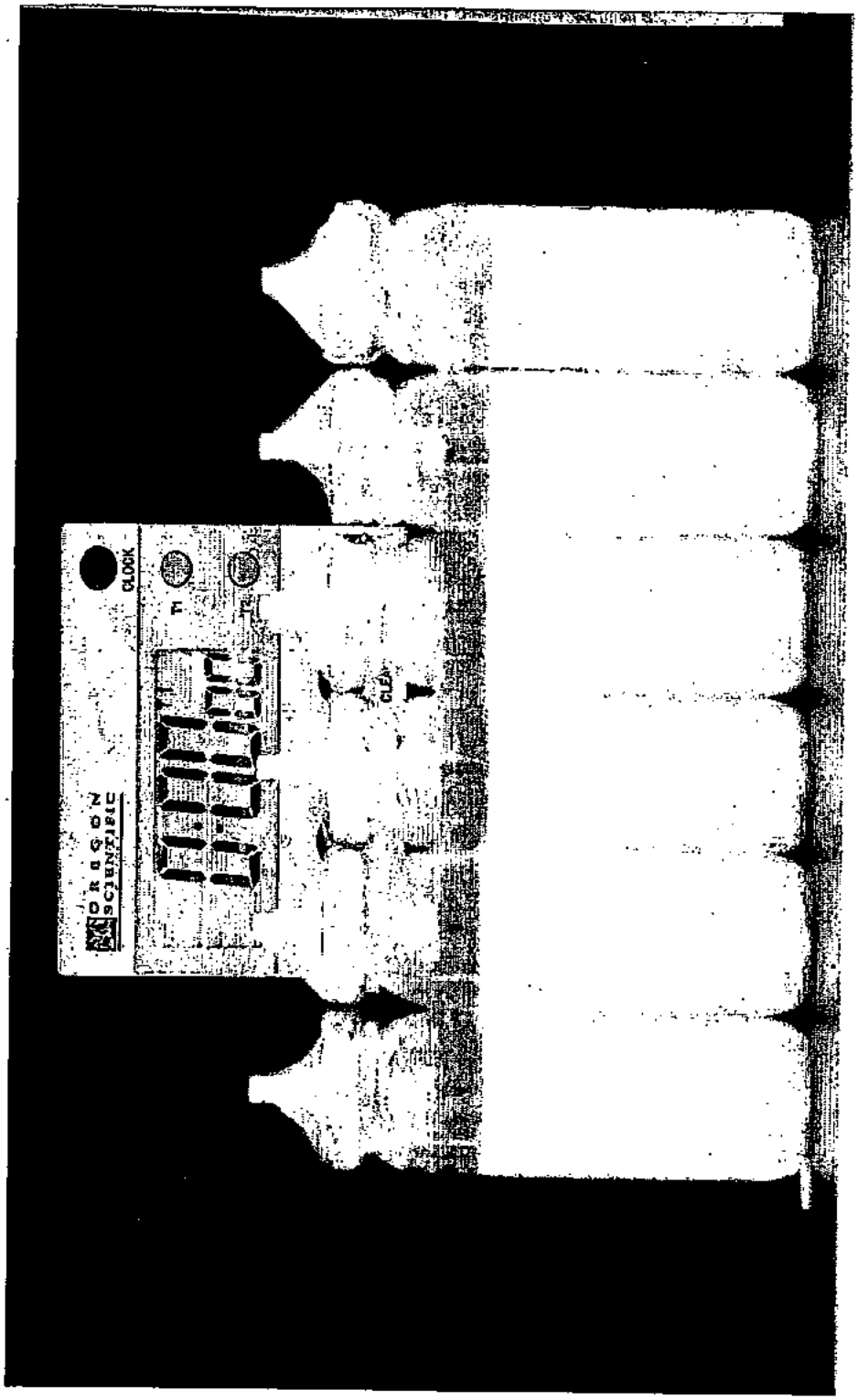


Fig. 13/16

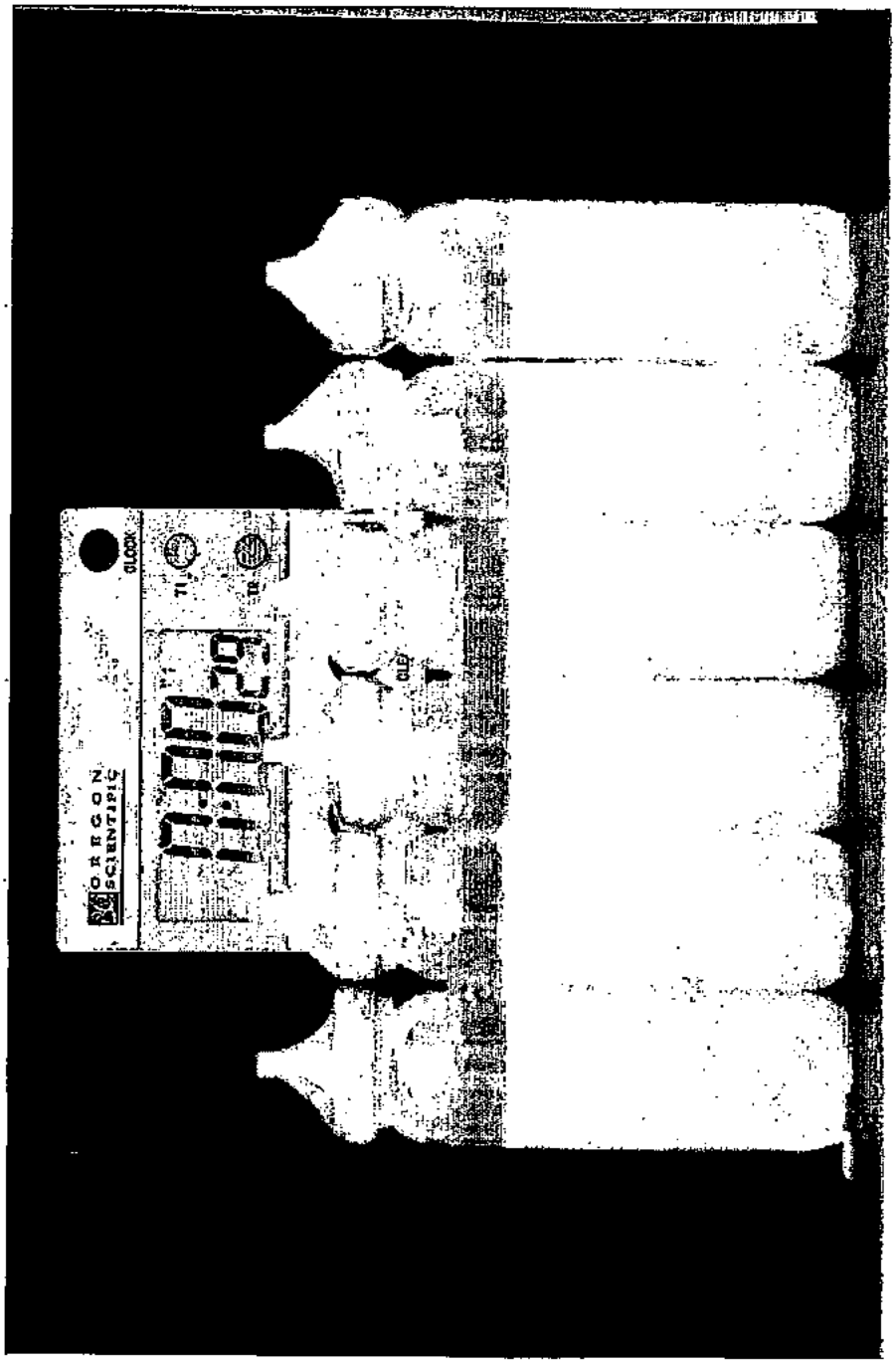


Fig 14/16

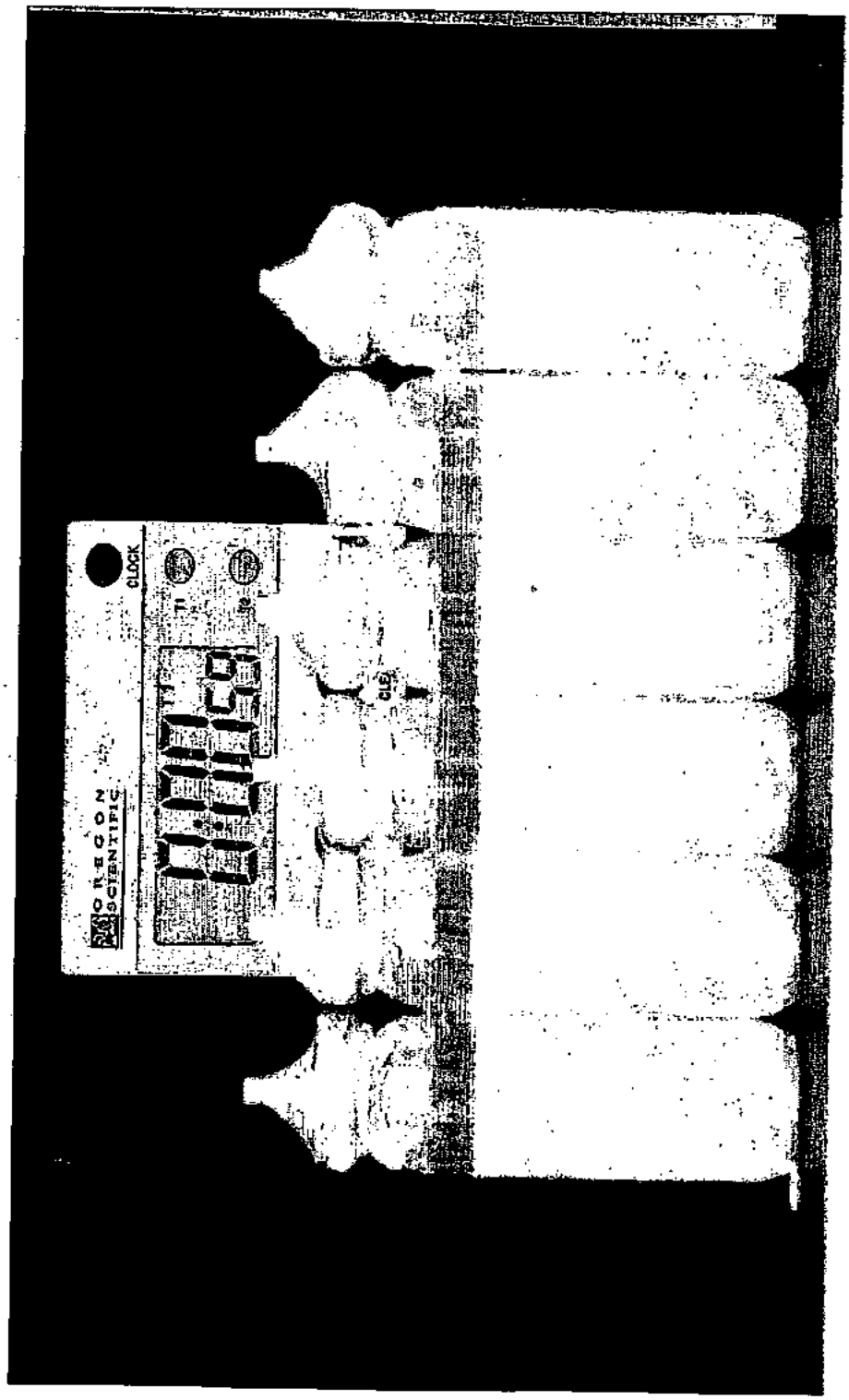
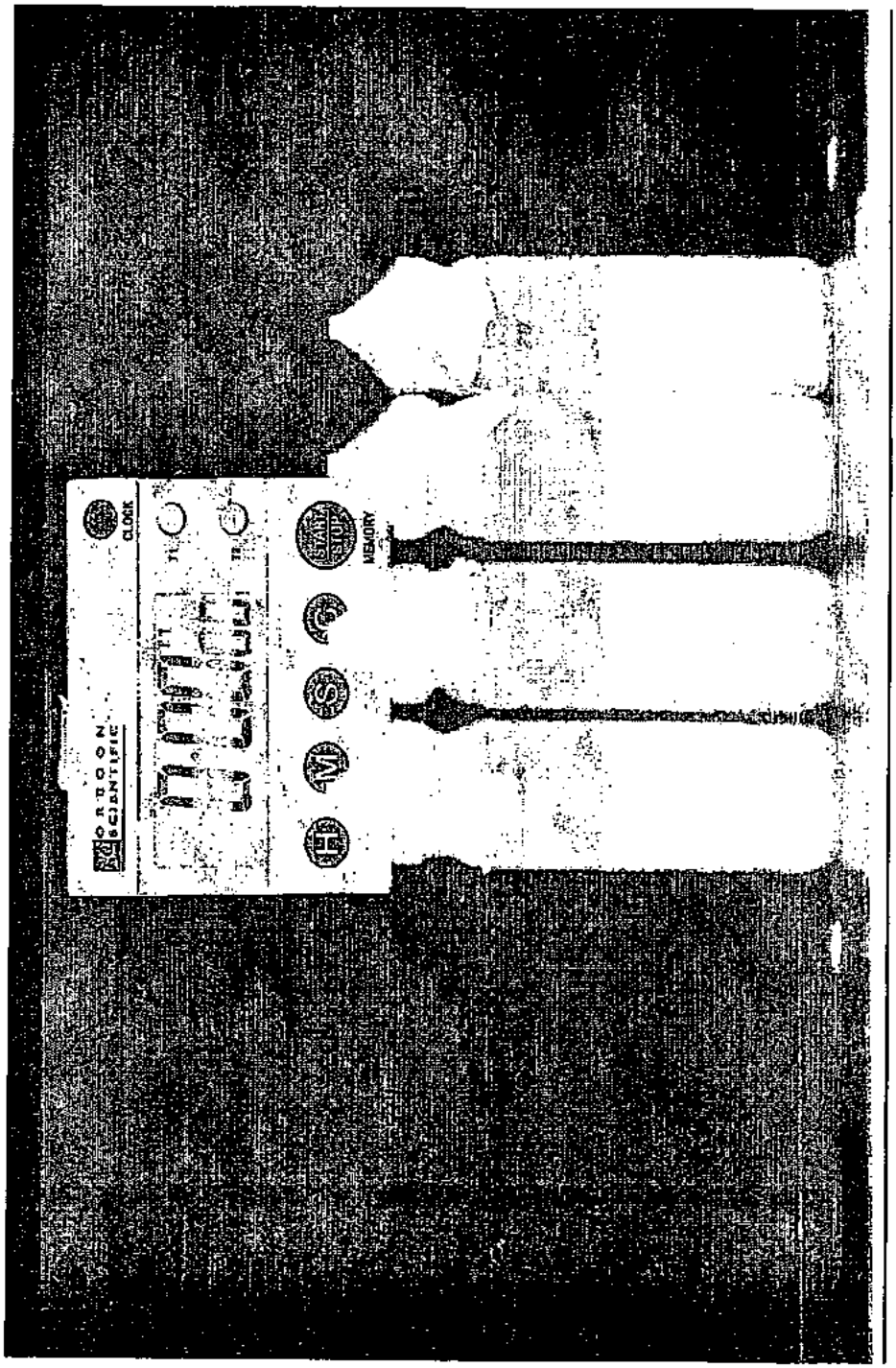
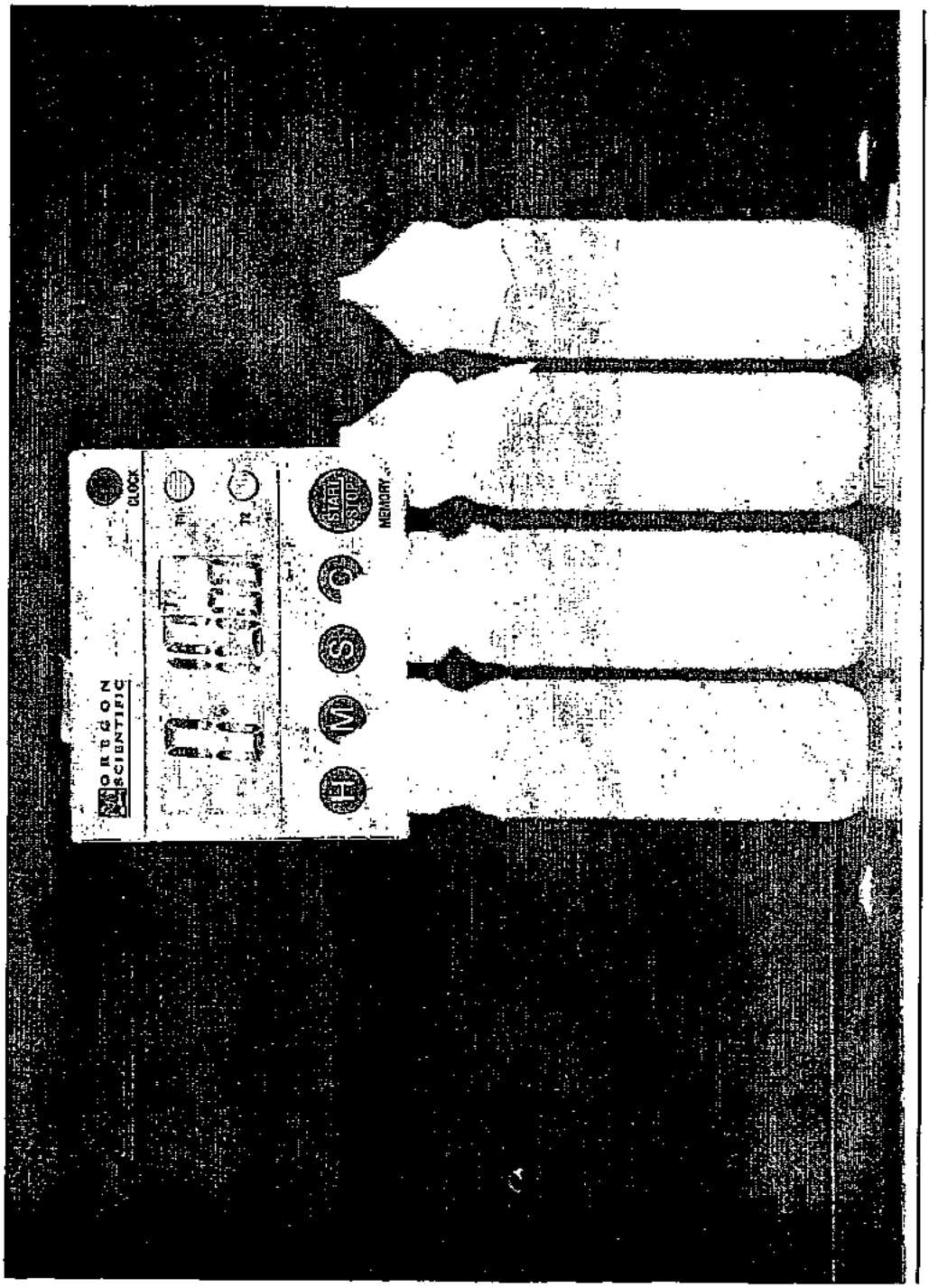


Fig. 15/16



PEG concn = left – right 0.005, 0.05, 0.35 and 0.5 % w/w

Fig. 16/16



COMBINED DECLARATION AND POWER OF ATTORNEY

As a below-named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated next to my name.

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter that is claimed and for which a patent is sought on the invention entitled:

COMPOSITION FOR INHALATION

the specification of which:

☐ is attached hereto.

OR

☐ was filed on _____ with Express Mail No. (Application Number not yet known).

OR

☐ was filed on 29 January 2003 (29.01.2003)as United States Application Number or PCT International Application Number PCT/SE2003/000156 and was amended on _____ (if applicable).

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information which is material to patentability as defined in 37 CFR §1.56.

I hereby claim the benefit under Title 35, United States Code, §119(e)(1) of any United States provisional application(s) listed below:

U.S. Serial No.	Filing Date	Status

I hereby claim the benefit under Title 35, United States Code, §120 of any United States application(s), or §365(c) of any PCT International application designating the United States, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application or PCT International application in the manner provided by the first paragraph of Title 35, United States Code, §112, I acknowledge the duty to disclose all information I know to be material to patentability as defined in Title 37, Code of Federal Regulations, §1.56(a) which became available between the filing date of the prior application and the national or PCT international filing date of this application:

U.S. Serial No.	Filing Date	Status

I hereby claim foreign priority benefits under Title 35, United States Code, §119(a)-(d) or §365(b) of any foreign application(s) for patent or inventor's certificate, or §365(a) of any PCT International application designating at least one country other than the United States of America, listed below and have also identified below, by checking the box, any foreign application for patent or inventor's certificate or any PCT international application(s) designating at least one country other than the United States of America filed by me on the same subject matter having a filing date before that of the application(s) of which priority is claimed:

Country	Application No.	Filing Date	Priority Claimed
SE	0200312-7	01 February 2002 (01.02.2002)	☒Yes ☐No
			☐Yes ☐No

I hereby appoint all registered practitioners associated with **Customer Number 26164** to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith, and direct that all correspondence be addressed to:

Customer Number 26164

Direct all telephone calls to JANIS K. FRASER, Ph.D., J.D., Reg. No. 34,819, at telephone number (617) 542-5070.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

1-00

Full Name of Inventor: Nayna GOVIND

Inventor's Signature: N-Govind Date: 30/6/04

Residence Address: Leicestershire, Great Britain

Citizenship: Great Britain

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2-00

Full Name of Inventor: Maria MARLOW

Inventor's Signature: M. Marlow Date: 30/06/04

Residence Address: Leicestershire, Great Britain

Citizenship: Great Britain

Post Office Address: AstraZeneca R&D Charnwood, Bakewell Road, Loughborough, Leicestershire LE11 5RH Great Britain GBX

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CONFIRMATION NO. 7568

SERIAL NUMBER	FILING OR 371(c) DATE	CLASS	GROUP ART UNIT	ATTORNEY DOCKET NO.
10/502,685	07/27/2004 RULE	424	1616	06275-410US1

APPLICANTS

Nayna Govind, Loughborough, UNITED KINGDOM;
Maria Marlow, Loughborough, UNITED KINGDOM;

**** CONTINUING DATA ***************************

This application is a 371 of PCT/SE03/00156 01/29/2003

**** FOREIGN APPLICATIONS *********************

SWEDEN 0200312-7 02/01/2002

Foreign Priority claimed	STATE OR COUNTRY	SHEETS DRAWING	TOTAL CLAIMS	INDEPENDENT CLAIMS
☐ yes ☐ no 35 USC 119 (a-d) conditions met ☐ yes ☐ no ☐ Met after Allowance Verified and Acknowledged _____ Examiner's Signature Initials	UNITED KINGDOM	16	12	1

ADDRESS

26164

TITLE

Composition for inhalation

FILING FEE RECEIVED	
1080	FEES: Authority has been given in Paper No. _____ to charge/credit DEPOSIT ACCOUNT No. _____ for following:

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☐ 1.16 Fees (Filing)
☐ 1.17 Fees (Processing Ext. of time)
☐ 1.18 Fees (Issue)
☐ Other _____
☐ Credit

PATENT APPLICATION SERIAL NO. 10/502685

U.S. DEPARTMENT OF COMMERCE
PATENT AND TRADEMARK OFFICE
FEE RECORD SHEET

07/30/2004 GFREYE 00000138 10502685
01 FC:1611 1080.00 OP

PTO-1556
(5/87)

*U.S. Government Printing Office: 2002 — 489-267/69033

PATENT APPLICATION FEE DETERMINATION RECORD

Effective October 1, 2003

Application or Docket Number

10/502685

CLAIMS AS FILED - PART I

	(Column 1)	(Column 2)
TOTAL CLAIMS		
FOR	NUMBER FILED	NUMBER EXTRA
TOTAL CHARGEABLE CLAIMS	12 minus 20=	* —
INDEPENDENT CLAIMS	1 minus 3 =	* —
MULTIPLE DEPENDENT CLAIM PRESENT	— ☐	

* If the difference in column 1 is less than zero, enter "0" in column 2

SMALL ENTITY TYPE ☐ OR OTHER THAN SMALL ENTITY

RATE	FEE		RATE	FEE
BASIC FEE		OR	BASIC FEE	1080
XS 9=		OR	XS18=	
X43=		OR	X86=	
+145=		OR	+290=	
TOTAL		OR	TOTAL	1080

CLAIMS AS AMENDED - PART II

AMENDMENT A	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA
Total	*	Minus	**	=
Independent	*	Minus	***	=
FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM ☐				

SMALL ENTITY OR OTHER THAN SMALL ENTITY

RATE	ADDITIONAL FEE		RATE	ADDITIONAL FEE
XS 9=		OR	XS18=	
X43=		OR	X86=	
+145=		OR	+290=	
TOTAL ADDIT. FEE		OR	TOTAL ADDIT. FEE	

AMENDMENT B	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA
Total	*	Minus	**	=
Independent	*	Minus	***	=
FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM ☐				

RATE	ADDITIONAL FEE		RATE	ADDITIONAL FEE
XS 9=		OR	X$18=	
X43=		OR	X86=	
+145=		OR	+290=	
TOTAL ADDIT. FEE		OR	TOTAL ADDIT. FEE	

AMENDMENT C	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA
Total	*	Minus	**	=
Independent	*	Minus	***	=
FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM ☐				

RATE	ADDITIONAL FEE		RATE	ADDITIONAL FEE
X$ 9=		OR	X$18=	
X43=		OR	X86=	
+145=		OR	+290=	
TOTAL ADDIT. FEE		OR	TOTAL ADDIT. FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than "20", enter "20."
*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3."
The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.

Attorney's Docket No.: 06275-410US1 / 100629-1P US
DT12 Rec'd PCT/PTO 27 JUL 2004

IN THE UNITED STATES RECEIVING OFFICE

Applicant : Nayna Govind et al.
Serial No. : Unassigned
Filed : Herewith
Title : COMPOSITION FOR INHALATION

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Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

PRELIMINARY AMENDMENT

Prior to examination, please amend the application as indicated on the following pages (a total of 5, including this page).

Amendments to the Specification appear at page 2.

Amendments to the Claims appear at pages 3-4.

Remarks appear at page 5.

CERTIFICATE OF MAILING BY EXPRESS MAIL

Express Mail Label No. EV382036625US

July 27, 2004
Date of Deposit

Amendments to the Specification:

Please insert the following paragraph on page 1 after the title:

CROSS-REFERENCE TO RELATED APPLICATIONS

This application is a national phase application under 35 U.S.C. § 371 of PCT International Application No. PCT/SE2003/000156, filed on January 29, 2003, which claims priority to Swedish Application Serial No. 0200312-7, filed February 1, 2002.

Amendments to the Claims:

This listing of claims replaces all prior versions and listings of claims in the application:

Listing of Claims:

1. (Original) A pharmaceutical composition comprising formoterol, budesonide, HFA 227, PVP and PEG.

2. (Original) A formulation according to claim 1 characterised in that the PVP is present from about 0.0005 to about 0.05 %w/w and the PEG is present from about 0.05 to about 0.35% w/w.

3. (Currently Amended) A pharmaceutical composition according to claim 1 [or 2]in which the PVP is PVP K25.

4. (Currently Amended) A pharmaceutical composition according to claim 1[to 3] in which the PVP is present in an amount of 0.001% w/w.

5. (Currently Amended) A pharmaceutical composition according to ~~any one of claims 1 to 4~~claim 1 in which the PEG is PEG 1000.

6. (Currently Amended) A pharmaceutical composition according to ~~any one of claims 1 to 5~~claim 1 in which the PEG is present in an amount of 0.3% w/w.

7. (Currently Amended) A pharmaceutical composition according to ~~any one of claims 1 to 6~~claim 1 in which formoterol is in the form of its fumarate dihydrate salt.

8. (Currently Amended) A pharmaceutical composition according to ~~any one of claims 1 to 7~~claim 1 in which the formoterol is in the form of the single R, R-enantiomer.

9. (Currently Amended) A pharmaceutical composition according to ~~any one of claims 1 to 8~~claim 1 in which the second active ingredient is the 22R-epimer of budesonide.

10. (Currently Amended) A pharmaceutical composition according to ~~any one of claims 1 to 9~~claim 1 for use for the treatment or prophylaxis of a respiratory disorder.

11. (Currently Amended) A pharmaceutical composition according to ~~any one of claims 1 to 9~~claim 1 for use for the treatment or prophylaxis of asthma, rhinitis or COPD.

12. (Currently Amended) A method of treating a respiratory disorder in a mammal which comprises administering to a patient a pharmaceutical composition according to ~~any one of claims 1 to 9~~claim 1.

REMARKS

The amendment to the specification merely inserts a cross-reference to related applications.

Claims 1-12 are pending. Amendments to claims 3-12 merely remove multiple dependencies and correct punctuation. No new matter has been added.

Applicant asks that all claims be examined in view of the amendments to the claims.

Please apply any charges to deposit account 06-1050, referencing attorney-docket no.06275-410US1.

Respectfully submitted,

Date: July 27, 2004

Janis K. Fraser, Ph.D., J.D.
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Applicants submit the references listed on the attached form PTO-1449 and enclose copies of all listed documents other than U.S. patents. A copy of a communication from a foreign patent office in a counterpart application is also enclosed.

This statement is being filed with the application. Please apply any charges or credits to Deposit Account No. 06-1050, referencing Attorney Docket No. 06275-410US1.

Respectfully submitted,

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U.S. Patent Documents

Examiner Initial	Desig. ID	Document Number	Publication Date	Patentee	Class	Subclass	Filing Date If Appropriate
	AA	6,004,537	12/21/1999	Blondino et al.			
	AB						
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Foreign Patent Documents or Published Foreign Patent Applications

Examiner Initial	Desig. ID	Document Number	Publication Date	Country or Patent Office	Class	Subclass	Translation Yes	Translation No
	AJ	EP 0 534 731	03/31/1993	Europe				
	AK	WO 93/05765	04/01/1993	WIPO				
	AL	WO 93/11773	06/24/1993	WIPO				
	AM	WO 98/21175	05/22/1998	WIPO				
	AN	WO 01/78693	10/25/2001	WIPO				
	AO	WO 02/03958	01/17/2002	WIPO				

Other Documents (include Author, Title, Date, and Place of Publication)

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	AP	
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(54) Pressurised aerosol compositions.

(57) A pressurised aerosol composition comprising a liquefied hydrofluoroalkane, a powdered medicament dispersable therein and a polymer soluble in the liquefied hydrofluoroalkane, wherein the polymer includes recurring structural units, the units being selected from amide containing units and carboxylic acid ester containing units.

EP 0 534 731 A1

This invention relates to pressurised aerosol compositions, in particular compositions of inhalation medicaments.

Pressurised aerosols for the administration of medicaments, and indeed for other applications, conventionally contain one or more liquefied chlorofuorocarbons (CFC's) as propellant. Such materials are suitable for use in such applications since they have the right vapour pressures (or can be mixed in the right proportions to achieve a vapour pressure in the right range) and are essentially taste- and odour-free.

In recent years there has been increasing concern about the depletion of the ozone layer in the upper atmosphere. This is believed to be due to the release into the atmosphere of CFC's and has led to a search for alternative agents for use in all applications of CFC's. To this end, aerosols for many applications are now pressurised using pressurised gases such as nitrogen or hydrocarbons. However, such propellants are generally not suitable for use in the administration of inhalation medicaments since they are toxic and/or the pressure within the canister falls each time the device is used which leads to unreproducible dosing.

The use of hydrofuorocarbons as aerosol propellants has also been suggested. However, considerable difficulties have been encountered in finding suspending agents which are soluble in hydrofuoroalkanes and capable of stabilising medicament suspensions.

Surprisingly, we have found that certain polymers are both soluble in the aerosol propellants and capable of stabilising medicament compositions.

Thus, according to the invention, we provide a pressurised aerosol composition comprising a liquefied hydrofuoroalkane, a powdered medicament dispersable therein and a polymer soluble in the liquefied hydrofuoroalkane, wherein the polymer includes recurring structural units, the units being selected from amide containing units and carboxylic acid ester containing units.

The polymer may be a homopolymer, that is the polymer consists of the same recurring structural units, or it may be a copolymer, that is the polymer contains recurring units in addition to either amide containing units or carboxylic acid ester units. The polymer may also be a copolymer of amide containing units and carboxylic acid ester units. Such copolymers may be either block copolymers or random copolymers.

We prefer polymers which include recurring structural units containing an amide group. We particularly prefer the amide containing unit to be 1-ethylenepyrrolidin-2-one. We especially prefer the polymer to be a homopolymer containing recurring 1-ethylene-pyrrolidin-2-one, that is polyvinylpyrrolidone.

In general, we have found that polyvinylpyrrolidones having a wide range of average molecular weights give acceptable suspensions. Although polymers can be characterised by their weight average molecular weights, viscosity average molecular weights or number average molecular weights, it is more usual to characterise polymers, in particular polymers such as polyvinylpyrrolidone, by K values, in which K is determined from viscosity measurements using the Fikentscher equation (H. Fikentscher, *Cellusochemie*, 1932, **13**, 58-64 and 71-74). In particular we prefer the polymer to have a K value of from 10 to 150, more preferably 15 to 120. Particular K values and ranges that may be mentioned include 10-14, 15-18, 29-32, 88-100 and 115-125.

Suitable polymers containing carboxylic acid ester containing recurring structural units include polyvinylacetate and copolymers of vinyl acetate and vinyl pyrrolidone, that is polyvinylpyrrolidone/vinyl acetate copolymer. We have found that polyvinylacetate with a weight average molecular weight of 250,000 gives particularly stable suspensions.

Other polymers that may be mentioned include acrylic acid/methacrylic acid ester copolymers, especially those in which the methyl and ethyl ester groups have been replaced with a low content of trimethylammoniumethyl groups, preferably at a ratio of 1:20, especially at a ratio of 1:40. We have found that such copolymers having a weight average molecular weight of 150,000 give stable suspensions.

The amount of polymer in the composition will depend on the active ingredient to be dispersed, its concentration and the particular polymer selected. However, in general the amount of polymer is from 0.00001 to 10% w/w, more preferably 0.0001 to 5% w/w and especially 0.001 to 1% w/w.

The compositions may, in addition to the polymer, contain other excipients, in particular excipients intended to improve valve lubrication and excipients to modify favour. Particular lubricants that may be mentioned include polyethoxylated compounds, especially polyethylene glycol. We prefer polyethylene glycol having a mean molecular weight of from 200 to 3000, preferably 400 to 2000, eg 1500. Other polyethoxylated compounds that may be used as lubricants include polysorbates, eg polysorbate 80, and alkyl aryl polyether alcohols, eg tyloxapol. Other lubricating excipients that may be mentioned include high molecular weight fully halogenated chlorofuorocarbons and esters of medium chain fatty acids. The amount of lubricant in the composition will depend on the other components of the composition, the active ingredient, the nature of the valve, etc. In general, we prefer a concentration of 0.01 to 4% w/w and more preferably 0.1 to 2% w/w.

Flavour modifying excipients that may be added to the composition include peppermint oil, menthol, Dentomint (Dentomint is a tradename), saccharin and saccharin sodium. When the favour modifying excipient is a solid, preferably it is micronised. The concentration will depend on the individual composition and the flavour

modifying excipient. In general, we prefer a concentration of 0.005 to 4% w/w; more preferably 0.01 to 1% w/w.

By the term 'hydrofuoroalkane' we mean a compound of general formula

$$C_xH_yF_z$$

in which x is an integer from 1 to 3, y+z=2x+2 and y and z are both at least 1.

Particular hydrofuoroalkanes of interest are CF_3CFH_2 (Propellant 134a), CH_3CHF_2 (Propellant 152a) and CF_3CHFCF_3 (Propellant 227). We particularly prefer compositions including propellant 227.

In general the vapour pressure of the propellant mixture should be in the range suitable and permitted for aerosol propellants. The vapour pressure may be varied by mixing one or more hydrofuoroalkanes and/or some other suitable vapour pressure modifying agent in appropriate proportions.

We prefer the vapour pressure of the mixture to be in the range 20 to 100 psig, more preferably 40 to 80 psig, eg about 60 psig.

In certain cases we have found it advantageous to add to the compositions excipients capable of increasing the solubility of the polymer or of other excipients, in the propellant. In general we have found that the polymers selected have a solubility in the propellant of at least 0.0001% w/w, preferably at least 0.001% w/w, particularly 0.01% w/w and especially 0.1% w/w. Excipients capable of increasing the solubility of the polymer include liquid excipients which are more polar than the liquefied propellant, where polarity is defined in terms of relative Kauri butanol values, as described in European patent application 0 372 777. Particular excipients that may be mentioned include alcohols eg ethanol and isopropanol. However, in contrast to the teaching of EP 0 372 777, we have found that only very small quantities of such excipients are required. In particular we have found that good compositions can be prepared in propellant 134a with polyvinylpyrrolidone as polymer with a variety of active ingredients and less than 10% w/w, preferably less than 5% w/w, more preferably less than 2% w/w, eg 0.2% w/w ethanol.

Medicaments which may be dispersed in the propellant mixture according to the invention include any medicaments which are conventionally administered to the lung and/or nose by inhalation of a pressurised aerosol formulation. Such medicaments include drugs for use in the prophylactic or remedial treatment of reversible obstructive airways disease, eg drugs such as sodium cromoglycate, nedocromil sodium, inhaled steroids, eg beclomethasone dipropionate, fluticasone propionate, budesonide and tipredane, and bronchodilators, eg salbutamol, reproterol, terbutaline, formoterol, pirbuterol, isoprenaline, salmeterol, fenoterol and salts thereof, and anticholinergic agents such as ipratropium bromide, oxitropium bromide and atropine and combinations of two or more of these agents, eg a combination of a prophylactic agent with a bronchodilator, eg sodium cromoglycate with salbutamol.

Other medicaments that may be mentioned include antihistamines, eg clemastine, pentamidine and salts thereof, acetyl-β-methylcholine bromide, peptide hormones such as insulin and amylin, bradykinin antagonists, PLA_2 inhibitors, PAF antagonists, lipoxygenase inhibitors, leukotriene antagonists, CNS active drugs, such as NMDA antagonists, glutamate antagonists, CCK agonists and antagonists; macrolide compounds including FK 506, rapamycin, cyclosporin and structurally related compounds, vitamins, vaccines, eg MMR vaccine and polio vaccine and vectors for gene therapy, eg plasmids containing genes intended to correct genetic disorders such as cystic fibrosis.

Where the medicament is intended for delivery to the lung, it preferably has a particle size distribution such that a high proportion of the particles are of a size capable of penetrating deep into the lung. In particular, the medicament is preferably in a form having a mass median diameter of from 0.01 to 10 μm, more preferably from 0.1 to 4 μm, eg about 2 or 3 μm.

The amount of medicament in the composition will depend on the nature of the active ingredient and the condition to be treated. However, the composition preferably comprises from 0.01 to 15% w/w, preferably from 0.1 to 10% w/w, and most preferably from 0.5 to 5% w/w medicament.

According to a further aspect of the invention there is provided a method of producing a pressurised aerosol composition as herein described, which comprises dispersing the powdered medicament and the polymer in the liquefied hydrofluoroalkane.

In particular, the compositions may be produced by cold fill or pressure fill techniques. In cold filling, the ingredients are placed in a cooled mixing vessel, cooled liquefied propellant added and a dispersion produced by vigorous stirring. Alternatively, a slurry may be prepared of the ingredients in a portion of cooled liquid propellant and the remainder of the liquefied propellant added under vigorous stirring. Aliquots of the dispersed composition are then filled into cooled aerosol cans and sealed with a suitable valve, eg a metering valve.

In pressure filling, the ingredients are placed in a pressure vessel, liquefied propellant added under pressure through a valve and a dispersion of the ingredients in the liquefied dispersed composition are then filled, under pressure, through the valve into suitable cans provided with appropriate valves, eg metering valves.

The compositions according to the invention are advantageous in that the solubility of the polymer is such as to ensure good dispersion of the medicament and smooth operation of the aerosol valve.

The compositions of the present invention may also be advantageous in that they are substantially taste- and odour-free and have suitable vapour pressures for the administration of medicaments by inhalation, yet are environmentally safe and acceptable, especially when compared with compositions including chlorofluorocarbons. In addition, they may be less irritant than corresponding compositions including conventional surfactants such as oleic acid and sorbitan trioleate.

The performance of the compositions according to the present invention can be assessed using the following test procedures:

1. Settling times

A glass bottle containing the composition is gently shaken five times and then stood upright. The time interval between standing the bottle upright and the first appearance of flocculation or separation of powder in the propellant determined (S_1). Timing is continued until complete separation, defined as when three lines of standard newspaper print can be read through the propellant from the top or bottom, depending on whether the active ingredient floats or sinks (S_2). In some compositions, complete separation does not occur. For these compositions, a turbidity factor ranging from 1 to 5 is determined, 1 denoting that a small proportion of the active ingredient is suspended and 5 denoting that the majority of the active ingredient is suspended.

2. Dispersion Tests

Dispersion testing on compositions formulated in cans having a metering valve can be assessed using a glass multistage liquid impinger, eg of the type described by J.H. Bell *et al, J. Pharm. Sci.*, 1971, **60**(10), 1559.

3. Lubrication

The lubricating effects of the composition can be assessed by filling the formulation into a can and closing the can with a modified metering valve from which the return spring has been removed. The stem of the valve is subjected to a compression force and the reading recorded in Newtons. This gives a measure of the lubricating efficacy of the composition.

4. Dose uniformity

Dose uniformity is assessed by discharging a metered dose aerosol can containing the composition into a filter tube which has sufficient air flowing through it to entrain all the dose. The tube is washed out with a suitable solvent and the amount of medicament assayed. The medicament entrained on the mouthpiece is also washed off and assayed. The variation of dose evaluated throughout the life of the can is a measure of dose uniformity. In a variation of this test, dose uniformity after standing can be assessed by shaking the aerosol can, allowing to stand for a predetermined time and assessing dose in the manner described above.

5. Caking potential

Compositions to be assessed are filled into plastic coated glass bottles. The assessment is carried out by allowing the samples to be stored for a period of time in order that complete sedimentation and compaction of the powder mass can take place, eg 3 months. After that period, the glass bottles are shaken by gentle twisting of the hand to totally invert the bottles. The number of bottle inversions required to completely resuspend the drug is noted. The number gives a measure of the degree of compaction of the composition. Since ease of drug particle redispersion is essential for dose uniformity, any composition requiring more than 5 shakes suggests possible problems in long-term storage.

The invention will now be illustrated, but in no way limited, by the following Examples.

Examples

Method

The required amounts of micronised active ingredient, suspending agent and other excipients, were weighed into plastic coated glass bottles and crimped with an appropriate valve. The desired amount of liquefied propellant was then transferred using a transfer button and the contents of the bottle sonicated to ensure thorough mixing. Unless otherwise stated, the fill volume for the bottles was 20 ml.

Materials

Active Ingredients

All active ingredients were micronised. In general, the active ingredients were anhydrous, although nedocromil sodium and sodium cromoglycate were used in their equilibrium hydrated form which each contain about 10% w/w water at room temperature.

Polyethyleneglycols (PEG)

The average molecular weight of the polyethyleneglycol used is indicated by the number 200, 400, etc following PEG.

Halocarbon oil

Halocarbon oil is the proprietary name given to a series of high molecular weight fully halogenated chlorofuorocarbons of chlorotrifuoroethylene telomers obtainable from Halocarbon Products Corporation, New Jersey, USA.

Miglyols

Miglyol®neutral oils

Miglyol® neutral oils are esters of medium chain fatty acids and are sometimes referred to as fractionated coconut oils. Miglyol is a trademark of Hüls AG. The following oils were used.

Miglyol® 810

A triglyceride of fractionated C_8/C_{10} coconut oil fatty acids classified by the CTFA as caprylic/capric triglyceride. It meets the requirements of the British Pharmacopoeia 1988 for the monograph "Fractionated Coconut Oil". It is a low viscosity oil of neutral taste and smell, with a turbidity point below 0°C.

Miglyol® 829

A glyceryl ester of fractionated C_8/C_{10} coconut fatty acids linked to succinic acid and is classified by the CTFA as caprylic/capric/diglyceryl succinate. It has a turbidity point below -30°C, is soluble in alcohol, has a viscosity of approximately 250 mPa.s and a density of approximately 1.

Miglyol® 840

A propylene glycol diester of saturated vegetable fatty acids with C_8/C_{10} chain lengths, classified by the CFTA as propyleneglycol dicaprylate/dicaprate. It meets the requirements of the German Pharmacopoeia, DAR9, 1st supplement, for the monograph "Propyleneglycoloctanoatodecanoate". It has a turbidity point below -30°C and is soluble in 90% ethanol.

Polyvinylpyrrolidones

All polyvinylpyrrolidones used were essentially linear homopolymers formed by the free radical polymerisation of N-vinylpyrrolidone. PVP(K29/32), PVP(K90), PVP(K120), PVP(C15) and PVP(C30) refer to the polyvinylpyrrolidones obtainable from GAF Chemical Corporation and sold under the Trade Mark **PLASDONE®**. PVP/17PF refers to **KOLLIDON** 17PF, a polyvinylpyrrolidone available from BASF (**KOLLIDON** is a registered Trade Mark).

The manufacturing processes for polyvinylpyrrolidone and the other polymers used herein produce polymer mixtures containing molecules of unequal chain length and thus different molecular weights. Such polymers are usually characterised by their K values, in which K is determined from viscosity measurements using the Fikentscher equation (H. Fikentscher, *Cellusochemie*, 1932, 13, 58-64 and 71-74). The polymers can also be characterised by their average molecular weights ($\overline{M}w$), viscosity average molecular weights ($\overline{M}v$) and number average molecular weights ($\overline{M}n$).

Characterising data for the polyvinylpyrrolidones used were as follows:

	K	$\overline{M}w$	$\overline{M}v$	$\overline{M}n$
PVP 17 PF	15-18	9000	-	2500
K29/32	29-32	-	-	-
K90	94±6	1,280,000	63000	-
K120	120±5	2,800,000	1,450,000	-
C15	17±1	10500	7000	3000
C30	30.5±1	62500	3800	16500

Polyvinylpyrrolidone/vinylacetate copolymers

Polyvinylpyrrolidone/vinylacetate copolmers are obtainable from GAF Chemical Corporation. The E- and I- series of PVP/VA copolymers were supplied as 50% solutions in ethanol and isopropanol respectively. S-630 refers to the white, spray dried polymer of PVP/VA having the characteristics set out below. Characterising data for PVP/VA used:

		K value	VP/VA ratio
PVP/VA	S-630	30-50	60/40
	E-535	30-50	50/50
	I-535	25-35	50/50
	E-335	25-35	30/70

Acrylic acid/methacrylic acid ester copolymers

The acrylic acid/methacrylic acid ester copolmers used were copolmers synthesized from acrylic and methacrylic acid ethyl and methyl esters with a low content of quaternary ammonium groups. The molar ratio of these ammonium groups to the neutral (meth)acrylic acid esters is 1:40. The weight average molecular weight is approximately 150000. The polymer used was **EUDRAGIT** RS PM, obtainable from Röhn Pharma GmbH. (**EUDRAGIT** is a registered Trade Mark).

Polyvinylacetate

The polyvinylacetate used had a weight average molecular weight of about 26,000.

A. Compositions containing polyvinylpyrrolidone and propellant 227

The following active ingredients were formulated at the concentration shown with PVP in propellant 227 **PLASDONE** C30 (**PLASDONE** is a registered Trade Mark of GAF Chemicals Corporation).

a) with 0.05% w/w PVP(C-30)		
1.	Terbutaline sulphate	5mg/ml
2.	Beclomethasone dipropionate	5mg/ml
3.	Salbutamol sulphate	4mg/ml
4.	Fluticasone propionate	4mg/ml
5.	Reproterol hydrochloride	10mg/ml
6.	Fenoterol hydrobromide	4mg/ml
7.	Sodium cromoglycate	10mg/ml
8.	Sodium cromoglycate	50mg/ml
9.	Ipratropium bromide	0.8mg/ml
10.	Pentamidine isoethionate	4mg/ml
11.	Clemastine	4mg/ml
12.	Acetyl-β-methylcholine bromide	10mg/ml
13.	Budesonide	4mg/ml

b) with 0.1% w/v PVP(17PF)		
1.	Fenoterol hydrobromide	4mg/ml
2.	Terbutaline sulphate	5mg/ml
3.	Salbutamol sulphate	4mg/ml

c) with 0.025% w/v PVP(C30)		
1.	Tipredane	10mg/ml

B. Compositions containing polyvinylpyrrolidone/vinyl acetate copolymer in propellant 227

The following active ingredients were formulated in propellant 227 at the concentrations shown.

a)	with 0.05% w/v PVP/VA S-630	
1.	Terbutaline sulphate	5mg/ml
2.	Beclomethasone dipropionate	5mg/ml
3.	Salbutamol sulphate	4mg/ml
4.	Fluticasone propionate	4mg/ml
5.	Reproterol hydrochloride	10mg/ml

	6.	Fenoterol hydrobromide	4mg/ml
	7.	Sodium cromoglycate	10mg/ml
	8.	Sodium cromoglycate	50mg/ml
	9.	Ipratropium bromide	0.8mg/ml
	10.	Acetyl-β-methylcholine bromide	10mg/ml
	11.	Budesonide	4mg/ml
	b)	with 0.025% w/v PVP/VA S-630	
	1.	Tipredane	10mg/ml

C. Compositions containing PVP or PVP/VA, propellant 227 and polyethylene glycol

The following active ingredients were formulated in propellant 227 at the concentration shown with 0.5 % w/v PEG600.

a) with 0.05% w/v PVP(C30)		
1.	Salbutamol sulphate	4mg/ml
2.	Sodium cromoglycate	50mg/ml
3.	Reproterol hydrochloride	10mg/ml

b) with 0.05% w/v PVP/VA S-630		
1.	Salbutamol sulphate	4mg/ml
2.	Sodium cromoglycate	50mg/ml
3.	Reproterol hydrochloride	10mg/ml
4.	Budesonide	4mg/ml

c) with 0.1% w/v PVP(17PF)		
1.	Terbutaline sulphate	5mg/ml
2.	Fenoterol hydrobromide	4mg/ml

D. Compositions containing acrylic acid/methacrylic acid ester copolymers and propellant 227

The following active ingredients were formulated at the concentration shown with 0.1% w/v **EUDRAGIT RS** (**EUDRAGIT** is a Trade Mark of Röhn Pharma GmbH) in propellant 227.

a)	1.	Terbutaline	5mg/ml
	2.	Beclomethasone dipropionate	5mg/ml
	3.	Salbutamol sulphate	4mg/ml
	4.	Fluticasone	4mg/ml

	5.	Reproterol hydrochloride	10mg/ml
	6.	Fenoterol	4mg/ml
	7.	Sodium cromoglycate	10mg/ml
	8.	Ipratropium bromide	0.8mg/ml
	9.	Clemastine	4mg/ml
	10.	Acetyl-β-methylcholine bromide	10mg/ml
b)	<u>compositions including 0.5%w/w PEG 600</u>		
	11.	Beclomethasone dipropionate	5mg/ml
	12.	Sodium cromoglycate	50mg/ml
	13.	Reproterol hydrochloride	10mg/ml
	14.	Fenoterol hydrobromide	4mg/ml

E. Compositions in propellant 134a

The following active ingredients were formulated at the concentration shown in propellant 134a.

1.	Tipredane	10mg/ml
	PVP(C30)	0.1% w/w
	ethanol	5.0% w/w
2.	Tipredane	10mg/ml
	PVP(C30)	0.1% w/w
	ethanol	10.0% w/w
3.	Nedocromil sodium	20mg/ml
	PVP(C30)	0.1%/ w/w
	ethanol	5.0% w/w
4.	Nedocromil sodium	20mg/ml
	PVP(C30)	0.1% w/w
	ethanol	10.0% w/w
5.	Tipredane	10mg/ml
	PVP/VA S-630	0.1% w/w
	ethanol	5.0% w/w
6.	Tipredane	10mg/ml
	PVP(C30)	0.25% w/w
	ethanol	5.0% w/w
7.	Tipredane	10mg/ml
	PVP(C30)	0.5% w/w
	ethanol	5.0% w/w

8.	Nedocromil sodium	20mg/ml
	PVP/VA S-630	0.1% w/w
	ethanol	5.0% w/w
9.	Nedocromil sodium	20mg/ml
	PVP/C30	0.25% w/w
	ethanol	5.0% w/w
10.	Nedocromil sodium	20mg/ml
	PVP(C30)	0.5% w/w
	ethanol	5.0% w/w
11.	Tipredane	10mg/ml
	PVP(C30)	0.1% w/w
	PEG 600	0.5% w/w
	ethanol	5.0% w/w
12.	Tipredane	10mg/ml
	PVP(C30)	0.1% w/w
	PEG 600	0.5% w/w
	ethanol	10.0% w/w
13.	Nedocromil sodium	20mg/ml
	PVP(C30)	0.1% w/w
	PEG 600	0.5% w/w
	ethanol	5.0% w/w
14.	Nedocromil sodium	20mg/ml
	PVP(C30)	0.1% w/w
	PEG 600	0.5% w/w
	ethanol	10.0% w/w
15.	Nedocromil sodium	20mg/ml
	PVP(C30)	0.05% w/w
	PEG 600	0.5% w/w
	ethanol	0.2% w/w
16.	Beclomethasone dipropionate	5mg/ml
	PVP/VA S-630	0.1% w/w
	ethanol	2.0% w/w
17.	Beclomethasone dipropionate	5mg/ml
	PVP/VA S-630	0.1% w/w
	ethanol	5.0% w/w
18.	Beclomethasone	

dipropionate	5mg/ml
PVP(C30)	0.1% w/w
ethanol	5.0% w/w

F. Compositions containing polyvinylacetate

a) in propellant 134a		
1.	Tipredane	10mg/ml
	Polyvinylacetate	0.042% w/w
2.	Nedocromil sodium	20mg/ml
	Polyvinylacetate	0.042% w/w

b) in propellant 227		
1.	Tipredane	10mg/ml
	Polyvinylacetate	0.035%w/w
2.	Nedocromil sodium	20mg/ml
	Polyvinylacetate	0.035% w/w

G. Compositions using polyvinylpyrrolidone of different K values

The following active ingredients were formulated in propellant 227 at the concentrations shown, with 0.1% w/w polyvinylpyrrolidone having the K value shown:

a) PVP(K29/32)		
1.	Tipredane	10mg/ml
2.	Nedocromil sodium	20mg/ml
3.	Sodium cromoglycate	20mg/ml
4.	Reproterol hydrochloride	4mg/ml
5.	Salbutamol sulphate	4mg/ml

b) PVP(K90)		
1.	Tipredane	10mg/ml
2.	Nedocromil sodium	20mg/ml

c) PVP(K120)		
1.	Tipredane	10mg/ml
2.	Nedocromil sodium	20mg/ml

d) PVP(C15)		
1.	Tipredane	10mg/ml
2.	Nedocromil sodium	20mg/ml

H. Compositions using polyvinylpyrrolidone/vinylacetate copolymers of different vinylpyrrolidone/vinylacetate ratios

Tipredane and nedocromil sodium were formulated in propellant 227 at the concentrations shown, with 0.1 % w/w PVP/VA having the vinylpyrrolidone/vinylacetate ratio shown.

a)Nedocromil sodium 20mg/ml		
1.	PVP/VA E-535	(50/50)
2.	PVP/VA I-535	(50/50)
3.	PVP/VA E-335	(30/70)

b) Tipredane 10mg/ml		
1.	PVP/VA E-535	(50/50)
2.	PVP/VA I-535	(50/50)
3.	PVP/VA E-335	(30/70)

I. Further tipredane formulations

Ex	Tipredane (mg/ml)	PVP/VA S-630 % w/w	PVP/C30 % w/w	Propellant
1	4	0.0025	-	134a
2	4	0.01	-	134a
3	4	0.025	-	134a
4	4	0.05	-	134a
5	10	0.0025	-	134a
6	10	0.01	-	134a
7	10	0.025	-	134a
8	10	0.05	-	134a
9	30	0.0025	-	134a
10	30	0.01	-	134a
11	30	0.025	-	134a
12	30	0.05	-	134a
13	4	0.0025	-	227
14	4	0.01	-	227
15	4	0.025	-	227
16	4	0.05	-	227
17	10	0.0025	-	227
18	10	0.01	-	227
19	10	0.025	-	227
20	10	0.05	-	227
21	30	0.0025	-	227
22	30	0.01	-	227
23	30	0.025	-	227
24	30	0.05	-	227
25	4	-	0.0025	134a

26	4	-	0.01	134a
27	4	-	0.025	134a
28	4	-	0.05	134a
29	10	-	0.0025	134a
30	10	-	0.01	134a
31	10	-	0.025	134a
32	10	-	0.05	134a
33	30	-	0.0025	134a
34	30	-	0.01	134a
35	30	-	0.025	134a
36	30	-	0.05	134a
37	4	-	0.0025	227
38	4	-	0.01	227
39	4	-	0.025	227
40	4	-	0.05	227
41	10	-	0.0025	227
42	10	-	0.01	227
43	10	-	0.025	227
44	10	-	0.05	227
45	30	-	0.0025	227
46	30	-	0.01	227
47	30	-	0.025	227
48	30	-	0.05	227

J. Compositions containing flavouring agents

The following compositions were made up in propellant 227, with 0.1% w/w PVP/VA S-630.

1.	Nedocromil sodium	20mg/ml
	peppermint oil	0.1% w/w
2.	Nedocromil sodium	20mg/ml
	menthol	0.05% w/w
	saccharin	0.03% w/w
3.	Tipredane	10mg/ml
	menthol	0.05% w/w
	saccharin	0.03% w/w

K. Compositions containing additional excipients

The following composition was made up in propellant 227, to examine the effects of different excipients as valve lubricants.

a)	Nedocromil sodium	20mg/ml
	PVP/C30	0.1% w/w

	Lubricant		0.5% w/w
	Menthol		0.05% w/w
	Saccharin, micronised		0.03% w/w
	Lubricants:		
	PEG 200		
	PEG 400		
	PEG 600		
	PEG 1000		
	Miglyol 810		
	Miglyol 829		
	Miglyol 840		
	Ethyl oleate		
	Halocarbon oil 27		
	Tyloxapol		
	Polysorbate 80		
b)	Nedocromil sodium		20mg/ml
	PVP (C30)		0.10% w/w
	PEG 1500		0.20% w/w
	Menthol		0.05% w/w
	Saccharin, micronised		0.03% w/w
c)	Tipredane		10.0mg/ml
	PVP (C30)		0.10% w/w
	Lubricant		0.50% w/w
	Lubricants:	PEG 600	
		PEG 1000	
d)	Tipredane		10.0mg/ml
	PVP (C30)		0.10% w/w
	Lubricant		0.20% w/w
	Lubricants:	PEG 600	
		PEG 1000	
		PEG 1500	

Claims

1. A pressurised aerosol composition comprising a liquefied hydrofluoroalkane, a powdered medicament dispersable therein and a polymer soluble in the liquefied hydrofluoroalkane, wherein the polymer includes recurring structural units, the units being selected from amide containing units and carboxylic acid ester containing units.

2. A composition according to Claim 1, wherein the polymer contains recurring structural units containing an amide group.

3. A composition according to Claim 1 or Claim 2, wherein the polymer includes recurring 1-ethylene-pyrrolidin-2-one units.

4. A composition according to any one of Claims 1 to 3, wherein the polymer is polyvinylpyrrolidone.

5. A composition according to any one of Claims 1 to 3, wherein the polymer is a copolymer containing recurring 1-ethylene-pyrrolidin-2-one units.

6. A composition according to any one of Claims 1 to 3 or Claim 5, wherein the polymer is polyvinylpyrrolidone/vinyl acetate copolymer.

7. A composition according to Claim 1, wherein the polymer is polyvinylacetate or a copolymer of acrylic acid and methacrylic acid esters.

8. A composition according to any one of the preceding claims, wherein the concentration of polymer is from 0.00001 to 10% w/w.

9. A composition according to any one of the preceding claims, wherein the medicament is selected from one or more of terbutaline sulphate, beclomethasone dipropionate, salbutamol sulphate, fluticasone propionate, reproterol hydrochloride, fenoterol hydrobromide, sodium cromoglycate, nedocromil sodium, tipredane, pentamidine isoethionate, clemastine, acetyl-β-methylcholine bromide and budesonide.

10. A process for the preparation of a composition according to Claim 1, which comprises dispersing the powdered medicament and the polymer in the liquefied hydrofluoroalkane.

European Patent Office

EUROPEAN SEARCH REPORT

Application Number
EP 92 30 8657

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.5)
D,Y	EP-A-0 372 777 (RIKER LABORATORIES INC) 13 June 1990 * claims 1,12 *	1-10	A61K9/00 A61K9/12
Y	WO-A-8 705 211 (BURGHART KURT) 11 September 1987 * the whole document *	1-10	

TECHNICAL FIELDS SEARCHED (Int. Cl.5)

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The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
THE HAGUE	28 OCTOBER 1992	VENTURA AMAT A.

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(54) Title: PRESSURISED AEROSOL COMPOSITIONS

(57) Abstract

A pressurised aerosol composition comprising a liquefied hydrofluoroalkane, a powdered medicament dispersable therein and a polymer soluble in the liquefied hydrofluoroalkane, wherein the polymer includes recurring structural units, the units being selected from amide containing units and carboxylic acid ester containing units.

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Pressurised Aerosol Compositions

This invention relates to pressurised aerosol compositions, in particular compositions of inhalation medicaments.

Pressurised aerosols for the administration of medicaments, and indeed for other applications, conventionally contain one or more liquefied chlorofluorocarbons (CFC's) as propellant. Such materials are suitable for use in such applications since they have the right vapour pressures (or can be mixed in the right proportions to achieve a vapour pressure in the right range) and are essentially taste- and odour-free.

In recent years there has been increasing concern about the depletion of the ozone layer in the upper atmosphere. This is believed to be due to the release into the atmosphere of CFC's and has led to a search for alternative agents for use in all applications of CFC's. To this end, aerosols for many applications are now pressurised using pressurised gases such as nitrogen or hydrocarbons. However, such propellants are generally not suitable for use in the administration of inhalation medicaments since they are toxic and/or the pressure within the canister falls each time the device is used which leads to unreproducible dosing.

The use of hydrofluorocarbons as aerosol propellants has also been suggested. However, considerable difficulties have been encountered in finding suspending agents which are soluble in hydrofluoroalkanes and capable of stabilising medicament suspensions.

Surprisingly, we have found that certain polymers are both soluble in the aerosol propellants and capable of stabilising medicament compositions.

Thus, according to the invention, we provide a pressurised aerosol composition comprising a liquefied hydrofluoroalkane, a powdered medicament dispersable therein and a polymer soluble in the liquefied hydrofluoroalkane, wherein the polymer includes recurring structural units, the units being selected from amide containing units and carboxylic acid ester containing units.

The polymer may be a homopolymer, that is the polymer consists of the same recurring structural units, or it may be a copolymer, that is the polymer contains recurring units in addition to either amide containing units or carboxylic acid ester units. The polymer may also be a copolymer of amide containing units and

carboxylic acid ester units. Such copolymers may be either block copolymers or random copolymers.

We prefer polymers which include recurring structural units containing an amide group. We particularly prefer the amide containing unit to be 1-ethylene-pyrrolidin-2-one. We especially prefer the polymer to be a homopolymer containing recurring 1-ethylene-pyrrolidin-2-one, that is polyvinylpyrrolidone.

In general, we have found that polyvinylpyrrolidones having a wide range of average molecular weights give acceptable suspensions. Although polymers can be characterised by their weight average molecular weights, viscosity average molecular weights or number average molecular weights, it is more usual to characterise polymers, in particular polymers such as polyvinylpyrrolidone, by K values, in which K is determined from viscosity measurements using the Fikentscher equation (H. Fikentscher, *Cellusochemie*, 1932, 13, 58-64 and 71-74). In particular we prefer the polymer to have a K value of from 10 to 150, more preferably 15 to 120. Particular K values and ranges that may be mentioned include 10-14, 15-18, 29-32, 88-100 and 115-125.

Suitable polymers containing carboxylic acid ester containing recurring structural units include polyvinylacetate and copolymers of vinyl acetate and vinyl pyrrolidone, that is polyvinylpyrrolidone/vinyl acetate copolymer. We have found that polyvinylacetate with a weight average molecular weight of 250,000 gives particularly stable suspensions.

Other polymers that may be mentioned include acrylic acid/methacrylic acid ester copolymers, especially those in which the methyl and ethyl ester groups have been replaced with a low content of trimethylammoniumethyl groups, preferably at a ratio of 1:20, especially at a ratio of 1:40. We have found that such copolymers having a weight average molecular weight of 150,000 give stable suspensions.

The amount of polymer in the composition will depend on the active ingredient to be dispersed, its concentration and the particular polymer selected. However, in general the amount of polymer is from 0.00001 to 10% w/w, more preferably 0.0001 to 5% w/w and especially 0.001 to 1% w/w.

The compositions may, in addition to the polymer, contain other excipients, in particular excipients intended to improve valve lubrication and excipients to modify flavour. Particular lubricants that may be mentioned include polyethoxylated

compounds, especially polyethylene glycol. We prefer polyethylene glycol having a mean molecular weight of from 200 to 3000, preferably 400 to 2000, eg 1500. Other polyethoxylated compounds that may be used as lubricants include polysorbates, eg polysorbate 80, and alkyl aryl polyether alcohols, eg tyloxapol. Other lubricating excipients that may be mentioned include high molecular weight fully halogenated chlorofluorocarbons and esters of medium chain fatty acids. The amount of lubricant in the composition will depend on the other components of the composition, the active ingredient, the nature of the valve, etc. In general, we prefer a concentration of 0.01 to 4% w/w and more preferably 0.1 to 2% w/w.

Flavour modifying excipients that may be added to the composition include peppermint oil, menthol, Dentomint (Dentomint is a tradename), saccharin and saccharin sodium. When the flavour modifying excipient is a solid, preferably it is micronised. The concentration will depend on the individual composition and the flavour modifying excipient. In general, we prefer a concentration of 0.005 to 4% w/w; more preferably 0.01 to 1% w/w.

By the term 'hydrofluoroalkane' we mean a compound of general formula

$$C_xH_yF_z$$

in which x is an integer from 1 to 3, y+z=2x+2 and y and z are both at least 1.

Particular hydrofluoroalkanes of interest are CF_3CFH_2 (Propellant 134a), CH_3CHF_2 (Propellant 152a) and CF_3CHFCF_3 (Propellant 227). We particularly prefer compositions including propellant 227.

In general the vapour pressure of the propellant mixture should be in the range suitable and permitted for aerosol propellants. The vapour pressure may be varied by mixing one or more hydrofluoroalkanes and/or some other suitable vapour pressure modifying agent in appropriate proportions.

We prefer the vapour pressure of the mixture to be in the range 20 to 100 psig, more preferably 40 to 80 psig, eg about 60 psig.

In certain cases we have found it advantageous to add to the compositions excipients capable of increasing the solubility of the polymer or of other excipients, in the propellant. In general we have found that the polymers selected have a solubility in the propellant of at least 0.0001% w/w, preferably at least 0.001% w/w, particularly 0.01% w/w and especially 0.1% w/w. Excipients capable of increasing the solubility of the polymer include liquid excipients which are more polar than the liquefied

propellant, where polarity is defined in terms of relative Kauri butanol values, as described in European patent application 0 372 777. Particular excipients that may be mentioned include alcohols eg ethanol and isopropanol. However, in contrast to the teaching of EP 0 372 777, we have found that only very small quantities of such excipients are required. In particular we have found that good compositions can be prepared in propellant 134a with polyvinylpyrrolidone as polymer with a variety of active ingredients and less than 10% w/w, preferably less than 5% w/w, more preferably less than 2% w/w, eg 0.2% w/w ethanol.

Medicaments which may be dispersed in the propellant mixture according to the invention include any medicaments which are conventionally administered to the lung and/or nose by inhalation of a pressurised aerosol formulation. Such medicaments include drugs for use in the prophylactic or remedial treatment of reversible obstructive airways disease, eg drugs such as sodium cromoglycate, nedocromil sodium, inhaled steroids, eg beclomethasone dipropionate, fluticasone propionate, budesonide and tipredane, and bronchodilators, eg salbutamol, reproterol, terbutaline, formoterol, pirbuterol, isoprenaline, salmeterol, fenoterol and salts thereof, and anticholinergic agents such as ipratropium bromide, oxitropium bromide and atropine and combinations of two or more of these agents, eg a combination of a prophylactic agent with a bronchodilator, eg sodium cromoglycate with salbutamol.

Other medicaments that may be mentioned include antihistamines, eg clemastine, pentamidine and salts thereof, acetyl-β-methylcholine bromide, peptide hormones such as insulin and amylin, bradykinin antagonists, PLA_2 inhibitors, PAF antagonists, lipoxygenase inhibitors, leukotriene antagonists, CNS active drugs, such as NMDA antagonists, glutamate antagonists, CCK agonists and antagonists; macrolide compounds including FK 506, rapamycin, cyclosporin and structurally related compounds, vitamins, vaccines, eg MMR vaccine and polio vaccine and vectors for gene therapy, eg plasmids containing genes intended to correct genetic disorders such as cystic fibrosis.

Where the medicament is intended for delivery to the lung, it preferably has a particle size distribution such that a high proportion of the particles are of a size capable of penetrating deep into the lung. In particular, the medicament is

preferably in a form having a mass median diameter of from 0.01 to 10 μm, more preferably from 0.1 to 4 μm, eg about 2 or 3 μm.

The amount of medicament in the composition will depend on the nature of the active ingredient and the condition to be treated. However, the composition preferably comprises from 0.01 to 15% w/w, preferably from 0.1 to 10% w/w, and most preferably from 0.5 to 5% w/w medicament.

According to a further aspect of the invention there is provided a method of producing a pressurised aerosol composition as herein described, which comprises dispersing the powdered medicament and the polymer in the liquefied hydrofluoroalkane.

In particular, the compositions may be produced by cold fill or pressure fill techniques. In cold filling, the ingredients are placed in a cooled mixing vessel, cooled liquefied propellant added and a dispersion produced by vigorous stirring. Alternatively, a slurry may be prepared of the ingredients in a portion of cooled liquid propellant and the remainder of the liquefied propellant added under vigorous stirring. Aliquots of the dispersed composition are then filled into cooled aerosol cans and sealed with a suitable valve, eg a metering valve.

In pressure filling, the ingredients are placed in a pressure vessel, liquefied propellant added under pressure through a valve and a dispersion of the ingredients in the liquefied dispersed composition are then filled, under pressure, through the valve into suitable cans provided with appropriate valves, eg metering valves.

The compositions according to the invention are advantageous in that the solubility of the polymer is such as to ensure good dispersion of the medicament and smooth operation of the aerosol valve.

The compositions of the present invention may also be advantageous in that they are substantially taste- and odour-free and have suitable vapour pressures for the administration of medicaments by inhalation, yet are environmentally safe and acceptable, especially when compared with compositions including chlorofluorocarbons. In addition, they may be less irritant than corresponding compositions including conventional surfactants such as oleic acid and sorbitan trioleate.

The performance of the compositions according to the present invention can be assessed using the following test procedures:

1. **Settling times**

A glass bottle containing the composition is gently shaken five times and then stood upright. The time interval between standing the bottle upright and the first appearance of flocculation or separation of powder in the propellant determined (S_1). Timing is continued until complete separation, defined as when three lines of standard newspaper print can be read through the propellant from the top or bottom, depending on whether the active ingredient floats or sinks (S_2). In some compositions, complete separation does not occur. For these compositions, a turbidity factor ranging from 1 to 5 is determined, 1 denoting that a small proportion of the active ingredient is suspended and 5 denoting that the majority of the active ingredient is suspended.

2. **Dispersion Tests**

Dispersion testing on compositions formulated in cans having a metering valve can be assessed using a glass multistage liquid impinger, eg of the type described by J.H. Bell *et al*, *J. Pharm. Sci.*, 1971, 60(10), 1559.

3. **Lubrication**

The lubricating effects of the composition can be assessed by filling the formulation into a can and closing the can with a modified metering valve from which the return spring has been removed. The stem of the valve is subjected to a compression force and the reading recorded in Newtons. This gives a measure of the lubricating efficacy of the composition.

4. **Dose uniformity**

Dose uniformity is assessed by discharging a metered dose aerosol can containing the composition into a filter tube which has sufficient air flowing through it to entrain all the dose. The tube is washed out with a suitable solvent and the amount of medicament assayed. The medicament entrained on the mouthpiece is also washed off and assayed. The variation of dose evaluated throughout the life of the can is a measure of dose uniformity. In a variation of this test, dose uniformity after standing can be assessed by shaking the aerosol can, allowing to stand for a predetermined time and assessing dose in the manner described above.

5. **Caking potential**

Compositions to be assessed are filled into plastic coated glass bottles. The assessment is carried out by allowing the samples to be stored for a period of time in

order that complete sedimentation and compaction of the powder mass can take place, eg 3 months. After that period, the glass bottles are shaken by gentle twisting of the hand to totally invert the bottles. The number of bottle inversions required to completely resuspend the drug is noted. The number gives a measure of the degree of compaction of the composition. Since ease of drug particle redispersion is essential for dose uniformity, any composition requiring more than 5 shakes suggests possible problems in long-term storage.

The invention will now be illustrated, but in no way limited, by the following Examples.

Examples

Method

The required amounts of micronised active ingredient, suspending agent and other excipients, were weighed into plastic coated glass bottles and crimped with an appropriate valve. The desired amount of liquefied propellant was then transferred using a transfer button and the contents of the bottle sonicated to ensure thorough mixing. Unless otherwise stated, the fill volume for the bottles was 20 ml.

Materials

Active ingredients

All active ingredients were micronised. In general, the active ingredients were anhydrous, although nedocromil sodium and sodium cromoglycate were used in their equilibrium hydrated form which each contain about 10% w/w water at room temperature.

Polyethyleneglycols (PEG)

The average molecular weight of the polyethyleneglycol used is indicated by the number 200, 400, etc following PEG.

Halocarbon oil

Halocarbon oil is the proprietary name given to a series of high molecular weight fully halogenated chlorofluorocarbons of chlorotrifluoroethylene telomers obtainable from Halocarbon Products Corporation, New Jersey, USA.

Miglyols

Miglyol® neutral oils

Miglyol® neutral oils are esters of medium chain fatty acids and are sometimes referred to as fractionated coconut oils. Miglyol is a trademark of Hüls AG. The following oils were used.

Miglyol® 810

A triglyceride of fractionated C_8/C_{10} coconut oil fatty acids classified by the CTFA as caprylic/capric triglyceride. It meets the requirements of the British Pharmacopoeia 1988 for the monograph "Fractionated Coconut Oil". It is a low viscosity oil of neutral taste and smell, with a turbidity point below 0°C.

Miglyol® 829

A glyceryl ester of fractionated C_8/C_{10} coconut fatty acids linked to succinic acid and is classified by the CTFA as caprylic/capric/diglyceryl succinate. It has a turbidity point below -30°C, is soluble in alcohol, has a viscosity of approximately 250 mPa.s and a density of approximately 1.

Miglyol® 840

A propylene glycol diester of saturated vegetable fatty acids with C_8/C_{10} chain lengths, classified by the CFTA as propyleneglycol dicaprylate/dicaprate. It meets the requirements of the German Pharmacopoeia, DAR9, 1st supplement, for the monograph "Propyleneglycoloctanoatodecanoate". It has a turbidity point below -30°C and is soluble in 90% ethanol.

Polyvinylpyrrolidones

All polyvinylpyrrolidones used were essentially linear homopolymers formed by the free radical polymerisation of N-vinylpyrrolidone. PVP(K29/32), PVP(K90), PVP(K120), PVP(C15) and PVP(C30) refer to the polyvinylpyrrolidones obtainable from GAF Chemical Corporation and sold under the Trade Mark **PLASDONE®**. PVP/17PF refers to **KOLLIDON** 17PF, a polyvinylpyrrolidone available from BASF (**KOLLIDON** is a registered Trade Mark).

The manufacturing processes for polyvinylpyrrolidone and the other polymers used herein produce polymer mixtures containing molecules of unequal chain length and thus different molecular weights. Such polymers are usually characterised by their K values, in which K is determined from viscosity measurements using the Fikentscher equation (H. Fikentscher, *Cellusochemie*, 1932, 13, 58-64 and 71-74). The polymers can also be characterised by their average molecular weights ($\bar{M}w$),

viscosity average molecular weights ($\overline{M}v$) and number average molecular weights ($\overline{M}n$).

Characterising data for the polyvinylpyrrolidones used were as follows:

	K	$\overline{M}w$	$\overline{M}v$	$\overline{M}n$
PVP 17 PF	15-18	9000	-	2500
K29/32	29-32	-	-	-
K90	94±6	1,280,000	63000	-
K120	120±5	2,800,000	1,450,000	-
C15	17±1	10500	7000	3000
C30	30.5±1	62500	3800	16500

Polyvinylpyrrolidone/vinylacetate copolymers

Polyvinylpyrrolidone/vinylacetate copolymers are obtainable from GAF Chemical Corporation. The E- and I- series of PVP/VA copolymers were supplied as 50% solutions in ethanol and isopropanol respectively. S-630 refers to the white, spray dried polymer of PVP/VA having the characteristics set out below.

Characterising data for PVP/VA used:

		K value	VP/VA ratio
PVP/VA	S-630	30-50	60/40
	E-535	30-50	50/50
	I-535	25-35	50/50
	E-335	25-35	30/70

Acrylic acid/methacrylic acid ester copolymers

The acrylic acid/methacrylic acid ester copolymers used were copolymers synthesized from acrylic and methacrylic acid ethyl and methyl esters with a low content of quaternary ammonium groups. The molar ratio of these ammonium groups to the neutral (meth)acrylic acid esters is 1:40. The weight average molecular weight is approximately 150000. The polymer used was **EUDRAGIT** RS PM, obtainable from Röhn Pharma GmbH. (**EUDRAGIT** is a registered Trade Mark).

Polyvinylacetate

The polyvinylacetate used had a weight average molecular weight of about 26,000.

A. Compositions containing polyvinylpyrrolidone and propellant 227

The following active ingredients were formulated at the concentration shown with PVP in propellant 227 **PLASDONE** C30 (**PLASDONE** is a registered Trade Mark of GAF Chemicals Corporation).

a) with 0.05% w/w PVP(C-30)

1.	Terbutaline sulphate	5mg/ml
2.	Beclomethasone dipropionate	5mg/ml
3.	Salbutamol sulphate	4mg/ml
4.	Fluticasone propionate	4mg/ml
5.	Reproterol hydrochloride	10mg/ml
6.	Fenoterol hydrobromide	4mg/ml
7.	Sodium cromoglycate	10mg/ml
8.	Sodium cromoglycate	50mg/ml
9.	Ipratropium bromide	0.8mg/ml
10.	Pentamidine isoethionate	4mg/ml
11.	Clemastine	4mg/ml
12.	Acetyl-β-methylcholine bromide	10mg/ml
13.	Budesonide	4mg/ml

b) with 0.1% w/v PVP(17PF)

1.	Fenoterol hydrobromide	4mg/ml
2.	Terbutaline sulphate	5mg/ml
3.	Salbutamol sulphate	4mg/ml

c) with 0.025% w/v PVP(C30)

1.	Tipredane	10mg/ml

B. Compositions containing polyvinylpyrrolidone/vinyl acetate copolymer in propellant 227

The following active ingredients were formulated in propellant 227 at the concentrations shown.

a) with 0.05% w/v PVP/VA S-630

1.	Terbutaline sulphate	5mg/ml
2.	Beclomethasone dipropionate	5mg/ml
3.	Salbutamol sulphate	4mg/ml
4.	Fluticasone propionate	4mg/ml
5.	Reproterol hydrochloride	10mg/ml

	6.	Fenoterol hydrobromide	4mg/ml
	7.	Sodium cromoglycate	10mg/ml
	8.	Sodium cromoglycate	50mg/ml
	9.	Ipratropium bromide	0.8mg/ml
	10.	Acetyl-β-methylcholine bromide	10mg/ml
	11.	Budesonide	4mg/ml
	b)	with 0.025% w/v PVP/VA S-630	
	1.	Tipredane	10mg/ml

C. **Compositions containing PVP or PVP/VA, propellant 227 and polyethylene glycol**

The following active ingredients were formulated in propellant 227 at the concentration shown with 0.5% w/v PEG600.

	a)	with 0.05% w/v PVP(C30)	
	1.	Salbutamol sulphate	4mg/ml
	2.	Sodium cromoglycate	50mg/ml
	3.	Reproterol hydrochloride	10mg/ml
	b)	with 0.05% w/v PVP/VA S-630	
	1.	Salbutamol sulphate	4mg/ml
	2.	Sodium cromoglycate	50mg/ml
	3.	Reproterol hydrochloride	10mg/ml
	4.	Budesonide	4mg/ml
	c)	with 0.1% w/v PVP(17PF)	
	1.	Terbutaline sulphate	5mg/ml
	2.	Fenoterol hydrobromide	4mg/ml

D. **Compositions containing acrylic acid/methacrylic acid ester copolymers and propellant 227**

The following active ingredients were formulated at the concentration shown with 0.1% w/v **EUDRAGIT RS** (**EUDRAGIT** is a Trade Mark of Röhn Pharma GmbH) in propellant 227.

a)	1.	Terbutaline	5mg/ml
	2.	Beclomethasone dipropionate	5mg/ml
	3.	Salbutamol sulphate	4mg/ml
	4.	Fluticasone	4mg/ml

5.	Reproterol hydrochloride	10mg/ml
6.	Fenoterol	4mg/ml
7.	Sodium cromoglycate	10mg/ml
8.	Ipratropium bromide	0.8mg/ml
9.	Clemastine	4mg/ml
10.	Acetyl-β-methylcholine bromide	10mg/ml

b) compositions including 0.5%w/w PEG 600

11.	Beclomethasone dipropionate	5mg/ml
12.	Sodium cromoglycate	50mg/ml
13.	Reproterol hydrochloride	10mg/ml
14.	Fenoterol hydrobromide	4mg/ml

E. Compositions in propellant 134a

The following active ingredients were formulated at the concentration shown in propellant 134a.

1.	Tipredane	10mg/ml
	PVP(C30)	0.1% w/w
	ethanol	5.0% w/w
2.	Tipredane	10mg/ml
	PVP(C30)	0.1% w/w
	ethanol	10.0% w/w
3.	Nedocromil sodium	20mg/ml
	PVP(C30)	0.1%/ w/w
	ethanol	5.0% w/w
4.	Nedocromil sodium	20mg/ml
	PVP(C30)	0.1% w/w
	ethanol	10.0% w/w
5.	Tipredane	10mg/ml
	PVP/VA S-630	0.1% w/w
	ethanol	5.0% w/w
6.	Tipredane	10mg/ml
	PVP(C30)	0.25% w/w
	ethanol	5.0% w/w
7.	Tipredane	10mg/ml
	PVP(C30)	0.5% w/w
	ethanol	5.0% w/w

8.	Nedocromil sodium	20mg/ml
	PVP/VA S-630	0.1% w/w
	ethanol	5.0% w/w
9.	Nedocromil sodium	20mg/ml
	PVP/C30	0.25% w/w
	ethanol	5.0% w/w
10.	Nedocromil sodium	20mg/ml
	PVP(C30)	0.5% w/w
	ethanol	5.0% w/w
11.	Tipredane	10mg/ml
	PVP(C30)	0.1% w/w
	PEG 600	0.5% w/w
	ethanol	5.0% w/w
12.	Tipredane	10mg/ml
	PVP(C30)	0.1% w/w
	PEG 600	0.5% w/w
	ethanol	10.0% w/w
13.	Nedocromil sodium	20mg/ml
	PVP(C30)	0.1% w/w
	PEG 600	0.5% w/w
	ethanol	5.0% w/w
14.	Nedocromil sodium	20mg/ml
	PVP(C30)	0.1% w/w
	PEG 600	0.5% w/w
	ethanol	10.0% w/w
15.	Nedocromil sodium	20mg/ml
	PVP(C30)	0.05% w/w
	PEG 600	0.5% w/w
	ethanol	0.2% w/w
16.	Beclomethasone dipropionate	5mg/ml
	PVP/VA S-630	0.1% w/w
	ethanol	2.0% w/w
17.	Beclomethasone dipropionate	5mg/ml
	PVP/VA S-630	0.1% w/w
	ethanol	5.0% w/w
18.	Beclomethasone	

dipropionate	5mg/ml
PVP(C30)	0.1% w/w
ethanol	5.0% w/w

F. **Compositions containing polyvinylacetate**

a) **in propellant 134a**

1.	Tipredane	10mg/ml
	Polyvinylacetate	0.042% w/w
2.	Nedocromil sodium	20mg/ml
	Polyvinylacetate	0.042% w/w

b) **in propellant 227**

1.	Tipredane	10mg/ml
	Polyvinylacetate	0.035% w/w
2.	Nedocromil sodium	20mg/ml
	Polyvinylacetate	0.035% w/w

G. **Compositions using polyvinylpyrrolidone of different K values**

The following active ingredients were formulated in propellant 227 at the concentrations shown, with 0.1% w/w polyvinylpyrrolidone having the K value shown:

a) **PVP(K29/32)**

1.	Tipredane	10mg/ml
2.	Nedocromil sodium	20mg/ml
3.	Sodium cromoglycate	20mg/ml
4.	Reproterol hydrochloride	4mg/ml
5.	Salbutamol sulphate	4mg/ml

b) **PVP(K90)**

1.	Tipredane	10mg/ml
2.	Nedocromil sodium	20mg/ml

c) **PVP(K120)**

1.	Tipredane	10mg/ml
2.	Nedocromil sodium	20mg/ml

d) **PVP(C15)**

1.	Tipredane	10mg/ml
2.	Nedocromil sodium	20mg/ml

H. **Compositions using polyvinylpyrrolidone/vinylacetate**

copolymers of different vinylpyrrolidone/vinylacetate ratios

Tipredane and nedocromil sodium were formulated in propellant 227 at the concentrations shown, with 0.1% w/w PVP/VA having the vinylpyrrolidone/vinylacetate ratio shown.

a) **Nedocromil sodium 20mg/ml**

1. PVP/VA E-535 (50/50)
2. PVP/VA I-535 (50/50)
3. PVP/VA E-335 (30/70)

b) **Tipredane 10mg/ml**

1. PVP/VA E-535 (50/50)
2. PVP/VA I-535 (50/50)
3. PVP/VA E-335 (30/70)

I. Further tipredane formulations

Ex	Tipredane (mg/ml)	PVP/VA S-630 % w/w	PVP/C30 % w/w	Propellant
1	4	0.0025	-	134a
2	4	0.01	-	134a
3	4	0.025	-	134a
4	4	0.05	-	134a
5	10	0.0025	-	134a
6	10	0.01	-	134a
7	10	0.025	-	134a
8	10	0.05	-	134a
9	30	0.0025	-	134a
10	30	0.01	-	134a
11	30	0.025	-	134a
12	30	0.05	-	134a
13	4	0.0025	-	227
14	4	0.01	-	227
15	4	0.025	-	227
16	4	0.05	-	227
17	10	0.0025	-	227
18	10	0.01	-	227
19	10	0.025	-	227
20	10	0.05	-	227
21	30	0.0025	-	227
22	30	0.01	-	227
23	30	0.025	-	227
24	30	0.05	-	227
25	4	-	0.0025	134a

26	4	-	0.01	134a
27	4	-	0.025	134a
28	4	-	0.05	134a
29	10	-	0.0025	134a
30	10	-	0.01	134a
31	10	-	0.025	134a
32	10	-	0.05	134a
33	30	-	0.0025	134a
34	30	-	0.01	134a
35	30	-	0.025	134a
36	30	-	0.05	134a
37	4	-	0.0025	227
38	4	-	0.01	227
39	4	-	0.025	227
40	4	-	0.05	227
41	10	-	0.0025	227
42	10	-	0.01	227
43	10	-	0.025	227
44	10	-	0.05	227
45	30	-	0.0025	227
46	30	-	0.01	227
47	30	-	0.025	227
48	30	-	0.05	227

J. **Compositions containing flavouring agents**

The following compositions were made up in propellant 227, with 0.1% w/w PVP/VA S-630.

1.	Nedocromil sodium	20mg/ml
	peppermint oil	0.1% w/w
2.	Nedocromil sodium	20mg/ml
	menthol	0.05% w/w
	saccharin	0.03% w/w
3.	Tipredane	10mg/ml
	menthol	0.05% w/w
	saccharin	0.03% w/w

K. **Compositions containing additional excipients**

The following composition was made up in propellant 227, to examine the effects of different excipients as valve lubricants.

a)	Nedocromil sodium	20mg/ml
	PVP/C30	0.1% w/w

	Lubricant		0.5% w/w
	Menthol		0.05% w/w
	Saccharin, micronised		0.03% w/w
	Lubricants:		
	PEG 200		
	PEG 400		
	PEG 600		
	PEG 1000		
	Miglyol 810		
	Miglyol 829		
	Miglyol 840		
	Ethyl oleate		
	Halocarbon oil 27		
	Tyloxapol		
	Polysorbate 80		
b)	Nedocromil sodium		20mg/ml
	PVP (C30)		0.10% w/w
	PEG 1500		0.20% w/w
	Menthol		0.05% w/w
	Saccharin, micronised		0.03% w/w
c)	Tipredane		10.0mg/ml
	PVP (C30)		0.10% w/w
	Lubricant		0.50% w/w
	Lubricants:	PEG 600	
		PEG 1000	
d)	Tipredane		10.0mg/ml
	PVP (C30)		0.10% w/w
	Lubricant		0.20% w/w
	Lubricants:	PEG 600	
		PEG 1000	
		PEG 1500	

Claims

1. A pressurised aerosol composition comprising a liquefied hydrofluoroalkane, a powdered medicament dispersable therein and a polymer soluble in the liquefied hydrofluoroalkane, wherein the polymer includes recurring structural units, the units being selected from amide containing units and carboxylic acid ester containing units.

2. A composition according to Claim 1, wherein the polymer contains recurring structural units containing an amide group.

3. A composition according to Claim 1 or Claim 2, wherein the polymer includes recurring 1-ethylene-pyrrolidin-2-one units.

4. A composition according to any one of Claims 1 to 3, wherein the polymer is polyvinylpyrrolidone.

5. A composition according to any one of Claims 1 to 3, wherein the polymer is a copolymer containing recurring 1-ethylene-pyrrolidin-2-one units.

6. A composition according to any one of Claims 1 to 3 or Claim 5, wherein the polymer is polyvinylpyrrolidone/vinyl acetate copolymer.

7. A composition according to Claim 1, wherein the polymer is polyvinylacetate or a copolymer of acrylic acid and methacrylic acid esters.

8. A composition according to any one of the preceding claims, wherein the concentration of polymer is from 0.00001 to 10% w/w.

9. A composition according to any one of the preceding claims, wherein the medicament is selected from one or more of terbutaline sulphate, beclomethasone dipropionate, salbutamol sulphate, fluticasone propionate, reproterol hydrochloride, fenoterol hydrobromide, sodium cromoglycate, nedocromil sodium, tipredane, pentamidine isoethionate, clemastine, acetyl-β-methylcholine bromide and budesonide.

10. A process for the preparation of a composition according to Claim 1, which comprises dispersing the powdered medicament and the polymer in the liquefied hydrofluoroalkane.

INTERNATIONAL SEARCH REPORT

International Application No PCT/GB 92/01749

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl. 5 A61K9/00; A61K9/12

II. FIELDS SEARCHED

Minimum Documentation Searched[7]

Classification System	Classification Symbols
Int.Cl. 5	A61K

Documentation Searched other than Minimum Documentation to the Extent that such Documents are included in the Fields Searched[8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

Category[10]	Citation of Document,[11] with indication, where appropriate, of the relevant passages[12]	Relevant to Claim No.[13]
Y	EP,A,0 372 777 (RIKER LABORATORIES INC.) 13 June 1990 cited in the application see claims 1,12	1-10
Y	WO,A,8 705 211 (BURGHART KURT) 11 September 1987 see the whole document	1-10

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IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
28 OCTOBER 1992	20. 11. 92
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	Mme Dagmar FRANK

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ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO. GB 9201749 SA 64798

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Patent document cited in search report	Publication date	Patent family member(s)		Publication date
EP-A-0372777	13-06-90	AU-A-	4595689	14-06-90
		CA-A-	2004598	06-06-90
		EP-A-	0499344	19-08-92
		JP-A-	2200627	08-08-90
WO-A-8705211	11-09-87	AU-B-	597049	24-05-90
		AU-A-	7127987	28-09-87
		CA-A-	1293929	07-01-92
		DE-A-	3775960	27-02-92
		EP-A,B	0240484	07-10-87
		JP-T-	63503304	02-12-88
		US-A-	4869899	26-09-89
		ZA-A-	8701721	31-08-87

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(54) Title: NEW COMBINATION OF FORMOTEROL AND BUDESONIDE

(57) Abstract

Effective amounts of formoterol (and/or a physiologically acceptable salt and/or solvate thereof) and budesonide are used in combination for simultaneous, sequential or separate administration by inhalation in the treatment of respiratory disorder.

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New combination of formoterol and budesonide.

Field of the invention

This invention relates to improvements in the treatment of mild as well as severe asthma and other respiratory disorders. More particularly, it relates to the use of a bronchodilator in combination with a steroidal anti-inflammatory drug for the treatment of respiratory disorders such as asthma, and to pharmaceutical compositions containing the two active ingredients. It emphasizes the use of a long-acting bronchodilator which provides rapid relief of symptoms.

Background of the invention

There have recently been significant advances in our understanding of asthma. Despite many advances, both in awareness of the disease by doctors and patients alike, coupled with the introdction of very powerful and effective anti-asthma drugs, asthma remains a poorly understood and often poorly treated disease. Previously, contraction of airway smooth muscles has been regarded as the most important feature of asthma. Recently there has been a marked change in the way asthma is managed, stemming from the fact that asthma is recognized as a chronic inflammatory disease. Uncontrolled airway inflammation may lead to mucosal damage and structural changes giving irrversible narrowing of the airways and fibrosis of the lung tissue. Therapy should therefore be aimed at controlling symptoms so that normal life is possible and at the same time provide basis for treating

the underlying inflammation.

The most common cause for poor control of asthma is poor compliance with the long-term management of chronic asthma, particularly with prophylatic treatments, such as inhaled steroids, which do not give immediate symptom relief. Patients will readily take β_2-agonist inhalers, since these provide rapid relief of symptoms, but often do not take prophylactic therapy, such as inhaled steroids, regularly because there is no immediate symptomatic benefit. They also counteract down regulation of β_2-adrenoceptor agonists.

Formoterol, (N-[2-hydroxy-5-[1-hydroxy-2-[[2-(4-methoxyphenyl)-1-methylethyl]amino]ethyl]phenyl] formamide), is an adrenoceptor agonist which selectively stimulates β_2-receptors, thus producing relaxation of bronchial smooth muscle, inhibition of the release of endogenous spasmogens, inhibition of oedema caused by endogenous mediators, and increased mucociliary clearence. Inhaled formoterol fumarate acts rapidly, usually within minutes which gives the patient immediate confirmation that he has taken an adequat dose and thereby avoiding overdosing of both β-agonist and steroid. Inhaled formoterol also exerts a prolonged bronchodilation, which in clinical trials has been demonstrated as up to 12 hours.

Budesonide, (16,17-butylidenebis(oxy)-11,21-dihydroxypregna-1,4-diene-3,20-dione), may be given in a high inhaled dose (up to 2 mg daily) with very low systemic effects, possibly because of its rapid metabolism. The high rapid systemic elimination of budesonide is due to extensive and rapid hepatic metabolism. Long term clinical studies have shown that inhaled budesonide is a pharmacologically safe drug. High doses of inhaled budesonide are highly effective and well

tolerated when used in oral steroid replacement therapy. Budesonide represents a logical safe and effective therapy for long term control of asthma.

The inhaled route of administration enables the dose to be delivered directly to the airways. By this type of administration, it is possible to give a small dose and thereby minimizing unwanted side-effects. The drawbacks of the currently available bronchodilators are their relatively short duration of action. By using a compound with long duration e.g. formoterol it would be possible to avoid the nocturnal asthma, which so often causes considerable anxiety and debility to the patients. Formoterol gives less nocturnal waking than the commonly used short-acting agonists like salbutamol, terbutaline and the like. Formoterol has been registered for oral administration in Japan since 1986.

Pharmaceutical combinations of long-acting β_2-agonists and steroids are disclosed in two European applications, EP 416950 which discloses the combination of salmeterol and beclomethasone, and EP 416951 which discloses the combination of salmeterol and fluticasone propionate.

In Ann. Allergy 1989, 63 (3), p. 220-224 the use of a β_2-agonist, i.e. formoterol and a steroid, i.e. budesonide seperately are mentioned. It is not disclosed a pharmaceutical combination including both formoterol and budesonide, or the use of the two compounds in combination therapy. The use of a β_2-agonist and a steroid separately is also mentoined in Lung (1990), 168, no. supp, p. 105-110.

Outline of the Invention

The present invention is based on the concept of a novel combination therapy whereby formoterol (and/or a

physiologically acceptable salt and/or solvate thereof) and budesonide are administrated simultaneously, sequentially or seperately by inhalation. This combination has not only a greater efficiency and duration of bronchodilator action but the combination also has a rapid onset of action. This new feature is of utmost importance in order to establish a higher compliance for patients and it provides a rescue medicine thereby avoiding the necessity for the patient of carrying two different inhalers. This simplifies life for patients considerably and makes life more comfortable and secure. The rapid onset of the long-acting β_2-agonist gives the patient immediate confirmation that he has taken an adequate dose and thereby avoiding overdosing of both β_2-agonist and steroid. Since the use of formoterol instead of salmoterol gives a much more rapid onset the combinations according to the invention have a number of advantages compared to the combinations disclosed i EP 416950 and EP 41651. The combination according to present invention permits a twice daily dosing regime as a basic treatment of asthma, particularly nocturnal asthma.

The present invention provides a medicament containing, separately, or together, (i) formoterol (and/or a physiologically acceptable salt and/or solvate thereof) and (ii) budesonide for simultaneous, sequential or separate administration by inhalation in the treatment of respiratory disorder.

The invention also provides a pharmaceutical composition for administration by inhalation in the treatment of respiratory disorder which composition comprises formoterol (and/or a physiologically acceptable salt and/or solvate thereof) and budesonide.

According to another aspect of the invention there are provided pharmaceutical compositions comprising effective

amounts of formoterol (and/or a physiologically acceptable salt and/or solvate thereof) and budesonide as a combined preperation for simultaneous, sequential or seperate administration by inhalation in the treatment of respiratory disorder.

The invention further provides formoterol (and/or a physiologically acceptable salt and/or solvate thereof) and budesonide for use in combination therapy by simultaneous, sequential or seperate administration by inhalation in the treatment of respiratory disorder.

Further the invention provides the use of formoterol (and/or a physiologically acceptable salt and/or solvate thereof) in the manufacture of a medicament for combination therapy where formoterol (and/or a physiologically acceptable salt and/or solvate thereof) and budesonide are administered simultaneously, sequentially or seperately by inhalation in the treatment of respiratory disorder and the use of budesonide in the manufacture of a medicament for combination therapy where formoterol (and/or a physiologically acceptable salt and/or solvate thereof) and budesonide are administered simultaneously, sequentially or separately by inhalation in the treatment of respiratory disorder.

The invention additionally relates to the use of formoterol (and/or a physiologically acceptable salt and/or solvate thereof) and budesonide in the manufacture of a medicament for combination therapy for simultaneous, sequential or seperate administration of formoterol and budesonide by inhalation in the treatment of respiratory disorder.

According to a further feature of the invention there is provided a method of treating respiratory disorder which comprises the simultaneous, sequential or separate

administration by inhalation of effective amounts of formoterol (and/or a physiologically acceptable salt and/or solvate thereof) and budesonide.

Suitable physiologically salts of formoterol include acid addition salts derived from inorganic and organic acids, such as the hydrochloride, hydrobromide, sulphate, phosphate, maleate, fumarate, tartrate, citrate, benzoate, 4-methoxybenzoate, 2- or 4-hydroxybenzoate, 4-chlorobenzoate, p-toluenesulphonate, methanesulphonate, ascorbate, salicylate, acetate succinate, lactate, glutarate, gluconate, tricarballylate, hydroxynaphthalenecarboxylate or oleate. Formoterol is preferably used in the form of its fumarate salt and as a dihydrate.

The ratio of formoterol to budesonide used according to the invention is preferably within the range of 1:4 to 1:70. The two drugs may be administered separately in the same ratio.

The intended dose regimen is a twice daily administration, where the suitable daily dose of formoterol is in the range of 6 to 100 µg with a preferred dose of 6-48 µg and the suitable daily dose for budesonide is 50 to 4800 µg with a preferred dose of 100-1600 µg. The particular dose used will strongly depend on the patient (age, weight etc) and the severity of the disease (mild, moderate, severe asthma etc).

For administration, the combination is suitably inhaled from a nebulizer, from a pressurized metered dose inhaler or as a dry powder from a dry powder inhaler (e.g. as sold under the trade mark Turbuhaler) or from a dry powder inhaler utilizing gelatine, plastic or other capsules, cartridges or blister packs.

A diluent or carrier, generally non-toxic and chemically inert to the medicament e.g. lactose, dextran, mannitol or glucose or any additives that will give the medicament a desired taste, can be added to the powdered medicament.

Examples of the preparation of suitable dosage forms according to the invention include the following: Formoterol fumarate dihydrate and budesonide (optionally premicronized) are mixed in the proportions given above. The agglomerated, free-flowing micronized mixture may be filled into dry powder inhaler such as sold under the trade mark Turbuhaler. When a capsule system issued, it is desirable to include a filler in the mixture.

The micronized mixture may be suspended or dissolved in a liquid propellant mixture which is kept in a container that is sealed with a metering valve and fitted into a plastic actuator. The propellants used may be chlorofluorocarbons of different chemical formulae. The most frequently used chlorofluorocarbon propellants are trichloromonofluoromethane (propellant 11), dichlorodifluoromethane (propellant 12), dichlorotetrafluoroethane (propellant 114), tetrafluoroethane (propellant 134a) and 1,1-difuoroethane (propellant 152a). Low concentrations of a surfactant such as sorbitan trioleate, lecithin, disodium dioctylsulphosuccinate or oleic acid may also be used to improve the physical stability.

The invention is further illustrated by way of example with reference to the following Examples.

Example 1 - Dry Powder Inhaler (Turbuhaler)

Active ingredient	Per dose
Formoterol (as fumarate dihydrate)	12 µg
Budesonide	200 µg

The storage unit of the inhaler is filled with sufficient for at least 200 doses.

Active ingredient	Per dose
Formoterol (as fumarate dihydrate)	24 µg
Budesonide	200 µg

The storage unit is filled with sufficient for at least 200 doses.

Active ingredient	Per dose
Formoterol (as fumarate dihydrate)	12 µg
Budesonide	100 µg

The storage unit is filled with sufficient for at least 200 doses.

Example 2 - Metered dose inhaler

Active ingredient	Per dose
Formoterol (as fumarate dihydrate)	12 µg
Budesonide	200 µg
Stabilizer	0.1 - 0.7 mg
Propellant	25 - 100 µl

Active ingredient	Per dose
Formoterol (as fumarate dihydrate)	24 µg
Budesonide	200 µg
Stabilizer	0.1 - 0.7 mg
Propellant	25 - 100 µl

Active ingredient	Per dose
Formoterol (as fumarate dihydrate)	12 µg
Budesonide	200 µg
Stabilizer	0.1 - 0.7 mg
Propellant	25 - 100 µl

Example 3 - Metered dose dry powder formulation

Active ingredient	Per dose
Formoterol (as fumarate dihydrate)	12 µg
Budesonide	200 µg
Lactose	up to 5, 12.5 or 25 mg

Active ingredient	Per dose
Formoterol (as fumarate dihydrate)	24 µg
Budesonide	200 µg
Lactose	up to 5, 12.5 or 25 mg

Active ingredient	Per dose
Formoterol (as fumarate dihydrate)	12 µg
Budesonide	100 µg
Lactose	up to 5, 12.5 or 25 mg

CLAIMS

1. A medicament containing, seperately or together, (i) formoterol (and/or a physiologically acceptable salt and/or solvate thereof) and (ii) budesonide for simultaneous, sequential or seperate administration by inhalation in the treatment of respiratory disorder.

2. A pharmaceutical composition for administration by inhalation in the treatment of respiratory disorder which composition comprises formoterol (and/or a physiologically acceptable salt and/or solvate thereof) and budesonide.

3. A pharmaceutical composition comprising effective amounts of formoterol (and/or a physiologically acceptable salt and/or solvate thereof) and budesonide as a combined preperation for simultaneous, sequential or separate administration by inhalation in the treatment of respiratory disorder.

4. Formoterol (and/or a physiologically acceptable salt and/or solvate thereof) and budesonide for use in combination therapy by simultaneous, sequential or separate administration by inhalation in the treatment of respiratory disorder.

5. The use of formoterol (and/or a physiologically acceptable salt thereof) in the manufacture of a medicament for combination therapy where formoterol (and/or physiologically acceptable salt and/or solvate thereof) and budesonide are administered simultaneously, sequentially or separately by inhalation in the treatment of respiratory disorder.

6. The use of budesonide in the manufacture of a medicament for combination therapy where formoterol

(and/or a physiologically acceptable salt and/or solvate thereof) and budesonide are administered simultaneously, sequentially or separately by inhalation in the treatment of respiratory disorder.

7. The use of formoterol (and/or a physiologically acceptable salt and/or solvate thereof) and budesonide in the manufacture of a medicament for combination therapy for simultaneous, sequential or separate administration of formoterol and budesonide by inhalation in the treatment of respiratory disorder.

INTERNATIONAL SEARCH REPORT

International Application No PCT/EP 92/02826

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl. 5 A61K31/57; //(A61K31/57,31:165)

II. FIELDS SEARCHED

Minimum Documentation Searched[7]

Classification System	Classification Symbols
Int.Cl. 5	A61K

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched[8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

Category[10]	Citation of Document,[11] with indication, where appropriate, of the relevant passages[12]	Relevant to Claim No.[13]
X	ANNALS OF ALLERGY vol. 63, no. 3, September 1989, pages 220 - 224 JEAN H. MARSAC ET AL. 'Inhaled beta agonists and inhaled steroids in the treatment of asthma' cited in the application see page 221, column 2; table 1 see page 221, column 3, line 11 - line 15 * page 223; summary *	1-7
X	LUNG (USA) vol. 168, no. SUPP, 1990, NEW YORK pages 105 - 110 NILS SVEDMYR 'The current place of beta-agonists in the management of asthma' cited in the application see abstract	1-7

[10] Special categories of cited documents :

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IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
07 APRIL 1993	28/4/93
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	LEHERTE C.F.M.

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(54) Title: PROCESS FOR THE PREPARATION OF OPTICALLY PURE ISOMERS OF FORMOTEROL

(57) Abstract

A method is disclosed for the preparation of optically pure isomes of formeterol, especially the (*R*,*R*)- and (*S*,*S*)-isomer, by the reaction of an optically pure 4-benzyloxy-3-formamidostyrene oxide with an optically pure 4-methoxy-α-methyl-*N*-(phenylmethyl)benzeneethanamine followed by debenzylation. Useful intermediates in the process are also disclosed, as is the novel *L*-tartrate salt of *R*,*R*-formoterol.

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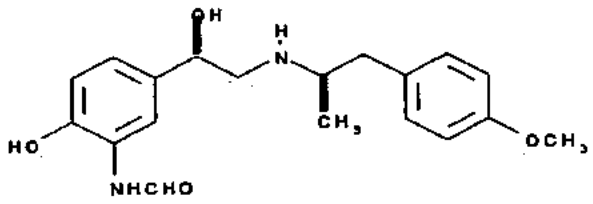
PROCESS FOR THE PREPARATION OF OPTICALLY PURE ISOMERS OF FORMOTEROL

Field of the Invention

The present invention relates to a method of preparation of optically pure isomers of formoterol, especially the (*R,R*)- and (*S,S*)-isomer, by the reaction of an optically pure 4-benzyloxy-3-formamidostyrene oxide with an optically pure 4-methoxy-α-methyl-*N*-(phenylmethyl)benzeneethanamine followed by debenzylation.

Background of the Invention

Formoterol, whose chemical name is (+/-) *N*-[2-hydroxy-5-[1-hydroxy-2[[2-(p-methoxyphenyl)-2-propyl]amino]ethyl]phenyl]-formamide, is a highly potent and β_2-selective adrenoceptor agonist having a long lasting bronchodilating effect when inhaled. The structure of formoterol is as shown:



Formoterol has two chiral centers in the molecule, each of which can exist in two possible configurations. This gives rise to four combinations: (*R,R*), (*S,S*), (*R,S*) and (*S,R*). (*R,R*) and (*S,S*) are mirror images of each other and are therefore enantiomers; (*R,S*) and (*S,R*) are similarly an enantiomeric pair. The mirror images of (*R,R*) and (*S,S*) are not, however, superimposable on (*R,S*) and (*S,R*), which are diastereomers. Formoterol is available commercially only as a racemic diastereomer, (*R,R*) plus (*S,S*) in a 1:1 ratio, and the generic name formoterol refers to this enantiomeric mixture. The racemic mixture that is commercially available for administration is a dihydrate of the fumarate salt.

The graphic representations of racemic, ambiscalemic and scalemic or enantiomerically pure compounds used herein are taken from Maehr J. Chem. Ed. 62, 114-120 (1985): solid and broken wedges are used to denote the absolute configuration of a chiral element; wavy lines indicate disavowal of any stereochemical implication which

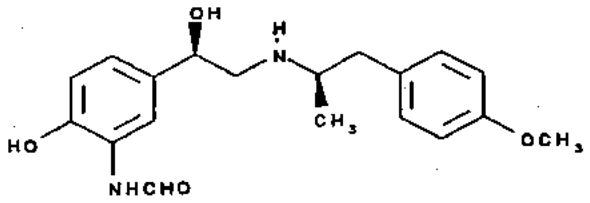
the bond it represents could generate; solid and broken bold lines are geometric descriptors indicating the relative configuration shown but denoting racemic character; and wedge outlines and dotted or broken lines denote enantiomerically pure compounds of indeterminate absolute configuration. Thus, the formula for formoterol above reflects the racemic nature of the commercial material, while among the structures below, those having open wedges are intended to encompass both of the pure enantiomers of that pair and those having solid wedges are intended to encompass the single, pure enantiomer having the absolute stereochemistry shown.

All four isomers of formoterol have been synthesized and briefly examined for relaxing activity on the guinea pig trachea [Murase *et al.*, Chem. Pharm. Bull. 26, 1123-1129 (1978). It was found that the (*R,R*)-isomer is the most potent, while the others are 3-14 times less potent. More recently, the four isomers have been examined with respect to their ability to interact in vitro with β-adrenoceptors in tissues isolated from guinea pig [Trofast *et al.*, Chirality 3, 443-450 (1991)]. The order of potency was (*R,R*) >> (*R,S*)= (*S,R*) > (*S,S*). It was found that the (*R,R*)-isomer is 1000-fold more potent than the (*S,S*)-isomer. Preliminary research indicates that administration of the pure (*R,R*)-isomer may offer an improved therapeutic ratio.

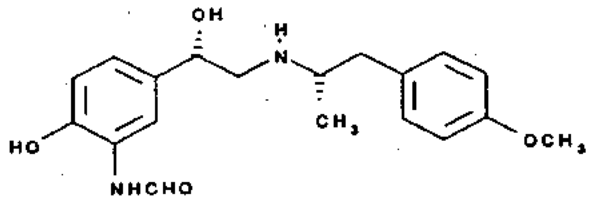
Two reports have been published describing the synthesis of all four isomers of formoterol. In the first report [Murase *et al. op. cit.*], the (*R,R*)- and (*S,S*)- isomers were obtained by diastereomeric crystallization of racemic formoterol with tartaric acid. In the second report [Trofast *et al. op. cit.*], racemic 4-benzyloxy-3-nitrostyrene oxide was coupled with an optically pure (*R,R*)- or (*S,S*)-*N*-(1-phenylethyl)-*N*-(1-(p-methoxyphenyl)-2-propyl)amine to give a diastereomeric mixture of formoterol precursors, which were then separated by semipreparative HPLC and transformed to the pure formoterol isomers. Both syntheses suffer long synthetic procedure and low overall yield and are impractical for large scale production of optically pure (*R,R*)- or (*S,S*)-formoterol. For example, the Trofast reference describes reacting 4.5 grams of the styrene oxide with 4.8 grams of the phenethylamine to produce 94 milligrams of the pure *S,S* enantiomer. Therefore, there exists a need for a more economical and efficient method of making optically pure formoterol.

Summary of the Invention

The processes of the invention provide a practical synthesis of optically pure formoterol, especially (*R*,*R*)- and (*S*,*S*)-formoterol.

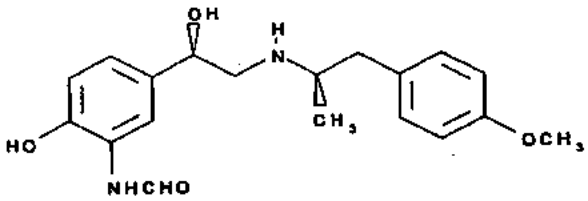


R,*R*-formoterol



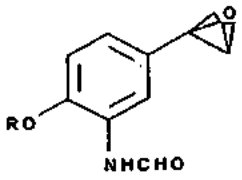
S,*S*-formoterol

In its broadest aspect, the invention relates to a process for preparing a compound of formula F



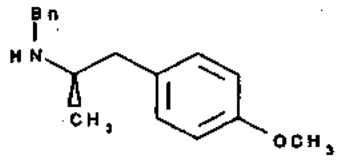
F

or a salt thereof, comprising the sequential steps of: (a) reacting a compound of formula



wherein R is benzyl or substituted benzyl,

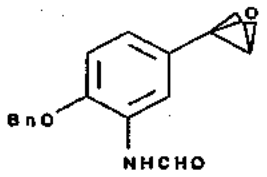
with a compound of formula FBA:



FBA

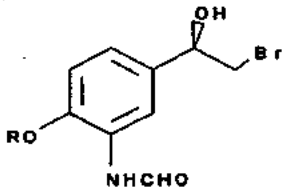
and (b) reducing with hydrogen gas in the presence of a noble metal catalyst.

The term "substituted benzyl" refers to any protecting group for a phenol that contains the benzyl (or phenylmethyl) nucleus substituted with one or more substituents that do not interfere with its function as a protecting group. Suitable substituents include: C_1 to C_6-alkyl, C_1 to C_6-alkoxyl, halogen and combinations thereof. In a particular embodiment, R is benzyl (Bn), and the compound is referred to herein as FAE:

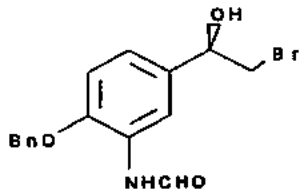


FAE

The epoxide may be produced *in situ* from the corresponding bromohydrin:

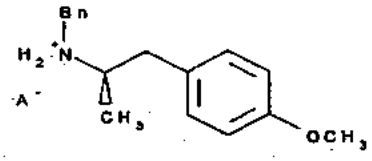


by treatment with a base, and the benzylamine may be produced *in situ* from a corresponding salt by treatment with a base. In one embodiment, the steps may be combined to provide a process wherein a compound of formula FBH3:



FBH3

a compound of formula FBA-HA:



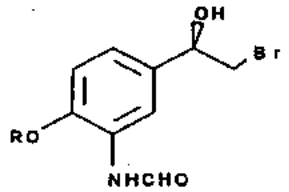
FBA-HA

and at least one equivalent of a base are combined to produce a mixture comprising an epoxide and a free base. The mixture of epoxide and free base is heated at a temperature sufficient to cause a reaction to produce a benzyl-protected aminoalcohol, and the benzyl-protected aminoalcohol is reduced with a source of hydrogen in the presence of a noble metal catalyst. In the above structure A^- is the anion of a conjugate acid HA having a pKa sufficient to protonate the amine.

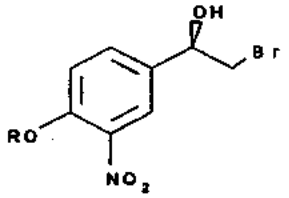
In the foregoing processes a preferred noble metal catalyst is palladium and a preferred base is an alkali metal carbonate, particularly potassium carbonate. The source of hydrogen may be hydrogen gas or a hydrogen-donating compound such as ammonium formate.

Suitable acid addition salts for the compounds of the present invention include for example, acetic, benzenesulfonic (besylate), benzoic, camphorsulfonic, citric, ethenesulfonic, fumaric, gluconic, glutamic, hydrobromic, hydrochloric, isethionic, lactic, maleic, malic, mandelic, methanesulfonic, mucic, nitric, pamoic, pantothenic, phosphoric, succinic, sulfuric, tartaric acid, p-toluenesulfonic, and the like. The mandelic acid salt is especially preferred for compounds of formula FBA; the tartrate and fumarate are preferred for formoterol enantiomers F.

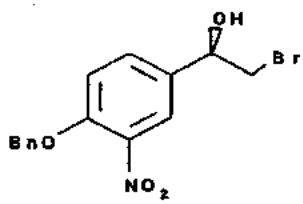
In another aspect, the invention relates to a process for synthesizing a compound of formula



comprising the sequential steps of (a) reducing 2-bromo-4'-RO-3'-nitroacetophenone with about one equivalent of borane-methyl sulfide in the presence of a catalytic amount of a single enantiomer of an oxazaborolidine reagent derived from a chiral aminoalcohol, preferably from *cis* 1-amino-2-indanol, to produce substantially enantiomerically pure α-(bromomethyl)-4-RO-3-nitrobenzenemethanol:



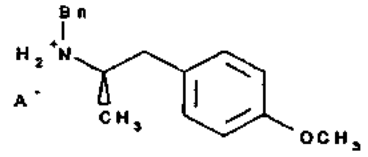
(b) reducing the α-(bromomethyl)-4-RO-3-nitrobenzenemethanol with hydrogen in the presence of a noble metal catalyst to produce an aniline; and (c) formylating the aniline with formic acid and acetic anhydride. A preferred noble metal catalyst for this process is platinum, derived from PtO_2. Steps (b) and (c) may be carried out without isolation of the aniline. In a preferred embodiment, R is benzyl and 2-bromo-4'-benzyloxy-3'-nitroacetophenone is reduced to produce substantially enantiomerically pure α-(bromomethyl)-4-phenylmethoxy-3-nitrobenzenemethanol (FBH):



In a more preferred embodiment the single enantiomer of an oxazaborolidine is derived from (1*R*,2*S*)-1-amino-2-indanol, which produces α-(bromomethyl)-4-phenylmethoxy-3-nitrobenzenemethanol of the *R* configuration. The oxazaborolidine

may be generated *in situ* from (1R,2S)-1-amino-2-indanol and two equivalents of borane-methyl sulfide.

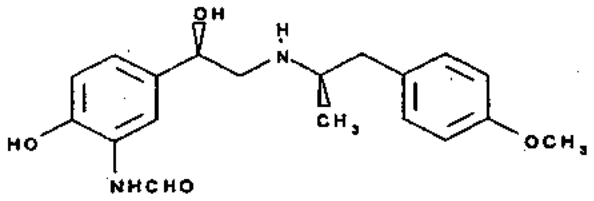
In another aspect, the invention relates to a process for preparing a substantially enantiomerically pure salt of 4-methoxy-α-methyl-*N*-(phenylmethyl)benzeneethanamine of formula FBA-HA



FBA-HA

comprising: (a) reducing 4-methoxyphenyl acetone with hydrogen in the presence of a platinum catalyst and about 1 equivalent of benzylamine in methanol; (b) adding about one equivalent of a single enantiomer of mandelic acid; (c) heating to obtain a methanolic solution; (d) cooling to obtain a crystalline solid phase; and (e) recovering the crystalline solid from the methanolic solution. If desired, one may convert the crystalline mandelic acid salt from step (e) to a salt of an acid other than mandelic acid by processes well known in the art.

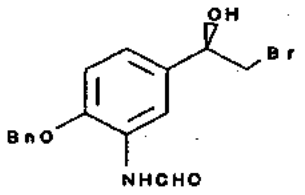
In another aspect, the invention relates to an overall process for preparing a compound of formula F:



F

from 2-bromo-4'-benzyloxy-3'-nitroacetophenone and 4-methoxy-α-methyl-*N*-(phenylmethyl)benzeneethanamine comprising the sequential steps of: (a) reducing 2-bromo-4'-benzyloxy-3'-nitroacetophenone with about one equivalent of borane-methyl sulfide in the presence of a catalytic amount of a single enantiomer of an oxazaborolidine derived from *cis* 1-amino-2-indanol to produce substantially enantiomerically pure α-

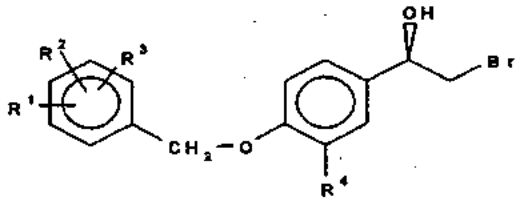
(bromomethyl)-4-phenylmethoxy-3-nitrobenzenemethanol (FBH); (b) reducing the α-(bromomethyl)-4-phenylmethoxy-3-nitrobenzenemethanol with hydrogen in the presence of a noble metal catalyst to produce an aniline FBH2; (c) formylating the aniline with formic acid and acetic anhydride to produce a compound of formula FBH3:



FBH3

(d) combining FBH3, a salt of 4-methoxy-α-methyl-*N*-(phenylmethyl)benzeneethanamine (FBA-HA) and at least one equivalent of a base to produce a mixture comprising an epoxide (FAE) and a free base (FBA); (e) heating the mixture of epoxide and free base at a temperature sufficient to cause a reaction to produce a benzyl-protected aminoalcohol (DBF); and (f) reducing the benzyl-protected aminoalcohol with hydrogen gas in the presence of a noble metal catalyst.

In another aspect, the invention relates to compounds of formula:



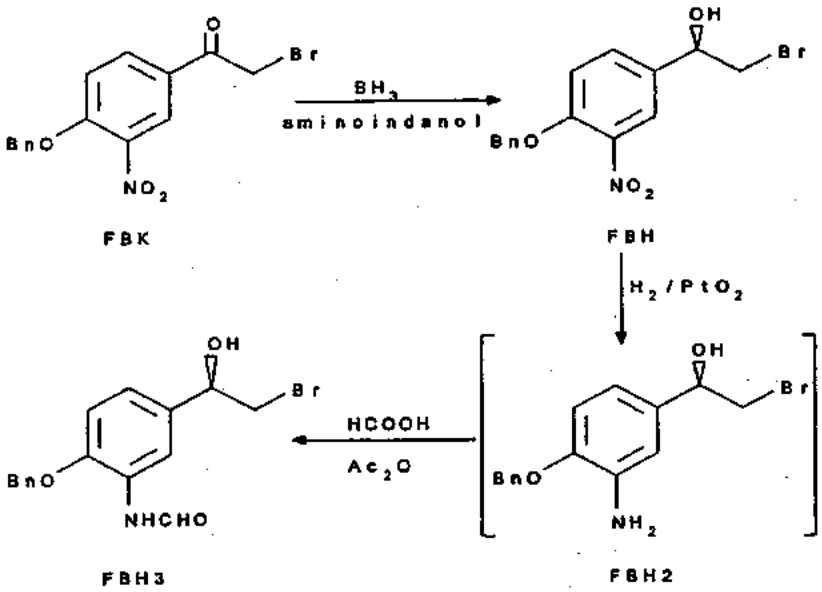
wherein each of R^1, R^2 and R^3 is independently chosen from the group consisting of hydrogen, C_1 to C_6-alkyl, C_1 to C_6-alkoxyl, and halogen and R^4 is $-NO_2$, $-NH_2$ or -NHCHO. The compounds are useful as intermediates in the synthesis of single enantiomers of formoterol. The compounds in which all of R^1, R^2 and R^3 are hydrogen are preferred.

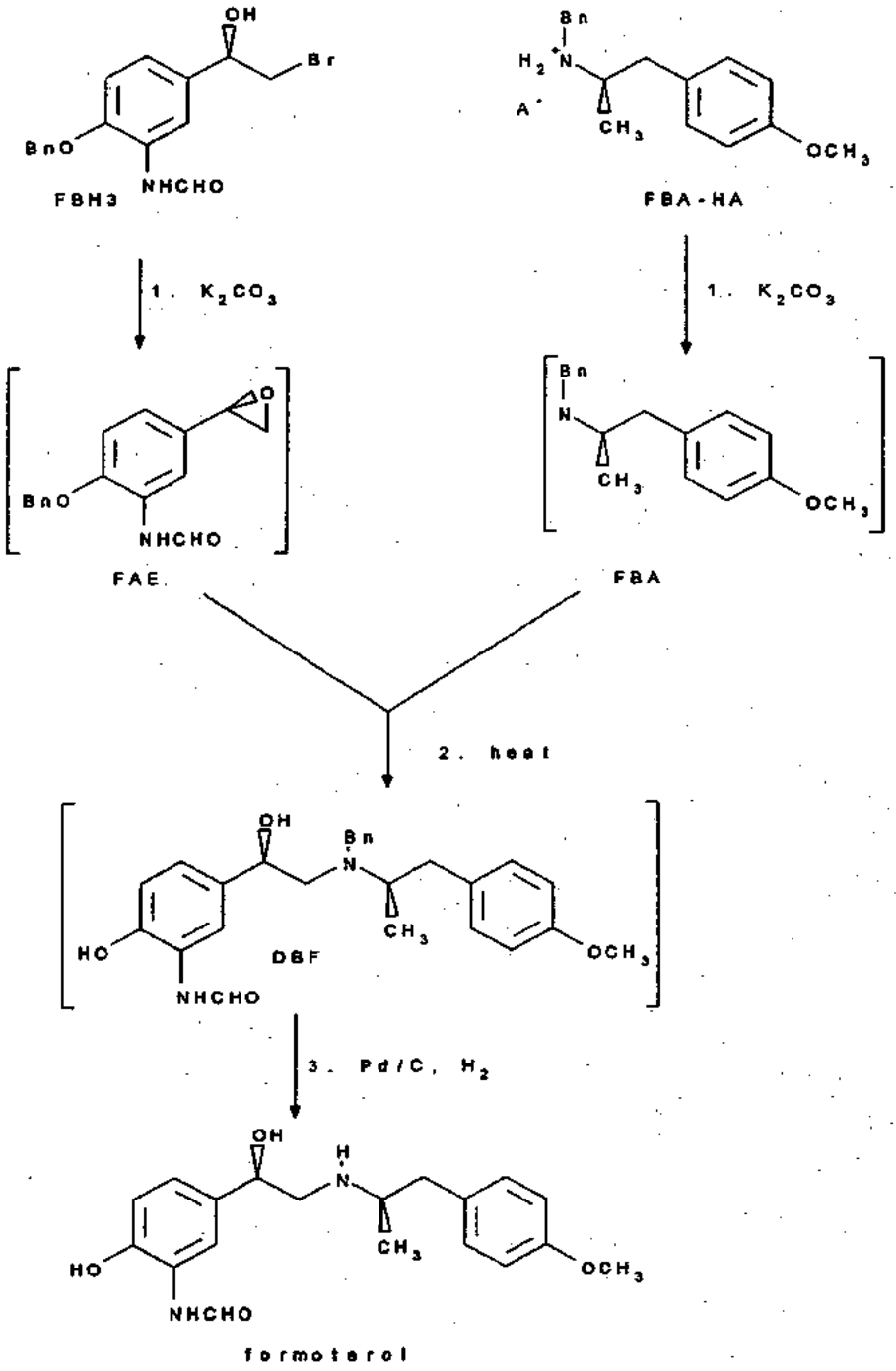
In another aspect, the invention relates to the *L*-(+)-tartrate salt of *R,R*-formoterol, which is unexpectedly superior to other salts of *R,R*-formoterol in that it is easy to handle, pharmaceutically innocuous and non-hygroscopic. The *D*-(-)-tartrate salt of *S,S*-formoterol possesses similar advantages.

Detailed Description

The present invention relates to a more practical and efficient process for the preparation of optically pure isomers of formoterol. This method is particularly advantageous in comparison with known methods because it utilizes optically pure precursors that are readily available by simple resolution and asymmetric reduction. The overall sequence is set forth in Scheme 1, wherein R has been exemplified as benzyl. The same sequence could be used to produce other intermediates in which R is substituted benzyl by beginning with the appropriate starting material analogous to FBK. Brackets indicate intermediates that could be isolated but are not usually isolated in the integrated process.

Scheme 1




OH
Br
BnO
NHCHO
FBH3
Bn
H2N
A-
CH3
OCH3
FBA-HA
1. K2CO3
1. K2CO3
O
BnO
NHCHO
FAE
Bn
N
CH3
OCH3
FBA
2. heat
OH
Bn
N
HO
CH3
OCH3
NHCHO
DBF
3. Pd/C, H2
OH
H
N
HO
CH3
OCH3
NHCHO
formoterol

In the process described above, the optically pure 4-methoxy-α-methyl-*N*-(phenylmethyl)benzene-ethanamine, also called 2-*N*-benzylamino-1-(p-methoxyphenyl)propane (FBA), is obtained by resolution of the racemic compound with *L*- or (*D*)-mandelic acid using a modification of the procedure of Kraft, *et al.* [Rec. Trav. Chim. Pays-Bas 85, 607 (1966)]. The racemic *N*-benzylamine compound was prepared by the reductive amination of p-methoxyphenylacetone with *N*-benzylamine under catalytic hydrogenation, but other reductive conditions using methods known in the art could be used. (*See,* Houben-Weyl's Methoden der Org. Chem. Band IV/1c, p427.)

The invention encompasses a process for making optically pure formoterol from optically pure 4-benzyloxy-3-formamidostyrene oxide (FAE) comprising the coupling and hydrogenation described above in combination with a method for the preparation of the optically pure styrene oxides. According to this aspect the optically pure styrene oxide is obtained by: (a) reduction of 2'-bromo-4-benzyloxy-3-nitroacetophenone with borane stereoselectively in the presence of a chiral oxazaborolidine catalyst to give the corresponding optically active bromohydrin [*See,* Hong, *et al.*, Tetrahedron Lett. 35, 6631(1994)] and U.S. Patent 5,495,821]; (b) reduction of the 3-nitro group in the bromohydrin with a reducing agent to the amino group followed by formylation with formic acid or formic acid/acetic anhydride (Ac_2O) to give the 3-formamido bromohydrin FBH3; and (c) conversion of the 3-formamido bromohydrin to the corresponding 4-benzyloxy-3-formamidostyrene oxide FAE with a base.

The optically pure 2-*N*-benzylamino-1-(p-methoxyphenyl)propane (FBA) is obtained by resolution of the racemic compound with *L*- or (*D*)-mandelic acid. The resolution of racemic *N*-benzylamine compound is performed using one equivalent of *L*- or *D*-mandelic acid in an alcohol solvent such as methanol (MeOH). Optically pure benzylamine mandelic acid salt (FBA-MA) is obtained after four or five crystallizations. The free *N*-benzylamine compound is then obtained by treating the mandelic acid salt with a base such as aq. NaOH or aq. Na_2CO_3 or aq. NH_3 in the presence of an inert organic solvent such as *t*-butyl methyl ether (MTBE) or ethyl acetate (EtOAc) followed by evaporation of the solvent. (*R*)-2-*N*-benzylamino-1-(p-methoxyphenyl)propane is obtained from the *L*-(+)-mandelic acid salt while the (*S*)-enantiomer is obtained from the *D*-(-)-mandelic acid salt. From the same lot of racemic *N*-benzylamine compound, both

(*R*)- and (*S*)-enantiomer can be obtained by using the appropriate mandelic acid.

The optically pure epoxide (FAE) is prepared from commercially available 4-benzyloxy-3-nitroacetophenone. Thus, the acetophenone may be bromonated with bromine in an inert organic solvent such as CH_3CN, MeOH or chloroform to give the α-bromoacetophenone. The bromoacetophenone is then reduced with a borane reducing agent such as BH_3·THF or BH_3Me_2S in the presence of a chiral oxazaborolidine catalyst such as *cis*-(1*R*,2*S*)-aminoindanol-B-Me catalyst to give the optically active bromohydrin after isolation by crystallization in >96% ee. The bromohydrin can be further enriched to >98% ee by recrystallization. The absolute configuration of the bromohydrin is determined by the chirality of the oxazaborolidine catalyst. The nitro group in the bromohydrin is selectively reduced to the amine group using a reducing agent known for selective nitro reduction, such as Sn, Fe with acid, $SnCl_2$ or by heterogeneous catalytic hydrogenation in the presence of a noble metal catalyst such as PtO_2 or Pt/C. The amine group is then formylated with a mixture of formic acid and acetic anhydride without racemization, and the resulting compound is converted to optically pure 4-benzyloxy-3-formamidostyrene oxide with a base such as aq. NaOH or K_2CO_3 in an alcohol solvent or solvent mixture such as MeOH/THF. The epoxide obtained can be purified by recrystallization from an inert organic solvent or solvent mixture, preferably from EtOAc/heptane or toluene/heptane.

The optically pure 2-*N*-benzylamino-1-(*p*-methoxyphenyl) propane (FBA) is reacted with optically pure 4-benzyloxy-1-formamidostyrene oxide without racemization to give an optically pure N,O-di-benzylformoterol intermediate (DBF), and the N,O-di benzyl group of the dibenzylformoterol is removed by hydrogenation in the presence of a hydrogenation catalyst, to give optically pure formoterol. Alternatively, the dibenzylformoterol is obtained directly from the reaction of optically pure 2-*N*-benzylamino-1-(p-methoxyphenyl)propane with the optically pure 1-(4'-benzyloxy-3'-formamidophenyl)-2-bromoethanol (FBH3) in the presence of a base whereby the epoxide (FAE) is formed *in situ*.

For the synthesis of optically pure formoterol, the optically pure *N*-benzylamine sidechain may be coupled with the epoxide without solvent at temperature in the range of

100-140° C, or in a high boiling inert solvent under reflux. Suitable solvents include toluene, *t*-butanol, *t*-amylalcohol, and methyl isobutylketone (MIBK). The resulting dibenzylformoterol (DBF) can be purified by column chromatography or by recrystallization as salt of an organic acid such as fumaric acid. It can also be used directly without purification for the de-benzylation reaction to form formoterol.

The dibenzylformoterol product is converted by catalytic hydrogenation in the presence of Pd catalyst such as Pd/C directly to optically pure formoterol. This reaction is preferably performed in an alcohol solvent such as methanol, ethanol, or 2-propanol at 40-60 psi of hydrogen pressure and 15-30°C for 2-15 hours. Although the formoterol product can be isolated as the fumaric acid salt by adding fumaric acid to the reaction solution after removal of the catalyst, a product of higher purity is obtained if the formoterol is recovered and purified as the tartrate salt and then converted to the fumarate. Alternatively, the hydrogenation (de-benzylation) can be performed in the presence of the appropriate organic acid in an alcohol solvent such as MeOH under similar conditions. The resulting formoterol acid salt is then isolated by crystallization by addition of a less polar co-solvent after filtration to remove the catalyst.

In a specific synthesis, the enantioselective reduction of FBK was done with 15 mol% AIBMe catalyst at -15°C. The bromohydrin was isolated after aqueous work-up with enantioselectivities ranging from 96-98% isomeric purity. The catalyst AIBMe was generated from aminoindanol and trimethylboroxine, followed by azeotropic removal of by-products using toluene. When the FBH was not purified by crystallization, 2-4% of minor isomer was carried through the synthetic sequence and caused lower yields in the last step. In those cases it was necessary to crystallize with *L*-tartaric acid 3-4 times at the last step in order to obtain the desired enantiomeric purity (>99.5%) of formoterol tartaric acid salt.

The chiral amine, 4-methoxy-α-methyl-*N*-(phenylmethyl)benzeneethanamine, was synthesized by a reductive amination procedure followed by a novel resolution procedure with mandelic acid. A concentration of 0.4M appears to be the optimal concentration and provides the product after 3-4 crystallizations in isomeric purities of 99.5-100%.

In Scheme 1, the aniline (FBH2) can be isolated as an intermediate and then transformed to the epoxide, but FBH2 has a tendency to oxidize when exposed to air. Therefore, there is an advantage to not isolating the FBH2 and instead hydrogenating in THF, which allows the formylation directly after filtration of the catalyst. The formamidobromohydrin (FBH3), as a highly crystalline compound, can be isolated from the reaction mixture without aqueous work-up. Using pure FBH3 and forming the epoxide provides crystalline FAE.

The epoxide opening reaction was conducted as neat reaction with the free amine to give the penultimate precursor dibenzylformoterol (DBF), as an oil with a purity of 85-87%. The reaction may also be run in toluene, 2-propanol or t-amyl alcohol.

Crude DBF can be converted to formoterol tartrate, which can be crystallized in high yields and high purities, and formoterol fumarate can be generated by salt switch from the purified formoterol tartrate. Although formoterol fumarate can also be crystallized directly from the hydrogenation mixture in high yields, subsequent crystallizations do not remove a major impurity.

In the enantioselective reduction of FBK to FBH, an AIBMe catalyst consistently gives slightly higher selectivities than the AIBH, but it is more difficult to prepare, more expensive and the optimum process temperature is lower than that of the AIBH process.

Epoxide formation from FBH3 and release of the free base from the benzylamine FBA-HA may be accomplished in separate steps. However, since both reactions require a base, a combination of both steps into a one pot procedure is possible and simplifies the process.

Experimental

2-Bromo-4'-benzyloxy-3'-nitroacetophenone (**FBK**)

A 5-liter flask was charged with 300 g (1.1 mol) of 4-benzyloxy-3-nitroacetophenone and 3 liters of acetonitrile. The mixture was heated to 50° C to form a clear solution, and 180 g of bromine (1.6 mol) was added in one portion. The reaction was stirred at 50° for 15-25 minutes, during which time the deep red color changed to pale orange and TLC (ethyl acetate/hexane 3:7) showed no remaining starting material. Without heating, 200 to 300 mL of acetonitrile, along with the byproduct hydrogen bromide, were distilled from the reaction under vacuum. During the course of the

distillation, the temperature dropped to about 15° and the product precipitated as a yellow solid. The reaction was stirred at 0-5° for two hours and the product filtered off and washed with acetonitrile. The resulting 2-bromo 4'-benzyloxy-3'nitroacetophenone was dried in vacuum to yield 242 g (63%) of off-white solid having a melting point of 136°C.

R-α-(bromomethyl)-4-phenylmethoxy-3-nitrobenzemethanol (**FBH**)

A 2-liter flask was charged with 2.5 g (17 mmol) of (1*R*,2*S*)-aminoindanol in 50 mL of THF under argon. While cooling to maintain a temperature below 25° C, 3.4 mL (34 mmol) of a 10 mol solution of borane methyl sulfide was added over a period of 5 minutes and the reaction stirred for ten minutes at 25° C to complete formation of the catalyst. To this catalyst solution the ketone and reducing agent were added simultaneously. From separate reservoirs were added (1) a solution of 120 g of FBK (0.34 mol) in 950 mL of THF and (2) 24 mL of 10 M borane-methyl sulfide. Addition was over a period of 3 hours at 25° C. The reaction was cooled on an ice bath and 100 mL of methanol was added over a period of 15 minutes. The reaction mixture was concentrated under vacuum to a volume of about 200 mL, and 650 mL of toluene was added to dissolve the residue. The solution was washed with 0.2 M sulfuric acid and then water. If desired the aminoindanol may be recovered from the aqueous acidic phase. The organic phase was dried over sodium sulfate, filtered and concentrated to a weight of 240-260 g. A total of 100 mL of heptane was added to the mixture with stirring at 50-60°, then cooled to 15-20° and filtered. Although the wet filter cake may be used in the next step without drying, the solid was dried under vacuum to give 95-108 g of (*R*)-FBH as an off white solid, melting point 68° C.

N-[5-(2-bromo-1-hydroxyethyl)-2-(phenylmethoxy)phenyl]formamide (**FBH3**)

A solution of 100 g (0.28 mol) of (*R*) FBH in 200 mL of THF and 200 mL of toluene was hydrogenated in a Parr hydrogenator in the presence of 1 g of platinum oxide catalyst at 45-50 psi for 7-13 hours until hydrogen uptake ceased. The reaction mixture was filtered through a bed of diatomaceous earth and a solution of 21.5 g (0.48 mol) of formic acid and 33 g (0.32 mol) of acetic anhydride, which had been pre-mixed, was added to the filtrate, which was maintained at 10-15° C by external cooling. The solution

was stirred for 20 minutes at 10-25° C and then concentrated to about 300 mL at 30° C. One hundred milliliters of toluene was added and the reaction was stirred at 15° C for 15 minutes. The resulting slurry was filtered to provide 75 g (76% yield of (*R*)-FBH3 melting point 130°C, isomeric purity 99-99.5%. The product is also sometimes referred to as 2-bromo-(4'-benzyloxy-3'-formamidophenyl)ethanol.

N-[5-oxiranyl-2-(phenylmethoxy)phenyl]formamide (FAE)

If it is desired to isolate the epoxide, as opposed to generating it in situ in the next step, the following procedure may be used: a solution of 28 g of the aniline FBH2 from platinum catalyzed reduction of the nitro compound FBH was treated with a mixture of 17 mL of the mixed formic/acetic anhydride, concentrated to dryness and dissolved in 200 mL of methanol. The methanolic solution was treated with 60 g of potassium carbonate, stirred at 30 minutes and concentrated under vacuum. The resulting residue was triturated with 400 mL of ethyl acetate, washed with water and brine, decolorized with carbon and dried over sodium sulfate. The drying agent and carbon were filtered off and the filtrate concentrated to give 19.3 g (86% yield) of the epoxide FAE as an oil, which solidified on standing (95.4% ee; m.p. 64-65° C).

(*R*,*R*)-Formoterol-*L*-tartrate

A 2-liter flask was charged with 70 g of (*R*)FBH3 (0.2 mol) 76.5 g of (*R*)-FBA-*L*-MA (0.19 mol), 70 g of potassium carbonate (0.5 mol), 400 mL of THF and 400 mL of methanol. The mixture was stirred at 25° for 1-2 hours and the reaction followed by HPLC. When the starting material (FBH3) content was below 2%, the mixture was concentrated to dryness at 30-35° C under vacuum. To the residue were added in order, first 600 mL of toluene and then 600 mL of water. The slurry was stirred 10 minutes, the phases were separated and the organic phase was dried over sodium sulfate. The toluene solution was filtered free of drying agent and concentrated to 110 g. The residue, which was shown by HPLC to be a 1:1 mixture of FAE and FBA, was stirred under argon atmosphere at 110-130° C for 24 hours. To the hot mixture was added 400 mL of ethanol to obtain a clear solution of (*R*,*R*)DBF. The solution was cooled to 25°, transferred to a Parr hydrogenator and hydrogenated at 45-50 psi in the presence of 10 g of 5% palladium

on carbon until hydrogen uptake was complete (3-4 hours). The mixture was filtered through a pad of diatomaceous earth washed with 200 mL of 2-propanol, and 28.5 g of *L*-tartaric acid (0.19 mol) and 60 mL of water was added to the filtrate. The mixture was heated to 60-80° C until a clear solution was formed. As soon as the clear solution formed, heating was discontinued and the mixture was cooled to 25°, at which temperature it was held for 1-2 hours. It was then further cooled to 0-5° for 1 hour and the product collected by filtration. The product was dried under vacuum to provide 70-80 g of (*R,R*) formoterol *L*-tartrate as an off white powder. The tartrate salt was dissolved in 700-800 mL of hot 80% aqueous 2-propanol, cooled as before and filtered again. The second recrystallization provided 60-70 g of (*R,R*) formoterol *L*-tartrate as an off-white powder having a melting point between 179 and 184 depending upon purity. A product having a chemical purity of 99.8% and an enantiomeric purity of 99.7% exhibits a melting point of 184° C.

(*R,R*) Formoterol Fumarate

A 2-liter flask was charged with 650 mL of water and 60 g of (*R,R*) formoterol *L*-tartrate (0.12 mol). The mixture was stirred and 52 g of sodium bicarbonate (0.6 mol) was added in small portions. The product was extracted into 250 mL of ethyl acetate, dried over sodium sulfate, filtered and concentrated to give 56 g of the free base. The free base was dissolved in 260 mL of isopropyl alcohol and 7.0 g of fumaric acid (60 mmol) was added followed by 130 mL of 2-propanol. The mixture was heated to 50-60° until a clear solution was formed and then cooled as above to crystallize the fumarate salt. The product was filtered and washed with 2-propanol to provide 44 g of (*R,R*) formoterol fumarate as white crystals having a chemical purity greater than 98% and an enantiomeric purity greater than 99.5%.

4-Methoxy-α-methyl-*N*-(phenlymethyl)benzene ethanamine *L*-mandelic acid salt (**FBA-*L*-MA**)

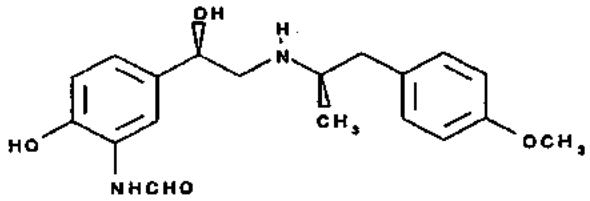
To 800 mL of methanol were added 328 g of 4-methoxy-phenylacetone (2 mol) and 214 g of *N*-benzylamine (2 mol). The imine formation was exothermic and the solution warmed to 45° C. After reaction was complete, the solution was hydrogenated at

50 psi for 6-8 hours in the presence of 3.3 g of 5% platinum on carbon catalyst. When the hydrogen uptake had stopped, the reaction was filtered through diatomaceous earth, and the filter cake was washed with 200 mL of methanol. The combined filtrates were placed in a 6-liter flask and diluted with 4.2 liters of methanol. Three hundred four grams of (*S*)-*L*-mandelic acid (2 mol) was added and the mixture heated with stirring to reflux to obtain a clear solution. The solution was cooled to room temperature, stirred at room temperature for two hours and the mandelic acid salt filtered off. The recrystallization was repeated three times to obtain 60-70 g of (*R*)-FBA-*L*-MA having isomeric purity greater than 99.8% and a melting point of 164°C.

Claims

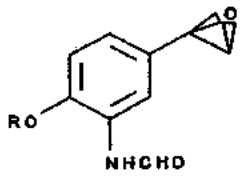
We claim:

1. A process for preparing a compound of formula

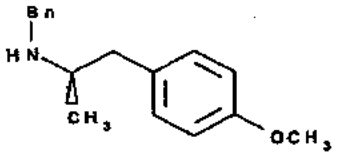


or a salt thereof, comprising the sequential steps of:

(a) reacting a compound of formula



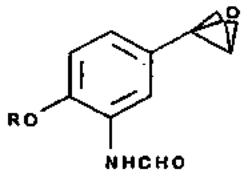
with a compound of formula



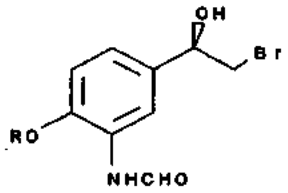
wherein R is benzyl or substituted benzyl, and

(b) reducing with a source of hydrogen in the presence of a noble metal catalyst.

2. A process according to claim 1 wherein said compound of formula

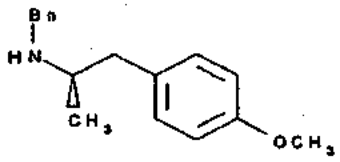


is produced *in situ* from the corresponding bromohydrin



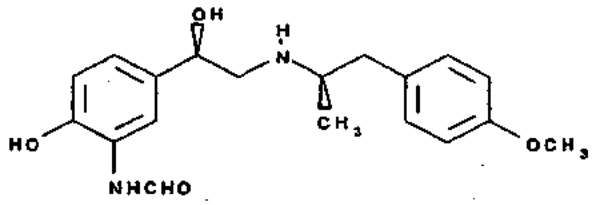
by treatment with a base.

3. A process according to claim 1 wherein said compound of formula



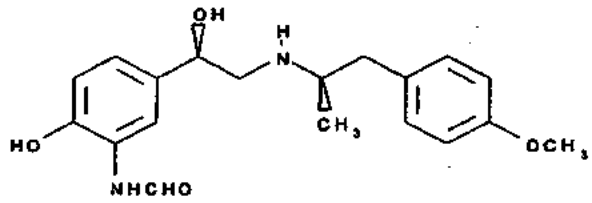
is produced *in situ* from a corresponding salt by treatment with a base.

4. A process according to claim 1 wherein said compound of formula



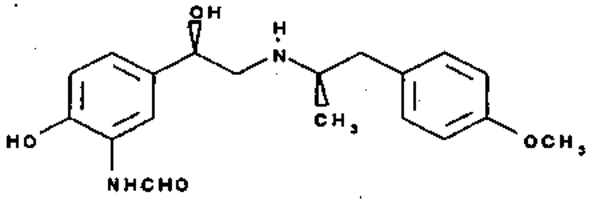
is of the *R,R* configuration.

5. A process according to claim 1 wherein said compound of formula



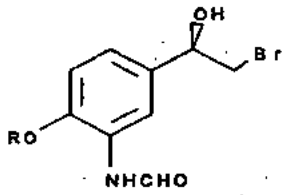
is of the *S,S* configuration.

6. A process for preparing a compound of formula

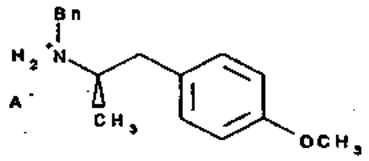


or salt thereof, comprising the sequential steps of:

(a) combining a compound of formula



a compound of formula



wherein R is benzyl or substituted benzyl and A^- is an acid counter ion, and at least one equivalent of a base to produce a mixture comprising an epoxide and a free base;

(b) heating said mixture of an epoxide and a free base at a temperature sufficient to cause a reaction to produce a benzyl-protected aminoalcohol; and

(c) reducing said benzyl-protected aminoalcohol with hydrogen gas in the presence of a noble metal catalyst.

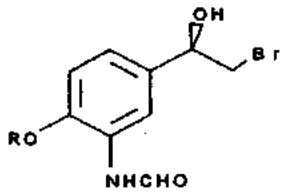
7. A process according to any of claims 1, 2, 3, 4 or 6 wherein said noble metal catalyst is palladium.

8. A process according to any of claims 2, 3, or 6 wherein said base is an alkali metal carbonate.

9. A process according to any of claims 1 to 6 wherein said salt is a tartrate salt.

10. A process according to any of claims 1 to 6 wherein said salt is a fumarate salt.

11. A process for synthesizing a compound of formula



wherein R is benzyl or substituted benzyl, comprising the sequential steps of:

(a) reducing 2-bromo-4'-RO-3'-nitroacetophenone with about one equivalent of borane-methyl sulfide in the presence of a catalytic amount of a single enantiomer of an oxazaborolidine reagent to produce substantially enantiomerically pure α-(bromomethyl)-4-RO-3-nitrobenzenemethanol

(b) reducing said α-(bromomethyl)-4-RO-3-nitrobenzenemethanol with hydrogen in the presence of a noble metal catalyst to produce an aniline; and

(c) formylating said aniline with formic acid and acetic anhydride.

12. A process according to claim 11 wherein said oxazaborolidine reagent is generated *in situ* from (1R,2S)-1-amino-2-indanol and two equivalents of borane-methyl sulfide.

13. A process according to claim 11 wherein said noble metal catalyst is platinum and said oxazaborolidine is derived from *cis* 1-amino-2-indanol.

14. A process according to claim 11 wherein steps (b) and (c) are carried out without isolation of said aniline.

15. A process according to claim 11 wherein said single enantiomer of an oxazaborolidine is derived from (1*R*,2*S*)-1-amino-2-indanol, and said substantially enantiomerically pure α-(bromomethyl)-4-RO-3-nitrobenzenemethanol is *R*-α-(bromomethyl)-4-phenylmethoxy-3-nitrobenzenemethanol.

16. A process for preparing a substantially enantiomerically pure salt of 4-methoxy-α-methyl-*N*-(phenylmethyl)benzeneethanamine comprising:

(a) reducing 4-methoxyphenyl acetone with hydrogen in the presence of a platinum catalyst and about 1 equivalent of benzylamine in methanol;

(b) adding about one equivalent of a single enantiomer of mandelic acid;

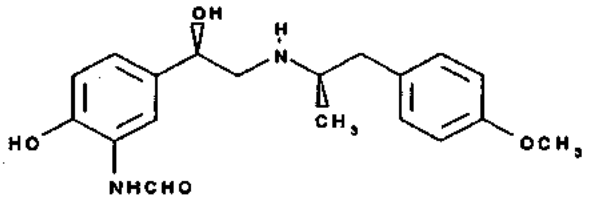
(c) heating to obtain a methanolic solution;

(d) cooling to obtain a crystalline solid phase; and

(e) recovering said crystalline solid from said methanolic solution.

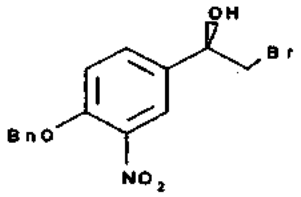
17. A process according to claim 16 comprising the additional step of converting said crystalline solid from step (e) to a salt of an acid other than mandelic acid.

18. A process for preparing a compound of formula



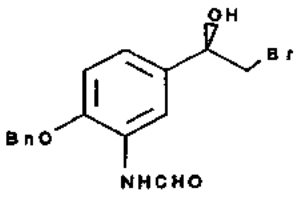
comprising the sequential steps of:

(a) reducing 2-bromo-4'-benzyloxy-3'-nitroacetophenone with about one equivalent of borane-methyl sulfide in the presence of a catalytic amount of a single enantiomer of an oxazaborolidine derived from *cis* 1-amino-2-indanol to produce substantially enantiomerically pure α-(bromomethyl)-4-phenylmethoxy-3-nitrobenzenemethanol:

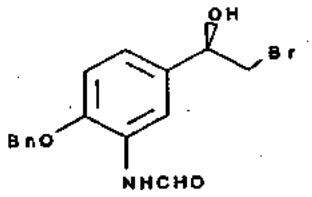


(b) reducing said α-(bromomethyl)-4-phenylmethoxy-3-nitrobenzenemethanol with a source of hydrogen in the presence of a noble metal catalyst to produce an aniline;

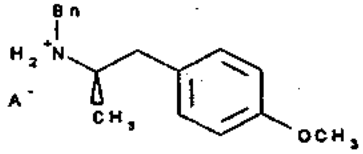
(c) formylating said aniline with formic acid and acetic anhydride to produce a compound of formula



(d) combining said compound of formula



a compound of formula

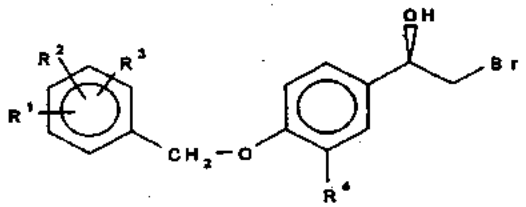


wherein A^- is an acid counter ion, and at least one equivalent of a base to produce a mixture comprising an epoxide and a free base;

(e) heating said mixture of an epoxide and a free base at a temperature sufficient to cause a reaction to produce a benzyl-protected aminoalcohol; and

(f) reducing said benzyl-protected aminoalcohol with hydrogen gas in the presence of a noble metal catalyst.

19. A compound of formula:



wherein each of R^1, R^2 and R^3 is independently chosen from the group consisting of hydrogen, C_1 to C_6-alkyl, C_1 to C_6-alkoxyl, and halogen and R^4 is $-NO_2$, $-NH_2$ or -NHCHO.

20. A compound according to claim 19 wherein all of R^1, R^2 and R^3 are hydrogen.

21. The *L*-(+)-tartrate salt of R,R-formoterol.

22. The *D*-(-)-tartrate salt of *S,S*-formoterol.

INTERNATIONAL SEARCH REPORT

Inter nal Application No
PCT/US 97/20472

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07C231/18 C07C233/43 C07C213/02 C07C217/86 C07C233/25
C07C205/37

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07C

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	ROBERT HETT ET AL.: "Enantio- and Diastereoselective Synthesis of all Four Stereoisomers of Formotero " TETRAHEDRON LETTERS, vol. 38, no. 7, February 1997, OXFORD GB, pages 1125-1128, XP002057058 see page 1126, scheme 2; page 1127 --- -/--	16,19-22

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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"P" document published prior to the international filing date but later than the priority date claimed

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1

Date of the actual completion of the international search	Date of mailing of the international search report
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Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Zervas, B

INTERNATIONAL SEARCH REPORT

Inter nal Application No
PCT/US 97/20472

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	CHEMICAL ABSTRACTS, vol. 127, no. 12, 22 September 1997 Columbus, Ohio, US; abstract no. 161695m, SHIRO MIYOSHI ET AL.: "Preparation of tricyclic compounds as beta-3 adrenaline receptor antagonists." page 654; column 1; XP002057061 see abstract; CAS-Registry Nos.: 193761-53-4 and 188690-82-6 & WO 97 25311 A (ASAHI KASEI) 17 July 1997 ---	19
X	K. MURASE ET AL.: "Absolute Configurations of Four Isomers of 3-Formamido-4-hydroxy-alpha''N-(p-methoxy-alpha-methylphenethyl)amino!methyl!benzyl Alcohol, a Potent beta-Adrenoreceptor Stimulant" CHEMICAL AND PHARMACEUTICAL BULLETIN, vol. 26, no. 4, April 1978, TOKYO JP, pages 1123-1125, XP002057059 cited in the application see page 1123, last paragraph; page 1126 table 1; page 1127, line 20 from the bottom - page 1128, line 14	21,22
A	see page 1127 - page 1129 ---	1-20
A	JAN TROFAST ET AL.: "Steric Aspects of Agonism and Antagonism at beta-Adrenoreceptors: Synthesis of and Pharmacological Experiments With the Enantiomers of Formoterol and Their Diastereomers " CHIRALITY, vol. 3, no. 6, 1991, pages 443-450, XP002057060 cited in the application see page 444, column 1, line 7 - page 445, column 2, line 54 ---	1-22
A	WO 92 05147 A (ASTRA) 2 April 1992 see the whole document -----	1-22

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inter nal Application No
PCT/US 97/20472

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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		AU 652386 B	25-08-94
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		BG 97576 A	31-03-94
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		EP 0550612 A	14-07-93
		ES 2084831 T	16-05-96
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		PL 166434 B	31-05-95
		RU 2079486 C	20-05-97
		SK 22793 A	07-07-93
		US 5434304 A	18-07-95

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(74) Agents: **MINOJA, Fabrizio** et al.; Bianchetti Bracco Minoja S.r.l., Via Rossini, 8, I-20122 Milano (IT).

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WO 01/78693 A2

(54) Title: PHARMACEUTICAL FORMULATIONS FOR DRY POWDER INHALERS IN THE FORM OF HARD-PELLETS

(57) Abstract: The invention provides a formulation to be administered as dry powder for inhalation suitable for efficacious delivery of active ingredients into the low respiratory tract of patients suffering of pulmonary diseases such as asthma. In particular, the invention provides a formulation to be administered as dry powder for inhalation freely flowable, which can be produced in a simple way, physically and chemically stable and able of delivering either accurate doses and high fine particle fraction of low strength active ingredients by using a high- or medium resistance device.

"PHARMACEUTICAL FORMULATIONS FOR DRY POWDER INHALERS IN THE FORM OF HARD-PELLETS"

PRIOR ART

Inhalation anti-asthmatics are widely used in the treatment of reversible airway obstruction, inflammation and hyperresponsiveness.

Presently, the most widely used systems for inhalation therapy are the pressurised metered dose inhalers (MDIs) which use a propellant to expel droplets containing the pharmaceutical product to the respiratory tract.

However, despite their practicality and popularity, MDIs have some disadvantages:

i) droplets leaving the actuator orifice could be large or have an extremely high velocity resulting in extensive oropharyngeal deposition to the detriment of the dose which penetrates into the lungs;
the amount of drug which penetrates the bronchial tree may be further reduced by poor inhalation technique, due to the common difficulty of the patient to synchronise actuation form the device with inspiration;

ii) chlorofluorocarbons (CFCs), such as freons contained as propellants in MDIs, are disadvantageous on environmental grounds as they have a proven damaging effect on the atmospheric ozone layer.

Dry powder inhalers (DPIs) constitute a valid alternative to MDIs for the administration of drugs to airways. The main advantages of DPIs are:

i) being breath-actuated delivery systems, they do not require co-ordination of actuation since release of the drug is dependent on the patient own inhalation;

ii) they do not contain propellants acting as environmental hazards;

iii) the velocity of the delivered particles is the same or lower than that of the flow of inspired air, so making them more prone to follow the air

flow than the faster moving MDI particles, thereby reducing upper respiratory tract deposition.

DPIs can be divided into two basic types:

i) single dose inhalers, for the administration of pre-subdivided single doses of the active compound;

ii) multidose dry powder inhalers (MDPIs), either with pre-subdivided single doses or pre-loaded with quantities of active ingredient sufficient for multiple doses; each dose is created by a metering unit within the inhaler.

On the basis of the required inspiratory flow rates (l/min) which in turn are strictly depending on their design and mechanical features, DPI's are also divided in:

i) low-resistance devices (> 90 l/min);

ii) medium-resistance devices (about 60 l/min);

iii) high-resistance devices (about 30 l/min).

The reported flow rates refer to the pressure drop of 4 KPa (KiloPascal) in accordance to the European Pharmacopoeia (Eur Ph).

Drugs intended for inhalation as dry powders should be used in the form of micronised powder so they are characterised by particles of few microns (μm) particle size. Said size is quantified by measuring a characteristic equivalent sphere diameter, known as aerodynamic diameter, which indicates the capability of the particles of being transported suspended in an air stream. Hereinafter, we consider as particle size the mass median aerodynamic diameter (MMAD) which corresponds to the aerodynamic diameter of 50 percent by weight of the particles. Respirable particles are generally considered to be those with diameters from 0.5 to 6 μm, as they are able of penetrating into the lower lungs, i.e. the bronchiolar and alveolar sites, where absorption takes place. Larger particles are mostly deposited in the oropharyngeal cavity so they

cannot reach said sites, whereas the smaller ones are exhaled.

Although micronisation of the active drug is essential for deposition into the lower lungs during inhalation, it is also known that the finer are the particles, the stronger are the cohesion forces. Strong cohesion forces hinder the handling of the powder during the manufacturing process (pouring, filling). Moreover they reduce the flowability of the particles while favouring the agglomeration and/or adhesion thereof to the walls. In multidose DPI's, said phenomena impair the loading of the powder from the reservoir to the aerosolization chamber, so giving rise to handling and metering accuracy problems.

Poor flowability is also detrimental to the respirable fraction of the delivered dose being the active particles unable to leave the inhaler and remaining adhered to the interior of the inhaler or leaving the inhaler as large agglomerates; agglomerated particles, in turn, cannot reach the bronchiolar and alveolar sites of the lungs. The uncertainty as to the extent of agglomeration of the particles between each actuation of the inhaler and also between inhalers and different batches of particles, leads to poor dose reproducibility as well.

In the prior art, one possible method of improving the flowing properties of these powders is to agglomerate, in a controlled manner, the micronised particles to form spheres of relatively high density and compactness. The process is termed spheronisation while the round particles formed are called pellets. When, before spheronisation, the active ingredient is mixed with a plurality of fine particles of one or more excipient, the resulting product has been termed as soft pellets.

Otherwise powders for inhalation could be formulated by mixing the micronised drug with a carrier material (generally lactose, preferably α-lactose monohydrate) consisting of coarser particles to give rise to so-called 'ordered mixtures'.

However, either ordered mixtures and pellets should be able to effectively release the drug particles during inhalation, in order to allow them to reach the target site into the lungs.

At this regard, it is well known that the interparticle forces which occur between the two ingredients in the ordered mixtures may turn out to be too high thus preventing the separation of the micronised drug particles from the surface of the coarse carrier ones during inhalation. The surface of the carrier particles is, indeed, not smooth but has asperities and clefts, which are high energy sites on which the active particles are preferably attracted to and adhere more strongly. In addition, ordered mixtures consisting of low strength active ingredients could also face problems of uniformity of distribution and hence of metering accurate doses.

On the other hand, soft pellets may reach a so high internal coherence as to compromise their breaking up into the small particles during inhalation; such drawback could be regarded as a particular critical step when high-resistance dry powder inhalers are used. With said inhalers, less energy is indeed available for breaking up the pellets into the small primary particles of the active ingredient. The soft pellets may also face some problems of handling during filling and use of the inhalers.

In consideration of all problems and disadvantages outlined, it would be highly advantageous to provide a formulation aimed at delivering low strength active ingredients after inhalation with a DPI device, preferably a high-resistance one and exhibiting: *i)* good uniformity of distribution of the active ingredient; *ii)* small drug dosage variation (in other words, adequate accuracy of the delivered doses); *iii)* good flowability; *iv)* adequate physical stability in the device before use; *v)* good performance in terms of emitted dose and fine particle fraction (respirable fraction).

Another requirement for an acceptable formulation is its adequate shelf-

life.

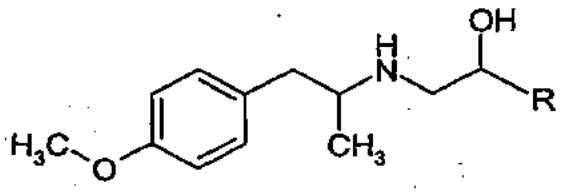
It is known that the chemical compounds can undergo chemico-physical alterations such as amorphisation, when subjected to mechanical stresses. Amorphous or partially amorphous materials, in turn, absorb water in larger amounts than crystalline ones (Hancock et al. *J. Pharm. Sci.* 1997, 86, 1-12) so formulations containing active ingredients, whose chemical stability is particularly sensitive to the humidity content, will benefit during their preparation by the use of as low as possible energy step treatment.

Therefore, it would be highly advantageous to provide a process for preparing said formulation in which a low energy step is envisioned during the incorporation of the active ingredient to the mixture in such a way to ensure adequate shelf life of the formulation suitable for commercial distribution, storage and use.

OBJECT OF THE INVENTION

It is an object of the invention to provide a formulation to be administered as dry powder for inhalation suitable for efficacious delivery of low strength active ingredients into the low respiratory tract of patients suffering of pulmonary diseases such as asthma. In particular , it is an object of the invention to provide a formulation to be administered as dry powder for inhalation freely flowable, which can be produced in a simple way, physically and chemically stable and able of delivering either accurate doses and high fine particle fraction of the following active ingredients:

long acting β2-agonists belonging to the formula sketched below



wherein R is preferably 1-formylamino-2-hydroxy- phen-5-yl (formoterol) or 8-hydroxy-2(1H)-quinolinon-5-yl (TA 2005) and its stereoisomers and their salts;

a corticosteroid selected from budesonide and its epimers, preferably its 22R epimer;

their mixture and their combination with other active ingredients such as for example beclometasone dipropionate

According to a first embodiment of the invention there is provided a powdery formulation comprising: i) a fraction of fine particle size constituted of a mixture of a physiologically acceptable excipient and magnesium stearate, the mixture having a mean particle size of less than 35 μm; ii) a fraction of coarse particles constituted of a physiologically acceptable carrier having a particle size of at least 90 μm , said mixture being composed of 90 to 99 percent by weight of the particles of excipient and 1 to 10 percent by weight of magnesium stearate and the ratio between the fine excipient particles and the coarse carrier particles being between 1:99 and 40:60 percent by weight; and the said mixture having been further mixed with the active ingredients mentioned above in micronised form or combination thereof.

In a preferred embodiment of the invention, the magnesium stearate particles partially coat the surface of either the excipient particles and the coarse carrier particles. Said feature could be achieved by exploiting the peculiar film forming properties of such water-insoluble additive, as also reported in the co-pending application WO 00/53157 of Chiesi. The coating can be established by scanning electron microscope and the degree of coating can be evaluated by means of the image analysis method.

It has been found indeed that the single features of adding either of a fraction with a fine particle size of the physiologically acceptable excipient or magnesium stearate is not enough for guaranteeing high fine particle doses of

the aforementioned active ingredients upon inhalation in particular by a high-resistance device. For significantly improving the aerosol performances, it is necessary that both said excipient with a suitable particle size fraction should be present in the formulation and that the magnesium stearate particles should, at least partially, coat the surface of either the excipient and the coarse carrier particles.

Moreover, it has been found that the particle size of the physiologically acceptable excipient, the main component of the mixture i) is of particular importance and that the best results in terms of aerosol performances are achieved when its particle size is less than 35 μm, preferably less than 30, more preferably less than 20, even more preferably less than 15 μm.

In a more preferred embodiment , the formulation of the invention is in the form of 'hard pellets' and they are obtained by subjecting the mixture to a spheronisation process.

By the term of 'hard pellets' we mean spherical or semi-spherical units whose core is made of coarse particles. The term has been coined for distinguishing the formulation of the invention from the soft pellets of the prior art which are constituted of only microfine particles (WO 95/24889, GB 1520247, WO 98/31353).

By the term 'spheronisation' we mean the process of rounding off of the particles which occurs during the treatment.

In an even more preferred embodiment of the invention, the coarse carrier particles have a particle size of at least 175 μm as well as a highly fissured surface. A carrier of the above mentioned particle size is particularly advantageous when the fine excipient particles constitute at least the 10 percent by weight of the final formulation.

It has been found that, whereas formulations containing conventional carriers and having fine particle contents of above 10% tend to have poor flow

properties, the formulations according to the invention have adequate flow properties even at fines contents (that is contents of active particles and of fine excipient particles) of up to 40 percent by weight.

The prior art discloses several approaches for improving the flowability properties and the respiratory performances of low strength active ingredients. WO 98/31351 claims a dry powder composition comprising formoterol and a carrier substance, both of which are in finely divided form wherein the formulation has a poured bulk density of from 0.28 to 0.38 g/ml. Said formulation is in the form of soft pellet and does not contain any additive.

EP 441740 claims a process and apparatus thereof for agglomerating and metering non-flowable powders preferably constituted of micronised formoterol fumarate and fine particles of lactose (soft pellets).

Furthermore several methods of the prior art were generally addressed at improving the flowability of powders for inhalation and/or reducing the adhesion between the drug particles and the carrier particles.

- GB 1,242,211, GB 1,381,872 and GB 1,571,629 disclose pharmaceutical powders for the inhalatory use in which the micronised drug (0.01 - 10 μm) is respectively mixed with carrier particles of sizes 30 to 80 μm, 80 to 150 μm, and less than 400 μm wherein at least 50% by weight of which is above 30 μm.
- WO 87/05213 describes a carrier, comprising a conglomerate of a solid water-soluble carrier and a lubricant, preferably 1% magnesium stearate, for improving the technological properties of the powder in such a way as to remedy to the reproducibility problems encountered after the repeated use of a high resistance inhaler device.
- WO 96/02231 claims a mixture characterised in that the micronised active compound is mixed with rough carrier particles having a particle size of 400 μm to 1000 μm. According to a preferred embodiment of the

invention, the components are mixed until the carrier crystals are coated with the fine particles (max. for 45 minutes). No example either with auxiliary additives and/or with low strength active ingredient is reported.

- EP 0,663,815 claims the addition of finer particles (< 10 μm) to coarser carrier particles (> 20 μm) for controlling and optimising the amount of delivered drug during the aerosolisation phase.
- WO 95/11666 describes a process for modifying the surface properties of the carrier particles by dislodging any asperities in the form of small grains without substantially changing the size of the particles. Said preliminary handling of the carrier causes the micronised drug particles to be subjected to weaker interparticle adhesion forces.
- In WO 96/23485, carrier particles are mixed with an anti-adherent or anti-friction material consisting of one or more compounds selected from amino acids (preferably leucine); phospholipids or surfactants; the amount of additive and the process of mixing are preferably chosen in such a way as to not give rise to a real coating. It appears that the presence of a discontinuous covering as opposed to a "coating" is an important and advantageous feature. The carrier particles blended with the additive are preferably subjected to the process disclosed in WO 95/11666.
- Kassem (London University Thesis 1990) disclosed the use of relatively high amount of magnesium stearate (1.5%) for increasing the 'respirable' fraction. However, the reported amount is too great and reduces the mechanical stability of the mixture before use.
- WO 00/28979 is addressed to the use of small amounts of magnesium stearate as additive for improving the stability to the humidity of dry powder formulations for inhalation.
- WO 00/33789 refers to an excipient powder for inhalable drugs

comprising a coarse first fraction (with at least 80% by weight having a particle size of at least 10 μm), a fine second fraction (with at least 90% by weight having a particle size of no more than 10 μm) and a ternary agent which is preferably a water-soluble surface-active agent with a preference for leucine.

In none of aforementioned documents the features of the formulation of the invention are disclosed and none of the teaching therein disclosed contributes to the solution of the problem according to the invention. All the attempts of obtaining stable powder formulations of low strength active ingredients endowed of good flowability and high fine particle fraction according to some of the teaching of the prior art, for example by preparation of ordered mixture, addition of a fine fraction, mere addition of additives, were indeed unsuccessful as demonstrated by the examples reported below. In particular, in the prior art it often occurred that the solutions proposed for a technical problem (i.e. improving dispersion of the drug particles) was detrimental to the solution of another one (i.e. improving flowability, mechanical stability) or *vice versa*.

On the contrary, the formulation of the invention shows either excellent rheological properties and physical stability and good performances in terms of fine particle fraction , preferably more than 40%. The cohesiveness between the partners has been indeed adjusted in such a way as to give sufficient adhesion force to hold the active particles to the surface of the carrier particles during manufacturing of the dry powder and in the delivery device before use, but to allow the effective dispersion of the active particles in the respiratory tract even in the presence of a poor turbulence as that created by high-resistance devices.

Contrary to what has been stated in the prior art (EP 441740), in the formulation of the invention the presence of an additive with lubricant

properties such as magnesium stearate, in a small amount, does not compromise the integrity of the pellets before use.

According to a second embodiment of the invention there are also provided processes for making the formulation of the invention, in such a way as that the magnesium stearate particles partially coat the surface of either the excipient particles and the coarse carrier particles with a degree of coating that can vary depending on the amount and particle size of the fine fraction and, in any case, is of at least 5%, preferably at least 15%.

According to a particular embodiment, there is provided a process including the steps of: i) co-micronising the excipient particles and the magnesium stearate particles such that to reduce their particle size below 35 μm, and contemporaneously making the additive particles partially coating the surface of the excipient particles; ii) spheronising by mixing the resulting mixture with the coarse carrier particles such that mixture particles adhere to the surface of the coarse carrier particles; iii) adding by mixing the active particles to the spheronised particles.

According to a further particular embodiment of the invention there is provided another process, said process including the steps of: i) mixing the excipient particles in the micronised form and the magnesium stearate particles in such a way as to make the additive particles partially coating the surface of the excipient particles; ii) spheronising by mixing the resulting mixture with the coarse carrier particles such that mixture particles adhere to the surface of the coarse carrier particles; iii) adding by mixing the active particles to the spheronised particles.

When the coarse carrier particles have a particle size of at least 175 μm and in a preferred embodiment a highly fissured surface, the formulation of the invention could also be prepared by: i) co-mixing the coarse carrier particles, magnesium stearate and the fine excipient particles for not less than two hours;

ii) adding by mixing the active particles to the mixture.

It has been indeed found that the particles need to be processed for at least two hours in order to either have a good fine particle fraction (respirable fraction) and no problem of sticking during the preparation.

In all process claimed, contrary to the prior art (WO 98/31351), the active ingredient is uniformly incorporated in the mixture by simple mixing so avoiding any potential mechanical stress which may disturb the cristallinity of its particles.

Advantageously, the coarse and fine carrier particles may be constituted of any pharmacologically acceptable inert material or combination thereof; preferred carriers are those made of crystalline sugars, in particular lactose; the most preferred are those made of α-lactose monohydrate. Advantageously the diameter of the coarse carrier particles is at least 100μm, more advantageously at least 145 μm, preferably at least 175 μm, more preferably between 175 and 400 μm, even more preferably between 210 and 355 μm.

When the diameter of the coarse carrier particles is at least 175 μm, the carrier particles have preferably a relatively highly fissured surface, that is, on which there are clefts and valleys and other recessed regions, referred to herein collectively as fissures.

The expression "relatively highly fissured" is used herein to mean that the ratio of a theoretical envelope volume of the particles, as calculated from the envelope of the particles, to the actual volume of the particles, that is, the volume defined by the actual surface of the particles (that ratio hereafter being referred to as the "fissure index"), is at least 1.25. The theoretical envelope volume may be determined optically, for example, by examining a small sample of the particles using an electron microscope. The theoretical envelope volume of the particles may be estimated via the following method. An electron micrograph of the sample may be divided into a number of grid squares of

approximately equal populations, each containing a representative sample of the particles. The population of one or more grids may then be examined and the envelope encompassing each of the particles determined visually as follows. Measure the Feret's diameter for each of the particles with respect to a fixed axis . The Feret's diameter for particles within a grid is measured relative to a fixed axis of the image, typically at least ten particles are measured for their Feret's diameter. Feret's diameter is defined as the length of the projection of a particle along a given reference line as the distance between the extreme left and right tangents that are perpendicular to the reference line. A mean Feret's diameter is derived. A theoretical mean envelope volume may then be calculated from this mean diameter to give a representative value for all the grid squares and thus the whole sample. Division of that value by the number of particles gives the mean value per particle. The actual volume of the particles may then be calculated as follows. The mean mass of a particle is calculated as follows. Take a sample of approximately 50 mg, record the precise weight to 0.1 mg . Then by optical microscopy determine the precise number of particles in that sample. The mean mass of one particle can then be determined. Repeat this five times to obtain a mean value of this mean.

Weigh out accurately a fixed mass of particles (typically 50 g), calculate the number of particles within this mass using the above mean mass value of one particle. Immerse the sample of particles in a liquid in which the particles are insoluble and, after agitation to remove trapped air, measuring the amount of liquid displaced. From this calculate the mean actual volume of one particle.

The fissure index is advantageously not less than 1.5, and is, for example, 2 or more.

An alternative method of determining whether carrier particles have appropriate characteristics is to determine the rugosity coefficient. The "rugosity coefficient" is used to mean the ratio of the perimeter of a particle

outline to the perimeter of the "convex hull". This measure has been used to express the lack of smoothness in the particle outline. The "convex hull" is defined as a minimum enveloping boundary fitted to a particle outline that is nowhere concave. (See "The Shape of Powder-Particle Outlines" A.E. Hawkins, Wiley 1993). The "rugosity coefficient"may be calculated optically as follows. A sample of particles should be identified from an electron micrograph as identified above. For each particle the perimeter of the particle outline and the associated perimeter of the "convex hull" is measured to provide the "rugosity coefficient". This should be repeated for at least ten particles to obtain a mean value. The mean "rugosity coefficient" is at least 1.25.

The additive is magnesium stearate. Advantageously, the amount of magnesium stearate in the final formulation is comprised between at least 0.02 and not more than 1.5 percent by weight (which equates to 1.5 g per 100 g of final formulation), preferably at least 0.05 and not more than 1.0 percent by weight, more preferably between 0.1 and not more than 0.6 percent by weight, even more preferably between 0.2 and 0.4 percent by weight.

According to the invention the fraction with a fine particle size is composed of 90 to 99 percent by weight of the physiologically acceptable excipient and 1 to 10 percent by weight of magnesium stearate and the ratio between the fraction of fine particle size and the fraction of coarse carrier particle is comprised between 1:99 and 40:60 percent by weight, preferably between 5:95 and 30:70 percent by weight, even more preferably between 10:90 and 20:80 percent by weight.

In a preferred embodiment of the invention, the fraction with a fine particle size is composed of 98 percent by weight of α-lactose monohydrate and 2 percent by weight of magnesium stearate and the ratio between the fraction with a fine particle size and the coarse fraction made of α-lactose

monohydrate particles is 10:90 percent by weight, respectively.

Advantageously the formulation of the invention has an apparent density before settling of at least 0.5 g/ml, preferably from 0.6 to 0.7 g/ml and a Carr index of less than 25, preferably less than 15.

In one of the embodiment of the invention, the excipient particles and magnesium stearate particles are co-micronised by milling, advantageously in a ball mill for at least two hours, preferably until the final particle size of the mixture is less than 35 μm, preferably less than 30 μm, more preferably less than 15 μm. In a more preferred embodiment of the invention the particles are co-micronised by using a jet mill.

Alternatively, the mixture of the excipient particles with a starting particle size less than 35 μm, preferably less than 30 μm, more preferably less than 15 μm, with the magnesium stearate particles will be prepared by mixing the components in a high-energy mixer for at least 30 minutes, preferably for at least one hour, more preferably for at least two hours.

In a general way, the person skilled in the art will select the most proper size of the fine excipient particles either by sieving or by suitably adjusting the time of co-milling.

The spheronisation step will be carried out by mixing the coarse carrier particles and the fine particle fraction in a suitable mixer, e.g. tumbler mixers such as Turbula, rotary mixers or instant mixer such as Diosna for at least 5 minutes, preferably for at least 30 minutes, more preferably for at least two hours, even more preferably for four hours. In a general way, the person skilled in the art will adjust the time of mixing and the speed of rotation of the mixer to obtain homogenous mixture.

When the formulation of the invention is prepared by co-mixing the coarse carrier particles, magnesium stearate and the fine excipient particles all together, the process is advantageously carried out in a suitable mixer,

preferably in a Turbula mixer for at least two hours, preferably for at least four hours.

The ratio between the spheronised carrier and the drug (the active ingredient) will depend on the type of inhaler device used and the required dose.

The mixture of the spheronised carrier with the active particles will be prepared by mixing the components in suitable mixers like those reported above.

Advantageously, at least 90% of the particles of the drug have a particle size less than 10 μm, preferably less than 6 μm.

The process of the invention is illustrated by the following examples.

Example 1 -Hard-pellet formulation containing coarse lactose (CapsuLac 212-355 μm), a micronized pre-blend Lactose/Magnesium Stearate mixture obtained by jet milling and formoterol fumarate as active ingredient

a) Preparation of the formulation

α-Lactose monohydrate SpheroLac 100 (Meggle EP D30) with a starting particle size of 50 to 400 μm (d(v, 0.5) of about 170 μm) and magnesium stearate with a starting particle size of 3 to 35 μm (d(v, 0.5) of about 10 μm) in the ratio 98: 2 percent by weight were co-milled in a jet mill apparatus. At the end of the treatment, a significant reduction of the particle size was observed (blend A).

85 percent by weight of α-lactose monohydrate CapsuLac (212 - 355 μm) was placed in a 240 ml stainless steel container, then 15 percent by weight of blend A was added. The blend was mixed in a Turbula mixer for 2 hours at 42 r.p.m (blend B).

Micronised formoterol fumarate was added to the blend B and mixed in a Turbula mixer for 10 mins at 42 r.p.m. to obtain a ratio of 12 μg of active to 20 mg of carrier; the amount of magnesium stearate in the final formulation is 0.3

percent by weight. The final formulation (hard pellet formulation) was left to stand for 10 mins then transferred to amber glass jar.

b) Characterisation of the micronised mixture (blend A)

The micronized mixture (blend A) was characterised by particle size analysis (Malvern analysis), water contact angle and degree of molecular surface coating calculated according to Cassie *et al.* in Transaction of the Faraday Society 40; 546,1944.

The results obtained are reported in Table 1.

Table 1. Micronised mixture (blend A)

Particle size distribution (μm)	Malvern
d (v, 0.1)	1.58
d (v, 0.5)	4.19
d (v, 0.9)	9.64
Water contact angle	40°
Degree of coating	15% *

* α-Lactose monohydrate water contact angle 12°; magnesium stearate water contact angle 118°

c) Chemical and technological characterisation of the hard-pellet formulation

The formulation mixture was characterised by its density/flowability parameters and uniformity of distribution of the active ingredient.

The apparent volume and apparent density were tested according to the method described in the European Pharmacopoeia (Eur. Ph.).

Powder mixtures (100 g) were poured into a glass graduated cylinder and the unsettled apparent volume V_0 is read; the apparent density before settling (*dv*) was calculated dividing the weight of the sample by the volume V_0. After 1250 taps with the described apparatus, the apparent

volume after settling (V_{1250}) is read and the apparent density after settling *(ds)* was calculated.

The flowability properties were tested according to the method described in the Eur. Ph.

Powder mixtures (about 110 g) were poured into a dry funnel equipped with an orifice of suitable diameter that is blocked by suitable mean. The bottom opening of the funnel is unblocked and the time needed for the entire sample to flow out of the funnel recorded. The flowability is expressed in seconds and tenths of seconds related to 100g of sample.

The flowability was also evaluated from the Carr's index calculated according to the following formula:

$$\text{Carr's index (\%)} = \frac{ds - dv}{ds} \times 100$$

A Carr index of less than 25 is usually considered indicative of good flowability characteristics.

The uniformity of distribution of the active ingredient was evaluated by withdrawing 10 samples, each equivalent to about a single dose, from different parts of the blend. The amount of active ingredient of each sample was determined by High-Performance Liquid Chromatography (HPLC).

The results are reported in Table 2.

Table 2. Chemical and Technological Parameters of the hard pellet formulation

Apparent volume/density	
App. volume (V_0) before settling	156 ml
App. density (d_v) before settling	0.64 g/ml
App. volume (V_{1250}) after settling	138 ml
App. density (d_s) after settling	0.73 g/ml
Flowability	
Flow rate through 4 mm Ø	152 s/100g
Carr Index	12
Uniformity of distribution of active ingredient	
Mean value	
RSD	12.1 µg
	2.2 %

d) Determination of the aerosol performances.

An amount of powder for inhalation was loaded in a multidose dry powder inhaler (Pulvinal®- Chiesi Pharmaceutical SpA, Italy).

The evaluation of the aerosol performances was performed by using a modified Twin Stage Impinger apparatus, TSI (Apparatus of type A for the aerodynamic evaluation of fine particles described in FU IX, 4° supplement 1996). The equipment consists of two different glass elements, mutually connected to form two chambers capable of separating the powder for inhalation depending on its aerodynamic size; the chambers are referred to as higher (stage 1) and lower (stage 2) separation chambers, respectively. A rubber adaptor secures the connection with the inhaler containing the powder. The apparatus is connected to a vacuum pump which produces an air flow through the separation chambers and the connected inhaler. Upon actuation of

the pump, the air flow carries the particles of the powder mixture, causing them to deposit in the two chambers depending on their aerodynamic diameter. The apparatus used were modified in the Stage 1 Jet in order to obtained an aerodynamic diameter limit value, *dae*, of 5 μm at an air flow of 30 l/min, that is considered the relevant flow rate for Pulvinal® device. Particles with higher *dae* deposit in Stage 1 and particles with lower *dae* in Stage 2. In both stages, a minimum volume of solvent is used (30 ml in Stage 2 and 7 ml in Stage 1) to prevent particles from adhering to the walls of the apparatus and to promote the recovery thereof.

The determination of the aerosol performances of the mixture obtained according to the preparation process a) was carried out with the TSI applying an air flow rate of 30 l/min for 8 seconds.

After nebulization of 10 doses, the Twin Stage Impinger was disassembled and the amounts of drug deposited in the two separation chambers were recovered by washing with a solvent mixture, then diluted to a volume of 100 and 50 ml in two volumetric flasks, one for Stage 1 and one for Stage 2, respectively. The amounts of active ingredient collected in the two volumetric flasks were then determined by High-Performance Liquid Chromatography (HPLC). The following parameters, were calculated: *i)* the shot weight as mean expressed as mean and relative standard deviation (RSD) ii) the fine particle dose (FPD) which is the amount of drug found in stage 2 of TSI; *iii)* the emitted dose which is the amount of drug delivered from the device recovered in stage 1 + stage 2; *iv)* the fine particle fraction (FPF) which is the percentage of the emitted dose reaching the stage 2 of TSI.

The results in terms of aerosol performances are reported in Table 3.

Table 3. Aerosol performances

Shot weight mg (%)	Emitted dose µg	FPD µg	FPF %
20.0 (7.8)	9.40	4.44	47.2

The formulation of the invention shows very good flow properties as demonstrated by the Carr index; this parameter is very important to obtain consistency of the delivered dose when a multi-dose dry powder inhalers with powder reservoir is used. The aerosol performance of the formulation is very good as well with about 50% of the drug reaching the stage 2 of the TSI.

Example 2 -Hard-pellet formulation containing coarse lactose (CapsuLac 212-355 µm), a micronized pre-blend Lactose/Magnesium Stearate mixture obtained by ball milling and formoterol fumarate as active ingredient

Blend A was prepared as described in the Example 1 but using α-lactose monohydrate SorboLac 400 with a starting particle size below 30 µm (d(v, 0.5) of about 10 µm) and carrying out the co-micronisation in a ball milling apparatus for 2 hours.

Blend B was prepared according to the Example 1 but after mixing for 6 mins and then screening through a 355 µm sieve.

The hard pellet final formulation was prepared according to the Example 1.

The particle size distribution, the water contact angle and the degree of coating for the micronized mixture (blend A), and the uniformity of distribution of the active ingredient for the final formulation (blend B), determined as previously described, are reported in Table 4.

Analogous results were achieved after preparing blend B by mixing for 4 hours without screening through a sieve.

Table 4 . Characterisation of blends A and B

Micronised mixture (blend A)	
Particle size distribution (μm) Malvern	
d (v, 0.1)	0.72 μm
d (v, 0.5)	2.69 μm
d (v, 0.9)	21.98 μm
water contact angle	52 °
degree of coating	25%
Final formulation (blend B)	
Uniformity of distribution of the active ingredient	Mean = 11.84 μg
	RSD = 1.83 %

The in-vitro performances, determined as previously described, are reported in Table 5.

Table 5. Aerosol performances

Shot weight mg (%)	Emitted dose μg	FPD μg	FPF %
20.8 (6.9)	8.57	4.28	49.9

As it can be appreciated from the results, also such formulation show excellent characteristics either in terms of flowability properties and in terms of aerosol performances.

Example 3 – Determination of the suitable amount of Magnesium stearate to be added in the formulation

Samples of pre-blends were prepared as described in Example 2 in a ball milling apparatus for 2 hours using α-Lactose monohydrate SorboLac 400 (Meggle microtose) with a starting particle size below 30 μm (d(v, 0.5) of about 10 μm) and magnesium stearate with a starting particle size of 3 to 35

μm (d(v, 0.5) of about 10 μm) in the ratio 98:2, 95:5 and 90:10 percent by weight (blends A).

Blends B and the hard pellet final formulation were prepared as previously described; the amount of magnesium stearate in the final formulations turns out to be 0.3, 0.75 and 1.5 percent by weight, respectively. The uniformity of distribution of active ingredient and the in-vitro aerosol performance were determined as previously described. The results obtained are reported in Table 6.

Table 6. Uniformity of distribution and *in-vitro* aerosol performances

	Mg stearate 0.3 %	**Mg stearate 0.75 %**	**Mg stearate 1.5 %**
Content uniformity			
- Mean (μg)	11.84	-	-
- RSD (%)	1.83	-	-
Shot weight			
- Mean (mg)	20.8	24.7	23.0
- RSD (%)	6.9	6.5	2.4
Emitted dose (μg)	8.57	10.1	11.1
FPD (μg)	4.28	3.5	3.6
FPF (%)	49.9	35	32

In all cases, good performances in terms of fine particle dose are obtained, in particular with 0.3 percent by weight of magnesium stearate in the final formulation.

Examples 4 – Ordered mixtures powder formulations

Powders mixtures were prepared by mixing of commercially available α-lactose monohydrate with different particle size and formoterol fumarate to

obtain a ratio of 12 μg of active to 20 mg of carrier. Blending was carried out in glass mortar for 30 mins. The uniformity of distribution of active ingredient and the in-vitro aerosol performances were determined as previously described. The results are reported In Table 7.

Table 7. Uniformity of distribution and *in-vitro* aerosol performances

	Spherolac 100 (63-90 μm)	Spherolac 100 (90-150 μm)	Spherolac 100 (150-250 μm)	Pharmatose 325 M (30–100 μm)
Content uniformity				
- Mean (μg)	11.89	11.81	12.98	11.90
- RSD (%)	3.88	2.17	9.03	10.10
Shot weight				
- Mean (mg)	25.28	25.23	22.02	22.40
- RSD (%)	7.73	3.39	6.93	22.00
Emitted dose (μg)	11.10	10.30	8.50	7.80
FPD (μg)	1.40	0.70	0.60	1.20
FPF (%)	12.6	6.8	7.1	15.4

The results indicate that, upon preparation of ordered mixtures containing formoterol fumarate as active ingredient according to the teaching of the prior art, the performances of the formulations are very poor.

Example 5 - Powders formulations containing different amounts of fine lactose particles.

Carrier A - α-Lactose monohydrate Spherolac 100 (90-150 μm) and Sorbolac 400 with a particle size below 30 μm (d(v, 0.5) of about 10 μm) in the ratio 95:5 percent by weight were mixed in a mortar for 15 mins.

Carrier B - α-Lactose monohydrate Spherolac 100 (90-150 μm) and micronised lactose (particle size below 5 μm) in the ratio 95:5 w/w were mixed in a mortar for 15 mins.

Carrier C - α-Lactose monohydrate Spherolac 100 (150-250 μm) and Sorbolac 400 with a particle size below 30 μm (d(v, 0.5) of about 10 μm) in the ratio 95:5 percent by weight were mixed in a mortar for 30 mins.

Carrier D - α-Lactose monohydrate Spherolac 100 (150-250 μm) and Sorbolac 400 particle size below 30 μm (d(v, 0.5) of about 10 μm) in the ratio 90:10 percent by weight were mixed in a mortar for 30 mins.

In the case of all the formulations tested, the carriers were mixed with formoterol fumarate in mortar for 15 mins to obtain a ratio of 12 μg of active to 25 mg of carrier.

The results in terms of content uniformity and in-vitro aerosol performances are reported in Table 8.

Table 8. Content uniformity and *in-vitro* aerosol performances

	Carrier A	Carrier B	Carrier C	Carrier D
Content uniformity				
- Mean (μg)	10.96	10.50	11.86	-
- RSD (%)	1.80	15.01	7.10	-
Shot weight				
- Mean (mg)	23.46	25.29	25.7	19.53
- RSD (%)	51.43	4.19	3.77	32.02
Emitted dose (μg)	10.40	9.5	10.1	5.92
FPD (μg)	1.60	2.3	2.3	1.30
FPF (%)	15.8	24.4	22.68	21.6

The results indicate that the performances of such formulations as well are very poor.

Example 6 -"Hard-pellet formulation containing coarse lactose (PrismaLac 40 fraction below 355 μm) and fine lactose"

α-Lactose monohydrate PrismaLac 40 with a particle size below 355 μm and Sorbolac 400 with a particle size below 30 μm (d(v, 0.5) of about 10 μm) in the ratio 60:40 percent by weight were first manually agitated for 10 mins to promote aggregation and then blended in a Turbula mixer for 30 mins at 42 r.p.m. The spheronised particles were mixed with formoterol fumarate in a Turbula mixer for 30 mins at 42 r.p.m. to obtain a ratio of 12 μg of active to 15 mg of carrier.

The results in terms of uniformity of distribution of active ingredient and in-vitro aerosol performances are reported in Table 9.

Table 9. Uniformity of distribution of active ingredient and *in-vitro* aerosol performances

	Spheronised particles
Content uniformity	
- Mean (μg)	11.90
- RSD (%)	18.46
Shot weight	
- Mean (mg)	18.10
- RSD (%)	6.80
Emitted dose (μg)	11.10
FPD (μg)	2.10
FPF (%)	18.9

The results indicate that the formulation without magnesium stearate has very poor performance.

Example 7 – Effect of the addition of magnesium stearate by simple mixing

Formulation A - α–Lactose monohydrate Pharmatose 325 M (30 –100 μm) and magnesium stearate in the ratio 99.75:0.25 percent by weight were blended in a Turbula mixer for 2 hours at 42 r.p.m. The blend was mixed with formoterol fumarate in a Turbula mixer for 30 mins at 42 r.p.m. to obtain a ratio of 12 μg of active to 25 mg of carrier.

Formulation B – as reported above but α–Lactose monohydrate SpheroLac 100 (90-150 μm) instead of Pharmatose 325 M.

Formulation C - α-Lactose monohydrate PrismaLac 40 (with a particle size below 355 μm) and micronised lactose with a particle size below 5 μm in the ratio 40:60 percent by weight were mixed in a Turbula mixer for 60 mins at 42 r.p.m. 99.75 percent by weight of the resulting blend and 0.25 percent by weight of magnesium stearate were mixed in a Turbula mixer for 60 mins at 42 r.p.m. The resulting blend was finally mixed with formoterol fumarate in a Turbula mixer for 30 mins at 42 r.p.m. to obtain a ratio of 12 μg of active to 15 mg of carrier.

Formulation D – Sorbolac 400 with a particle size below 30 μm (d(v, 0.5) of about 10 μm) and magnesium stearate in the ratio 98: 2 percent by weight were mixed in a high shear mixer for 120 mins (blend A). 85% percent by weight α-lactose monohydrate CapsuLac (212 – 355 μm) and 15% percent by weight of blend A were mixed in Turbula for 2 hours at 42 r.p.m. (blend B); the amount of magnesium stearate in the final formulation is 0.3 percent by weight. Micronised formoterol fumarate was placed on the top of blend B and mixed in a Turbula mixer for 10 mins at 42 r.p.m. to obtain a ratio of 12 μg of active to 20 mg of carrier.

Formulation E – Micronized lactose with a particle size below 10 μm (d(v, 0.5) of about 3 μm) and magnesium stearate in the ratio 98: 2 percent by weight were mixed in a Sigma Blade mixer for 60 mins (blend A). 85 percent

by weight of α-lactose monohydrate CapsuLac (212 – 355 μm) and 15 percent by weight of blend A were mixed in Turbula for 2 h at 42 r.p.m. (blend B); the amount of magnesium stearate in the final formulation is 0.3 percent by weight. Micronised formoterol fumarate was placed on the top of blend B and mixed in a Turbula mixer for 10 mins at 42 r.p.m. to obtain a ratio of 12 μg of active to 20 mg of carrier.

The results in terms of uniformity of distribution of active ingredient and in-vitro aerosol performances are reported in Table 10.

Table 10. Uniformity of distribution of active ingredient and *in-vitro* aerosol performances

	Formulations A	Formulations B	Formulations C	Formulations D	Formulations E
Content uniformity					
- Mean (μg)	7.96	10.50	9.10	10.68	11.32
- RSD (%)	2.16	8.30	24.90	2.80	3.0
Shot weight					
- Mean (mg)	24.10	26.50	12.50	22.07	21.87
- RSD (%)	34.60	8.20	15.30	2.50	4.0
Emitted dose (μg)	6.10	7.60	9.60	8.60	9.93
FPD (μg)	0.60	0.90	1.60	3.38	4.80
FPF (%)	9.8	11.8	16.7	39.3	48.37

Formulations were magnesium stearate is added, by simple mixing, to the total amount of lactose (formulations A-B-C) show very poor performance; no significant differences in the performance of the formulations were observed using lactose of different particle size.

Formulations were magnesium stearate is added by a high energy mixing to a small amount of fine lactose (blend A of the formulations D and E) show a

significant increase in the performances. In addition, the particle size of the fine lactose used has a significant effect on the deaggregation properties of the final formulation; in fact, formulation E prepared using a micronized lactose shows a significant improved performance compared with formulation D.

Example 8 - Effect of the amount of micronized pre-blend in the final formulation

αLactose monohydrate SpheroLac 100 (Meggle EP D30) with a starting particle size of 50 to 400 μm (d(v, 0.5) of about 170 μm) and magnesium stearate with a starting particle size of 3 to 35 μm (d(v, 0.5) of about 10 μm) in the ratio 98: 2 percent by weight were co-milled in a jet mill apparatus (blend A) Different ratios of α-lactose monohydrate Capsulac (212-355 μm) and blend A were placed in a stainless steel container and mixed in a Turbula mixer for four hours at 32 r.p.m. (blends B)

Micronised formoterol fumarate was placed on the top of blends B and mixed in a Turbula mixer for 30 mins at 32 r.p.m. to obtain a ratio of 12 μg of active to 20 mg total mixture. The amount of magnesium stearate in the final formulation ranges between 0.05 and 0.6 percent by weight.

The results in terms of uniformity of distribution of active ingredient and in-vitro aerosol performances are reported in Table 11.

Table 11. Uniformity of distribution of active ingredient and in-vivo aerosol performance

	Ratio 97.5 : 2.5	Ratio 95 : 5	Ratio 92.5 : 7.5	Ratio 90 : 10	Ratio 80 : 20	Ratio 70 : 30
Content uniformity						
- Mean (μg)	11.29	12.25	11.53	11.93	11.96	12.00
- RSD (%)	3.8	5.7	1.5	2.5	2.0	2.0
Shot weight						
- Mean (mg)	19.27	20.26	20.38	21.05	22.39	22.48
- RSD (%)	4.7	3.3	3.2	4.3	3.5	3.7
Emitted dose (μg)	10.58	9.20	10.65	9.18	9.63	9.88
FPD (μg)	4.18	5.10	6.78	5.9	5.33	5.28
FPF (%)	39.4	55.4	63.6	64.3	55.3	53.4

The results indicate that the performances of all the formulations are good.

Example 9 -Hard-pellet formulation containing coarse lactose (CapsuLac 212-355 μm), a micronized pre-blend Lactose/magnesium stearate mixture obtained by jet milling and budesonide as active ingredient

Blends A and B were prepared as described in the Example 1.

Micronised budesonide was added to the blend B and mixed in a Turbula mixer for 30 mins at 42 r.p.m. to obtain a ratio of 200 μg of active to 20 mg of carrier; the amount of magnesium stearate in the final formulation is 0.3 percent by weight . The final formulation (hard pellet formulation) was left to stand for 10 mins.

The results in terms of uniformity of distribution of active ingredient and in-vitro aerosol performances are reported in Table 12.

Table 12. Uniformity of distribution of active ingredient and *in-vitro* aerosol performances.

Content uniformity	
- Mean (μg)	201.60
- RSD (%)	1.60
Shot weight	
- Mean (mg)	19.47
- RSD (%)	3.90
Emitted dose (μg)	178.10
FPD (μg)	71.6
FPF (%)	40.3

The results demonstrate that the teaching of the present invention could also be applied to the preparation of a powdery formulation of budesonide provided of good performances in term of fine particle fraction.

Example 10 - Formulation containing lactose 90-150 μm, a micronized pre-blend Lactose/magnesium stearate mixture obtained by jet milling and formoterol as active ingredient

α–Lactose monohydrate SpheroLac 100 (Meggle EP D30) with a starting particle size of 50 to 400 μm (d(v, 0.5) of about 170 μm) and magnesium stearate with a starting particle size of 3 to 35 μm (d(v, 0.5) of about 10 μm) in the ratio 98: 2 percent by weight were co-milled in a jet mill apparatus (blend A).

92.5 percent by weight of α-lactose monohydrate Spherolac with a starting particle size of 90 to 150 μm (d(v, 0.5 of about 145 μm) and 7.5 percent by weight of blend A were placed in a stainless steel container and mixed in a Turbula mixer for four hours at 32 r.p.m. (blends B)

Micronised formoterol fumarate was placed on the top of blends B, and

mixed in a Turbula mixer for 30 mins at 32 r.p.m. to obtain a ratio of 12 μg of active to 20 mg total mixture. The amount of magnesium stearate in the final formulation is 0.15 percent by weight.

The results in terms of uniformity of distribution of active ingredient and in-vitro aerosol performances are reported in Table 13.

Table 13. Uniformity of distribution of active ingredient and *in-vitro* aerosol performances.

Content uniformity	
- Mean (μg)	11.75
- RSD (%)	1.50
Shot weight	
- Mean (mg)	-
- RSD (%)	-
Emitted dose (μg)	-
FPD (μg)	5.71
FPF (%)	45.2

From the reported results, it can be appreciated that, as long as the fraction of fine particles is less than 10 percent by weight, the performances of a formulation containing standard lactose as coarse carrier fraction and a fine particle fraction excipient obtained either by co-milling or by co-mixing, are very good.

Example 11 -Hard-pellet formulation containing coarse lactose (CapsuLac 212-355 μm), a micronized pre-blend Lactose/magnesium stearate mixture obtained by jet milling and the combination formoterol/beclometasone dipropionate (BDP) as active ingredient

Blends A and B were prepared as described in the Example 1.

Micronised formoterol and BDP were added to the blend B and mixed in

a Turbula mixer for 30 mins at 42 r.p.m. to obtain a ratio of 12 μg and 200 μg of active, respectively, to 20 mg of carrier. The amount of magnesium stearate in the final formulation is 0.3 percent by weight. The final formulation (hard pellet formulation) was left to stand for 10 mins.

The results in terms of uniformity of distribution of the active ingredients and in-vitro aerosol performances are reported in Table 14.

Table 14. Uniformity of distribution of the active ingredients and *in-vitro* aerosol performances.

Content uniformity	
Mean formoterol (μg)	11.93
RSD (%)	1.4
Mean BDP (μg)	190.0
RSD (%)	1.1
FPF formoterol (%)	47.2
FPF BDP (%)	40.4

The results indicate that, even in presence of a combination of active ingredients, the performances of the formulation are very good.

Example 12 –Effect of the time of mixing

Different blends were prepared by co-mixing CapsuLac 212-355 μm, micronized lactose with a particle size below 10 μm (d(v, 0.5) of about 3 μm) and magnesium stearate in the ratio 89.8:10:0.2 percent by weight, in a Turbula mixer (32 r.p.m.) at increasing mixing time (1, 2 and 4 hours).

Micronised formoterol fumarate was placed on the top of each blend and mixed in a Turbula mixer for 30 mins at 32 r.p.m. to obtain a ratio of 12 μg of active to 20 mg total mixture.

The results in terms of fine particle fraction (FPF) are reported in Table

Table 15 – Effect of the mixing time on FPF

Time of mixing	Fine particle fraction (%)
1 hour	21.0
2 hours	34.2
4 hours	40.5

The results indicate that good performances in terms of fine particle fraction are achieved after mixing for at least two hours.

CLAIMS

1. A powder for use in a dry powder inhaler, the powder comprising i) a fraction of fine particle size constituted of a mixture of a physiologically acceptable excipient and magnesium stearate, the mixture having a mean particle size of less than 35 μm; ii) a fraction of coarse particles constituted of a physiologically acceptable carrier having a particle size of at least 100 μm, said mixture (i) being composed of 90 to 99 percent by weight of particles of excipient and 1 to 10 percent by weight of magnesium stearate and the ratio between the fine excipient particles and the coarse carrier particles being between 1:99 and 40:60 percent by weight; and the said mixture having been further mixed with one or more active ingredient in micronised form selected from budesonide and its epimers, formoterol, TA 2005 and its stereoisomers, their salts and their combination.

2. A powder according to claim 1 wherein the active ingredient is the 22 R epimer of budesonide.

3. A powder according to claim 1 wherein the active ingredient is a combination of formoterol or TA-2005 with a corticosteroid selected from budesonide and its epimers and beclometasone dipropionate.

4. A powder according to claims 1-3, wherein the magnesium stearate particles partially coat the surface of either the excipient particles and the coarse carrier particles.

5. A powder according to claims 1-4, wherein the particle size of the fraction of fine particle size is less than 15 μm.

6. A powder according to claims 1-5 characterized in that the fraction of coarse carrier particles has a particle size of at least 175 μm, the fraction of fine particle size is composed of 98 percent by weight of particles of excipient and 2 percent by weight of magnesium stearate and the ratio between the fine

excipient particles and the coarse carrier particles is 10:90 percent by weight.

7. A powder according to claims 1-6 wherein the coarse carrier particles have a "fissure index" of at least 1.25

8. A powder according to any preceding claim wherein the physiological acceptable excipient is one or more crystalline sugars.

9. A powder according to any preceding claim wherein the the physiological acceptable excipient is α-lactose monohydrate.

10. A process for making a powder according to claims 1-9, said process including the steps of:

a) co-micronising the excipient particles and the magnesium stearate particles such that to significantly reduce their particle size and contemporaneously making the magnesium stearate particles coating the surface of the excipient particles;

b) spheronising by mixing the resulting mixture with the coarse carrier particles such that mixture particles adhere to the surface of the coarse carrier particle;

c) adding by mixing the active particles in the micronized form to the spheronised particles.

11. A process according to claim 10 wherein step a) is carried out by milling preferably by using a jet mill.

12. A process for making a powder according to claims 1-9, said process including the steps of:

a) mixing in high-energy mixer the excipient particles of a starting particle size less than 35 μm and the magnesium stearate particles in such a way as to make the magnesium stearate particles partially coating the surface of the excipient particles;

b) spheronising by mixing the resulting mixture with the coarse carrier particles such that mixture particles adhere to the surface of

the coarse carrier particles;

c) adding by mixing the active particles in the micronised form to the spheronised particles.

13. A process according to claim 12 wherein the excipient particles of step a) have a starting particle size of less than 15 μm.

14. A process of making a powder according to claims 1-9, said process including the steps of a) co-mixing the coarse carrier particles, magnesium stearate and the fine excipient particles; b) adding by mixing the active particles in the micronised form to the mixture wherein the fraction of coarse carrier particles has a particle size of at least 175 μm and the co-mixing a) is carried for at least two hours.

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(54) Title: NOVEL AEROSOL FORMULATION CONTAINING A POLAR FLUORINATED MOLECULE

(57) Abstract: The present invention relates to a stable pharmaceutical aerosol formulation intended for inhalation. The formulation contains an active substance, an aerosol propellant, a polar flurorinated molecule and an excipient. The preferred propellant is HFA 134a or HFA 227 or a mixture thereof.

NOVEL AEROSOL FORMULATION CONTAINING A POLAR FLUORINATED MOLECULE

The present invention relates to a pharmaceutical aerosol formulation for the administration of a pharmaceutically active substance by inhalation.

Pressurised metered dose inhalers (pMDI's) are known in the art. Long standing problems with pMDI's containing suspension formulations include creaming of the suspension, coarse drug suspension, drug flocculation and adhesion to dispensing device.

It has now surprisingly been found that these problems can be overcome with a novel pharmaceutical formulation containing a polar fluorinated molecule in conjunction with a suitable excipient. The formulations of the invention give rise to improved aerosol drug suspension characteristics, i.e. increase of phase separation times (creaming or sedimentation), production of a finer suspension, reduction of particles adhesion to the can walls and inhibition of particle flocculation.

In a first aspect the invention therefore provides a pharmaceutical formulation comprising a drug, an aerosol propellant, a polar fluorinated molecule and an excipient soluble in the polar fluorinated molecule.

Suitable drugs which can be used in the formulation of the invention include all drugs that can be administered via the inhalation route, for example steroids, peptides, oligonucleotides, small organic moecules etc., in particular those administered via a pMDI. Such drugs, which are not limited to those for treating respiratory diseases, include those suitable for administration by nasal delivery and nebulised delivery.

In preferred embodiements, the invention provides stable dispersion for the pulmonary or nasal delivery of one or more bioactive molecules, for local or systemic administration, comprising a fluorinated molecule and an excipient in a propellant or propellant mixture.

The biocative agent may be selected from any therapeutic or diagnostic agent. For example it may be from the group of antiallergics, bronchodilators, bronchoconsitrictors, pulmonary lung surfactants, analgesics, antibiotics, leukotrine inhibitors or antagonists, anticholinergics, mast cell inhibitors, antihistamines, antiinflammatories, antineoplastics, anaesthetics, anti-tuberculars, imaging agents, cardiovascular agents, enzymes, steroids, genetic material, viral vectors, antisense agents, proteins, peptides and combinations thereof.

Examples of specific drugs which can be formulated according to the invention include mometasone, ipratropium bromide, tiotropium and salts thereof, salemeterol, fluticasone propionate, beclomethasone dipropionate, reproterol, clenbuterol, rofleponide and salts, nedocromil, sodium cromoglycate, flunisolide, budesonide, formoterol fumarate dihydrate, Symbicort™ (budesonide and formoterol), Viozan™, 3-[2-(4-hydroxy-2-oxo-3H-1,3-benzothiazol-7-yl)ethylamino]-N-[2-[2-(4-methylphenyl)ethoxy)ethyl]propansulphonamide, terbutaline, terbutaline sulphate, salbutamol base and sulphate, fenoterol, 3-[2-(4-Hydroxy-2-oxo-3H-1,3-benzothiazol-7-yl)ethylamino]-N-[2-[2-(4-methylphenyl)ethoxy]ethyl]propanesulphonamide, hydrochloride. All of the above compounds can be in free base form or as pharmaceutically acceptable salts as known in the art.

Suitable aerosol propellants include those known in the art such as hydrofluoroalkane propellants including 1,1,1,2-tetrafluorethane (P134a) or 1,1,1,2,3,3,3-heptafluoropropane (P227). Preferred propellants include P134a or P227 or a mixture of P134a and P227, in particular a density-matched mixture of the two.

Suitable polar fluorinated molecules include those commercially available from companies such as Apollo chemicals and Fluorochem. Preferably the polar fluorinated molecules are pharmaceutically acceptable and are non-toxic and non-irritant. Suitable polar fluorinated molecules must be miscible in sufficient quantity in the propellant and to be able to solubilise the excipient. The fluorinated molecules are preferably liquid at room temperature, although solids are also possible. Preferably the polar fluorinated molecules are linear, more preferably with a short carbon chain. Most preferably the polar fluorinated molecules have oxygen functionality, i.e. contain an oxygen containing group including fluorinated alcohols, ethers, carboxylic acid, esters, aldehydes and ketones, amines and their mixtures, and any other fluorinated compounds with oxygen based functional groups.

Suitable examples of polar fluorinated molecules include:
n Butyl Pentafluoropropionate, Ethyl Perfluoro n-Dodecanoate, Fluorinert (FC-75), 2,2,3,3,3 Pentafluoropropyl Methyl Ether, Methyl Perfluorodecanoate, 2H Perfluoro-5,8,11-Trimethyl-3,6,9,12-Tetrafluoropropylether, Fluorad (FC-430), 1,1,2,2, Tetrafluoroethyl 2,2,3,3 Tetrafluoropropylether, 1H,1H,2H,2H Perfluorooctan-1-ol, 4,4,4 Trifluorobutan-1-ol, Fomblin (MF 402), Fomblin (ZDOL), Perfluoroheptanoic Anhydride, Methyl Perfluoro 2,5,8,11-Tetramethyl 3,6,9,12, Tetraoxapentadecanoate, N,N-Diethyl-2,3,3,3 Tetrafluoropropionamide, Ethyl 11H-Perfluoroundecanoate, 1H,1H,2H,3H,3H Perfluoro-1,2-Nonandiol, 1H,1H, Perfluorononan-1-ol,

Aflunox (606, 1406, 2507, 6008, 14013), Allyl Heptafluorobutyrate, Allyl Heptafluoroisopropyl Ether, Allyl 1,1,2,3,3,3-Hexafluoropropyl Ether, Allyl Perfluoroheptanoate, Allyl Perfluorooctanoate, Allyl 1H,1H Perfluorooctyl Ether, Allyl Perfluoropentanoate, 4-Amino-2,2-Difluorobutyric Acid, 2-Amino-3-Fluorobutyric Acid, 4-Amino-2-Fluorobutyric Acid, 2-Amino-4-Iminoheptafluoropent-2-ene, 2-Amino-4,4,4-Trifluorobutyric Acid, 3-Amino-4,4,4-Trifluorobutyric Acid, 1,1-Bis(diethylamino)tetrafluoro-1-Propene, Bis(heptafluoroisopropyl)ketone, Bis(hexafluoroisopropyl)maleate, Bis(hexafluoroisopropyl)itaconate, Bis[2-iodo-3-(perfluorooctyl)propyladipate, Bis(pefluorooctyl)itaconate, Bis(perfluorooctyl)maleate, Bis(2,2,2-trifluoroethyl)itaconate, Bis(2,2,2-trifluoroethyl)maleate, 1H,1H-2,5-Bis(trifluoromethyl)-3,6-Dioxaundecafluorononanol, 3,3-Bis(trifluoromethyl)-3-Hydroxypropionic Acid, 2,2 Bis (trifluoromethyl) Propionic Acid, n-Butyl-1,1,2,2-Tetrafluoroethyl Ether, n-Butyl Trifluoroacetate, tert-Butyl Trifluoroacetate, 1,1,1,5,5,6,6,7,7,7-Decafluoro-2,4-Heptanedione, 1H,1H,6H-Decfluorohexan-1-ol, 2H,3H-Decafluoropentane, Diethyl Difluoromalonate, 2,2-Difluoroethanol, 2,2-Difluoroethyl acetate, 2,2-Difluoroethyalamine, DL-4,4-Difluoroglutamic acid, 2,2-Difluoromalonamide, Difluoromethyl, 2,2,3,3,3-Pentafluoropropyl Ether, Difluoromethyl 2,2,2-Trifluoroethyl Ether, Difluoromethy 2,2,2-Trifluoroethyl Ether, 1,3-Difluoro-2-propanol, Dimethyl, Hexafluoroglutarate, Dimethyl Octafluoroadipate, Dimethyl Perfluoroazelate, Dimethyl Perfluoro-1,10-decanedicarboxylate, Dimethyl Perfluorosebacate, Dimethyl Perfluorosuberate, Dimethyl Tetrafluorosuccinate, Dimethyl 2,2,2-Trifluoropropionyl Carbinol, 4-Ethoxy-1,1,2-Trifluorobut-1-ene, Ethyl 3-Amino-4,4,4-trifluorocrotonate, Ethyl Ethoxymethylene-3-oxo-4,4,4-trifluorobutyrate, Ethyl 4-Fluoro-3-methyl-2-pentenoate, Ethyl 2-Fluoropropionate, Ethyl Heptafluorobutyrate, Ethyl Heptafluorobutyrylacetate, Ethyl 3-Hydroxy-4,4,4-trifluorobutyrate, Ethyl 2-Methyl-3-hydroxy-4,4,4-trifluorobutyrate, Ethyl Pentafluoropropionate, Ethyl Perfluoroheptanoate, Ethyl Perfluoro-n-dodecanoate including all compounds like CnF2n+1CO2CH2CH3, n= 4 to 16 (some H substitution possible in the CF chain, and double bonds), Ethyl Perfluoro-n-dodecanoate, Ethyl 7H-Perfluoroheptanoate, Ethyl Perfluorononanoate, Ethyl 9H-Perfluorononanoate, Ethyl Perfluorooctanoate, Ethyl Perfluoropentanoate, Ethyl 5H-Perfluoropentanoate, Ethyl 11H-Perfluoroundecanoate, Ethyl 1,1,2,2-Terafluoroethyl Ether, Ethyl 4,4,4-Trifluorobutyrate, Ethyl 3-(Trifluoromethyl)crotonate, Ethyl 4,4,4-Trifluoro-3-(trifluoromethyl)crotonate, Fluorinert (FC40, FC430, FC70, FC71, FC72, FC77, FC84, FC87, FC104, FC6001, FC6003), DL-2-Fluoro-3-alanine, 2-Fluoroethanol, D-Erythro-4-Fluoroglutamic Acid, 2-Fluoroethyl Methacrylate, DL-4-Fluoroglutamic Acid, L-Erythro-4-Fluoroglutamic Acid, D-Threo-4-Fluoroglutamic Acid, DL-Threo-4, Fluoroglutamic Acid, L-Threo-4-Fluoroglutamic Acid, DL-Erythro-4-Fluoroflutamine, L-Erythro-4-Fluoroglutamine, DL-Threo-4-Fluoroglutamine, DL-Erythro-4-

Fluoroisoglutamine, L-Erythro-4-Fluoroisoglutamine, DL-Threo-4-Fluoroisoglutamine, 3-Fluoro-DL-Norleucine, Flutec (PP1, PP2, PP3, PP9, PP10, PP11, PP25, PP50), Fomblin (M, Y (L-Vac), Y (H-Vac), Z15, MF402, ZDOL), Galden (HT70, HT85, HT90, HT100, HT110, HT135, HT200, HT230, HT250, HT270), 1H,1H Heptafluorobutan-1-ol, 1H,1H-Heptafluorobutyl Acetate, Heptafluorobutyramide, Heptafluorobutyric Acid, Heptafluorobutyric Anhydride, 4,4,5,5,6,6,6-Heptafluorohexanoic Acid, 4,4,5,5,6,6,6-Heptafluorohexan-1-ol, 4,4,5,5,6,6,6-Heptafluorohex-2-en-1-ol, Heptafluorosiopropyl Methyl Ether, 1,1,1,3,5,5,5-Heptafluoropentane-2,4-dione, Heptafluoropenta-2-ol, 2-Heptafluoropropoxy-2,3,3,3-tetrafluoropropan-1-ol, Heptafluoropropyl Methyl Ether, Heptafluoropropyl 1,2,2,2-tetrafluoroethyl Ether, Heptafluoropropyl Trifluorovinyl Ether, 2,2,3,4,4,4-Hexafluorobutan-1-ol, 2,2,3,3,4,4-Hexafluorobutan-1-ol, 2,2,3,4,4,4, Hexafluorobutyl Difluoromethyl Ether, 2,2,3,4,4,4-Hexafluorobutyl Methacrylate, Hexafluoroglutaramide, Hexafluoroglutaric Acid, Hexafluoroisopropanol, 1,1,1,3,3,3-Hexafluoroisopropyl Acrylate, mono-Hexafluoroisopropyl Itaconate, mono-Hexafluoroisopropyl Maleate, 1,1,1,3,3,3-Hexafluoroisopropyl methacrylate, Hexafluoroisopropyl Methyl Ether, Hexafluoroisopropylurethane-N-ethyl Methacrylate, Hexafluoroleucine, Hexafluoro-2-methylisopropanol; Hexafluoro-1,5-pentanediol, 3,3,4,5,5,5-Hexafluoropentan-2-ol, 1,1,2,3,3,3-Hexafluoropropyl Ethyl Ether, 1,1,2,3,3,3-Hexafluoropropyl Methyl Ether, 4,4,4,6,6,6-Hexafluoro-4-(trifluoromethyl)hexan-1-ol, 4,5,5,6,6,6-Hexafluoro4-(trifluoromethyl) hex-2-enoic Acid, 4,5,5,6,6,6-Hexafluoro-4-(trifluoromethyl) hex-2-en-1-ol, Hexafluoro-DL-valine, Isopropyl Trifluoroacetate, N, Methylbis(heptafluorobutyramide), Methyl Heptafluorobutyrate, Methyl Heptafluoropropyl Ketone, Methyl 2,2,3,3,4,4-hexafluorobutyrate, Methyl 2-hydroxy-2-(trifluoromethyl)pen-4-enoate, N-Methyl-N, methoxytrifluoroacetamide, Methyl Nonafluorobutyl Ether, Methyl Nonafluorobutyl Ketone, Methyl 2,2,3,3,4,4,5,5-octafluoropentanoate, Methyl Pentafluorobut-3-enoate, Methyl Pentafluoropropionate, Methyl Pentafluoropropionylacetate, Methyl Perfluorodecanoate, Methyl Perfluorododecanoate, Methyl Perfluoroheptanoate, Methyl 7H-Perfluoroheptanoate, Methy Perfluorohexadecanoate, Methyl Perfluoro(2-methyl-3-oxahexanoate), Methyl Perfluorononanoate, Methyl Perfluorooctadecanoate, Methyl Perfluoropentadecanoate, Methyl Perfluorotetradecanoate, Methyl Perfluoro-2,5,8,11-tetramethyl-3,6,9,12-tetraoxapentadecanoate, Methyl Perfluorotridecanoate, Methyl Perfluoroundecanoate, Methyl 2,3,3,3-Tetrafluoropropionate, Methyl Trifluoroacetate, Methyl 4,4,4-trifluoroacetoacetate, 2-Methyl-4,4,4-trifluorobutanol, Methyl 4,4,4,-trifluorocrotonate, Methyl 2-(trifluoromethyl), 3,3,3-trifluoropropionate, Methyl Trifluoropropenoate, Methyl Trifluoropyruvate, (Nonafluoro-n-butyl)epoxide, 2-(Nonafluorobutyl)ethyl acrylate, 2-(Nonafluorobutyl)ethyl methacrylate, 6-(nonafluorobutyl)hexanol, 3-(Nonafluorobutyl)-2-hydroxypropyl Acrylate, 3-(Nonafluoro-n-butyl)prop-2-enol, 3-(Nonafluoro-n-butyl)1,2,-

propenoxide, 1H,1H,2H,2H-Nonafluorohexan-1-ol, 1H,1H-Nonafluoropentan-1-ol, 2,2,3,3,4,4,5,5-Octafluoro-1,6-hexanediol, 2,2,3,3,4,4,5,5-Octafluorohexane-1,6-diacrylate, 2,2,3,3,4,4,5,5, Octafluorohexane-1,6-diamethacrylate, 3,3,4,4,5,5,6,6-Octafluoro-1,8-octanediol, 1H,1H,1H-Octafluoropenta-1-ol, 2,2,3,3,4,4,5,5 Octofluoro-1,6-hexanediol, 1,1,1,2,2-Pentafluorobutan-2-ol, 1,1,1,2,2-Pentafluoro-6,6-dimethyl-3,5-heptadione, 6-(Pentafluoroethyl)hexan-1-ol, 4,4,5,5,5-Pentafluoropentan-1-ol, 2,2,3,3,3-Pentafluoropropan-1-ol, Pentafluoropropionaldehyde Hydrate, Pentafluoropropionaldehyde Methyl Hemiacetal, Pentafluoropropionamide, 2,2,3,3,3-Pentafluoropropyl Acrylate, 2,2,3,3,3-Pentafluoropropyl Methacrylate, 2,2,3,3,3-Pentafluoropropyl Methyl Ether, 2,2,3,3,3-Pentafluoropropyl 1,1,2,2-Tetrafluoroethyl Ether, 1H,1H,10H,10H-Perfluoro-1,10-decanediol, 1H,1H-Perfluorodecan-1-ol, 1H,1H,2H,2H-Perfluorodecan-1-ol, 1H,1H,2H,2H-Perfluorodecanethiol, 1H,1H,2H,2H-Perfluorodecyl Acrylate, 1H,1H,2H,2H-Perfluorodecyl Methacrylate, 3-(Perfluoro-n-decyl)prop-2-enol, 3-(Perfluoro-n-decyl)-1,2-propenoxide, 1H,1H-Perfluoro-(3,7-dimethyloctan-1-ol), 2H-Perfluoro-(5,8-dimethyl-3,6,9-trioxadodecane), 1H,1H,12H,12H-perfluoro-1,12-dodecanediol, 1H,1H-Perfluorododecan-1-ol, 1H,1H,2H,2H-Perfluorododecan-1-ol, 1H,1H,2H,2H-Perfluorododecyl Acrylate, 1H,1H,2H,2H-Perfluorododecyl Methacrylate, 7H-Perfluoroheptanal, 7H-Perfluoro-1,1-heptanediol, Perfluoroheptanoic Anhydride, 1H,1H-Perfluoroheptan-1-ol, 1H,1H,7H-Perfluoroheptan-1-ol, Perfluoroheptoxypoly(propyloxy) Acrylate, Perfluoroheptoxypoly(propyloxy) Methacrylate, 1H,1H,7H-Perfluoroheptyl Methacrylate, 1H,1H-Perfluorohexadecan-1-ol, 3 Perfluorohexy-2-Hydroxypropyl Methacrylate, 2-(Perfluoro-n-hexyl)acetaldehyde Dimethyl Acetal, 3-Perfluorohexyl-2-hydroxypropyl Acrylate, 3-Perfluorohexyl-2-hydroxypropyl Methacrylate, 3-(Perfluorohexyl)propan-1-ol, 3-(Perfluoro-n-hexyl)prop-2-enol, 3-(Perfluoro-n-hexyl)-1,2-propenoxide, 11-(Perfluoro-n-hexyl)undecanol, 11-(Perfluoro-n-hexyl)undec-10-enol, 6, (Perfluorosiopropyl)hexan-1-ol, 3-(Perfluoro-3-methylbutyl)-2-hydroxy Propyl Acrylate, 3-(Perfluoro-3-methylbutyl)-2-hydroxy Propyl Methacrylate, 1H,1H,2H,2H-Perfluoro-9-methyldecan-1-ol, 2-(Perfluoro-9-methyldecyl)ethyl Acrylate, 2H-perfluoro-5-methyl-3,6-dioxanonane, 1H,1H,2H,2H-Perfluoro-11-methyldodecan-1-ol, Perfluoro-(2-methylhept-3-ene-5-one), 1H,1H,2H,2H, Perfluoro-5-methylhexan-1-ol, 2-(Perfluoro-5-methylhexyl)ethyl Acrylate, 2 (perfluoro-5-methylhexyl)ethyl Methacrylate3-(Perfluoro-5-methylhexyl)-2-hydroxypropyl Acrylate, 3-(Perfluor-5-methylhexyl)-2-hydroxypropyl Methacrylate, 1H,1H,2H,2H,-Perfluoro-7-methylocatn-1-ol, 2-(Perfluoro-7-methyloctyl)ethyl Acrylate, 2-(Perfluoro-7-methyloctyl)ethyl Methacrylate, 6-(Perfluoro-7-methyloctyl)hexanol, 3-(Perfluoro-7-methyloctyl)-2-hydroxypropyl Acrylate, 3-(Perfluoro-7-methyloctyl)-2-hydroxypropyl Methacrylate, 1H,1H,2H,3H,3H-Perfluoro-1,2-nonanediol, 1H,1H,9H,9H-Perfluoro-1,9-nonanediol, 1H,1H-Perfluorononan-1-ol, 1H,1H,9H-perfluorononan-1-ol, 1H,1H,9H-

Perfluorononon-1-ene, 1H,1H,9H-Perfluorononyl Acrylate, 1H,2H,9H-Perfluorononyl Methacrylate, 1H,1H-Perfluorooctadecan-1-ol, 1H,1H,8H,8H-Perfluoro-1,8-octanediol, n-Perfluoroctanoic acid Ammonium Salt, 1H,1H-Perfluorooctan-1-ol, 1H,1H,2H,2H-Perfluorooctan-1-ol, 1H,1H,8H-Perfluorooctan-1-ol, Perfluorooctoxy-poly(isobutoxy)-2-chloropropoxy-1,2-propyl Diacrylate, 2-(Perfluoro-n-octyl)acetaldehyde, 2-(Perfluoro-n, octyl)acetaldehyde Diethyl Acetate, Perfluorooctyl Acrylate, 1H,1H-Perfluorooctyl Acrylate, 1H,1H,2H,2H-Perfluorooctyl Acrylate, 6-(Perfluorooctyl)hexanol, 3-(Perfluorooctyl)-2-hydroxypropyl Acrylate, 3-(Perfluorooctyl)-2-hydroxypropyl Methacrylate, mono-Perfluorooctyl Itaconate, mono-Perfluorooctyl Maleate, Perfluorooctyl Methacrylate, 1H,1H-Perfluorooctyl Methacrylate, 3-(Perfluorooctyl)propanol, 3-(Perfluorooctyl)prop-2-enol, 11-(Pefluoro-n-octyl)undec-10-en-1-ol, 1H,1H,5H,5H-Perfluoropentyl-1,5-dimethacrylate, Pefluoropolyether linear & PFO-XR75, Perfluorosebacic Acid, 1H,1H-Perfluorotetradecan-1-ol, 1H,1H,13H-Perfluorotridecan-1-ol, Perfluoro-2-trifluoromethyl-4-oxanonane, Perfluoro-(3,5,5-trimethylhexanoic)acid, 1H,1H-Perfluoro(3,5,5-trimethylhexan-1-ol), 2H-Perfluoro-(5,8,11-trimethyl-3,6,9,12-tetraoxatetradecane), 1H,1H,2H,3H,3H-Perfluoro-1,2,-undecanediol, Perfluoroundecanoic Acid, 1H,1H-Perfluoroundecan-1-ol, 1H,1H,11H-Perfluoroundecan-1-ol, 1H,1H,11H-Perfluoroundecyl Acrylate, 1H,1H,11H-Perfluoroundecyl Methacrylate, Polyperfluoroethylene glycol Diacrylate, Polyperfluoroethylene glycol Dimethacrylate, Sodium Heptafluorobutyrate, Sodium Pentafluoropropionate, 2,2,3,3-Tetrafluoro-1,4-butanediacrylate, 2,2,3,3-Tetrafluoro1,4,butanedimethacrylate, 1,1,3,3-Tetrafluorodimethyl Ether, 1,1,2,2-Tetrafluoroethyl 2,2,3,3-tetrafluoropropyl Ether, 1,1,2,2, Tetrafluoroethyl 2,2,2-trifluoroethyl Ether, 1122 Tetrafluoroethyl 222 Trifluoroethyl Ether, 1,2,2,2-Tetrafluoroethyl Trifluoromethyl Ether, 4,5,5,5-Tetrafluoro-4-(heptafluoropropoxy)pentanoic Acid, 4,5,5,5-Tetrafluoro-4-(heptafluoropropoxy)pentan-1-ol, Tetrafluorosuccinic acid, 4,5,5,5-Tetrafluoro-4-(trifluoromethoxy)pentan-1-ol, 4,5,5,5-Tetrafluoro-4-(trifluoromethy)pentan-1-ol, 4,5,5,5-Tetrafluoro-4-(trifluoromethyl)pent-2-en-1-ol, N-(N-Trifluoroacetyl-L-cysteinyl)glycine Methyl Ester, DL-3,3,3-Trifluoro-2-alanine, 4,4,4-Trifluorobutan-1-ol, 1,1,1-Trifluorobutan-2-one, 4,4,4-Trifluorobutan-2-one, 4,4,4-Trifluorobut-2-en-1-ol, 1,1,2-Trifluoro-2-chloroethyl 2,2,2-trifluoroethyl ether, 4,4,4-Trifluorocrotonamide, 4,4,4-Trifluoro-3,3-dimethoxybutanol, 2,2,2-Trifluoroethanol, 2,2,2-Trifluoroethyl Butyrate, 1,2,2-Trifluoroethyl Trifluoromethyl Ether, 1,1,1-Trifluoro-2,4-hexanedione, Beta-Trifluoromethylcrotonic Acid, DL-2-(Trifluoromethyl)leucine, DL-2-(Trifluoromethyl)norleucine, DL-2-(Trifluoromethyl)norvaline, 2-(Trifluoromethyl)propan-2-ol, 6,6,6-Trifluoronorleucine, 5,5,5-Trifluoronorvaline, 1,1,1-Trifluoropropan-2-ol, 3,3,3-Trifluoropropan-1-ol, 1,1,1-Trifluoro-2-propyl Acetate, 4,4,4-Trifluoro-3-(trifluoromethyl)butan-1-ol, 2-Allyl Hexafluorosiopropanol, Butyl

Difluoroacetate, n-Butyl Pentafluoropropionate, tert-Butyl Pentafluoropropionate, N,N-Diethyl-2,3,3,3-tetrafluoropropionamide, 22 Difluoroethyl Trifluoromethyl Ether, 1-(Ethoxy)nonafluorobutane, 3-Fluoropropan-1-ol, 3H-Heptafluoro-2,2,4,4-tetrahydroxy Pentane, 2,2,3,3,4,4-Hexafluoro-1,5-pentyl Diacrylate, 1,1,2,3,3,3-Hexafluoropropyl 2,2,2-trifluoro Ethyl Ether, Methyl 2,2-Difluoro-3-oxopentanoate, Methyl 2, Methoxytetrafluoropropionate, Methyl Perfluoro-2,5,8,11-tetramethyl-3,6,9,12-tetraoxapentadecanoate, Methyl 3,3,3-Trifluoro-DL-lactate, 3,3,4,4,4-Pentafluorobutan-2-one, Pentafluorodiemethyl Ether, Pentafluoroethyl Methyl Ether, 2,2,3,3,3-Pentafluoropropyl Trifluoromethyl Ether, 2-(Perfluoroalkyl)ethanol, Perfluoroallylfluorosulphate, Perfluoro-2,5,8,11,14,17,20-heptamethyl-3,6,9,12,15,18-hexaoxahenelcosanoyl Fluoride, Mono-Perfluorooctyl Itaconate, 2H-Perfluoro-5,8,11,14,17-pentamethyl-3,6,9,12,15,18-hexaoxahenicosane, Perfluoropolyether Dinitrile, Polyfluoropolyethyleneacrylate, Polyfluoropolyethylenemethacrylate, 2,2,2-Trifluoroethyl Trifluoromethyl Ether, Perflurodecaline, Perfluorooctyl Bromide, di-Chloro-octyl Bromide and 1H,1H,5H Ocrafluoro-1-pentanol.

Preferably the fluorinated polar molecule is n-Butyl Pentafluoropropionate, Ethyl Perfluoro n-Dodecanoate, Fluorinert (FC-75), 2,2,3,3,3 Pentafluoropropyl Methyl Ether, Methyl Perfluorodecanoate, 2H Perfluoro-5,8,11-Trimethyl-3,6,9,12-Tetrafluoropropylether, Fluorad (FC-430), 1,1,2,2, Tetrafluoroethyl 2,2,3,3 Tetrafluoropropylether, 1H,1H,2H,2H Perfluorooctan-1-ol, 4,4,4 Trifluorobutan-1-ol, Fomblin (MF 402), Fomblin (ZDOL), Perfluoroheptanoic Anhydride, Methyl Perfluoro 2,5,8,11-Tetramethyl 3,6,9,12, Tetraoxapentadecanoate, N,N-Diethyl-2,3,3,3 Tetrafluoropropionamide, Ethyl 11H-Perfluoroundecanoate, 1H,1H,2H,3H,3H Perfluoro-1,2-Nonandiol, 1H,1H, Perfluorononan-1-ol or 1,1,2,2 Tetrafluoroethyl 2,2,2 Trifluoroethyl ether.

Even more preferred fluorinated molecules are 1H,1H,2H,2H Perfluorooctan-1-ol and 1,1,2,2 Tetrafluoroethyl 2,2,2 Trifluoroethyl ether.

The excipient for use in the formulation can be a surfactant or a polymer and combinations thereof, copolymers are particularly favoured. The excipient can either be soluble or miscible in the polar fluorinated molecule. Suitable excipients include:

Acrylidone 1005, Crodesta F160, Methoxy PEG Amine, Methoxy PEG carboxymethyl, 4 arms PEG, Cholic acid, MYRJ 52 P, APG-810-XL, APG-1014-XL, Glucopon 215, Glucopon 600, Brij 52, Gum Xanthan, Salicylic Acid, D-Lacotose monohydrate, α Lactose monohydrate, Lecithin egg, Carrageean, Sokalan CO5, Eudragit RLPO, Eudragit RSPO, Eudragit E100, Eudragit S100, Eudragit L100, Poly (DL-lacide coGlycolide), Gantrez S-97

BF, Gantrez AN-119, Gantrez AN-169, Myristic acid, Poly (lactide EO Lactid), Poly (methyl methacrylate-β -ethylene oxide), Lactose, Carboxymethyl cellulose Sodium Salt, 1-O-n-Octyl β D glucopyranoside, AOT DI-CF4H, Dioctyl-sulfosuccinate sodium salt (AOT), Phospholipon 100, Crodesta F10, Crodesta SL 40, APG 3399, Methoxy-PEG-DSPE MW 2000, Methoxy-PEG-DSPE MW 5000, N Dodecyl β D Maltoside, N Octyl β D Glucopyranoside, α cyclodextrin, β cyclodextrin hydrate, β cyclodextrin, ϒ cyclodextrin hydrate, ϒ cyclodextrin, ϒ cyclodextrin hydrate, Deoxycholic acid, Taurocholic acid, D-Mannitol, Poly (Methyl Methacrylate), Montanov 202, Montanov 68 EC, n Dodecyl β D Glucopyranoside, N Decyl β D Glucopyranoside, n Decyl β D Maltopyranoside, Glucamate DOE-120, Glucate SS, Glucamate SSE-20, Glucam DOE-120, Glucam P10, Glucam E20, Glucam P20 disteared, Glucam P20, Glucquat 125, Brij 30, Brij 96, Crodasinic LS 30, Crossential L99, Copolymer VC 713, Copolymer 958, Glucopon 650 EC, α Tocopherol, PVP K30, K25 and Plasdone K-29/32, PEG 600 and 1000, Three-Arm Poly (ethylene glycol),

lactose based compounds (eg Poly (lactide –co glycolide), Lactitol, Lactose, Cellulose based compounds (e.g. Carboxymethylcellulose, Cellulose, Hydroxypropyl cellulose), Faty acids (e.g. Castor oil), PEG and derivatives (e.g. Star PEG), Sugar compounds (e.g. Alkyl polyglucosides, Methyl glucosides, Sucrose esters, such as Berol AG6202, Glucopon chemical range, Montanov 68, Montanov 202, Grilloten LSE87, Crodesta chemical range), Poly(ethylene Oxide) compounds (e.g. Hydroxy terminated Three-Arm Polyethylene oxide, Hydroxy terminated Eight-Arm Polyethylene oxide, Carboxy terminated Eight-Arm Polyethylene Oxide, 4 Arms Star Polyethylene Oxide, Poly(methyl methacrylate b-ethylene oxide), Poly(t-butyl methacrylate –b-ethylene oxide), Poly(lactide-ethylene oxide-lactide triblock copolymer), Ω -Diacrylonyl terminated poly(lactide-ethylene oxide-lactide) triblock copolymer, Poly(lactone-β-ethylene oxide-β-lactone) triblock copolymer, Poly(ethylene oxide-β-caprolactone), Poly(ethylene oxide-β-propylene oxide) also known as PEO-PPO copolymers, Poly(methy methacrylate-β-ethylene oxide) also known as PMMA-PEO copolymers)). Further examples include Citric acid, Dibutyl Sebacate, Edetic acid, Glyceryl monooleate & monostearate, Glycofinol, Crodamol chemical range, Maltitol, Maltodextrin, Triglyceride, Polymethacrylate, Polyosyethylene alkyl ether, Sodium citrate dihydrate, Sorbitol, Mirj and Brij chemical range, Pluronic chemical range, Acrylidone 1005, Fluorinated AOT with different degrees of fluorination, Cholic acid, Copolymer 958, Copolymer VC713, Crossential L99, Crodasinic LS30, AOT Sodium salt, Phospholipon 100H, Salycilic acid, Sokalan CO5, Poly (lactide co glycolide), Poly(ethylene -β- methyl methacrylate), Poly(ethylene -β-2- vinyl pyridine), Poly(ethylene-β-4-vinyl pyridine), Poly(methyl methacrylate -β- sodium acrylate), Poly(methyl methacrylate-β-sodium methacrylate), PEG derivative compounds (Amino acid – PEG, Carboxyl – PEG copolymers, Methoxy PEG amine, Methoxy PEG

carboxymethyl, Branched PEG 4 arms, star PEG, PEG-PLA-PEG triblock copolymer etc...), sugar branched cyclodextrins derivatives, PEO cyclodextrins derivatives, and Dendrimer-PEO-Dendrimer triblock-copolymers.

Preferably the excipient is PEG based. Preferred excipients include Methoxy-PEG-DSPE MW 5000, Eudragit E100, Glucamate DOE 120, Methoxy-PEG-DSPE MW 2000, Acrylidone 1005, Crodesta F160, Methoxy PEG Amine, Methoxy PEG carboxymethyl, 4 arms PEG, Cholic acid, MYRJ 52 P, APG-810-XL, APG-1014-XL, Glucopon 215, Glucopon 600, Brij 52, Gum Xanthan, Salicylic Acid, D-Lacotose monohydrate, α Lactose monohydrate, Lecithin egg, Carrageean, Sokalan CO5, Eudragit RLPO, Eudragit RSPO, Eudragit E100, Eudragit S100, Eudragit L100, Poly (DL-lacide coGlycolide), Gantrez S-97 BF, Gantrez AN-119, Gantrez AN-169, Myristic acid, Poly (lactide EO Lactid), Poly (methyl methacrylate-β-ethylene oxide), Lactose, Carboxymethyl cellulose Sodium Salt, 1-O-n-Octyl β D glucopyranoside, AOT DI-CF4H, Dioctyl-sulfosuccinate sodium salt (AOT), Phospholipon 100, Crodesta F10, Crodesta SL 40, APG 3399, Methoxy-PEG-DSPE MW 2000, Methoxy-PEG-DSPE MW 5000, N Dodecyl β D Maltoside, N Octyl β D Glucopyranoside, α cyclodextrin, β cyclodextrin hydrate, β cyclodextrin, gamma cyclodextrin hydrate, gamma cyclodextrin, gamma cyclodextrin hydrate, Deoxycholic acid, Taurocholic acid, D-Mannitol, Poly (Methyl Methacrylate), Montanov 202, Montanov 68 EC, n Dodecyl β D Glucopyranoside, N Decyl β D Glucopyranoside, n Decyl β D Maltopyranoside, Glucamate DOE-120, Glucate SS, Glucamate SSE-20, Glucam DOE-120, Glucam P10, Glucam E20, Glucam P20 disteared, Glucam P20, Glucquat 125, Brij 30, Brij 96, Crodasinic LS 30, Crossential L99, Copolymer VC 713, Copolymer 958, Glucopon 650 EC, α Tocopherol, PVP K30, K25 and Plasdone K-29/32, PEG 600 and 1000, Three-Arm Poly (ethylene glycol).

Most preferably the excipient is Methoxy-PEG-DSPE MW 5000, Eudragit E100, Glucamate DOE 120 or Methoxy-PEG-DSPE MW 2000.

The grades of fluorinated molecules and excipients mentioned herein are purely indicative and do not limit the scope of this invention. Preferably the fluorinated molecules and excipients are pharmaceutically acceptable.

Other ingredients, for example other co-solvents, stabilisers, surfactants, lubricants, excipients, preservatives, buffers, antioxidants, sweeteners, water trapping agents, bulking agents, and taste masking agents may be included in the formulation of the present invention as desired.

The formulation of the present invention may be prepared, for example, by mixing the fluorinated polar molecule with the excipient, then adding the drug powder to the mixture. Propellant is then added to the drug slury, the formulation obtained is then dispensed in aliquots into specified pMDI which is suitable for nasal or pulmonary drug delivery by any known method, for example under pressure (addition of propellant under pressure) or by cold filling (addition of propellant at a temperature below its boiling point). The pharmaceutically active component may be processed in order to obtain a desired particle size distribution or specific surface properties. For example the pharmaceutically active component may be micronised by conventional methods prior to mixing, or the mixture of pharmaceutically active component may be micronised by conventional methods, after mixing.

Suitably the concentration of the fluorinated polar molecule is from 0.0001 to 55 % weight/weight, more preferably from 0.1 to 25%, and most preferably from 0.3 to 15%. The concentaration of excipient is suitably from 0.001% to 1%, preferably 0.01 to 1%.

The pMDI device for use with the formulation of the present invention preferably comprises a metal can, for example an aluminium can, closed with a suitable metering valve. Plastic and glass cans can also be used. Suitable cans, coated cans such as cans coated with a fluoropolymer, and metering valves are known in the art.

The pharmaceutical formulations of the present invention are useful for the local or systemic treatment of diseases and may be administered for example via the upper and lower respiratory tract, including by the nasal route. As such the present invention also provides the pharmaceutical aerosol formulation as defined herein for use in therapy; the use of the pharmaceutical aerosol formulation for the manufacture of a medicament for the treatment of diseases via the respiratory tract; and a method for the treatment of a patient in need of therapy, comprising administering to said patient a therapeutically effective amount of the pharmaceutical aerosol formulation of the present invention. It is expected that inflammatory diseases in the respiratory tract, for example asthma, rhinitis, COPD, alveolitis, bronchiolitis and bronchitis can be treated using the present pharmaceutical aerosol formulation.

The pharmaceutical formulation of the present invention is also useful for systemic delivery for many other non-respiratory diseases e.g. cancer, pain control, anaesthesia, infection, vaccinations etc.

In a further aspect the invention provides the use of a polar fluorinated molecule in conjunction with an excipient to reduce deposition and creaming of a pharmaceutical aerosol formulation, and to obtain easily a very fine stable suspension comprising a hydrofluoroalkane propellant having dispersed therein drug particulates.

In a further aspect the invention provides a pharmaceutical aerosol as described herein for use in therapy. The invention further provides a method of treatement of a patient in need of therapy comprising administering to said patient a therapeutically effective amount of a pharmaceutical aerosol formulation as described herein. In particular the invention provides a method of treating asthma, rhinitis and COPD.

The invention will now be illustrated in the following, non-limiting, examples.

Selection of Examples

A series of tests were performed to select novel formulation combinations. To select suitable fluorinated compounds, their solubility or miscibility in propellants HFA 134a and HFA 227 were tested (this is a pre-requisite for the fluorinated additive to play a suitable role in the formulation). Subsequently the solubility of selected excipients was tested in one of the fluorinated liquids (1H,1H,2H,2H Perfluorooctan-1-ol abbreviated as 4HPFOH). Finally 9 excipients (Methoxy-PEG-DSPE MW 2000, Methoxy-PEG-DSPE MW 5000, Glucamate DOE 120, Cholic Acid, APG 3399, AOT DI-HCF_6, 1 O n Octyl β D Glycopyranoside, 4 arms PEG, and Eudragit E100) were tested in the fluorinated liquids that were miscible in the propellant.

The results of this work are reported in the sections below. Adhesion pictures are shown in the Figures.

2.1 Miscibility and solubility of Fluorinated molecules in propellants

For a fluorinated compound to be useful in the novel aerosol formulation, it must preferably be fully miscible or soluble in the propellants at the concentration required. This also implies full miscibility in a mixture of the propellants.

The fluorinated chemical was weighed in a clear PET vial. The vial was then crimped, and subsequently pressure filled with one of the propellants until the desired total weight was reached.

The miscibility and solubility in HFA 227 and 134a are listed in Table 1. The values in brackets indicate the concentration at which the test was done. Solutions at concentrations below these limits are therefore monophasic. The concentrations quoted are not upper limits. It is perfectly possible for the fluorinated compounds to be miscible or soluble at higher concentrations. In the case of the Fluorad compound (C=9.09%w/w), the liquid was found to be insoluble at 9.09 %w/w. However this does not exclude that it could be miscible at a lower concentration, and therefore still be useful for the purpose of the invention.

NAME	Miscibility or solubility	
	HFA-134a	HFA-227
Ethyl Perfluoro n-Dodecanoate	Yes (C<9.24%w/w)	Yes (C<41.15%w/w)
Fluorinert(FC-75)	Yes (C<55.87%w/w)	Yes (C<50.94%w/w)
2,2,3,3,3 Pentafluoropropyl Methyl Ether	Yes (C<42.63%w/w)	Yes (C<33.49%w/w)
Methyl Perfluorodecanoate	Yes (C<42.63%w/w)	Yes (C<39.40%w/w)
2H Perfluoro-5,8,11-trimethyl-3,6,9,12-tetrafluoropropylether	Yes (C<43.49%w/w)	Yes (C<35.36%w/w)
Fluorad(FC-430)	No (C=9.09%w/w)	Yes (C<10.62%w/w)
1,1,2,2-tetrafluoroethyl 2,2,3,3 tetrafluoropropylether	Yes (C<40.30%w/w)	Yes (C<41.72%w/w)
1H,1H,2H,2H Perfluorooctan-1-ol (4HPFOH)	Yes (C<7.30%w/w)	Yes (C<5.17%w/w)
4,4,4 Trifluorobutan-1-ol	Yes (C<4.43%w/w)	Yes (C<4.63%w/w)
Fomblin MF 402	Yes (C<9.96%w/w)	Yes (C<9.93%w/w)
Fomblin ZDOL	Yes (C<9.93%w/w)	Yes (C<10.04%w/w)
Perfluoroheptanoic anhydride	Yes (C<9.89%w/w)	Yes (C<9.13%w/w)
Methyl perfluoro 2,5,9,11-Tetramethyl 3,6,9,12 Tetraoxapentadecanoate	Yes (C<10.37%w/w)	Yes (C<8.90%w/w)
N,N-diethyl-2,3,3,3 tetrafluoropropionamide	Yes (C<9.96%w/w)	Yes (C<9.2%w/w)
Ethyl 11H-Perfluoroundecanoate	Yes (C<4.93%w/w)	Yes (C<4.43%w/w)
1H,1H,2H,3H,3H Perfluoro-1,2-nonandiol	Yes (C<4.84%w/w)	Yes (C<3.71%w/w)
1H,1H, Perfluorononan-1-ol	Yes (C<4.55%w/w)	Yes (C<4.15%w/w)
n-Butyl Pentafluoropropionate	Yes	Yes

	(C=11.93%w/w)	(C=10.96%w/w)

Table 1: Miscibility or solubility of fluorinated molecules in propellants

The molecules listed in the chemicals list that do not appear in the following table did not show a solubility commensurate with the other compounds, therefore have not been included in this example section. However, they could still be used within the scope of this invention at a lower concentration range and cannot be excluded as potential systems.

2.2 Solubility of selected excipients in 4HPFOH

The second test carried out was to evaluate the solubility (or miscibility in the case of liquid samples) of some excipients in 4HPFOH.

The excipients were weighed in glass vials with a screw-on plastic cap. 4HPFOH was added at the required concentration, and the vial sealed with Teflon tape and the screw-on cap. The sample was sonicated and heated to quicken the solubilisation of the excipient. The vial was then allowed to cool down. Observations were subsequently made to asses their solubility (see Table 2 for results).

2.3 Solubility of a range of excipients in Fluorinated systems

The last test performed to determine a suitable list of excipients was to assess the solubility of some of the previous excipients in the miscible or soluble fluorinated liquids. Methoxy-PEG-DSPE MW 2000, Methoxy-PEG-DSPE MW 5000, Glucamate DOE 120, Eudragit E100, Cholic Acid, APG 3399, DI-HCF6, 1 O n Octyl β D Glycopyranoside, and 4 arms PEG were chosen for this purpose.

The solubilities were determined by weighing the excipient in a glass vial, adding the fluorinated liquid by weight and sealing the vial with Teflon tape and a screw-on cap. The samples were then heated and sonicated to speed up dissolution and allowed to cool down. Visual observations were made on the cold samples. The concentration of the solutions was 1 %w/w (unless otherwise stated). Therefore, compounds that are recorded as insoluble, are effectively insoluble at 1 %w/w, but could have a lower solubility. The choice of the 1 %w/w limit is arbitrary.

The observations on the solubilities are listed in Table 3, 4 and 5 below. Compounds which are soluble can be used as excipients in the novel formulation. For instance in the case of Methoxy-PEG-DSPE MW 2000, 5 fluorinated molecules can be used in

conjunction with the excipient at a concentration of at least 1 %w/w, and at lower concentrations for the 3 other fluorinated molecules.

Name	Concentration %w/w	Solubility or miscibility
Arlacel P135 USA	1.00	Yes
4 arms PEG	1.02	Yes
Brij 30	1.06	Yes
Brij 52	0.99	Yes
Brij 96	1.2	Yes
Cholic acid	0.11	Yes
Crossential L99	1.21	Yes
Deoxycholic acid	0.90	Yes
DI-CF4H	0.11	Yes
DI HCF2	0.98	Yes
DI HCF6	0.95	Yes
Dioctyl-sulfosuccinate sodium salt	0.096	Yes
Dodecyltrimethyl Ammonium Bromide	1.00	Yes
Eudragit E100	0.99	Yes
Eudragit RSPO	1.01	Yes
Glucamate DOE-120	1.16	Yes
Glucam E20	1.24	Yes
Glucam P20 disteared	1.18	Yes
Glucam P20	1.31	Yes
Glucquat 125	1.12	Yes
Methoxy PEG Amine	1	Yes
Methoxy PEG Propionic Acid	1.02	Yes
Methoxy PEG carboxymethyl	0.99	Yes
Methoxy-PEG-DSPE MW 2000	1.45	Yes
PEG-600	1.17	Yes
PEG 1000	0.98	Yes
MYRJ 52 P	0.99	Yes
N Octyl beta D Glucopyranoside	0.11	Yes
Nonyltrimethyl Ammonium Bromide	0.96	Yes
PVP K-25	0.95	Yes
PVP K-30	1	Yes
Plasdone K-29/32	1.08	Yes

Three-Arm Poly (ethylene glycol)	0.99	Yes

Table 2: Solubility of selected excipients in 4HPFOH

	Methoxy-PEG-DSPE MW 2000	Methoxy-PEG-DSPE MW 5000	Glucamate DOE 120
Fluorad	No	Yes	Yes
1,1,2,2-tetrafluoroethyl 2,2,3,3 tetrafluoropropylether	Yes	Yes	Yes
Fomblin MD 402	Yes	Yes	Yes
Fomblin ZDOL	Yes	Yes	No
Perfluoroheptanoic anhydride	No	Yes	Yes
Methyl perfluoro 2,5,9,11-Tetramethyl 3,6,9,12 Tetraoxapentadecanoate	Yes	No	Yes
N,N-diethyl-2,3,3,3 tetrafluoropropionamide	No	No	Yes
1,1,2,2 Tetrafluoroethyl 2,2,2 Trifluoroethyl ether	Yes	Yes	Yes

Table 3 Solubility of excipients in Fluorinated systems at 1 %w/w

	Cholic Acid	APG 3399	DI-HCF_6
Fluorad	No	No	Yes
1,1,2,2-tetrafluoroethyl 2,2,3,3 tetrafluoropropylether	No	No	No
Fomblin MD 402	No	No	Yes
Fomblin ZDOL	No	No	No
Perfluoroheptanoic anhydride	Yes	Yes	Yes
Methyl perfluoro 2,5,9,11-Tetramethyl 3,6,9,12 Tetraoxapentadecanoate	Yes	No	Yes
N,N-diethyl-2,3,3,3 tetrafluoropropionamide	No	No	Yes
1,1,2,2 Tetrafluoroethyl 2,2,2 Trifluoroethyl ether	No	No	Yes (0.1 %w/w)

Table 4 Solubility of excipients in Fluorinated systems at 1 %w/w, unless otherwise stated

5

	1 O n Octyl β D Glycopyranoside	4 arms PEG	Eudragit E100
Fluorad	No	No	No
1,1,2,2-tetrafluoroethyl 2,2,3,3 tetrafluoropropylether	Not tested	Yes	Yes
Fomblin MD 402	Yes	Yes	Yes
Fomblin ZDOL	Yes	Yes	Yes
Perfluoroheptanoic anhydride	Yes	Yes	Yes
Methyl perfluoro 2,5,9,11-Tetramethyl 3,6,9,12 Tetraoxapentadecanoate	No	Yes	No
N,N-diethyl-2,3,3,3 tetrafluoropropionamide	No	Yes	Yes
1,1,2,2 Tetrafluoroethyl 2,2,2 Trifluoroethyl ether	No	Yes	Yes

Table 5 Solubility of excipients in Fluorinated systems at 1 %w/w

From these results, it is possible to devise suitable excipient combinations that will form the novel formulation.

3 Examples selected

3.1 List of examples and controls

At least 29 novel formulations can be counted from the results in the previous tables, and many more can be elaborated from the previous lists of chemicals. The following combinations were especially assessed:

1- Budesonide with Methoxy-PEG-DSPE MW 5000 and 4HPFOH in HFA 227
2- Budesonide with Methoxy-PEG-DSPE MW 5000 and 4HPFOH in HFA 134a

3- Formoterol Fumarate Dihydrate with Methoxy-PEG-DSPE MW 5000 and 4HPFOH in HFA 227
4- Formoterol Fumarate Dihydrate with Methoxy-PEG-DSPE MW 5000 and 4HPFOH in HFA 134a
5- Budesonide with Eudragit E100 and 4HPFOH in HFA 227
6- Budesonide with Glucamate DOE 120 and 4HPFOH in HFA 227
7- Budesonide with Methoxy-PEG-DSPE MW 2000 and 4HPFOH in HFA 227
8- Formoterol Fumarate Dihydrate with Methoxy-PEG-DSPE MW 2000 and 4HPFOH in HFA 227
9- Terbutaline Sulphate with Methoxy-PEG-DSPE MW 2000 and 4HPFOH in HFA 227
10- 3-[2-(4-hydroxy-2-oxo-3H-1,3-benzothiazol-7-yl)ethylamino]-N-[2-[2-(4-methylphenyl)ethoxy)ethyl]propansulphonamide, with Methoxy-PEG-DSPE MW 2000 and 4HPFOH in HFA 227
11- Formoterol Fumarate Dihydrate with Glucamate DOE 120 and 1,1,2,2 Tetrafluoroethyl 2,2,2 Trifluoroethyl ether in HFA 227

A range of control samples were prepared to compare directly with the novel formulations, these were:

1- Formoterol Fumarate Dihydrate in HFA 227
2- Formoterol Fumarate Dihydrate in HFA 134a
3- Formoterol Fumarate Dihydrate with PEG 1000 and PVP K25 in a HFA 227 and 134a mix.
4- Terbutaline Sulphate in HFA 227
5- Terbutaline Sulphate in HFA 134a
6- Terbutaline Sulphate with PEG 600 and PVP K30 in HFA 227
7- Budesonide in HFA 227
8- Budesonide in HFA 134a
9- Budesonide with PEG 1000 and PVP K25 in HFA 227
10- 3-[2-(4-hydroxy-2-oxo-3H-1,3-benzothiazol-7-yl)ethylamino]-N-[2-[2-(4-methylphenyl)ethoxy)ethyl]propansulphonamide, in HFA 227
11- 3-[2-(4-hydroxy-2-oxo-3H-1,3-benzothiazol-7-yl)ethylamino]-N-[2-[2-(4-methylphenyl)ethoxy)ethyl]propansulphonamide, in HFA 134a

12- 3-[2-(4-hydroxy-2-oxo-3H-1,3-benzothiazol-7-yl)ethylamino]-N-[2-[2-(4-methylphenyl)ethoxy)ethyl]propansulphonamide, with PEG 600 and PVP K30 in HFA 227

All drug material used was micronised.

3.2 Samples preparation

Samples for adhesion and creaming tests were prepared in clear PET vials fitted with a continuous valve. The excipient and fluorinated molecule were mixed and the drug was weighed into the vial. The mixture of fluorinated molecule and excipient was then added to the drug. Once the continuous valve was manually crimped, the propellant was transferred through the valve under pressure to the desired weight. The samples were sonicated for at least 15 minutes, and left to stand for equilibration for up to 12 hours, before observations were made. The samples were then assessed and kept under standard laboratory conditions.

Samples for sizing were prepared in a similar fashion in 12 ml aluminium cans. The cans were then pierced and their content transferred in the measuring cell.

Examples 5 to 11 were prepared at 6 different concentrations to study the influence of the components concentrations.

3.3 Samples concentrations

The examples concentrations can be found below.

Example 1

Budesonide: 0.125 %w/w
Methoxy-PEG-DSPE MW 5000: 0.320 %w/w
4HPFOH: 31.7 %w/w
HFA 227: to 100 %w/w

Example 2

Budesonide: 0.174 %w/w
Methoxy-PEG-DSPE MW 5000: 0.286 %w/w
4HPFOH: 28.4 %w/w
HFA 134a: to 100 %w/w

Example 3

Formoterol Fumarate Dihydrate: 0.154%w/w
Methoxy-PEG-DSPE MW 5000: 0.320 %w/w
4HPFOH: 32.2 %w/w

HFA 227: to 100 %w/w

Example 4

Formoterol Fumarate Dihydrate: 0.220 %w/w
Methoxy-PEG-DSPE MW 5000: 0.317 %w/w
4HPFOH: 31.5 %w/w
HFA 134a: to 100 %w/w

Example 5

6 suspensions were prepared

Sample number	Concentration in HFA 227 of: (%w/w)		
	Budesonide	Eudragit E 100	4HPFOH
5.1	0.250	0.151	17.7
5.2	0.245	0.055	6.38
5.3	0.234	0.545	11.5
5.4	0.251	0.183	2.97
5.5	0.264	1.28	20.8
5.6	0.253	1.12	11.3

Example 6

6 suspensions were prepared

Sample number	Concentration in HFA 227 of: (%w/w)		
	Budesonide	Glucamate DOE-120	4HPFOH
6.1	0.262	0.166	18.3
6.2	0.267	0.062	6.88
6.3	0.255	1.12	11.3
6.4	0.264	1.33	21.2
6.5	0.262	0.569	12.1
6.6	0.256	0.192	3.05

Example 7

6 suspensions were prepared

Sample number	Concentration in HFA 227 of: (%w/w)		
	Budesonide	Methoxy-PEG-DSPE MW 2000	4HPFOH
7.1	0.239	0.193	17.1
7.2	0.260	0.078	6.9
7.3	0.249	0.966	11.1
7.4	0.25	1.13	20.0
7.5	0.26	0.519	12.1
7.6	0.255	0.172	3.06

Example 8

6 suspensions were prepared

Sample number	Concentration in HFA 227 of: (%w/w)		
	Formoterol Fumarate Dihydrate	Methoxy-PEG-DSPE MW 2000	4HPFOH
8.1	0.017	0.174	17.3
8.2	0.0174	0.069	6.85
8.3	0.0169	1.04	11.9
8.4	0.0174	0.171	3.04
8.5	0.0172	0.521	12.0
8.6	0.0176	1.19	21.1

Example 9

6 suspensions were prepared

Sample number	Concentration in HFA 227 of: (%w/w)		
	Terbutaline Sulphate	Methoxy-PEG-DSPE MW 2000	4HPFOH
9.1	0.282	0.165	16.4
9.2	0.312	0.047	4.7
9.3	0.288	0.71	8.2
9.4	0.299	1.154	20.9
9.5	0.295	0.51	11.8
9.6	0.294	0.169	3.06

Example 10

6 suspensions were prepared

Sample number	Concentration in HFA 227 of: (%w/w)		
	3-[2-(4-hydroxy-2-oxo-3H-1,3-benzothiazol-7-yl)ethylamino]-N-[2-[2-(4-methylphenyl)ethoxy)ethyl] propansulphonamide,	Methoxy-PEG-DSPE MW 2000	4HPFOH
10.1	0.043	0.209	18.5
10.2	0.045	0.082	7.2
10.5	0.043	1.021	11.7
10.6	0.043	1.163	20.7
10.7	0.043	0.521	12.1
10.8	0.042	0.170	3.03

Example 11

6 suspensions were prepared

Sample number	Concentration in HFA 227 of: (%w/w)		
	Fomoterol Fumarate Dihydrate	Glucamate DOE-120	1,1,2,2-tetrafluoroethyl-2,2,2-trifluoroethyl ether
11.1	0.017	0.063	6.98
11.2	0.017	0.159	18.4
11.3	0.016	0.198	3.16
11.4	0.016	0.587	12.1
11.5	0.017	1.10	12.1
11.6	0.017	1.3	22.2

Control 1

Formoterol Fumarate Dihydrate: 0.0167 %w/w

HFA 227: to 100 %w/w

Control 2

Formoterol Fumarate Dihydrate: 0.0167 %w/w

HFA 134a: to 100 %w/w

Control 3

Formoterol Fumarate Dihydrate: 0.0167 %w/w
PEG 1000: 0.1 %w/w
PVP K25: 0.001 %w/w
HFA 227: 25 %w/w
HFA 134a: to 100 %w/w

Control 4

Terbutaline Sulphate: 0.300 %w/w
HFA 227: to 100 %w/w

Control 5

Terbutaline Sulphate: 0.3 %w/w
HFA 134a: to 100 %w/w

Control 6

Terbutaline Sulphate: 0.299 %w/w
PEG 600: 0.03 %w/w
PVP K30: 0.005 %w/w
HFA 227: to 100 %w/w

Control 7

Budesonide: 0.260 %w/w
HFA 227: to 100 %w/w

Control 8

Budesonide: 0.259 %w/w
HFA 134a: to 100 %w/w

Control 9

Budesonide: 0.259 %w/w
PEG 1000: 0.3 %w/w
PVP K25: 0.001 %w/w
HFA 227: to 100 %w/w

Control 10

3-[2-(4-hydroxy-2-oxo-3H-1,3-benzothiazol-7-yl)ethylamino]-N-[2-[2-(4-methylphenyl)ethoxy)ethyl]propansulphonamide: 0.427 %w/w
HFA 227: to 100 %w/w

Control 11

3-[2-(4-hydroxy-2-oxo-3H-1,3-benzothiazol-7-yl)ethylamino]-N-[2-[2-(4-methylphenyl)ethoxy)ethyl]propansulphonamide: 0.428 %w/w
HFA 134a: to 100 %w/w

Control 12

3-[2-(4-hydroxy-2-oxo-3H-1,3-benzothiazol-7-yl)ethylamino]-N-[2-[2-(4-methylphenyl)ethoxy)ethyl]propansulphonamide: 0.428 %w/w
PEG 600: 0.3 %w/w
PVP K30: 0.0025 %w/w
HFA 227: to 100 %w/w

4 Assessment of examples

The novel formulation is especially useful to reduce drug adhesion to the can walls, reduce phase separation times and keep the suspension finely dispersed. Therefore 3 tests were performed: assessment of can wall adhesion, evaluation of creaming or sedimenting rates and sizing of the dispersion. The results were compared with the characteristics of the control samples.

Further tests were carried out to quantify the solubility of the drugs in the fluorinated liquids (the example chosen was 4HPFOH) and to check the degradation of the drugs in 4HPFOH.

4.1 Assessment of the extent of drug adhesion

The assessment of the adhesion of drugs to the can walls was done visually and recorded with a digital camera. The samples prepared in PET vials were observed after a couple of days storage. Their were shaken to enable re-dispersion of the creamed or sedimented layer. At this stage it is important to note that samples prepared with HFA 227 will tend to cream and can show some drug adhesion, whereas samples prepared with HFA 134a tend to sediment and because of it show very little adhesion in the head space. The PET vials were offset against a black background and in some cases allowed to settle before a picture was taken. The level of drug adhesion can be seen on the ring across the vial. The absence of a ring means no adhesion. Adhesion pictures can be found as Figures for the range of

samples prepared. Control samples with reference photographs have been collated as Figures.

The pictures are strong evidence of the benefits of the novel formulation. Two types of drug adhesion can be listed. Firstly, head space adhesion, where the particles are spread in the whole head space area (e.g. control 6). Secondly, adhesion at the propellant-gas interface, which will be referred to as ring adhesion (e.g. example 7.4). In all the controls, both types of adhesion were present. In the novel formulations however, the first kind of adhesion had disappeared in all but cases 5.6, 7.2, 10.2 and 10.6. Even in these cases, its extent was greatly limited. The ring adhesion did exist in some of the examples, but was very faint (e.g. 7.2 and 7.4).

The samples prepared with HFA 134a were on average better than the ones prepared with HFA 227. As mentioned before this is mostly due to the density difference. If the particles are not at the interface, and remain wetted in the liquid, they are not likely to adhere in the head space and form a dry ring or surface coating.

It is also interesting to note that for the 134a samples the novel formulation forms a milky suspension, i.e. a fine suspension, compared to the controls that tend to be coarser (see the grains in controls 2 and 3 for examples). Furthermore, the novel formulations are more stable than the controls as can be seen from the milky appearance of most of the examples. The creaming time for these samples was longer than the time required to set the vial and take the photograph (~ couple of minutes). This was not the case in many of the controls.

Budesonide examples 1, 2, 5, 6 and 7 must be compared with controls 7, 8 and 9 (Budesonide samples). For all the examples the novel formulation reduces drastically the amount of drug adhesion to the wall of the can. In all cases, except examples 5.6 and 7.2, there was virtually no drug on the can wall. Even in the case of examples 5.6 and 7.2, the adhesion was much less than in the control samples. There were instances where a small ring of particles was seen on the can wall, but even this was minimal compared to the controls.

Formoterol Fumarate Dihydrate examples 3, 4, 8 and 11 must be compared with controls 1, 2 and 3. Terbutaline Sulphate examples in series 9 must be compared with controls 4, 5 and 6. 3-[2-(4-hydroxy-2-oxo-3H-1,3-benzothiazol-7-yl)ethylamino]-N-[2-[2-(4-methylphenyl)ethoxy)ethyl]propansulphonamide examples in series 10 must be compared with control 10, 11 and 12. All these systems showed drastically improved performance over their respective control samples, similar to that described for Budesonide.

4.2 Assessment of the phase separation kinetics of the novel formulation

The phase separation kinetics of the novel formulation was assessed visually and with the OSCAR technique (Optical Suspension Characterisation). The OSCAR technique records the turbidity of a sample at two different heights as a function of time. Samples can be studied in situ, in the clear PET vials.

Photographic pictures of selected samples were taken at regular intervals to provide evidence of the slow phase separation kinetics. Samples prepared in HFA 227 creamed, whereas samples prepared in HFA 134a sedimented due to the density difference between the particles and the propellants.

Drug suspensions with no added stabilisers take a few seconds to a few minutes to be fully destabilised. The novel formulation however takes a much longer time to phase separate. It takes on average a couple of hours to form a separate solid phase layer. This is a significant improvement over the performance of other HFA formulations, and one of the major advantages of this novel formulation.

Examples 1, 2, 3 and 4 were studied with the OSCAR technique. In all 4 cases, the onset of detectable creaming was in excess of half an hour. For example 4, it is in excess of 3 hours. This is beyond the time scale usually observed in other formulations, in particular with the control samples, where creaming happens within a few minutes.

The other examples were studied visually. Pictures were recorded for all samples just after shaking and one hour after shaking. The picture titled "after shaking" are to be understood as pictures taken within one minute to one minute and a half after shaking of the first vial of the series. The systems were stable at one hour, and remained so well beyond that limit, extending to a couple of days in some instances. The control samples however had much reduced stability and on average creamed within half an hour after shaking. The level of instability was dependent on the concentration of additives. All suspensions had improved stability properties in the range of concentrations studied.

4.3 Assessment of the fineness of the novel formulation

Selected novel formulations were sized with a Mastersizer X in situ to demonstrate the absence of flocculation. The Mastersizer X is a laser light diffraction sizing apparatus developed by Malvern. A pressure cell assembly was adapted to be able to perform suspension sizing in propellant. Samples were prepared in 12 ml Aluminium cans fitted with a continuous valve, as described before in the creaming and adhesion section. These cans were then pierced and their content transferred in the measuring chamber with a purpose designed can piercer. 4 drugs were studied, Formoterol Fumarate Dihydrate, Budesonide, Terbutaline Sulphate and 3-[2-(4-hydroxy-2-oxo-3H-1,3-benzothiazol-7-yl)ethylamino]-N-[2-[2-(4-methylphenyl)ethoxy)ethyl]propansulphonamide. All drugs were micronised. They were formulated with Methoxy-PEG-DSPE MW 2000 and 4HPFOH in HFA 227. In addition, Formoterol Fumarate Dihydrate was sized in Glucamate DOE-120 and 1,1,2,2-tetrafluoroethyl-2,2,2-trifluoroethyl ether in HFA 227. The results could then be compared with sizing results of the same drugs in reference HFA formulations. The sizing results have been summarised in the tables below.

Formoterol Fumarate Dihydrate samples

Formoterol Fumarate Dihydrate was sized in 2 examples of the novel formulation. The first one is based on the combination Methoxy-PEG-DSPE MW 2000 and 4HPFOH in HFA 227. The second one is based on the combination Glucamate DOE-120 and 1,1,2,2-tetrafluoroethyl-2,2,2-trifluoroethyl ether in HFA 227. The HFA formulation used as a reference was based on a PEG 1000 and PVP K25 mixture in a HFA 134a and HFA 227 blend. Processing of the sizing data was done using the Mie theory. The refractive indices values necessary in the Mie theory were either known (for the 1st novel formulation) or approximated from the pure propellant values (2nd novel formulation and reference HFA formulation). The experimental concentrations are listed in Table 6.1, and the sizing results in Table 6.2.

1st Novel Formulation	2nd Novel Formulation	Reference HFA formulation
Methoxy-PEG-DSPE MW 2000 – 0.171 %w/w 4HPFOH – 3.053 %w/w FFD – 0.0174 %w/w HFA 227 to 100 %w/w	Glucamate DOE-120 – 1.25 %w/w 1,1,2,2-tetrafluoroethyl- 2,2,2-trifluoroethyl ether – 21.3 %w/w FFD – 0.049 %w/w HFA 227 to 100 %w/w	PEG 1000 – 0.099 %w/w PVP K25 – 0.00099 %w/w FFD – 0.0167 %w/ HFA 134a – 75.12 %w/w HFA 227 – 24.77 %w/w

Table 6.1 Concentrations of Formoterol Fumarate Dihydrate (FFD) samples sized with the

Mastersizer X

Sample	D(v,0.1)	D(v,0.5)	D(v,0.9)	D[4,3]	D[3,2]	Peaks	Span
1st novel Formulation	1.27	2.2	3.52	2.35	1.93	1	1.022
2nd novel Formulation	0.90	2.52	5.24	2.86	1.76	1	1.725
Reference HFA formulation	3.99	9.95	116.2	35.5	8.49	2	11.28

Table 6.2 Sizing results for the novel formulations and the reference HFA formulation of Formoterol Fumarate Dihydrate (FFD). Dimensions are expressed in μm. Span is [D(v,0.9)- D(v,0.1)]/ D(v,0.5).

The sizing results show that micronised FFD formulated in either new formulations has a narrower size distribution than in the reference HFA formulation, and the particles have a smaller average size. This is because in the novel formulation particles can exist as individual particles and not as clusters. Furthermore the novel formulations are monodisperse. This will have some effect on the performance of the pMDI, and it is expected that the ex-valve dose should be finer as well. A finely dispersed suspension is a good indicator of efficient suspending agents. The suspensions are well and truly stabilised by the added excipients.

Budesonide samples

2 Budesonide formulations were sized. The novel formulation was based on the combination Methoxy-PEG-DSPE MW 2000 and 4HPFOH in HFA 227. The reference sample was prepared with a PEG 1000 and PVP K25 mixture in HFA 227. Processing of the sizing data was done using the Mie theory. The refractive indices values necessary in the Mie theory were either known (novel formulation) or approximated from the pure propellant values (reference formulation). The experimental concentrations are listed in Table 7.1, and the sizing results on Table 7.2.

Novel Formulation	Reference HFA formulation
Methoxy-PEG-DSPE MW 2000 – 0.173 %w/w 4HPFOH – 3.095 %w/w Budesonide – 0.253 %w/w HFA 227 to 100 %w/w	PEG 1000 – 0.299 %w/w PVP K25 – 0.001 %w/w Budesonide – 0.256 %w/w HFA 227 to 100 %w/w

Table 7.1 Concentrations of Budesonide samples sized with the Mastersizer X

Sample	D(v,0.1)	D(v,0.5)	D(v,0.9)	D[4,3]	D[3,2]	Peaks	Span
Novel Formulation	0.53	2.13	3.68	2.20	1.30	1	1.479
Refrence HFA formulation	7.33	33.5	87.5	41.7	15.1	1	2.395

Table 7.2 Sizing results for the novel formulation and the reference HFA formulation of Budesonide. Dimensions are expressed in μm. Span is [D(v,0.9)- D(v,0.1)]/ D(v,0.5).

As for FFD, the sizing results show that micronised Budesonide formulated in the new formulation has a narrower size distribution than in the reference formulation, the particles have a smaller average size, and the size distribution is monodisperse.

Terbutaline sulphate samples

2 Terbutaline sulphate samples were sized. The novel formulation was based on the combination Methoxy-PEG-DSPE MW 2000 and 4HPFOH in HFA 227. The reference sample was prepared with a PEG 600 and PVP K30 mixture in HFA 227. Modelisation of the sizing data was done using the Mie theory. The refractive indices values necessary in the Mie theory were either known (novel formulation) or approximated from the pure propellant values (reference formulation). The experimental concentrations are listed in Table 8.1, and the sizing results on Table 8.2.

Novel Formulation	Reference HFA formulation
Methoxy-PEG-DSPE MW 2000 – 0.1743 %w/w 4HPFOH – 3.1126 %w/w Terbutaline Sulphate – 0.0831 %w/w HFA 227 to 100 %w/w	PEG 600 – 0.03 %w/w PVP K30 – 0.005 %w/w Terbutaline Sulphate – 0.0612 %w/w HFA 227 to 100 %w/w

Table 8.1 Concentrations of Terbutaline Sulphate samples sized with the Mastersizer X

Sample	D(v,0.1)	D(v,0.5)	D(v,0.9)	D[4,3]	D[3,2]	Peaks	Span
Novel Formulation	1.46	3.96	2.73	4.53	2.73	1	1.696
Refrence HFA formulation	5.68	13.6	40.4	23.1	10.6	1	2.543

Table 8.2 Sizing results for the novel formulation and the reference HFA formulation of Terbutaline Sulphate. Dimensions are expressed in μm. Span is [D(v,0.9)- D(v,0.1)]/ D(v,0.5).

As for FFD and Budesonide, the sizing results show that micronised Terbutaline sulphate formulated in the new formulation has a narrower size distribution than in the reference formulation, the particles are centred on a smaller average size, and the size distribution is monodisperse.

3-[2-(4-hydroxy-2-oxo-3H-1,3-benzothiazol-7-yl)ethylamino]-N-[2-[2-(4-methylphenyl)ethoxy)ethyl]propansulphonamide samples

Two 3-[2-(4-hydroxy-2-oxo-3H-1,3-benzothiazol-7-yl)ethylamino]-N-[2-[2-(4-methylphenyl)ethoxy)ethyl]propansulphonamide samples were sized. The novel formulation was based on the combination Methoxy-PEG-DSPE MW 2000 and 4HPFOH in HFA 227. The reference sample was prepared with a PEG 600 and PVP K30 mixture in HFA 227. Modelisation of the sizing data was done using the Mie theory. The refractive indices values necessary in the Mie theory were either known (novel formulation) or approximated from the pure propellant values (reference formulation). The experimental concentrations are listed in Table 9.1, and the sizing results on Table 9.2.

Novel Formulation	Reference HFA formulation
Methoxy-PEG-DSPE MW 2000 – 0.1743 %w/w 4HPFOH – 3.1126 %w/w 3-[2-(4-hydroxy-2-oxo-3H-1,3-benzothiazol-7-yl)ethylamino]-N-[2-[2-(4-methylphenyl)ethoxy)-ethyl]propansulphonamide, – 0.0831 %w/w HFA 227 to 100 %w/w	PEG 600 – 0.2941 %w/w PVP K30 – 0.0025 %w/w 3-[2-(4-hydroxy-2-oxo-3H-1,3-benzothiazol-7-yl)ethylamino]-N-[2-[2-(4-methylphenyl)ethoxy)-ethyl]propansulphonamide, – 0.1009 %w/w HFA 227 to 100 %w/w

Table 8.1 Concentrations of 3-[2-(4-hydroxy-2-oxo-3H-1,3-benzothiazol-7-yl)ethylamino]-N-[2-[2-(4-methylphenyl)ethoxy)ethyl]propansulphonamide samples sized with the Mastersizer X.

Sample	D(v,0.1)	D(v,0.5)	D(v,0.9)	D[4,3]	D[3,2]	Peaks	Span
Novel Formulation	1.53	3.14	39.9	10.6	2.76	2	12.23
Reference HFA formulation	5.9	22.2	136.3	42.1	12.9	2	5.860

Table 8.2 Sizing results for the novel formulation and the reference HFA formulation of 3-[2-(4-hydroxy-2-oxo-3H-1,3-benzothiazol-7-yl)ethylamino]-N-[2-[2-(4-methylphenyl)ethoxy)ethyl]propansulphonamide. Dimensions are expressed in μm. Span is [D(v,0.9)- D(v,0.1)]/ D(v,0.5).

As for FFD, Budesonide and Terbutaline sulphate, the sizing results show that micronised 3-[2-(4-hydroxy-2-oxo-3H-1,3-benzothiazol-7-yl)ethylamino]-N-[2-[2-(4-methylphenyl)ethoxy)ethyl]propansulphonamide formulated in the new formulation has a narrower size distribution than in the reference formulation, the particles have a smaller average size. Although the size distribution has in this case 2 peaks, the peak centred on 90 μm could be due to the approximation of the imaginary part of the medium refractive index, and may not be representative of the sample. It is this shoulder peak that leads to the high span value. Despite this results, the size distribution is still narrower and smaller than in the reference formulation.

4.4 Further tests: solubility of drug compounds in the novel formulation

This invention is concerned with the formulation of pMDI suspensions, but does not exclude the possibility of the formulation of a solution. Although most drug compounds are insoluble in the fluorinated systems, in some instances it is possible to solubilise the drug. Solubility tests were carried out on 4 different drugs in 4HPFOH: Formoterol Fumarate Dihydrate, Budesonide, Terbutaline Sulphate and 3-[2-(4-hydroxy-2-oxo-3H-1,3-benzothiazol-7-yl)ethylamino]-N-[2-[2-(4-methylphenyl)ethoxy)ethyl]-propansulphonamide.

Drug suspensions were prepared in sealed glass vials by weight. The suspensions were then allowed to rest over a couple of day to reach equilibrium. They were firstly assessed optically, and in the case of a possible solubility by UV-vis spectroscopy. The solutions were then filtered with 0.2 μm PTFE filters and studied by UV-Vis spectroscopy between 280 nm and 350 nm. A range of suspensions were prepared, to be able to reach saturation levels. Calibration curves were then drawn by plotting the absorbance as a function of concentration. The inflexion point at which the slope of the calibration plot changed was taken as the solubility limit. The experiment was carried out at least 3 times for each drug.

Formoterol Fumarate Dihydrate, Terbutaline Sulphate and 3-[2-(4-hydroxy-2-oxo-3H-1,3-benzothiazol-7-yl)ethylamino]-N-[2-[2-(4-methylphenyl)ethoxy)ethyl]-propansulphonamide are insoluble in 4HPFOH. Suspensions of the corresponding drug were observed optically at C= 0.1 ppm(w/w). At this concentration, particles were visible in the bulk of the solution. Their respective solubilities are therefore less than 0.1 ppm(w/w). I.e. the compounds can be considered as insoluble. Budesonide, however, is soluble in 4HPFOH. Its solubility limit measured by UV-Vis Spectroscopy is between 0.219 %w/w and 0.246 %w/w.

4.5 Further tests: stability of drug compounds in the novel formulation

The stability of Formoterol Fumarate Dihydrate and Budesonide in 4HPFOH were tested and compared with their stability in ethanol.

4 solutions were prepared in glass vials sealed with Teflon tape: Formoterol in 4HPFOH, Formoterol in ethanol, Budesonide in 4HPFOH and Budesonide in ethanol. The concentrations of Formoterol solutions were 0.792 %w/w in 4HPFOH and 1.365 %w/w in ethanol. The concentrations of Budesonide were 0.9315 %w/w in 4HPFOH and 1.215 %w/w in ethanol.

After 3 weeks storage, the levels of total impurity levels in excess of 0.01 % in the Formoterol solutions were 0.782 % for the ethanol solution, and 0.245 % in 4HPFOH. In the case of Budesonide, the levels of impurities were 0.23 %w/w in ethanol and 0.14 %w/w in 4HPFOH.

The impurities come from the degradation of the drug molecule in pure solvent. The total level of impurities in the fluorinated system was therefore up to 3 times less than in ethanol. Drug compounds are therefore more stable in the novel formulation than in other pMDI formulations that use co-solvents. This is yet an other distinct advantage of this novel formulation.

Explanation of Figures

Figures 1 – 58 show adhesion pictures for the samples prepared for the examples and controls as follows:

Figure	Example	Figure	Example	Figure	Example
1	1	21	7.5	41	11.1
2	2	22	7.6	42	11.2
3	2	23	8.1	43	11.3
4	4	24	8.2	44	11.4
5	5.1	25	8.3	45	11.5
6	5.2	26	8.4	46	11.6
7	5.3	27	8.5	**Figure**	**Control**
8	5.4	28	8.6	47	1
9	5.5	29	9.1	48	2
10	5.6	30	9.2	49	3
11	6.1	31	9.3	50	4
12	6.2	32	9.4	51	5
13	6.3	33	9.5	52	6
14	6.4	34	9.6	53	7
15	6.5	35	10.1	54	8
16	6.6	36	10.2	55	9
17	7.1	37	10.5	56	10
18	7.2	38	10.6	57	11
19	7.3	39	10.7	58	12
20	7.4	40	10.8		

Claims

1. A pharmaceutical formulation comprising a drug, an aerosol propellant, a polar fluorinated molecule and an excipient.

2. A pharmaceutical formulation as claimed in claim 1 for administration via the lung or nose.

3. A pharmaceutical aerosol formulation as claimed in claim 1 or 2 wherein the drug is selected from the group of antiallergics, bronchodilators, bronchoconsitrictors, pulmonray lung surfactants, analgesics, antibiotics leukotrine inhibitors or antagonists, anticholinergics, mast cell inhibitors, antihistamines, antiinflammatories, antineoplastics, anaesthetics, anti-tuberculars, imaging agents, cardiovascular agents, enzymes, steroids, genetic material, viral vectors, antisense agents, proteins, peptides and combinations thereof.

4. A pharmaceutical aerosol formulation as claimed in claim 1 to 3 wherein the drug is selected from budesonide, formoterol, Symbicort™ (budesonide and formoterol), Viozan™, 3-[2-(4-hydroxy-2-oxo-3H-1,3-benzothiazol-7-yl)ethylamino]-N-[2-[2-(4-methylphenyl)ethoxy)ethyl]propansulphonamide, terbutaline, salbutamol base and sulphate, fenoterol, or 3-[2-(4-Hydroxy-2-oxo-3H-1,3-benzothiazol-7-yl)ethylamino]-N-[2-[2-(4-methylphenyl)ethoxy]ethyl]propanesulphonamide and pharmaceutically acceptable salts thereof.

5. A pharmaceutical aerosol formulation as claimed in any one of claims 1 to 4 wherein the propellant is a fluorinated molecule.

6. A pharmaceutical aerosol formulation as claimed in any one of claims 1 to 5 wherein the propellant is HFA 134a or HFA 227 or a mixture of HFA 134a and HFA 227.

7. A pharmaceutical aerosol formulation as claimed in claim 1 to 6 wherein the polar fluorinated molecule is liquid at room temperature.

8. A pharmaceutical aerosol formulation as claimed in claim 1 to 7 wherein the polar fluorinated molecule is selected from:
n Butyl Pentafluoropropionate, Ethyl Perfluoro n-Dodecanoate, Fluorinert (FC-75),

2,2,3,3,3 Pentafluoropropyl Methyl Ether, Methyl Perfluorodecanoate, 2H Perfluoro-5,8,11-Trimethyl-3,6,9,12-Tetrafluoropropylether, Fluorad (FC-430), 1,1,2,2, Tetrafluoroethyl 2,2,3,3 Tetrafluoropropylether, 1H,1H,2H,2H Perfluorooctan-1-ol, 4,4,4 Trifluorobutan-1-ol, Fomblin (MF 402), Fomblin (ZDOL), Perfluoroheptanoic Anhydride, Methyl Perfluoro 2,5,8,11-Tetramethyl 3,6,9,12, Tetraoxapentadecanoate, N,N-Diethyl-2,3,3,3 Tetrafluoropropionamide, Ethyl 11H-Perfluoroundecanoate, 1H,1H,2H,3H,3H Perfluoro-1,2-Nonandiol, 1H,1H, Perfluorononan-1-ol, Aflunox (606, 1406, 2507, 6008, 14013), Allyl Heptafluorobutyrate, Allyl Heptafluoroisopropyl Ether, Allyl 1,1,2,3,3,3-Hexafluoropropyl Ether, Allyl Perfluoroheptanoate, Allyl Perfluorooctanoate, Allyl 1H,1H Perfluorooctyl Ether, Allyl Perfluoropentanoate, 4-Amino-2,2-Difluorobutyric Acid, 2-Amino-3-Fluorobutyric Acid, 4-Amino-2-Fluorobutyric Acid, 2-Amino-4-Iminoheptafluoropent-2-ene, 2-Amino-4,4,4-Trifluorobutyric Acid, 3-Amino-4,4,4-Trifluorobutyric Acid, 1,1-Bis(diethylamino)tetrafluoro-1-Propene, Bis(heptafluoroisopropyl)ketone, Bis(hexafluoroisopropyl)maleate, Bis(hexafluoroisopropyl)itaconate, Bis[2-iodo-3-(perfluorooctyl)propyladipate, Bis(pefluorooctyl)itaconate, Bis(perfluorooctyl)maleate, Bis(2,2,2-trifluoroethyl)itaconate, Bis(2,2,2-trifluoroethyl)maleate, 1H,1H-2,5-Bis(trifluoromethyl)-3,6-Dioxaundecafluorononanol, 3,3-Bis(trifluoromethyl)-3-Hydroxypropionic Acid, 2,2 Bis (trifluoromethyl) Propionic Acid, n-Butyl-1,1,2,2-Tetrafluoroethyl Ether, n-Butyl Trifluoroacetate, tert-Butyl Trifluoroacetate, 1,1,1,5,5,6,6,7,7,7-Decafluoro-2,4-Heptanedione, 1H,1H,6H-Decfluorohexan-1-ol, 2H,3H-Decafluoropentane, Diethyl Difluoromalonate, 2,2-Difluoroethanol, 2,2-Difluoroethyl acetate, 2,2-Difluoroethyalamine, DL-4,4-Difluoroglutamic acid, 2,2-Difluoromalonamide, Difluoromethyl, 2,2,3,3,3-Pentafluoropropyl Ether, Difluoromethyl 2,2,2-Trifluoroethyl Ether, Difluoromethy 2,2,2-Trifluoroethyl Ether, 1,3-Difluoro-2-propanol, Dimethyl, Hexafluoroglutarate, Dimethyl Octafluoroadipate, Dimethyl Perfluoroazelate, Dimethyl Perfluoro-1,10-decanedicarboxylate, Dimethyl Perfluorosebacate, Dimethyl Perfluorosuberate, Dimethyl Tetrafluorosuccinate, Dimethyl 2,2,2-Trifluoropropionyl Carbinol, 4-Ethoxy-1,1,2-Trifluorobut-1-ene, Ethyl 3-Amino-4,4,4-trifluorocrotonate, Ethyl Ethoxymethylene-3-oxo-4,4,4-trifluorobutyrate, Ethyl 4-Fluoro-3-methyl-2-pentenoate, Ethyl 2-Fluoropropionate, Ethyl Heptafluorobutyrate, Ethyl Heptafluorobutyrylacetate, Ethyl 3-Hydroxy-4,4,4-trifluorobutyrate, Ethyl 2-Methyl-3-hydroxy-4,4,4-trifluorobutyrate, Ethyl Pentafluoropropionate, Ethyl Perfluoroheptanoate, Ethyl Perfluoro-n-dodecanoate including all compounds like CnF2n+1CO2CH2CH3, n= 4 to 16 (some H substitution possible in the CF chain, and double bonds), Ethyl Perfluoro-n-dodecanoate, Ethyl 7H-Perfluoroheptanoate, Ethyl Perfluorononanoate, Ethyl 9H-Perfluorononanoate, Ethyl Perfluorooctanoate, Ethyl Perfluoropentanoate, Ethyl 5H-Perfluoropentanoate, Ethyl 11H-Perfluoroundecanoate, Ethyl 1,1,2,2-Terafluoroethyl

Ether, Ethyl 4,4,4-Trifluorobutyrate, Ethyl 3-(Trifluoromethyl)crotonate, Ethyl 4,4,4-Trifluoro-3-(trifluoromethyl)crotonate, Fluorinert (FC40, FC430, FC70, FC71, FC72, FC77, FC84, FC87, FC104, FC6001, FC6003), DL-2-Fluoro-3-alanine, 2-Fluoroethanol, D-Erythro-4-Fluoroglutamic Acid, 2-Fluoroethyl Methacrylate, DL-4-Fluoroglutamic Acid, L-Erythro-4-Fluoroglutamic Acid, D-Threo-4-Fluoroglutamic Acid, DL-Threo-4, Fluoroglutamic Acid, L-Threo-4-Fluoroglutamic Acid, DL-Erythro-4-Fluoroflutamine, L-Erythro-4-Fluoroglutamine, DL-Threo-4-Fluoroglutamine, DL-Erythro-4-Fluoroisoglutamine, L-Erythro-4-Fluoroisoglutamine, DL-Threo-4-Fluoroisoglutamine, 3-Fluoro-DL-Norleucine, Flutec (PP1, PP2, PP3, PP9, PP10, PP11, PP25, PP50), Fomblin (M, Y (L-Vac), Y (H-Vac), Z15, MF402, ZDOL), Galden (HT70, HT85, HT90, HT100, HT110, HT135, HT200, HT230, HT250, HT270), 1H,1H Heptafluorobutan-1-ol, 1H,1H-Heptafluorobutyl Acetate, Heptafluorobutyramide, Heptafluorobutyric Acid, Heptafluorobutyric Anhydride, 4,4,5,5,6,6,6-Heptafluorohexanoic Acid, 4,4,5,5,6,6,6-Heptafluorohexan-1-ol, 4,4,5,5,6,6,6-Heptafluorohex-2-en-1-ol, Heptafluorosiopropyl Methyl Ether, 1,1,1,3,5,5,5-Heptafluoropentane-2,4-dione, Heptafluoropenta-2-ol, 2-Heptafluoropropoxy-2,3,3,3-tetrafluoropropan-1-ol, Heptafluoropropyl Methyl Ether, Heptafluoropropyl 1,2,2,2-tetrafluoroethyl Ether, Heptafluoropropyl Trifluorovinyl Ether, 2,2,3,4,4,4-Hexafluorobutan-1-ol, 2,2,3,3,4,4-Hexafluorobutan-1-ol, 2,2,3,4,4,4, Hexafluorobutyl Difluoromethyl Ether, 2,2,3,4,4,4-Hexafluorobutyl Methacrylate, Hexafluoroglutaramide, Hexafluoroglutaric Acid, Hexafluoroisopropanol, 1,1,1,3,3,3-Hexafluoroisopropyl Acrylate, mono-Hexafluoroisopropyl Itaconate, mono-Hexafluoroisopropyl Maleate, 1,1,1,3,3,3-Hexafluoroisopropyl methacrylate, Hexafluoroisopropyl Methyl Ether, Hexafluoroisopropylurethane-N-ethyl Methacrylate, Hexafluoroleucine, Hexafluoro-2-methylisopropanol, Hexafluoro-1,5-pentanediol, 3,3,4,5,5,5-Hexafluoropentan-2-ol, 1,1,2,3,3,3-Hexafluoropropyl Ethyl Ether, 1,1,2,3,3,3-Hexafluoropropyl Methyl Ether, 4,4,4,6,6,6-Hexafluoro-4-(trifluoromethyl)hexan-1-ol, 4,5,5,6,6,6-Hexafluoro4-(trifluoromethyl) hex-2-enoic Acid, 4,5,5,6,6,6-Hexafluoro-4-(trifluoromethyl) hex-2-en-1-ol, Hexafluoro-DL-valine, Isopropyl Trifluoroacetate, N, Methylbis(heptafluorobutyramide), Methyl Heptafluorobutyrate, Methyl Heptafluoropropyl Ketone, Methyl 2,2,3,3,4,4-hexafluorobutyrate, Methyl 2-hydroxy-2-(trifluoromethyl)pen-4-enoate, N-Methyl-N, methoxytrifluoroacetamide, Methyl Nonafluorobutyl Ether, Methyl Nonafluorobutyl Ketone, Methyl 2,2,3,3,4,4,5,5-octafluoropentanoate, Methyl Pentafluorobut-3-enoate, Methyl Pentafluoropropionate, Methyl Pentafluoropropionylacetate, Methyl Perfluorodecanoate, Methyl Perfluorododecanoate, Methyl Perfluoroheptanoate, Methyl 7H-Perfluoroheptanoate, Methy Perfluorohexadecanoate, Methyl Perfluoro(2-methyl-3-oxahexanoate), Methyl Perfluorononanoate, Methyl Perfluorooctadecanoate, Methyl Perfluoropentadecanoate, Methyl Perfluorotetradecanoate, Methyl Perfluoro-2,5,8,11-tetramethyl-3,6,9,12-

tetraoxapentadecanoate, Methyl Perfluorotridecanoate, Methyl Perfluoroundecanoate, Methyl 2,3,3,3-Tetrafluoropropionate, Methyl Trifluoroacetate, Methyl 4,4,4-trifluoroacetoacetate, 2-Methyl-4,4,4-trifluorobutanol, Methyl 4,4,4,-trifluorocrotonate, Methyl 2-(trifluoromethyl), 3,3,3-trifluoropropionate, Methyl Trifluoropropenoate, Methyl Trifluoropyruvate, (Nonafluoro-n-butyl)epoxide, 2-(Nonafluorobutyl)ethyl acrylate, 2-(Nonafluorobutyl)ethyl methacrylate, 6-(nonafluorobutyl)hexanol, 3-(Nonafluorobutyl)-2-hydroxypropyl Acrylate, 3-(Nonafluoro-n-butyl)prop-2-enol, 3-(Nonafluoro-n-butyl)1,2,-propenoxide, 1H,1H,2H,2H-Nonafluorohexan-1-ol, 1H,1H-Nonafluoropentan-1-ol, 2,2,3,3,4,4,5,5-Octafluoro-1,6-hexanediol, 2,2,3,3,4,4,5,5-Octafluorohexane-1,6-diacrylate, 2,2,3,3,4,4,5,5, Octafluorohexane-1,6-diamethacrylate, 3,3,4,4,5,5,6,6-Octafluoro-1,8-octanediol, 1H,1H,1H-Octafluoropenta-1-ol, 2,2,3,3,4,4,5,5 Octofluoro-1,6-hexanediol, 1,1,1,2,2-Pentafluorobutan-2-ol, 1,1,1,2,2-Pentafluoro-6,6-dimethyl-3,5-heptadione, 6-(Pentafluoroethyl)hexan-1-ol, 4,4,5,5,5-Pentafluoropentan-1-ol, 2,2,3,3,3-Pentafluoropropan-1-ol, Pentafluoropropionaldehyde Hydrate, Pentafluoropropionaldehyde Methyl Hemiacetal, Pentafluoropropionamide, 2,2,3,3,3-Pentafluoropropyl Acrylate, 2,2,3,3,3-Pentafluoropropyl Methacrylate, 2,2,3,3,3-Pentafluoropropyl Methyl Ether, 2,2,3,3,3-Pentafluoropropyl 1,1,2,2-Tetrafluoroethyl Ether, 1H,1H,10H,10H-Perfluoro-1,10-decanediol, 1H,1H-Perfluorodecan-1-ol, 1H,1H,2H,2H-Perfluorodecan-1-ol, 1H,1H,2H,2H-Perfluorodecanethiol, 1H,1H,2H,2H-Perfluorodecyl Acrylate, 1H,1H,2H,2H-Perfluorodecyl Methacrylate, 3-(Perfluoro-n-decyl)prop-2-enol, 3-(Perfluoro-n-decyl)-1,2-propenoxide, 1H,1H-Perfluoro-(3,7-dimethyloctan-1-ol), 2H-Perfluoro-(5,8-dimethyl-3,6,9-trioxadodecane), 1H,1H,12H,12H-perfluoro-1,12-dodecanediol, 1H,1H-Perfluorododecan-1-ol, 1H,1H,2H,2H-Perfluorododecan-1-ol, 1H,1H,2H,2H-Perfluorododecyl Acrylate, 1H,1H,2H,2H-Perfluorododecyl Methacrylate, 7H-Perfluoroheptanal, 7H-Perfluoro-1,1-heptanediol, Perfluoroheptanoic Anhydride, 1H,1H-Perfluoroheptan-1-ol, 1H,1H,7H-Perfluoroheptan-1-ol, Perfluoroheptoxypoly(propyloxy) Acrylate, Perfluoroheptoxypoly(propyloxy) Methacrylate, 1H,1H,7H-Perfluoroheptyl Methacrylate, 1H,1H-Perfluorohexadecan-1-ol, 3 Perfluorohexy-2-Hydroxypropyl Methacrylate, 2-(Perfluoro-n-hexyl)acetaldehyde Dimethyl Acetal, 3-Perfluorohexyl-2-hydroxypropyl Acrylate, 3-Perfluorohexyl-2-hydroxypropyl Methacrylate, 3-(Perfluorohexyl)propan-1-ol, 3-(Perfluoro-n-hexyl)prop-2-enol, 3-(Perfluoro-n-hexyl)-1,2-propenoxide, 11-(Perfluoro-n-hexyl)undecanol, 11-(Perfluoro-n-hexyl)undec-10-enol, 6, (Perfluorosiopropyl)hexan-1-ol, 3-(Perfluoro-3-methylbutyl)-2-hydroxy Propyl Acrylate, 3-(Perfluoro-3-methylbutyl)-2-hydroxy Propyl Methacrylate, 1H,1H,2H,2H-Perfluoro-9-methyldecan-1-ol, 2-(Perfluoro-9-methyldecyl)ethyl Acrylate, 2H-perfluoro-5-methyl-3,6-dioxanonane, 1H,1H,2H,2H-Perfluoro-11-methyldodecan-1-ol, Perfluoro-(2-methylhept-3-ene-5-one), 1H,1H,2H,2H, Perfluoro-5-methylhexan-1-ol, 2-(Perfluoro-5-methylhexyl)ethyl Acrylate, 2 (perfluoro-5-

methylhexyl)ethyl Methacrylate3-(Perfluoro-5-methylhexyl)-2-hydroxypropyl Acrylate, 3-(Perfluor-5-methylhexyl)-2-hydroxypropyl Methacrylate, 1H,1H,2H,2H,-Perfluoro-7-methylocatn-1-ol, 2-(Perfluoro-7-methyloctyl)ethyl Acrylate, 2-(Perfluoro-7-methyloctyl)ethyl Methacrylate, 6-(Perfluoro-7-methyloctyl)hexanol, 3-(Perfluoro-7-methyloctyl)-2-hydroxypropyl Acrylate, 3-(Perfluoro-7-methyloctyl)-2-hydroxypropyl Methacrylate, 1H,1H,2H,3H,3H-Perfluoro-1,2-nonanediol, 1H,1H,9H,9H-Perfluoro-1,9-nonanediol, 1H,1H-Perfluorononan-1-ol, 1H,1H,9H-perfluorononan-1-ol, 1H,1H,9H-Perfluoronon-1-ene, 1H,1H,9H-Perfluorononyl Acrylate, 1H,2H,9H-Perfluorononyl Methacrylate, 1H,1H-Perfluorooctadecan-1-ol, 1H,1H,8H,8H-Perfluoro-1,8-octanediol, n-Perfluoroctanoic acid Ammonium Salt, 1H,1H-Perfluorooctan-1-ol, 1H,1H,2H,2H-Perfluorooctan-1-ol, 1H,1H,8H-Perfluorooctan-1-ol, Perfluorooctoxy-poly(isobutoxy)-2-chloropropoxy-1,2-propyl Diacrylate, 2-(Perfluoro-n-octyl)acetaldehyde, 2-(Perfluoro-n,octyl)acetaldehyde Diethyl Acetate, Perfluorooctyl Acrylate, 1H,1H-Perfluorooctyl Acrylate, 1H,1H,2H,2H-Perfluorooctyl Acrylate, 6-(Perfluorooctyl)hexanol, 3-(Perfluorooctyl)-2-hydroxypropyl Acrylate, 3-(Perfluorooctyl)-2-hydroxypropyl Methacrylate, mono-Perfluorooctyl Itaconate, mono-Perfluorooctyl Maleate, Perfluorooctyl Methacrylate, 1H,1H-Perfluorooctyl Methacrylate, 3-(Perfluorooctyl)propanol, 3-(Perfluorooctyl)prop-2-enol, 11-(Pefluoro-n-octyl)undec-10-en-1-ol, 1H,1H,5H,5H-Perfluoropentyl-1,5-dimethacrylate, Pefluoropolyether linear & PFO-XR75, Perfluorosebacic Acid, 1H,1H-Perfluorotetradecan-1-ol, 1H,1H,13H-Perfluorotridecan-1-ol, Perfluoro-2-trifluoromethyl-4-oxanonane, Perfluoro-(3,5,5-trimethylhexanoic)acid, 1H,1H-Perfluoro(3,5,5-trimethylhexan-1-ol), 2H-Perfluoro-(5,8,11-trimethyl-3,6,9,12-tetraoxatetradecane), 1H,1H,2H,3H,3H-Perfluoro-1,2,-undecanediol, Perfluoroundecanoic Acid, 1H,1H-Perfluoroundecan-1-ol, 1H,1H,11H-Perfluoroundecan-1-ol, 1H,1H,11H-Perfluoroundecyl Acrylate, 1H,1H,11H-Perfluoroundecyl Methacrylate, Polyperfluoroethylene glycol Diacrylate, Polyperfluoroethylene glycol Dimethacrylate, Sodium Heptafluorobutyrate, Sodium Pentafluoropropionate, 2,2,3,3-Tetrafluoro-1,4-butanediacrylate, 2,2,3,3-Tetrafluoro1,4,butanedimethacrylate, 1,1,3,3-Tetrafluorodimethyl Ether, 1,1,2,2-Tetrafluoroethyl 2,2,3,3-tetrafluoropropyl Ether, 1,1,2,2, Tetrafluoroethyl 2,2,2-trifluoroethyl Ether, 1122 Tetrafluoroethyl 222 Trifluoroethyl Ether, 1,2,2,2-Tetrafluoroethyl Trifluoromethyl Ether, 4,5,5,5-Tetrafluoro-4-(heptafluoropropoxy)pentanoic Acid, 4,5,5,5-Tetrafluoro-4-(heptafluoropropoxy)pentan-1-ol, Tetrafluorosuccinic acid, 4,5,5,5-Tetrafluoro-4-(trifluoromethoxy)pentan-1-ol, 4,5,5,5-Tetrafluoro-4-(trifluoromethy)pentan-1-ol, 4,5,5,5-Tetrafluoro-4-(trifluoromethyl)pent-2-en-1-ol, N-(N-Trifluoroacetyl-L-cysteinyl)glycine Methyl Ester, DL-3,3,3-Trifluoro-2-alanine, 4,4,4-Trifluorobutan-1-ol, 1,1,1-Trifluorobutan-2-one, 4,4,4-Trifluorobutan-2-one, 4,4,4-Trifluorobut-2-en-1-ol, 1,1,2-Trifluoro-2-chloroethyl 2,2,2-trifluoroethyl ether, 4,4,4-

Trifluorocrotonamide, 4,4,4-Trifluoro-3,3-dimethoxybutanol, 2,2,2-Trifluoroethanol, 2,2,2-Trifluoroethyl Butyrate, 1,2,2-Trifluoroethyl Trifluoromethyl Ether, 1,1,1-Trifluoro-2,4-hexanedione, Beta-Trifluoromethylcrotonic Acid, DL-2-(Trifluoromethyl)leucine, DL-2-(Trifluoromethyl)norleucine, DL-2-(Trifluoromethyl)norvaline, 2-(Trifluoromethyl)propan-2-ol, 6,6,6-Trifluoronorleucine, 5,5,5-Trifluoronorvaline, 1,1,1-Trifluoropropan-2-ol, 3,3,3-Trifluoropropan-1-ol, 1,1,1-Trifluoro-2-propyl Acetate, 4,4,4-Trifluoro-3-(trifluoromethyl)butan-1-ol, 2-Allyl Hexafluorosiopropanol, Butyl Difluoroacetate, n-Butyl Pentafluoropropionate, tert-Butyl Pentafluoropropionate, N,N-Diethyl-2,3,3,3-tetrafluoropropionamide, 22 Difluoroethyl Trifluoromethyl Ether, 1-(Ethoxy)nonafluorobutane, 3-Fluoropropan-1-ol, 3H-Heptafluoro-2,2,4,4-tetrahydroxy Pentane, 2,2,3,3,4,4-Hexafluoro-1,5-pentyl Diacrylate, 1,1,2,3,3,3-Hexafluoropropyl 2,2,2-trifluoro Ethyl Ether, Methyl 2,2-Difluoro-3-oxopentanoate, Methyl 2, Methoxytetrafluoropropionate, Methyl Perfluoro-2,5,8,11-tetramethyl-3,6,9,12-tetraoxapentadecanoate, Methyl 3,3,3-Trifluoro-DL-lactate, 3,3,4,4,4-Pentafluorobutan-2-one, Pentafluorodiemethyl Ether, Pentafluoroethyl Methyl Ether, 2,2,3,3,3-Pentafluoropropyl Trifluoromethyl Ether, 2-(Perfluoroalkyl)ethanol, Perfluoroallylfluorosulphate, Perfluoro-2,5,8,11,14,17,20-heptamethyl-3,6,9,12,15,18-hexaoxahenelcosanoyl Fluoride, Mono-Perfluorooctyl Itaconate, 2H-Perfluoro-5,8,11,14,17-pentamethyl-3,6,9,12,15,18-hexaoxahenicosane, Perfluoropolyether Dinitrile, Polyfluoropolyethyleneacrylate, Polyfluoropolyethylenemethacrylate, 2,2,2-Trifluoroethyl Trifluoromethyl Ether, Perflurodecaline, Perfluorooctyl Bromide, di-Chloro-octyl Bromide or 1H,1H,5H Octafluoro-1-pentanol.

9. A pharmaceutical aerosol formulation as claimed in any preceding claim, wherein the excipient is a PEG co-polymer.

10. A pharmaceutical aerosol formulation as claimed in any preceding claim, wherein the excipient is a PEG-phospholipid.

11. A pharmaceutical aerosol formulation as claimed in any preceding claim, wherein the excipient is selected from:

Acrylidone 1005, Crodesta F160, Methoxy PEG Amine, Methoxy PEG carboxymethyl, 4 arms PEG, Cholic acid, MYRJ 52 P, APG-810-XL, APG-1014-XL, Glucopon 215, Glucopon 600, Brij 52, Gum Xanthan, Salicylic Acid, D-Lacotose monohydrate, α Lactose monohydrate, Lecithin egg, Carrageean, Sokalan CO5, Eudragit RLPO, Eudragit RSPO, Eudragit E100, Eudragit S100, Eudragit L100, Poly (DL-lacide coGlycolide), Gantrez S-97 BF, Gantrez AN-119, Gantrez AN-169, Myristic acid, Poly (lactide EO Lactid), Poly

(methyl methacrylate-β -ethylene oxide), Lactose, Carboxymethyl cellulose Sodium Salt, 1-O-n-Octyl β D glucopyranoside, AOT DI-CF4H, Dioctyl-sulfosuccinate sodium salt (AOT), Phospholipon 100, Crodesta F10, Crodesta SL 40, APG 3399, Methoxy-PEG-DSPE MW 2000, Methoxy-PEG-DSPE MW 5000, N Dodecyl β D Maltoside, N Octyl β D Glucopyranoside, α cyclodextrin, β cyclodextrin hydrate, β cyclodextrin, Υ cyclodextrin hydrate, Υ cyclodextrin, Υ cyclodextrin hydrate, Deoxycholic acid, Taurocholic acid, D-Mannitol, Poly (Methyl Methacrylate), Montanov 202, Montanov 68 EC, n Dodecyl β D Glucopyranoside, N Decyl β D Glucopyranoside, n Decyl β D Maltopyranoside, Glucamate DOE-120, Glucate SS, Glucamate SSE-20, Glucam DOE-120, Glucam P10, Glucam E20, Glucam P20 disteared, Glucam P20, Glucquat 125, Brij 30, Brij 96, Crodasinic LS 30, Crossential L99, Copolymer VC 713, Copolymer 958, Glucopon 650 EC, α Tocopherol, PVP K30, K25 and Plasdone K-29/32, PEG 600 and 1000, Three-Arm Poly (ethylene glycol),

lactose based compounds (eg Poly (lactide –co glycolide), Lactitol, Lactose, Cellulose based compounds (e.g. Carboxymethylcellulose, Cellulose, Hydroxypropyl cellulose), Faty acids (e.g. Castor oil), PEG and derivatives (e.g. Star PEG), Sugar compounds (e.g. Alkyl polyglucosides, Methyl glucosides, Sucrose esters, such as Berol AG6202, Glucopon chemical range, Montanov 68, Montanov 202, Grilloten LSE87, Crodesta chemical range), Poly(ethylene Oxide) compounds (e.g. Hydroxy terminated Three-Arm Polyethylene oxide, Hydroxy terminated Eight-Arm Polyethylene oxide, Carboxy terminated Eight-Arm Polyethylene Oxide, 4 Arms Star Polyethylene Oxide, Poly(methyl methacrylate b-ethylene oxide), Poly(t-butyl methacrylate –b-ethylene oxide), Poly(lactide-ethylene oxide-lactide triblock copolymer), Ω -Diacrylonyl terminated poly(lactide-ethylene oxide-lactide) triblock copolymer, Poly(lactone-β-ethylene oxide-β-lactone) triblock copolymer, Poly(ethylene oxide-β-caprolactone), Poly(ethylene oxide-β-propylene oxide) also known as PEO-PPO copolymers, Poly(methy methacrylate-β-ethylene oxide) also known as PMMA-PEO copolymers)). Further examples include Citric acid, Dibutyl Sebacate, Edetic acid, Glyceryl monooleate & monostearate, Glycofinol, Crodamol chemical range, Maltitol, Maltodextrin, Triglyceride, Polymethacrylate, Polyosyethylene alkyl ether, Sodium citrate dihydrate, Sorbitol, Mirj and Brij chemical range, Pluronic chemical range, Acrylidone 1005, Fluorinated AOT with different degrees of fluorination, Cholic acid, Copolymer 958, Copolymer VC713, Crossential L99, Crodasinic LS30, AOT Sodium salt, Phospholipon 100H, Salycilic acid, Sokalan CO5, Poly (lactide co glycolide), Poly(ethylene -β- methyl methacrylate), Poly(ethylene -β-2- vinyl pyridine), Poly(ethylene-β-4-vinyl pyridine), Poly(methyl methacrylate -β- sodium acrylate), Poly(methyl methacrylate-β-sodium methacrylate), PEG derivative compounds (Amino acid – PEG, Carboxyl – PEG copolymers, Methoxy PEG amine, Methoxy PEG carboxymethyl, Branched PEG 4 arms, star PEG, PEG-PLA-PEG triblock copolymer),

sugar branched cyclodextrins derivatives, PEO cyclodextrins derivatives, and Dendrimer-PEO-Dendrimer triblock-copolymers, Methoxy-PEG-DSPE MW 5000, Eudragit E100, Glucamate DOE 120, Methoxy-PEG-DSPE MW 2000, Acrylidone 1005, Crodesta F160, Methoxy PEG Amine, Methoxy PEG carboxymethyl, 4 arms PEG, Cholic acid, MYRJ 52 P, APG-810-XL, APG-1014-XL, Glucopon 215, Glucopon 600, Brij 52, Gum Xanthan, Salicylic Acid, D-Lacotose monohydrate, α Lactose monohydrate, Lecithin egg, Carrageean, Sokalan CO5, Eudragit RLPO, Eudragit RSPO, Eudragit E100, Eudragit S100, Eudragit L100, Poly (DL-lacide coGlycolide), Gantrez S-97 BF, Gantrez AN-119, Gantrez AN-169, Myristic acid, Poly (lactide EO Lactid), Poly (methyl methacrylate-β-ethylene oxide), Lactose, Carboxymethyl cellulose Sodium Salt, 1-O-n-Octyl β D glucopyranoside, AOT DI-CF4H, Dioctyl-sulfosuccinate sodium salt (AOT), Phospholipon 100, Crodesta F10, Crodesta SL 40, APG 3399, Methoxy-PEG-DSPE MW 2000, Methoxy-PEG-DSPE MW 5000, N Dodecyl β D Maltoside, N Octyl β D Glucopyranoside, α cyclodextrin, β cyclodextrin hydrate, β cyclodextrin, gamma cyclodextrin hydrate, gamma cyclodextrin, gamma cyclodextrin hydrate, Deoxycholic acid, Taurocholic acid, D-Mannitol, Poly (Methyl Methacrylate), Montanov 202, Montanov 68 EC, n Dodecyl β D Glucopyranoside, N Decyl β D Glucopyranoside, n Decyl β D Maltopyranoside, Glucamate DOE-120, Glucate SS, Glucamate SSE-20, Glucam DOE-120, Glucam P10, Glucam E20, Glucam P20 disteared, Glucam P20, Glucquat 125, Brij 30, Brij 96, Crodasinic LS 30, Crossential L99, Copolymer VC 713, Copolymer 958, Glucopon 650 EC, α Tocopherol, PVP K30, K25 and Plasdone K-29/32, PEG 600 and 1000, Three-Arm Poly (ethylene glycol).

12. The use of a polar fluorinated molecule in conjunction with an excipient to reduce deposition and creaming of a pharmaceutical aerosol formulation, and obtain a very fine stable suspension comprising a hydrofluoroalkane propellant having dispersed therein drug particulates.

13. An aerosol can containing a formulation as claimed in any of claims 1 to 11.

14. A can according to claim 13 which is made of metal.

15. An aerosol can as claimed in claim 13 or 14 wherein the internal surfaces of the can are coated with a fluoropolymer.

16. A pharmaceutical aerosol formulation as claimed in any of claims 1 to 11 for use in therapy.

17. A pharmaceutical aerosol formulation as claimed in any of claims 1 to 11 for use in the treatment of asthma, rhinitis or COPD.

18. A method for the treatment of a patient in need of therapy, comprising administering to said patient a therapeutically effective amount of the pharmaceutical aerosol formulation as claimed in any of claims 1 to 11.

Figure 1/10

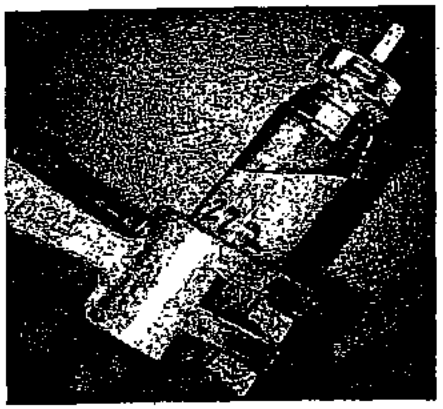


Figure 1 (Budesonide with Methoxy-PEG-DSPE MW 5000 in 4HPFOH and HFA 227)

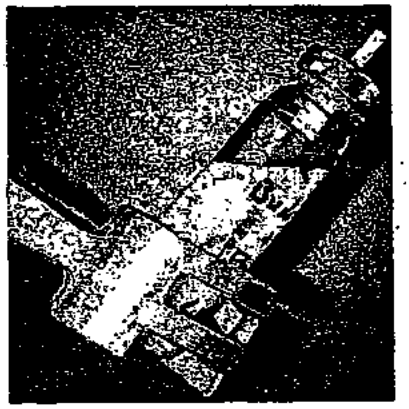


Figure 2 (Budesonide with Methoxy-PEG-DSPE MW 5000 in 4HPFOH and HFA 134a)

Figure 3 (Formoterol Fumarate Dihydrate with Methoxy-PEG-DSPE MW 5000 in 4HPFOH and HFA 227)

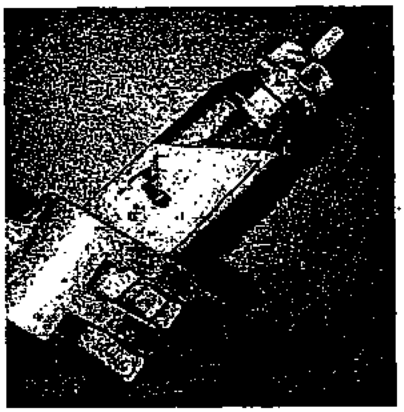


Figure 4 (Formoterol Fumarate Dihydrate with Methoxy-PEG-DSPE MW 5000 in 4HPFOH and HFA 134a)

Figure 2/10

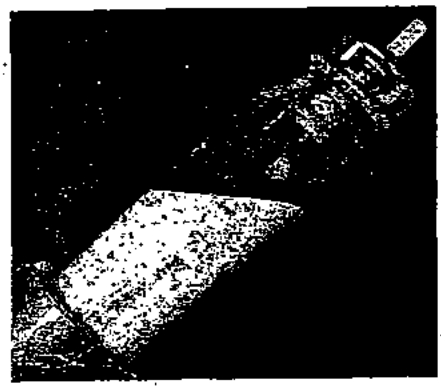


Figure 5

Figure 6

Figure 7

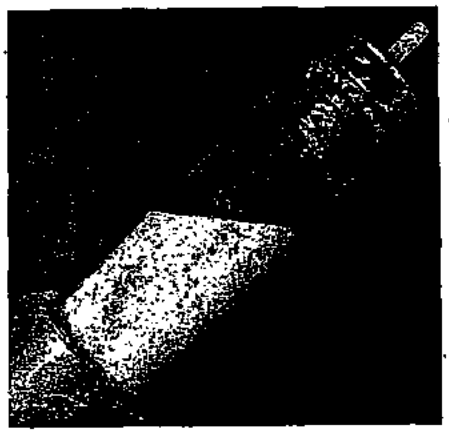


Figure 8

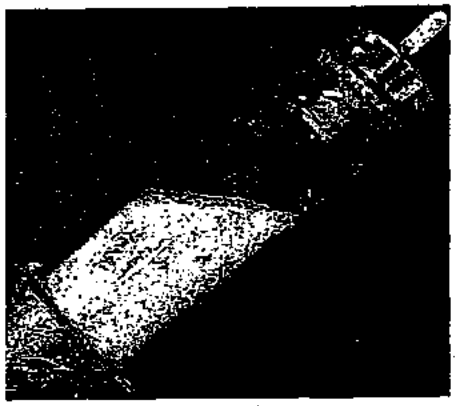


Figure 9

Figure 10

Figure 3/10

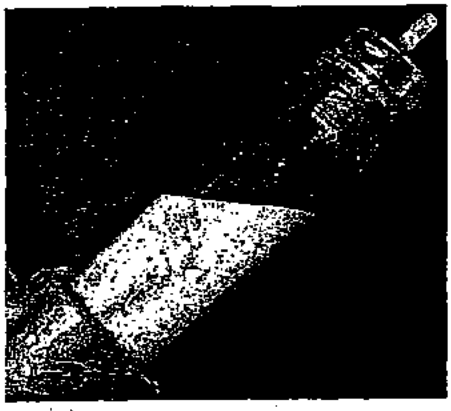


Figure 11

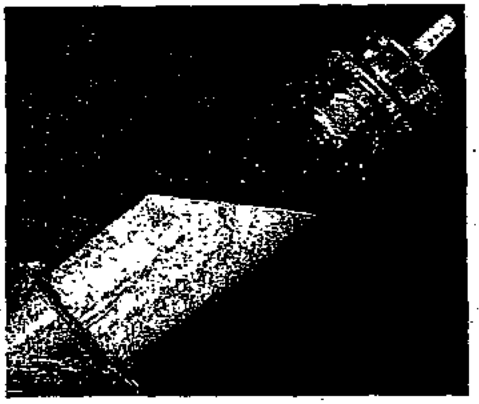


Figure 12

Figure 13

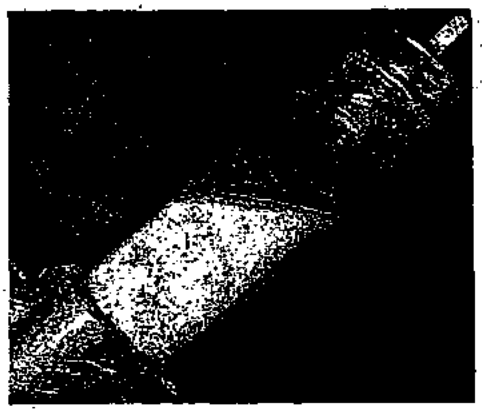


Figure 14

Figure 15

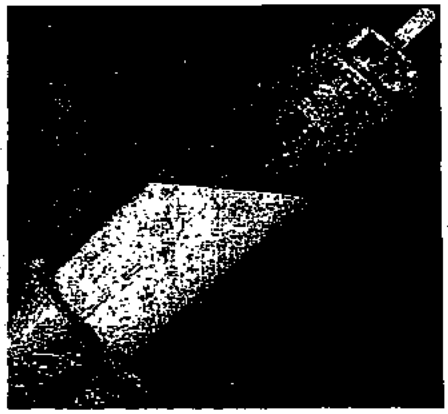


Figure 16

Figure 4/10

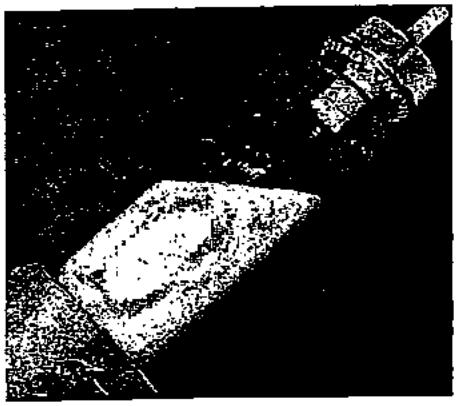


Figure 17

Figure 18

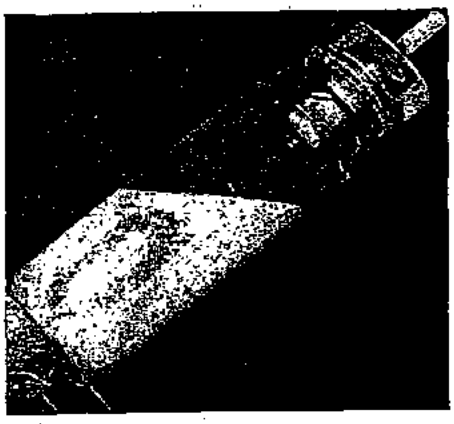


Figure 19

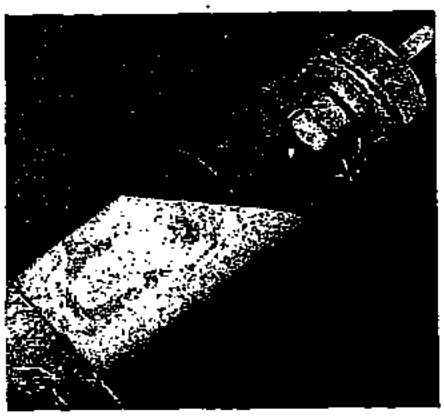


Figure 20

Figure 21

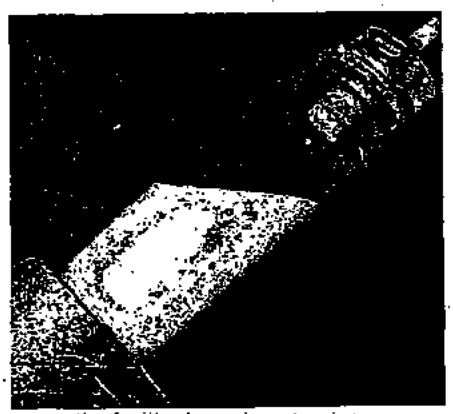
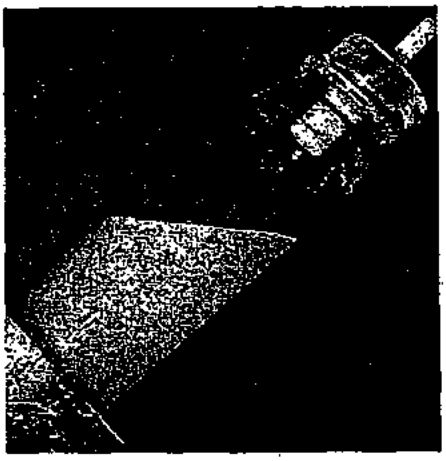


Figure 22

Figure 5/10

Figure 23



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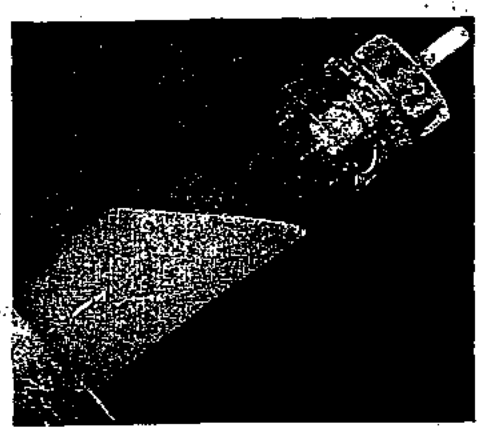

Figure 25

Figure 26

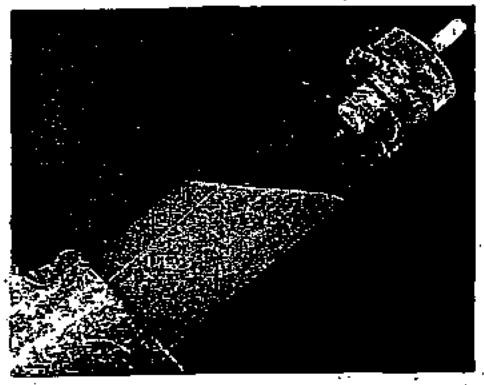

Figure 27

Figure 28

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Figure 29

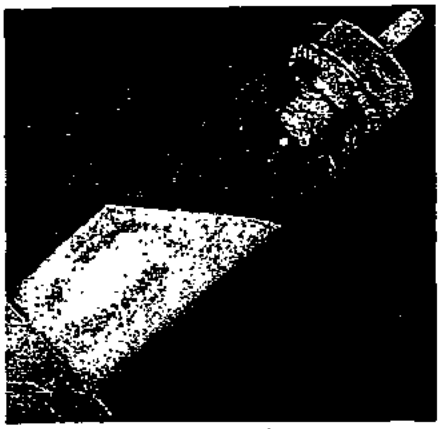

Figure 30

Figure 31

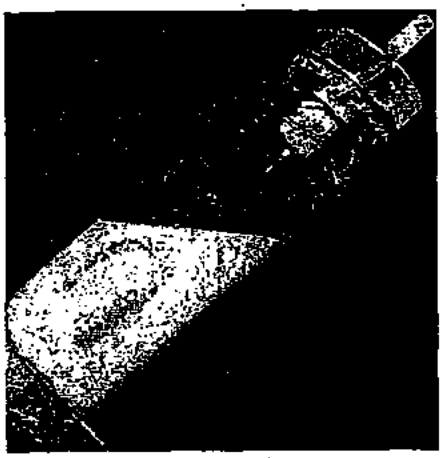

Figure 32

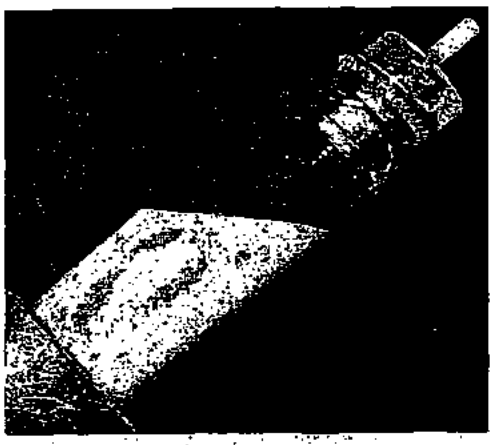

Figure 33

Figure 34

Figures 7/10

Figure 35

Figure 36

Figure 37

Figure 38

Figure 39

Figure 40

Figure 8/10

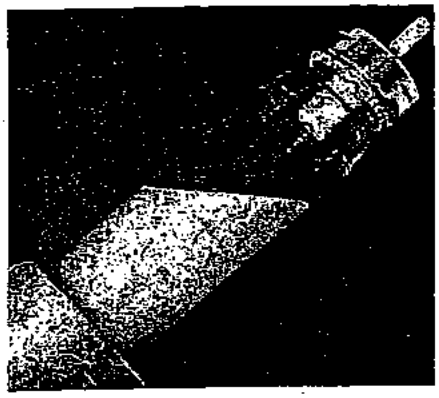

Figure 41

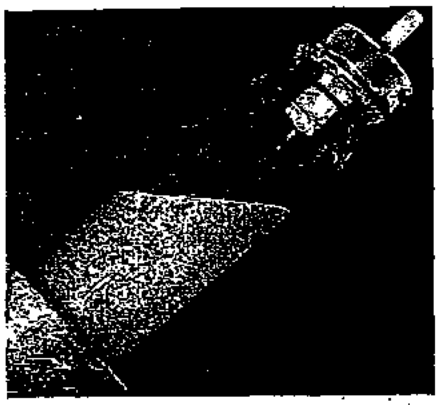

Figure 42

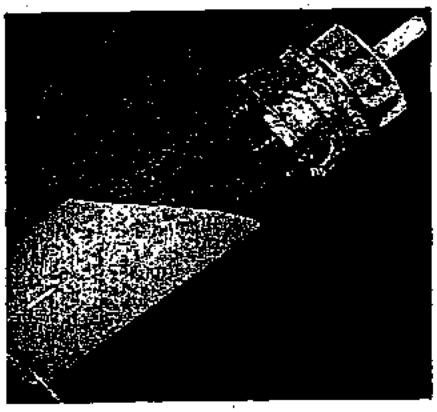

Figure 43

Figure 44

Figure 45

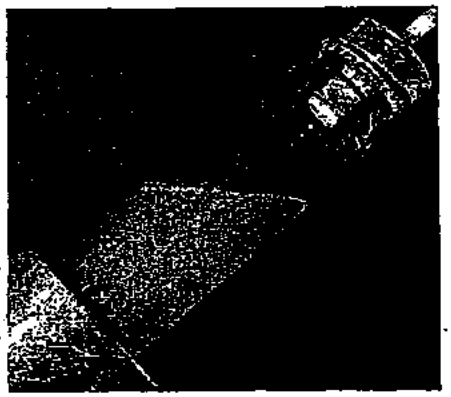

Figure 46

Figure 9/10

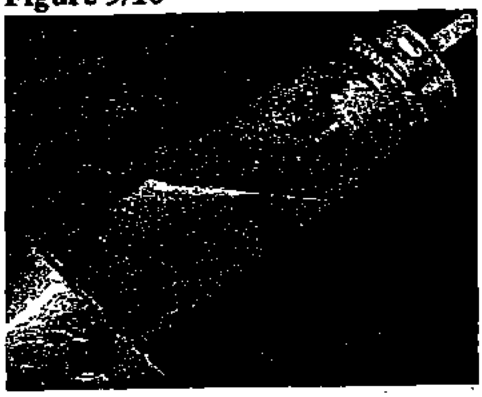

Figure 47 (Formoterol Fumarate Dihydrate in HFA 227)

Figure 48 (Formoterol Fumarate Dihydrate in HFA 134a)

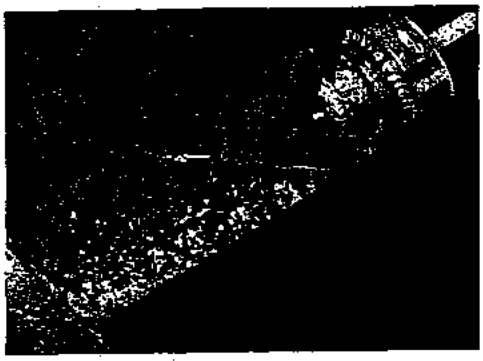

Figure 49 (Formoterol Fumarate with PEG 1000 and PVP K25 in a HFA 277 and HFA 134a mix)

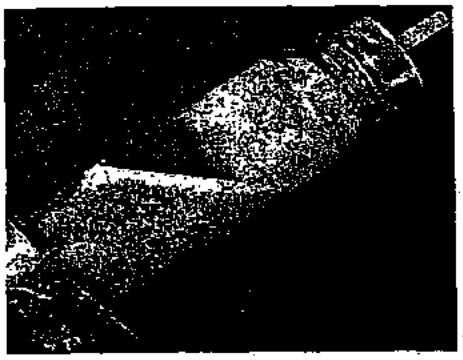

Figure 50 (Terbutaline Dihydrate sulphate in HFA 227)

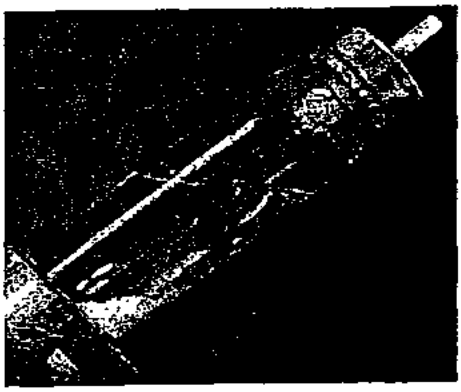

Figure 51 (Terbutaline Sulphate in HFA 134a)

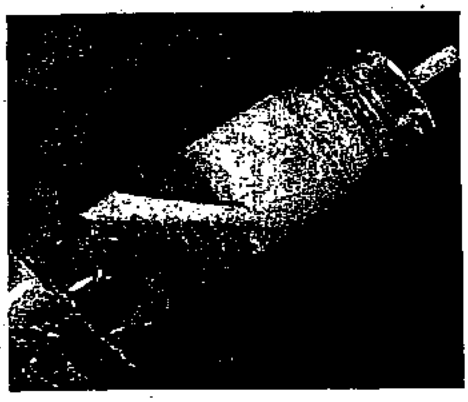

Figure 52 (Terbutaline with PEG 600 and PVP K30 in HFA 277)

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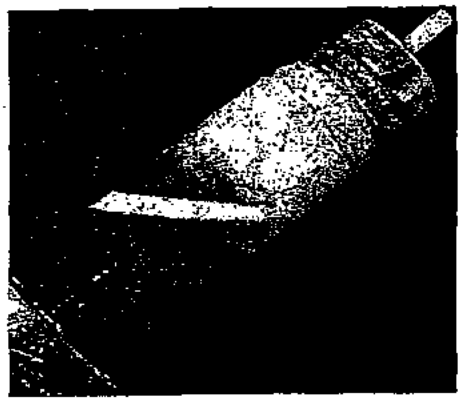

Figure 53 (Budesonide in HFA 227)

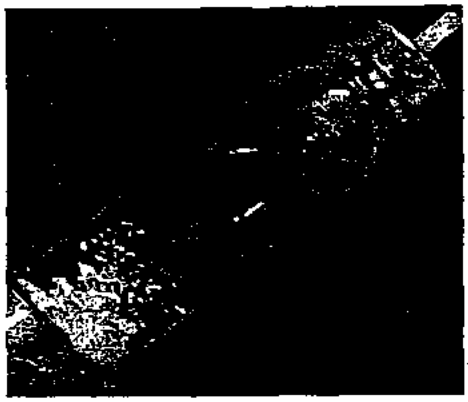

Figure 54 (Budesonide in HFA 134a)

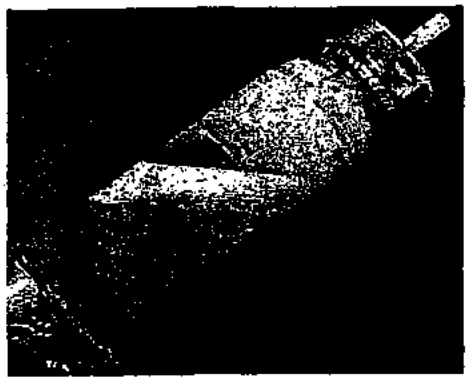

Figure 55 (Budesonide with PEG 1000 and PVP K25 in HFA 277)

Figure 56 (Viozan® in HFA 227)

Figure 57 (Viozan® in HFA 134a)

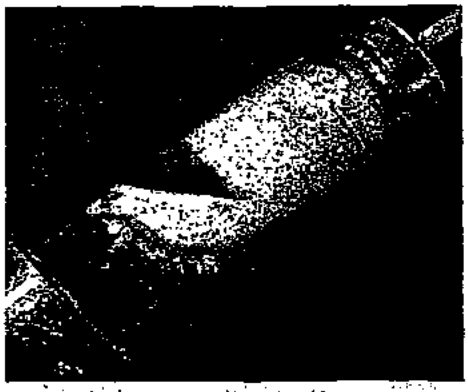

Figure 58 (Viozan® with PEG 600 and PVP K30 in HFA 277)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 01/01606

A. CLASSIFICATION OF SUBJECT MATTER

IPC7: A61K 9/12, A61K 9/72, A61K 47/24
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC7: A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO INTERNAL, WPI DATA, CA DATA, EMBASE, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	US 6149892 A (BRITTO), 21 November 2000 (21.11.00), column 1 - column 2; column 3, line 42 - line 46, and the examples --	1-18
X	US 5849265 A (LI-BOVET ET AL), 15 December 1998 (15.12.98), column 5 - column 6; column 7, line 39 - line 46, and the examples --	1-18
X	WO 9111173 A1 (FISONS PLC), 8 August 1991 (08.08.91), see especially pages nos. 6-7, the claims and the abstract --	1-18

[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
15 November 2001	16 -11- 2001
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer INGRID FALLENIUS/BS Telephone No. +46 8 782 25 00

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 01/01606

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	Anesth Analg, Volyme 88, 1999, Edmond I Eger II et al: "Minimum Alveolar Anesthetic Concentration of Fluorinated Alkanols in Rats: Relevance to Theories of Narcosis", pages 867-876 ---	1-18
A	US 3557294 A (ROBERT E. A. DEAR ET AL), 19 January 1971 (19.01.71) --- --------	1-18

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE01/01606

Box I **Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)**

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 18
because they relate to subject matter not required to be searched by this Authority, namely:

see next sheet*

2. ☒ Claims Nos.: 1-18
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

see next sheet**

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II **Observations where unity of invention is lacking (Continuation of item 2 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

*

Claim no. 18 relates to a method of treatment of the human or animal body by therapy. Rule. 39.1.(iv). Nevertheless, a search has been executed for this claim. The search has been based on the alleged effects of the composition.

**

Present claims 1-18 relate to an extremely large number of possible formulations. In fact, the claims contain so many options that a lack of clarity and conciseness within the meaning of Article 6 PCT arises to such an extent as to render a meaningful search of the claims impossible. Consequently, the search has been carried out for those parts of the application that appear to be clear and concise, namely the formulations recited in the examples.

INTERNATIONAL SEARCH REPORT

Information on patent family members

01/10/01

International application No.
PCT/SE 01/01606

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 6149892 A	21/11/00	AU 718851 B	20/04/00
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NOVEL COMPOSITION

Field of the invention

The present invention relates to a formulation comprising formoterol and budesonide for use in the treatment of inflammatory conditions/disorders, especially respiratory diseases such as asthma, COPD and rhinitis.

Background of the invention

Stability is one of the most important factors which determines whether a compound or a mixture of compounds can be developed into a therapeutically useful pharmaceutical product.

Combinations of formoterol and budesonide are known in the art, see for example WO 93/11773 discloses such a combination that is now marketed as Symbicort® in a dry powder inhaler. There are a variety of other inhalers by which a respiratory product can be administered, such as pressurised metered dose inhalers (pMDI's). Formulations for pMDI's may require certain excipients as disclosed in WO 93/05765.

It has now been found that certain HFA formulations comprising formoterol and budesonide together with polyvinylpyrrolidone (PVP) and polyethylene glycol (PEG) exhibit excellent physical suspension stability.

Description of the invention

In accordance with the present invention, there is provided a pharmaceutical composition comprising formoterol, budesonide, HFA 227, PVP and PEG characterised in that the PVP is present from about 0.0005 to about 0.03 %w/w and the PEG is present from about 0.05 to about 0.35% w/w.

Preferably the PVP is present in an amount of 0.001 % w/w. Preferably the PVP is PVP K25.

Preferably the PEG is present in an amount of 0.3 % w/w. Preferably the PEG is PEG 1000.

Preferably the concentrations of formoterol/budesonide are such that the formulation delivers formoterol/budesonide at 4.5/40 mcg, 4.5/80 mcg,4.5/160 mcg or 4.5/320mcg per actuation.

The formoterol can be in the form of a mixture of enantiomers. Preferably the formoterol is in the form of a single enantiomer, preferably the R;R enantiomer. The formoterol can be in the form of the free base, salt or solvate, or a solvate of a salt, preferably the formoterol is in the form of its fumarate dihydrate salt. Other suitable physiologically salts that can be used include chloride, bromide, sulphate, phosphate, maleate, tartrate, citrate, benzoate, 4-methoxybenzoate, 2- or 4-hydroxybenzoate, 4-chlorobenzoate, p-toluenesulphonate, benzenesulphonate, ascorbate, acetate, succinate, lactate, glutarate, gluconate, tricaballate, hydroxynapaphthalenecarboxylate or oleate.

Preferably the second active ingredient is budesonide, including epimers, esters, salts and solvates thereof. More preferably the second active ingredient is budesonide or an epimer thereof, such as the 22R-epimer of budesonide.

The pharmaceutical compositions according to the invention can be used for the treatment or prophylaxis of a respiratory disorder, in particular the treatment or prophylaxis of asthma, rhinitis or COPD.

In a further aspect the invention provides a method of treating a respiratory disorder, in particular asthma, rhinitis or COPD, in a mammal which comprises administering to a patient a pharmaceutical composition as herein defined.

The compositions of the invention can be inhaled from any suitable MDI device. Doses will be dependent on the severity of the disease and the type of patient, but are preferably 4.5/80 mcg or 4.5/160 mcg per actuation as defined above.

The invention is illustrated by the following examples.

Experimental section

Two methods can be used to evaluate physical suspension stability: Optical suspension characterisation (OSCAR) and TURBISCAN. Both methods are used to semi-quantify

sedimentation/creaming rates. For evaluation of physical suspension stability, formulations containing formoterol fumarate dihydrate, budesonide, PVP K25 and PEG 1000 in HFA-227 are prepared in polyethylene terephlate (PET) bottles crimped with a continuous valve. OSCAR measurements are performed using the PET bottles directly. For TURBISCAN analysis, the suspensions are transferred to custom designed pressure cells for measurement of light transmittance and backscattering.
Formulations containing formoterol fumarate dihydrate, budesonide, 0.001% w/w PVP K25 and either 0.1 % w/w or 0.3% PEG 1000 in HFA-227 were prepared in polyethylene terephlate (PET) bottles crimped with a continuous valve. For all formulations, the formoterol fumurate dihydrate concentration remained constant at 0.09mg/ml (equivalent to 4.5 mcg formoterol fumurate dihydrate per actuation) and the budesonide concentration varied between approximately 1mg/ml to 8 mg/ml (equivalent to 40 mcg to 320 mcg per actuation).

OSCAR analysis of these formulations gave relatively low light transmittance values at the lower sensor that is indicative of stable suspensions with low flocculation characteristics.

In addition product performance data for formulations containing formoterol fumurate dihydrate/budesonide at the following strengths, 4.5/80 mcg per actuation and 4.5/160 mcg per actuation, with 0.001% PVP K25 and either 0.1% or 0.3% PEG 1000 were stable for up to 12 months at 25°C/60% RH.

Data is given below.

OSCAR data for Symbicort pMDI formulations

Budesonide dose ex-actuator	Formoterol dose ex-actuator	PVP K25 concentration (% w/w in HFA-227)	Transmittance at lower sensor (mV)	PEG 1000 concentration (% w/w)	
				0.1	0.3
40 µg	4.5 µg	0.001	30 seconds		257
			60 seconds		264
80 µg	4.5 µg	0.001	30 seconds	202	
			60 seconds	240	
		0.002	30 seconds	184	
			60 seconds	185	
160 µg	4.5 µg	0.001	30 seconds	208	114
			60 seconds	304	191
		0.002	30 seconds	248	
			60 seconds	327	
320 µg	4.5 µg	0.001	30 seconds		475
			60 seconds		570
		0.002	30 seconds		930
			60 seconds		1443

Product performance data for Symbicort formulations containing 0.001% PVP K25 and 0.1% PEG 1000 in HFA-227

Product strength (µg) (FFD/budesonide/)	Fine particle fraction (% cumulative undersize for 4.7 µm cut-off)			
	Drug	Initial	25°C/60% RH 6 months	25°C/60% RH 12 months
4.5/80	Budesonide	51.3	52.8	62.0
	FFD	55.4	53.5	59.7
4.5/160	Budesonide	50.0	48.8	47.0
	FFD	54.2	52.1	51.3

Product performance data for Symbicort formulations containing 0.001% PVP K25 and 0.3% PEG 1000 in HFA-227

Product strength (µg) (FFD/budesonide)	Fine particle fraction (% cumulative undersize for 4.7 µm cut-off)			
	Drug	Initial	25°C/60% RH 6 months (FW)*	25°C/60% RH 12 months (FW)*
4.5/80	Budesonide	55.8	50.6	51.3
	FFD	64.2	57.6	58.7
4.5/160	Budesonide	48.7	50.2	52.3
	FFD	55.6	59.1	61.2

*Foil wrapped

Claims.

1. A pharmaceutical composition comprising formoterol, budesonide, HFA 227, PVP and PEG.

2. A formulation according to claim 1 characterised in that the PVP is present from about 0.0005 to about 0.05 %w/w and the PEG is present from about 0.05 to about 0.35% w/w.

3. A pharmaceutical composition according to claim 1 or 2 in which the PVP is PVP K25.

4. A pharmaceutical composition according to claim 1 to 3 in which the PVP is present in an amount of 0.001% w/w.

5. A pharmaceutical composition according to any one of claims 1 to 4 in which the PEG is PEG 1000.

6. A pharmaceutical composition according to any one of claims 1 to 5 in which the PEG is present in an amount of 0.3% w/w.

7. A pharmaceutical composition according to any one of claims 1 to 6 in which formoterol is in the form of its fumarate dihydrate salt

8. A pharmaceutical composition according to any one of claims 1 to 7 in which the formoterol is in the form of the single R,R-enantiomer.

9. A pharmaceutical composition according to any one of claims 1 to 8 in which the second active ingredient is the 22R-epimer of budesonide.

10. A pharmaceutical composition according to any one of claims 1 to 9 for use for the treatment or prophylaxis of a respiratory disorder.

11. A pharmaceutical composition according to any one of claims 1 to 9 for use for the treatment or prophylaxis of asthma, rhinitis or COPD.

12. A method of treating a respiratory disorder in a mammal which comprises administering to a patient a pharmaceutical composition according to any one of claims 1 to 9.

ABSTRACT

The invention relates to a formulation comprising formoterol and budesonide for use in the treatment of respiratory diseases

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(54) Title: COMPOSITION FOR INHALATION

(57) Abstract: The invention relates to a formulation comprising formoterol and budesonide for use in the treatment of respiratory diseases. The composition further contains HFA 227, PVP and PEG, preferably PVP K25 and PEG 1000.

Composition for inhalation

Field of the invention

The present invention relates to a formulation comprising formoterol and budesonide for use in the treatment of inflammatory conditions/disorders, especially respiratory diseases such as asthma, COPD and rhinitis.

Backgrounnd of the invention

Stability is one of the most important factors which determines whether a compound or a mixture of compounds can be developed into a therapeutically useful pharmaceutical product.

Combinations of formoterol and budesonide are known in the art, see for example WO 93/11773 discloses such a combination that is now marketed as Symbicort® in a dry powder inhaler. There are a variety of other inhalers by which a respiratory product can be administered, such as pressurised metered dose inhalers (pMDI's). Formulations for pMDI's may require certain excipients as disclosed in WO 93/05765.

It has now been found that certain HFA formulations comprising formoterol and budesonide together with polyvinylpyrrolidone (PVP) and polyethylene glycol (PEG) exhibit excellent physical suspension stability.

Description of the invention

In accordance with the present invention, there is provided a pharmaceutical composition comprising formoterol, budesonide, HFA 227, PVP and PEG characterised in that the PVP is present from about 0.0005 to about 0.03 %w/w and the PEG is present from about 0.05 to about 0.35% w/w.

Preferably the PVP is present in an amount of 0.001 % w/w. Preferably the PVP is PVP K25.

Preferably the PEG is present in an amount of 0.3 % w/w. Preferably the PEG is PEG 1000.

Preferably the concentrations of formoterol/budesonide are such that the formulation delivers formoterol/budesonide at 4.5/40 mcg, 4.5/80 mcg, 4.5/160 mcg or 4.5/320mcg per actuation.

The formoterol can be in the form of a mixture of enantiomers. Preferably the formoterol is in the form of a single enantiomer, preferably the R, R enantiomer. The formoterol can be in the form of the free base, salt or solvate, or a solvate of a salt, preferably the formoterol is in the form of its fumarate dihydrate salt. Other suitable physiologically salts that can be used include chloride, bromide, sulphate, phosphate, maleate, tartrate, citrate, benzoate, 4-methoxybenzoate, 2- or 4-hydroxybenzoate, 4-chlorobenzoate, p-toluenesulphonate, benzenesulphonate, ascorbate, acetate, succinate, lactate, glutarate, gluconate, tricaballate, hydroxynapaphthalenecarboxylate or oleate.
Preferably the second active ingredient is budesonide, including epimers, esters, salts and solvates thereof. More preferably the second active ingredient is budesonide or an epimer thereof, such as the 22R-epimer of budesonide.

The pharmaceutical compositions according to the invention can be used for the treatment or prophylaxis of a respiratory disorder, in particular the treatment or prophylaxis of asthma, rhinitis or COPD.
In a further aspect the invention provides a method of treating a respiratory disorder, in particular asthma, rhinitis or COPD, in a mammal, which comprises administering to a patient a pharmaceutical composition as herein defined.

The compositions of the invention can be inhaled from any suitable MDI device. Doses will be dependent on the severity of the disease and the type of patient, but are preferably 4.5/80 mcg or 4.5/160 mcg per actuation as defined above.

The concentration of PVP (0.001%w/w) used in this formulation has been found to give consistently stable formulations over the required dose range, incorporating a wide range of concentrations of the active components, and at a much lower concentration than indicated in the prior art.

The invention is illustrated by the following examples.

Experimental section

Two methods can be used to evaluate physical suspension stability: Optical suspension characterisation (OSCAR), and TURBISCAN. Both methods are used to semi-quantify sedimentation/creaming rates. OSCAR measurements are performed using the PET bottles directly. For TURBISCAN analysis, the suspensions are transferred to custom designed pressure cells for measurement of light transmittance and backscattering.

METHODOLOGY

OSCAR

Optical Suspension Characterisation (OSCAR) equipment is custom designed for the rapid and reproducible semi-quantification of metered dose inhaler suspension characteristics.

The OSCAR equipment utilises changes in light transmission with time, to characterise a pre-agitated suspension formulation (a schematic diagram of the equipment is shown in Figure 1). The equipment consists of a twin headed test assembly. The head on the left side of the equipment is used with dilute suspensions and the right for concentrated suspensions. The selector switch mounted between the two test heads is used to alternate concentration choice. The output from the selected test head is directed to the equipment mounted voltage display and to the computer for data logging. The analogue signals from photodetectors are digitised and the values collected in data files, these are then processed using a suitable software package. There are two equipment mounted voltage displays, one each for the upper and lower photodetectors. The upper and lower photodetectors are height adjustable and a position readout display is provided to indicate the set height for each test run.

The Reagecon Turbidity standards (2500-4000 NTU) are used to calibrate the sensitivity of the OSCAR equipment. In this case, the 3000 NTU turbidity calibration standard is used as a standard calibration check. However any of the turbidity standards can be used to adjust the sensitivity of the probes to a specific voltage appropriate to the formulation.

Samples for test on the OSCAR equipment are presented in PET bottles crimped with non-metering valves.

For background information and prior art for this method refer to papers from Drug Delivery to the Lungs IX, 1997, Method Development of the OSCAR technique for the characterization of metered dose inhaler formulations, Authors N. Govind, P. Lambert And Drug delivery to the Lungs VI, 1995, A Rapid Technique for Characterisation of the Suspension Dynamics of metered Dose Inhaler Formulations, Author, PA Jinks (3M Healthcare Ltd)

TURBISCAN

Turbiscan MA 2000 is a concentrated dispersion and emulsion stability and instability analyser, or a vertical scan macroscopic analyser. It consists of a reading head moving along a flat-bottomed, 5ml cylindrical glass cell, which takes readings of transmitted and backscattered light every 40 μm on a maximum sample height of 80mm. The scan can be repeated with a programmable frequency to obtain a macroscopic fingerprint of the sample.

The reading head uses a pulsed near infrared light source (wavelength = 850 nm) and two synchronous detectors:

Transmission detector: Picks up light transmitted through the solution in the tube, at 0°

Backscattering detector: Receives the light back scattered by the product at 135°.

The profile obtained characterises the samples homogenieity, concentration and mean particle diameter. It allows for quantification of the physical processes the sample is undergoing. As well as detecting destabilisation, Turbiscan allows comparison of, for example, the sedimentaion rate of different suspensions.

Turbiscan may be used in several modes, eg transmitted or backscattering modes. Turbiscan has been used here in these examples to measure the transmitted light as a funtion of time

Dispersion instability is the result of two physical processes: a) particle size increases as a result of the formation of aggregates, due to flocculation b) particle migration resulting in creaming or sedimentation. When a product is stable (ie no flocculation, creaming or

sedimentation), the transmitted and backscattered light will remain constant i.e. scans of these will show a constant level profile. If the product undergoes changes in particle size, variations in the transmitted/ backscattered light show as change in the direction of the scan from horizontal or steady state profile.

For pressurised systems a cell capable of handling pressurised samples is required. Such a cell was used for the evaluations of these HFA formulations. The scans were performed in the AUTO mode.

The % transmission averages shown in the figure (see later) were taken from a zone around the middle of the suspension sample.

INITIAL EVALUATION

For the initial evaluation, only OSCAR was used.

Formulations containing formoterol fumarate dihydrate, budesonide, 0.001% w/w PVP K25 and either 0.1 % w/w or 0.3% PEG 1000 in HFA-227 were prepared in polyethylene terephlate (PET) bottles crimped with a continuous valve. For all formulations, the formoterol fumurate dihydrate concentration remained constant at 0.09mg/ml (equivalent to 4.5 mcg formoterol fumurate dihydrate per actuation) and the budesonide concentration varied between approximately 1mg/ml to 8 mg/ml (equivalent to 40 mcg to 320 mcg per actuation).

Early OSCAR data for Symbicort pMDI formulations

Budesonide dose ex-actuator	Formoterol dose ex-actuator	PVP K25 concentration (% w/w)	Time seconds	Transmittance (mV) Lower sensor	
				PEG concn %w/w	
				0.1	0.3
40 µg	4.5 µg	0.001	30 seconds		257
			60 seconds		264
80 µg	4.5 µg	0.001	30 seconds	202	
			60 seconds	240	
		0.002	30 seconds	184	
			60 seconds	185	
160 µg	4.5 µg	0.001	30 seconds	208	114
			60 seconds	304	191
		0.002	30 seconds	248	
			60 seconds	327	
320 µg	4.5 µg	0.001	30 seconds		475
			60 seconds		570
		0.002	30 seconds		930
			60 seconds		1443

OSCAR analysis of these formulations gave relatively low light transmittance values at the lower sensor, which is indicative of stable suspensions with low flocculation characteristics. Early indications were that the 0.001% w/w PVP with 0.3% PEG 1000 would give the best suspension.

FURTHER EVALUATION: various concentrations of PVP K25 with a constant PEG 1000 concentration of 0.3% w/w.

OSCAR, Turbiscan and photographic methods were used to evaluate the formulations. OSCAR and Turbiscan techniques have been described earlier. Samples with varying concentrations of PVP were analysed to determine suspension stability over time.

PHOTOGRAPHIC ANALYSIS

For the photographic analysis , samples were prepared in PET bottles and photographed digitally over time, using a black background. These photographs (some of which are shown here) show the behaviour of the suspension over time and allow easy comparison of the effectiveness of the various concentrations of PVP. The concentration of PVP varied from 0.0001 to 0.05 % w/w. From left to right on the photographs the concentration of PVP is as follows:

0.0001 far left	0.0005	0.001	0.01	0.03	0.05 far right

DIGITAL PHOTOGRAPHY OF FORMULATIONS SHOWING DEGREE OF DISPERSION OVER TIME

Figures 9, 10 and 11 show Budesonide 160µg/shot, Formoterol 4.5µg/shot with various PVP K25 concentrations and 0.3% PEG 1000 at 0, 15, 30, and 60 seconds standing time.

Figures 12, 13 and 14 shows Budesonide 80µg/shot, Formoterol 4.5µg/shot with various PVP K25 concentrations and 0.3% PEG 1000 at 0, 30, and 60 seconds standing time.

TABLE OF DEGREEE OF DISPERSION OF SUSPENSIONS OVER TIME: (ALL SAMPLES)

Photographs were taken of all doses (320µg/4.5µg to 40µg/4.5µg) at 0, 15, 30, 60, 90 seconds, and 2, 5 and 10 minutes. As this produced too many photographs to reproduce here, a chart has been constructed to give a reprentation of the degree of dispersion over time.

If the sample was fully suspended, the sample was rated 0 e.g. at 0 minutes they were fully dispersed. From there, the samples have been rated in increments of 1-5 at 20% intervals to express the degree of dispersion i.e. 0 was fully suspended and 5 fully creamed. This allows some comparison across the whole dose range and PVP concentration range used.

(Note concentration of Formoterol is 4.5µg/shot in all the samples)

(Samples are all fully dispersed at 0 seconds and therefore all have a score of 0)

Fully dispersed – 0

More than 80% dispersed ie less than 20% clear liquid present 1

More than 60% dispersed ie less than 40% clear liquid present 2
Less than 40% dispersed ie more than 60% clear liquid present 3
Less than 20% dispersed ie more than 80% clear liquid present 4
Fully creamed 5

TABLE OF DEGREEE OF DISPERSION OF SUSPENSIONS OVER TIME: ALL SAMPLES

Dose	Time	PVP concentration (% w/w)					
µg/shot Budesonide	Sec/mins	0.0001	0.0005	0.001	0.01	0.03	0.05
320	15	2	1	0-1	0-1	0-1	0-1
	30	3	3	2	1-2	2	2
	60	4	4	3-4	2	3	3-4
	90	4	5	5	3	5	5
	2	5	5	4-5	4-5	5	5
	5	5	5	5	5	5	5
	10	5	5	5	5	5	5
160	15	3	2	0-1	0-1	2	2
	30	3	2	1	1	2	2
	60	5	4	1	2	4	5
	90	5	5	1	2	5	5
	2	5	5	1	2	5	5
	5	5	5	2	4	5	5
	10	5	5	2	4	5	5
80	15	2	1	0	0	1	1
	30	3	2	1	1	2	2
	60	4	2	1	1-2	3	3
	90	5	3	1-2	1-2	4	3
	2	5	3-4	1	1	5	4
	5	5	4	2	2	5	5
	10	5	5	3	3	5	5
40	15	1	1	0	0	1	2
	30	2	1	1	2	2	3
	60	1-2	1	1	2	2	3
	90	1-2	1-2	1-2	2	2-3	4
	2	2	2	2	3	4	5

	5	3	2	2	3	4	5
	10	4-5	3	2	4	5	5

Suspensions considered excellent are highlighted in bold.
It can be seen that the formulations with 0.001% w/w PVP gave the best suspension stability overall.

OSCAR DATA (Graphs of light transmission versus time)

Figure 2 shows the average OSCAR transmission readings (lower sensor only) for various concentrations of PVP K25. A low transmission reading indicates that the suspension is dispersed preventing light being transmitted. Hence, it can be seen that the lowest line is the most stable formulation. This is the 0.001% PVP sample.

In Figure 3, the bottom line, again with low transmission readings, clearly shows that the formulation containing 0.001% PVP is the most stable.

TURBISCAN DATA(Graphs of percentage (%) light transmission versus time)

Data from the Turbiscan can be intepretated in a similar vein to the OSCAR data in that a low percentage (%) transmission indicates the suspension is dispersed . The % transmission averages quoted here were taken from a zone around the middle of the suspension sample. In Figure 4 the most stable formulation is the lowest line with the lowest % transmission, i.e. the bold black line with 0.001%w/w PVP

Figures 5 and 6 show that the suspension with 0.001% w/w PVP is the most stable (bottom bold line) with the lowest % transmission.

FURTHER EVALUATION: Determination of the optimum PEG 1000 concentration.

For this evaluation, photography, turbiscan and force to fire data (valve performance) was used to determine the optimum PEG concentration.

Line1

METHODOLOGY - Force to fire (return force at 0.5mm stem return)

Force to fire testing was performed using the Lloyd LRX testing machine. The pMDI unit to be tested was placed valve down in a can holder on the lower platform of the unit. The upper crosshead was then moved to just above the base of the can. Can actuations were performed using a standard protocol. During measurement, force data is captured by means of the load cell located at the top of the upper crosshead. This program was designed to output the return force at 0.5mm stem return as this is the point at which the metering chamber is considered to refill.

A low return force is indicative of high friction and potential sticking problems. It also suggests there may be a problem with low actuation weights as the propellant enters the metering chamber more slowly and has time to vaporise. Force to fire testing was performed at preset actuations.

DATA

FORCE TO FIRE DATA

Figure 7 shows the effect of PEG 1000 concentration on stem return force for the 4.5/160 μg formoterol/budesonide formulation

This shows that at 120 actuations, the return force is greater for the 0.3% w/w PEG 1000 concentration than for the other concentrations of 0.5% and 0.1%. In general, the higher the return force the lesser the chance of the valve stem sticking. The above data shows that in this case 0.3% would be preferred.

TURBISCAN DATA

The Turbiscan data (figure 8) shows that there is little difference between the stability of suspensions made with varying levels of PEG 1000 except for the 0.005% w/w level which was unsatisfactory.

PHOTOGRAPHIC ANALYSIS

Digital photographs of suspensions containing Budesonide, Formoterol, HFA 227, 0.001%w/w PVP and varying levels of PEG 1000 show little variation in suspension stability over time (0 seconds to 10 minutes) except for the 0.005% w/w PEG level (in agreement with the Turbiscan data).

Figures 15 and 16 show Budesonide 80µg/shot, Formoterol 4.5µg/shot with 0.001% PVP K25 and various concentrations of PEG 1000 at 0 (1) and 10 minutes (2) standing time

PRODUCT PERFORMANCE DATA

In addition to the above, product performance data for formulations containing formoterol fumurate dihydrate/budesonide at the following strengths, 4.5/80 mcg per actuation and 4.5/160 mcg per actuation, with 0.001% PVP K25 and either 0.1% or 0.3% PEG 1000 were stable for up to 12 months at 25°C/60% RH.

Product performance data for Symbicort formulations containing 0.001% PVP K25 and 0.1% PEG 1000 in HFA-227

Product strength (µg) (FFD/budesonide)	**Fine particle fraction (% cumulative undersize for 4.7 µm cut-off)**			
	Drug	Initial	25°C/60% RH 6 months	25°C/60% RH 12 months
4.5/80	Budesonide	51.3	52.8	62.0
	FFD	55.4	53.5	59.7
4.5/160	Budesonide	50.0	48.8	47.0
	FFD	54.2	52.1	51.3

Product performance data for Symbicort formulations containing 0.001% PVP K25 and 0.3% PEG 1000 in HFA-227

Product strength (μg) (FFD/budesonide)	Fine particle fraction (% cumulative undersize for 4.7 μm cut-off)			
	Drug	Initial	25°C/60% RH 6 months	25°C/60% RH 12 months
4.5/80	Budesonide	55.8	50.6	51.3
	FFD	64.2	57.6	58.7
4.5/160	Budesonide	48.7	50.2	52.3
	FFD	55.6	59.1	61.2

Claims.

1. A pharmaceutical composition comprising formoterol, budesonide, HFA 227, PVP and PEG.

2. A formulation according to claim 1 characterised in that the PVP is present from about 0.0005 to about 0.05 %w/w and the PEG is present from about 0.05 to about 0.35% w/w.

3. A pharmaceutical composition according to claim 1 or 2 in which the PVP is PVP K25.

4. A pharmaceutical composition according to claim 1 to 3 in which the PVP is present in an amount of 0.001% w/w.

5. A pharmaceutical composition according to any one of claims 1 to 4 in which the PEG is PEG 1000.

6. A pharmaceutical composition according to any one of claims 1 to 5 in which the PEG is present in an amount of 0.3% w/w.

7. A pharmaceutical composition according to any one of claims 1 to 6 in which formoterol is in the form of its fumarate dihydrate salt

8. A pharmaceutical composition according to any one of claims 1 to 7 in which the formoterol is in the form of the single R, R-enantiomer.

9. A pharmaceutical composition according to any one of claims 1 to 8 in which the second active ingredient is the 22R-epimer of budesonide.

10. A pharmaceutical composition according to any one of claims 1 to 9 for use for the treatment or prophylaxis of a respiratory disorder.

11. A pharmaceutical composition according to any one of claims 1 to 9 for use for the treatment or prophylaxis of asthma, rhinitis or COPD.

12. A method of treating a respiratory disorder in a mammal which comprises administering to a patient a pharmaceutical composition according to any one of claims 1 to 9.

Fig 1/16

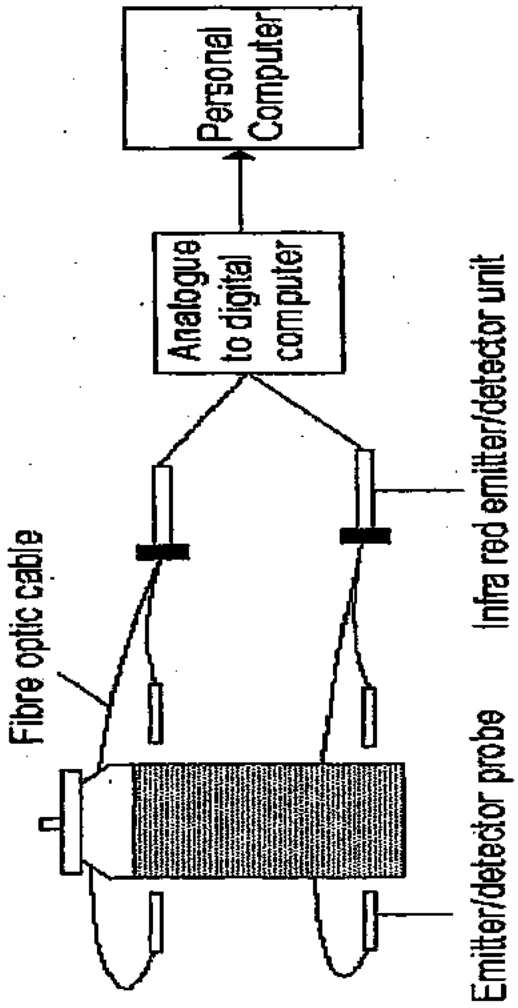


Figure 1: Schematic for OSCAR set-up

Fig 2/16

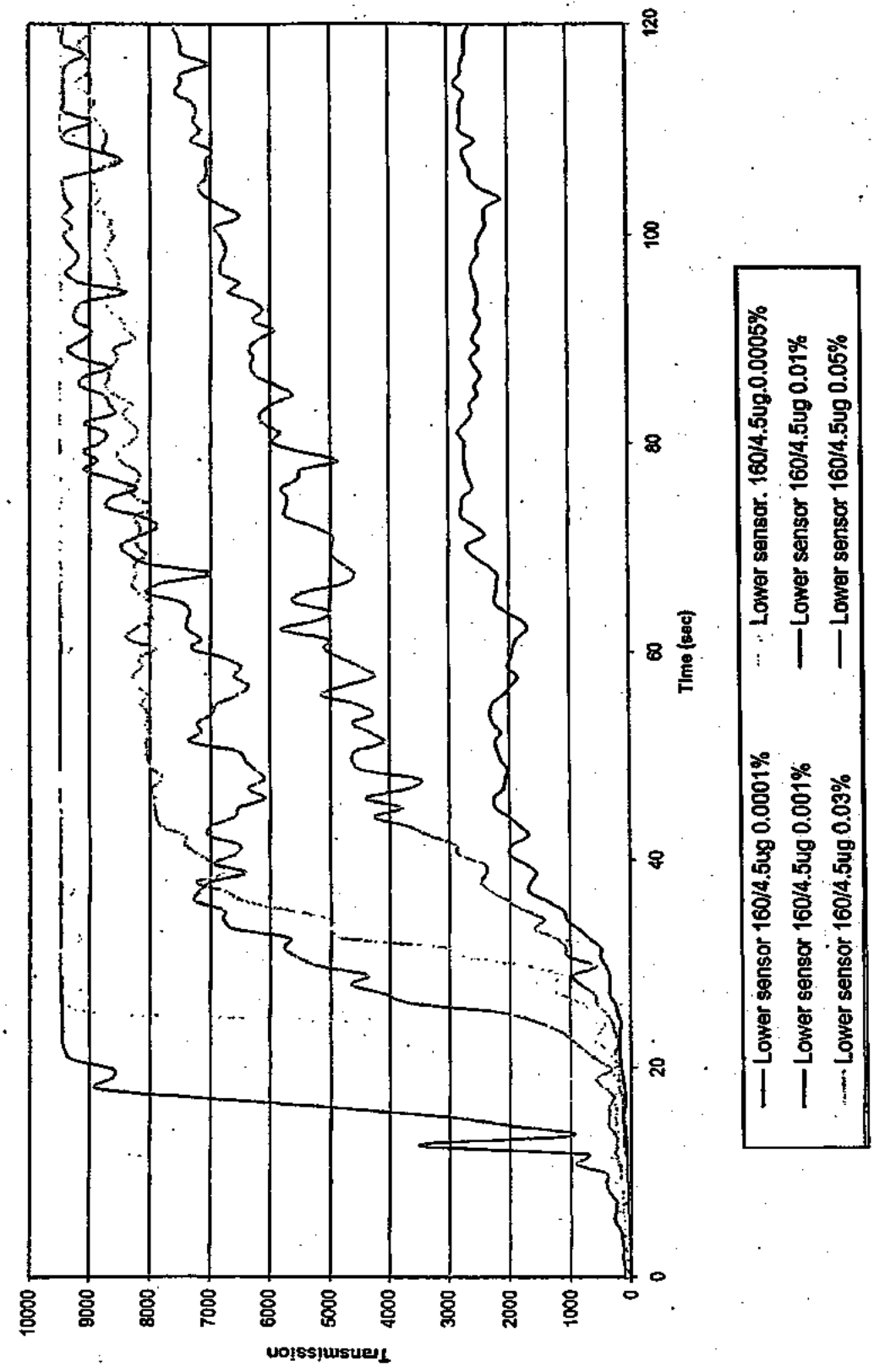


Figure 2: Averages of OSCAR data for formulation containing 160/4.5ug Budesonide/Formoterol. 0.3% w/w PEG 1000. 0.0001% - 0.05% w/w PVP K25.

Fig 3/16

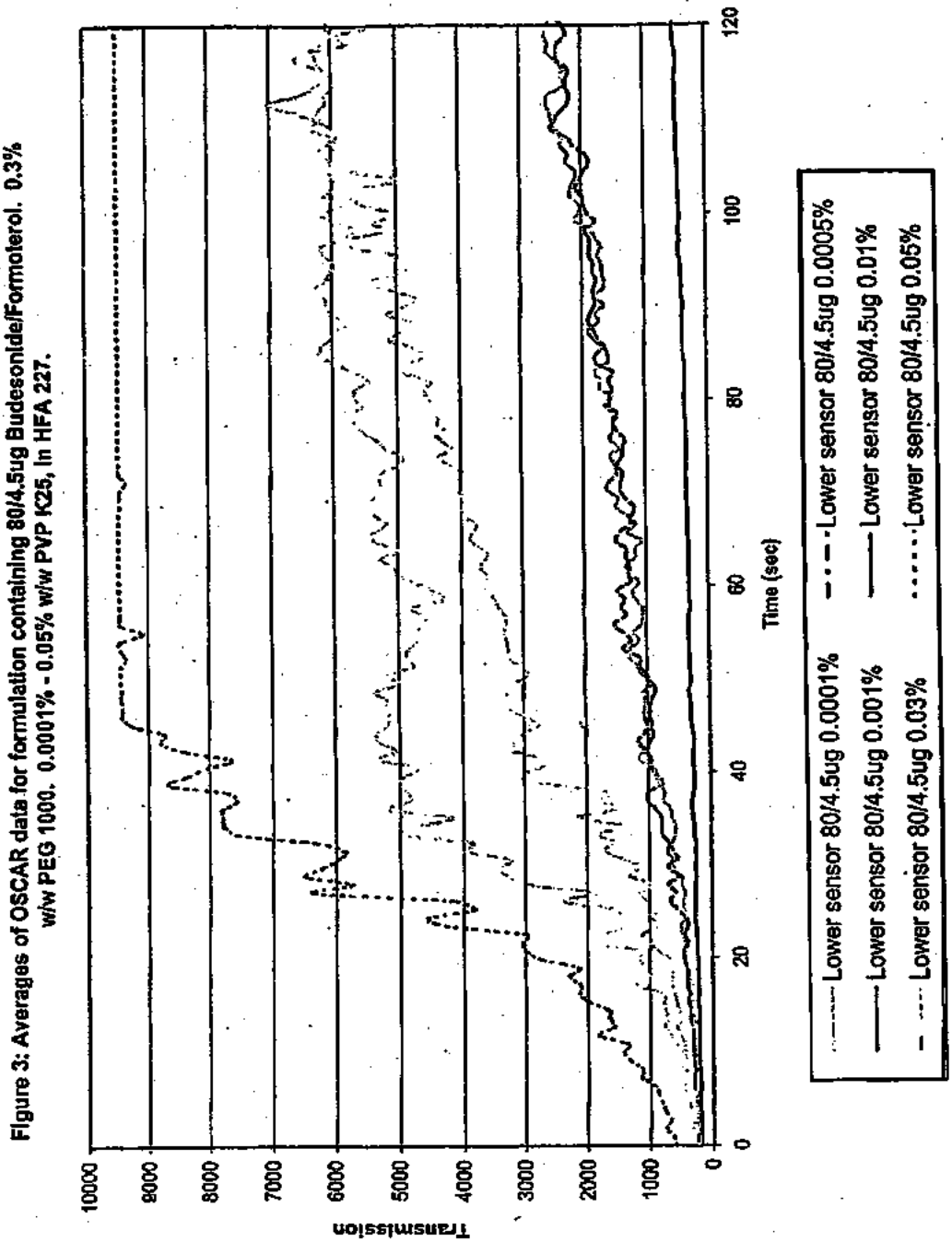


Figure 3: Averages of OSCAR data for formulation containing 80/4.5ug Budesonide/Formoterol. 0.3% w/w PEG 1000. 0.0001% - 0.05% w/w PVP K25, In HFA 227.

Fig 4/16

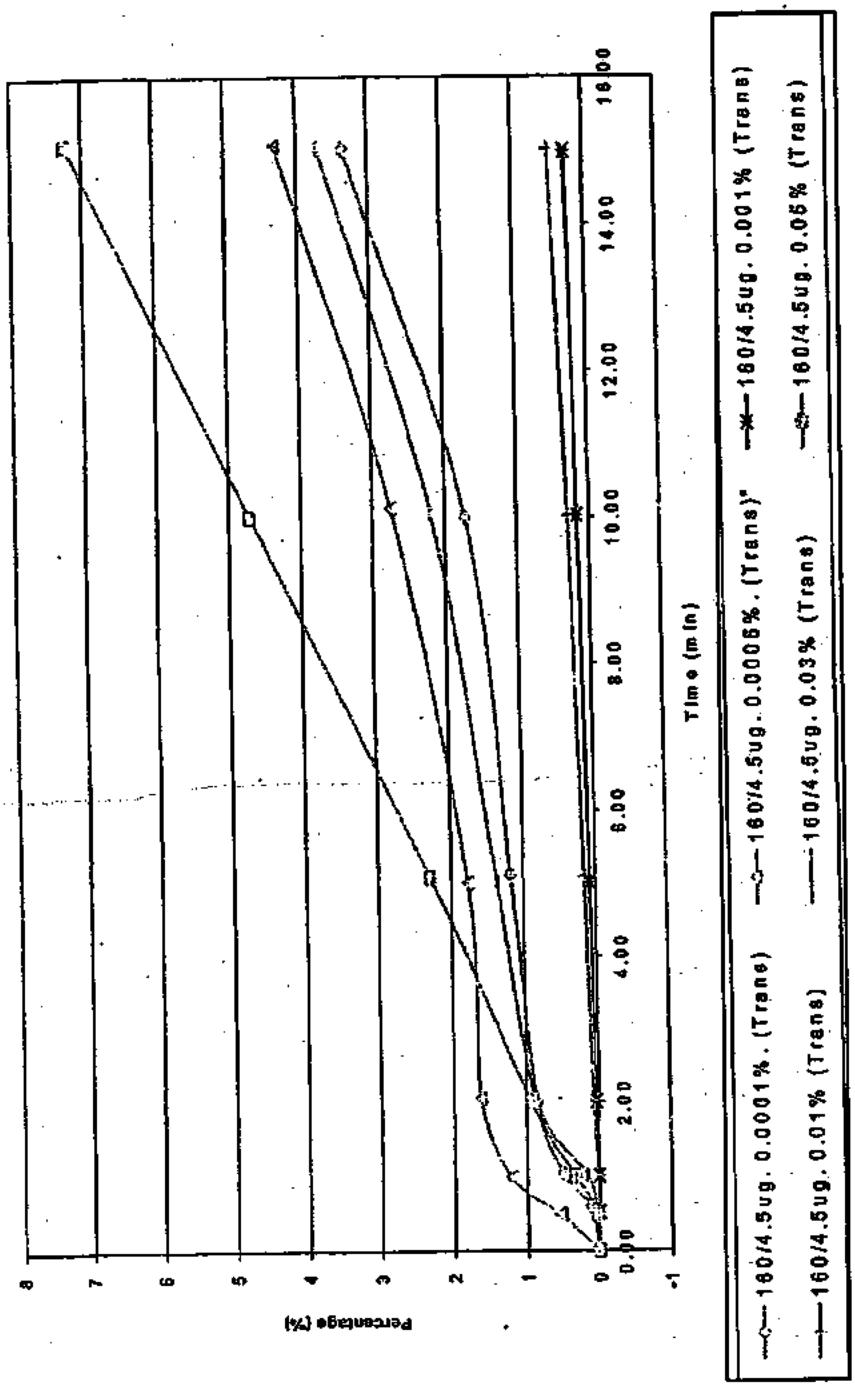


Figure 4: Averages of Turbiscan data for formulation containing 160/4.5ug Budesonide/Formoterol. 0.3% w/w PEG 1000, 0.0001% - 0.05% w/w PVP K25, in HFA 227.
Percentage (%)
Time (min)
160/4.5ug. 0.0001%. (Trans)
160/4.5ug. 0.0006%. (Trans)*
160/4.5ug. 0.001% (Trans)
160/4.5ug. 0.01% (Trans)
160/4.5ug. 0.03% (Trans)
160/4.5ug. 0.05% (Trans)

Fig 5/16

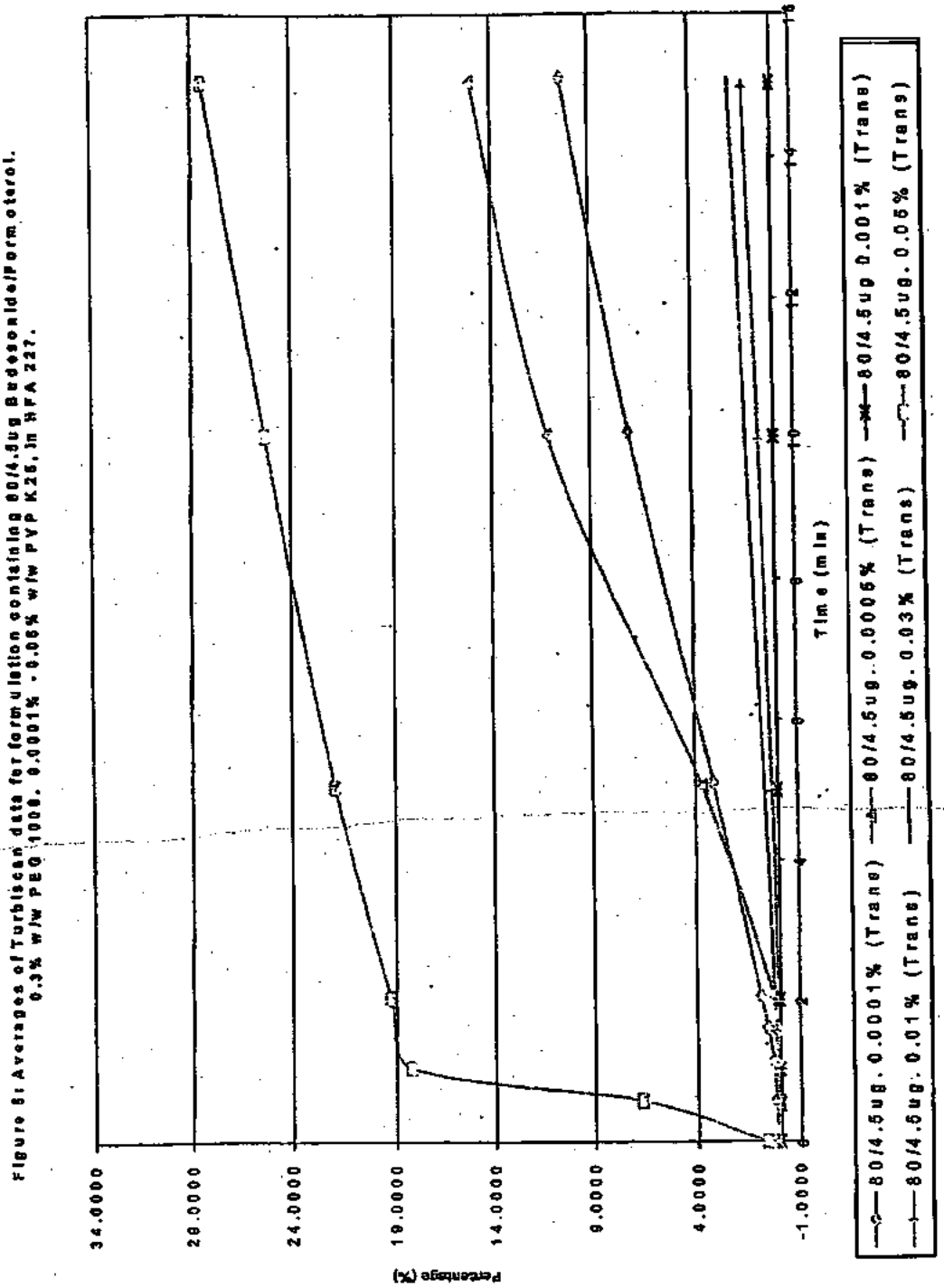


Figure 5: Averages of Turbiscan data for formulation containing 80/4.5ug Budesonide/Formoterol. 0.3% w/w PEG 1000, 0.0001% - 0.05% w/w PVP K25, in HFA 227.
Backscatter (%)
34.0000
29.0000
24.0000
19.0000
14.0000
9.0000
4.0000
-1.0000
Time (min)
80/4.5ug. 0.0001% (Trans)
80/4.5ug. 0.0006% (Trans)
80/4.5ug 0.001% (Trans)
80/4.5ug. 0.01% (Trans)
80/4.5ug. 0.03% (Trans)
80/4.5ug. 0.05% (Trans)

Fig 6/16

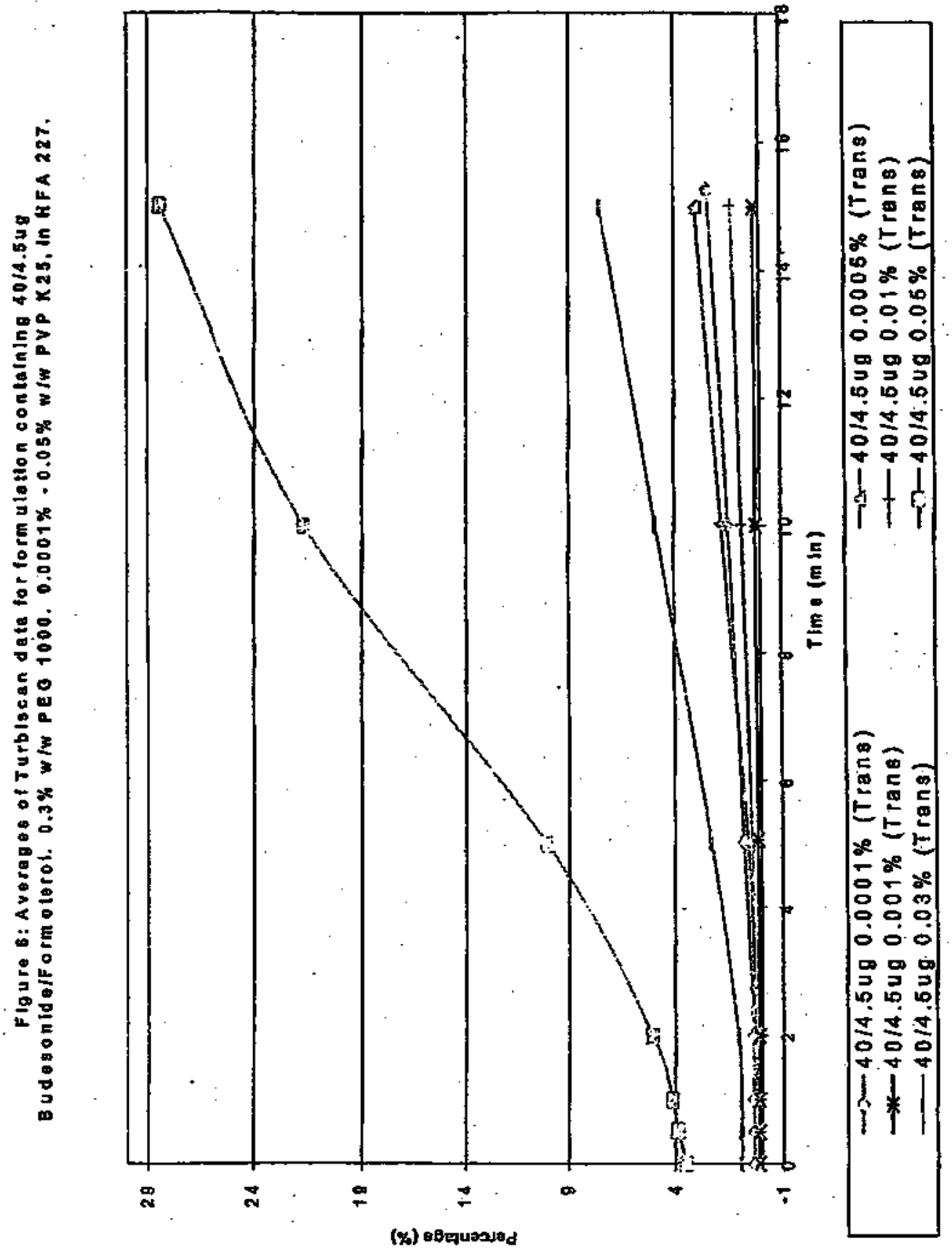


Figure 6: Averages of Turbiscan data for formulation containing 40/4.5ug Budesonide/Formoterol. 0.3% w/w PEG 1000, 0.0001% - 0.05% w/w PVP K25, in HFA 227.
Percentage (%)
Time (min)
40/4.5ug 0.0001% (Trans)
40/4.5ug 0.001% (Trans)
40/4.5ug 0.03% (Trans)
40/4.5ug 0.0005% (Trans)
40/4.5ug 0.01% (Trans)
40/4.5ug 0.05% (Trans)

Fig 7/16

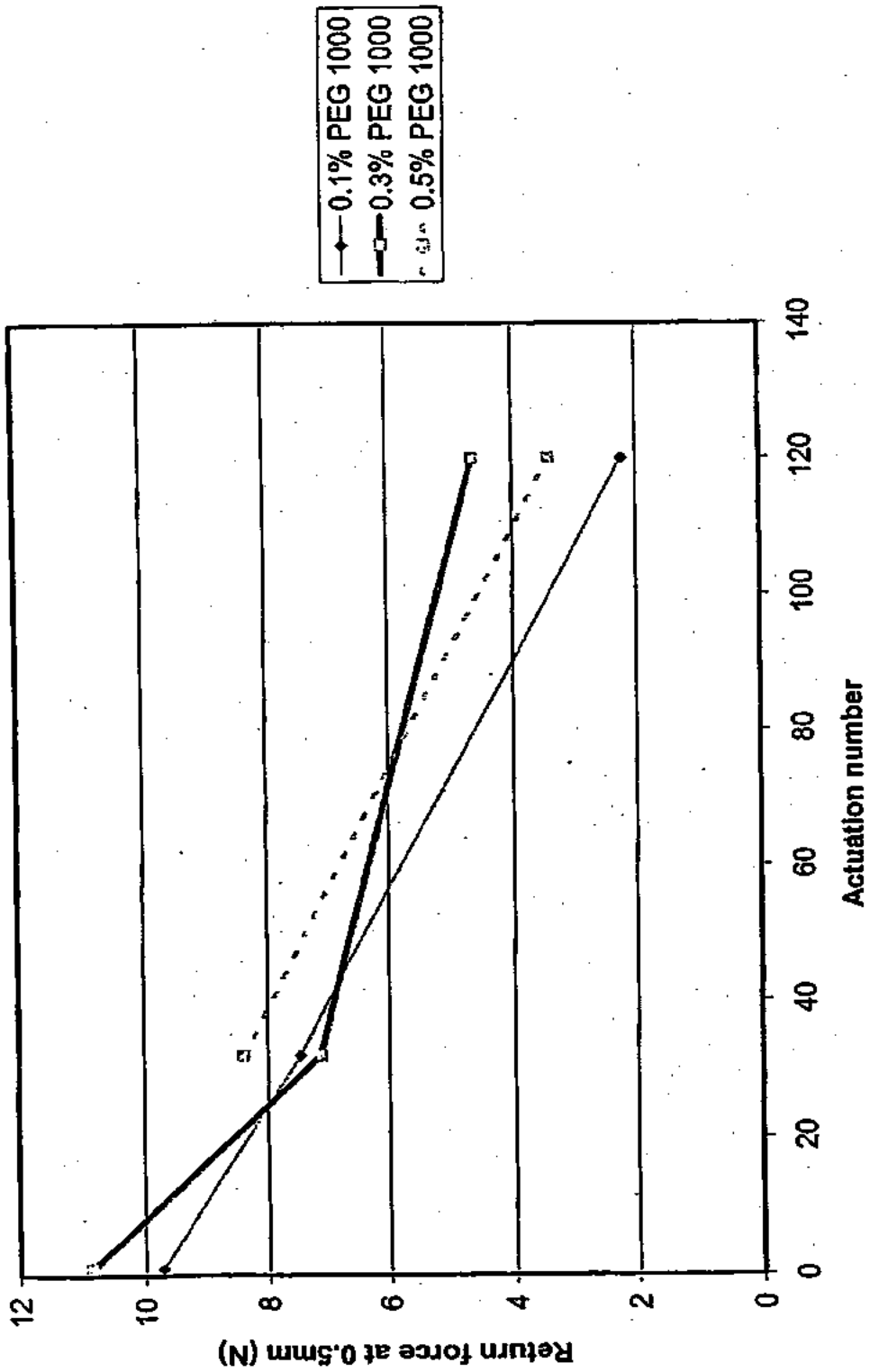

0.1% PEG 1000
0.3% PEG 1000
0.5% PEG 1000
Actuation number
0
20
40
60
80
100
120
140
Return force at 0.5mm (N)
12
10
8
6
4
2
0

Fig. 8/16

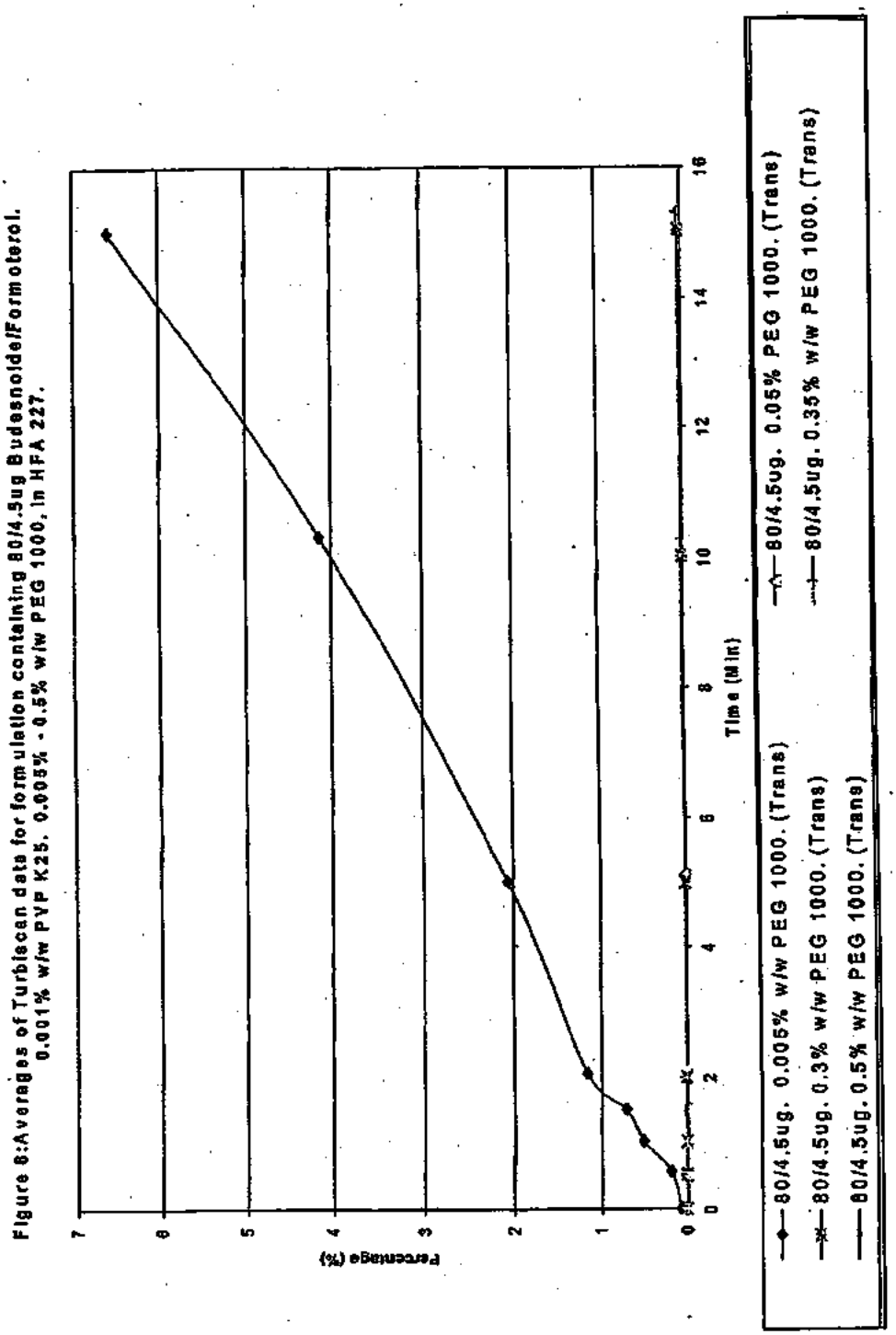


Figure 8:Averages of Turbiscan data for formulation containing 80/4.5ug Budesonide/Formoterol.
0.001% w/w PVP K25. 0.005% - 0.5% w/w PEG 1000, in HFA 227.
Percentage (%)
Time (Min)
80/4.5ug. 0.005% w/w PEG 1000. (Trans)
80/4.5ug. 0.3% w/w PEG 1000. (Trans)
80/4.5ug. 0.5% w/w PEG 1000. (Trans)
80/4.5ug. 0.05% PEG 1000. (Trans)
80/4.5ug. 0.35% w/w PEG 1000. (Trans)

Fig. 9/16

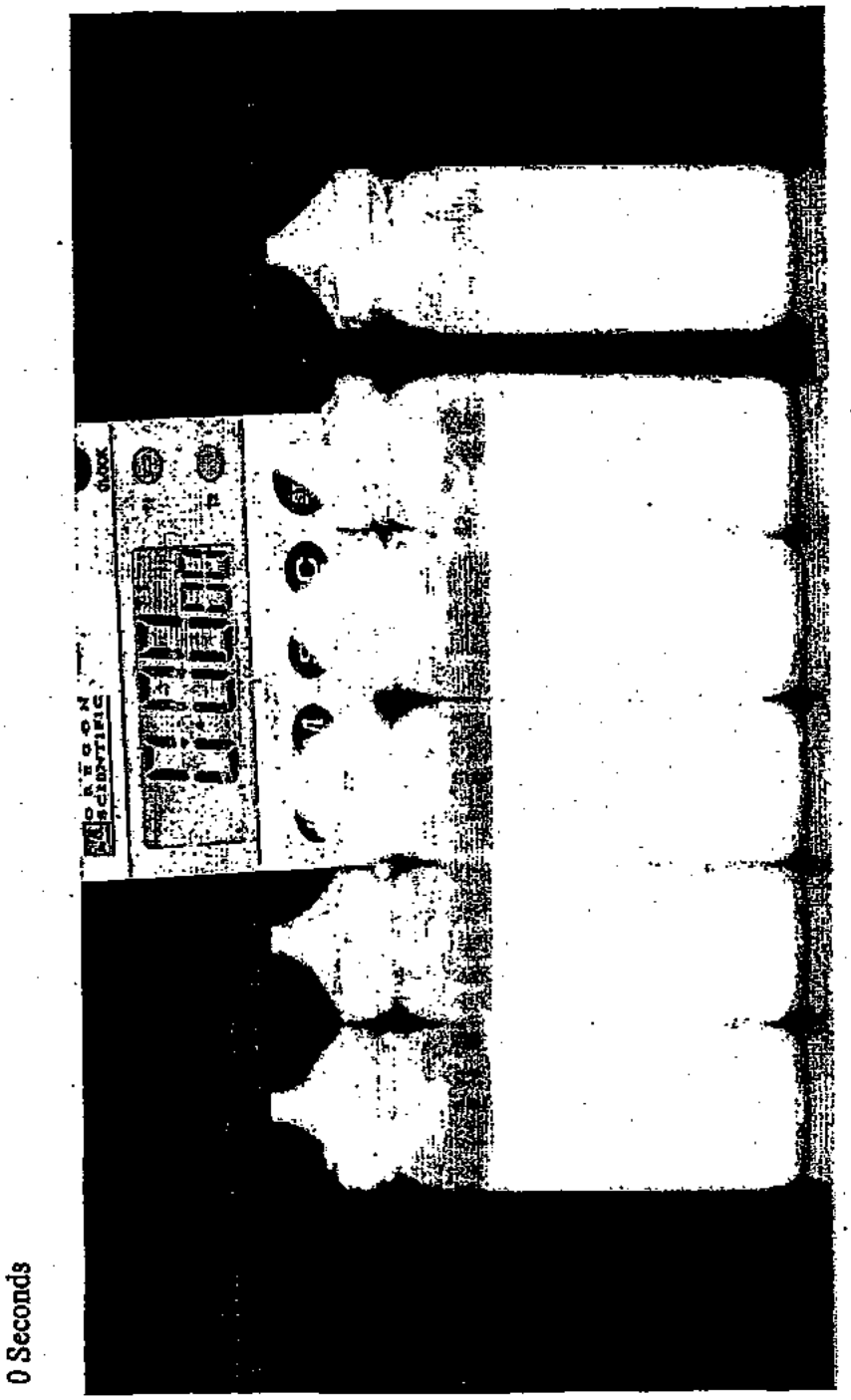


Fig. 10/16

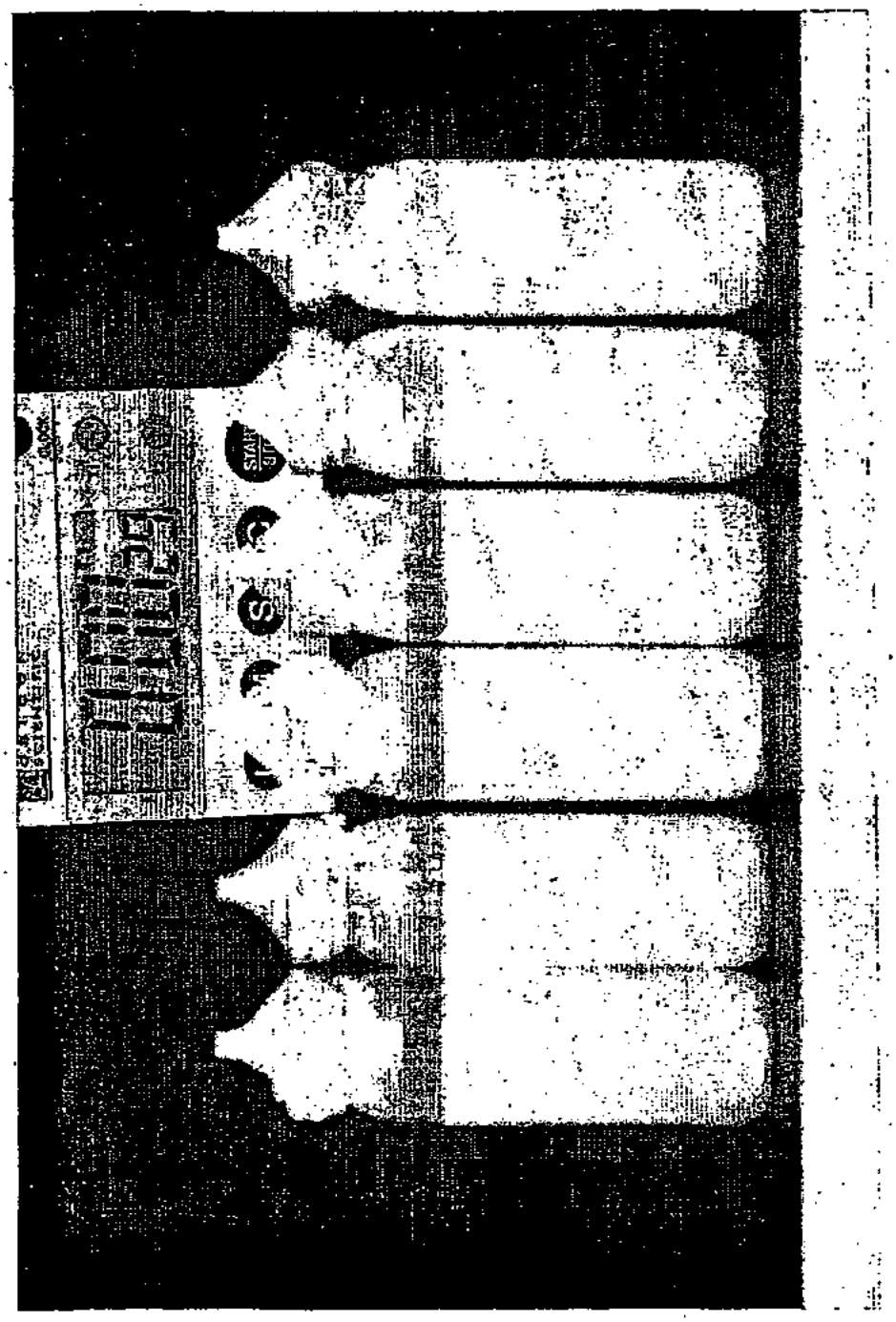


Fig. 11/16

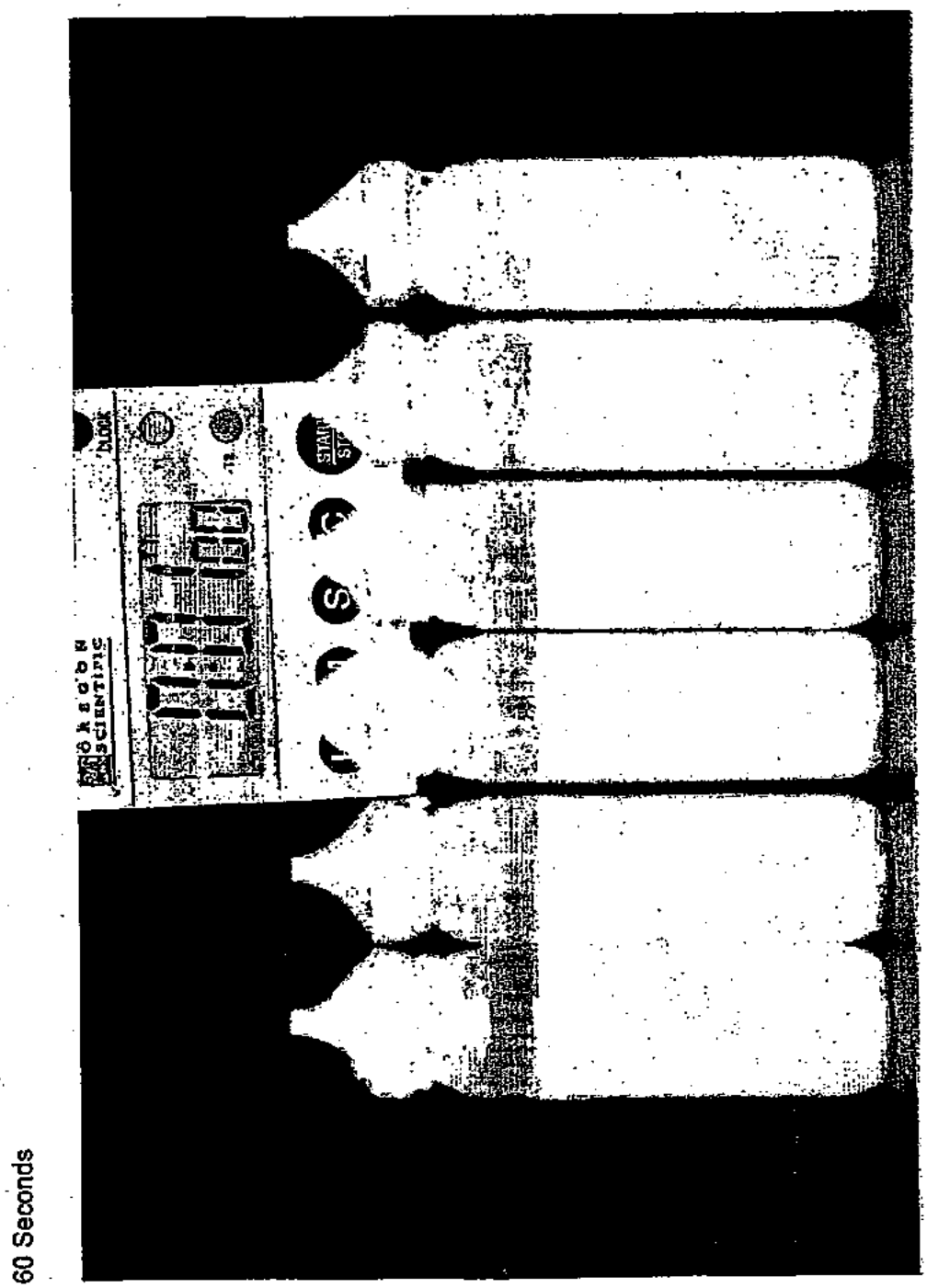


Fig. 12/16

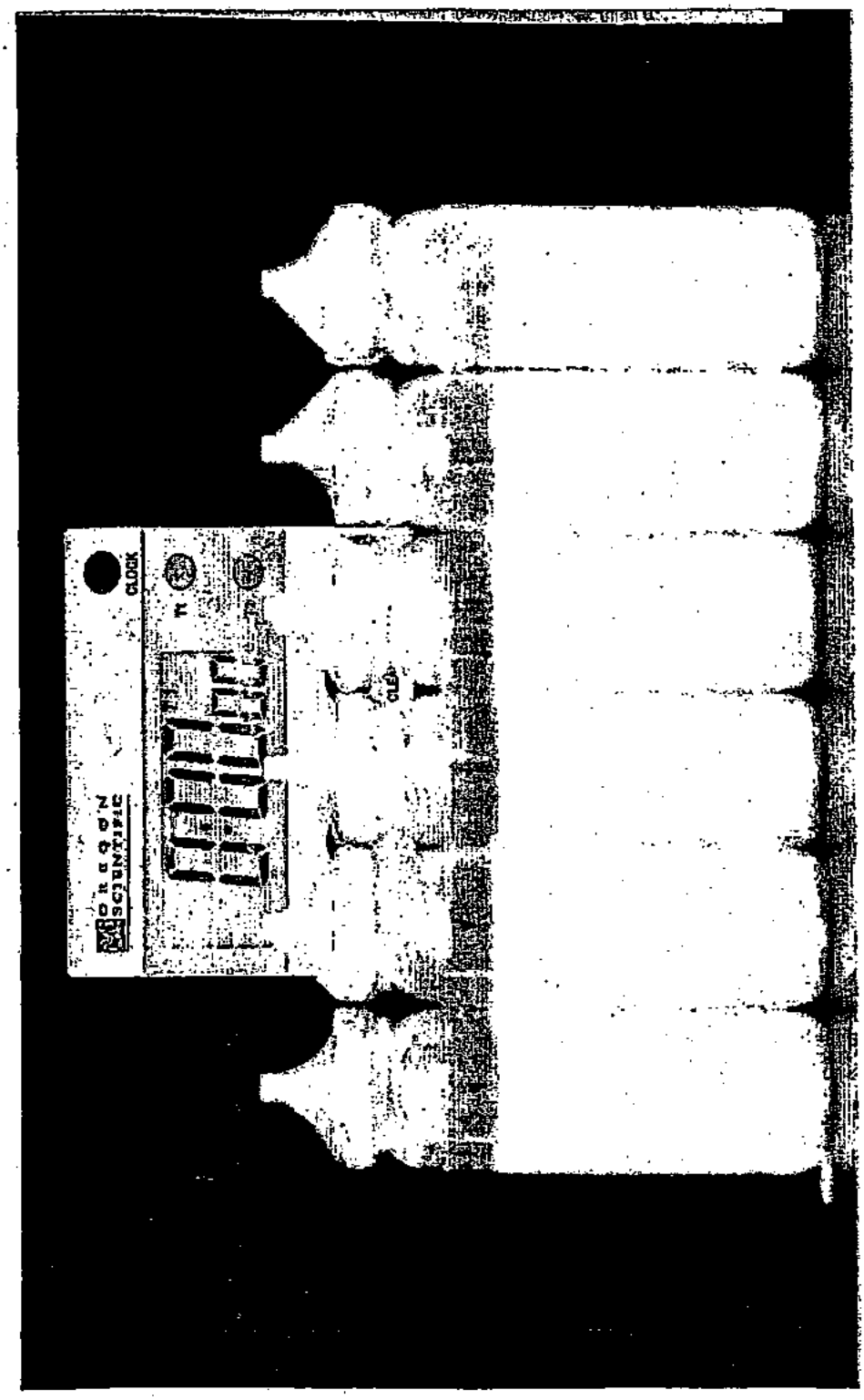


Fig. 13/16

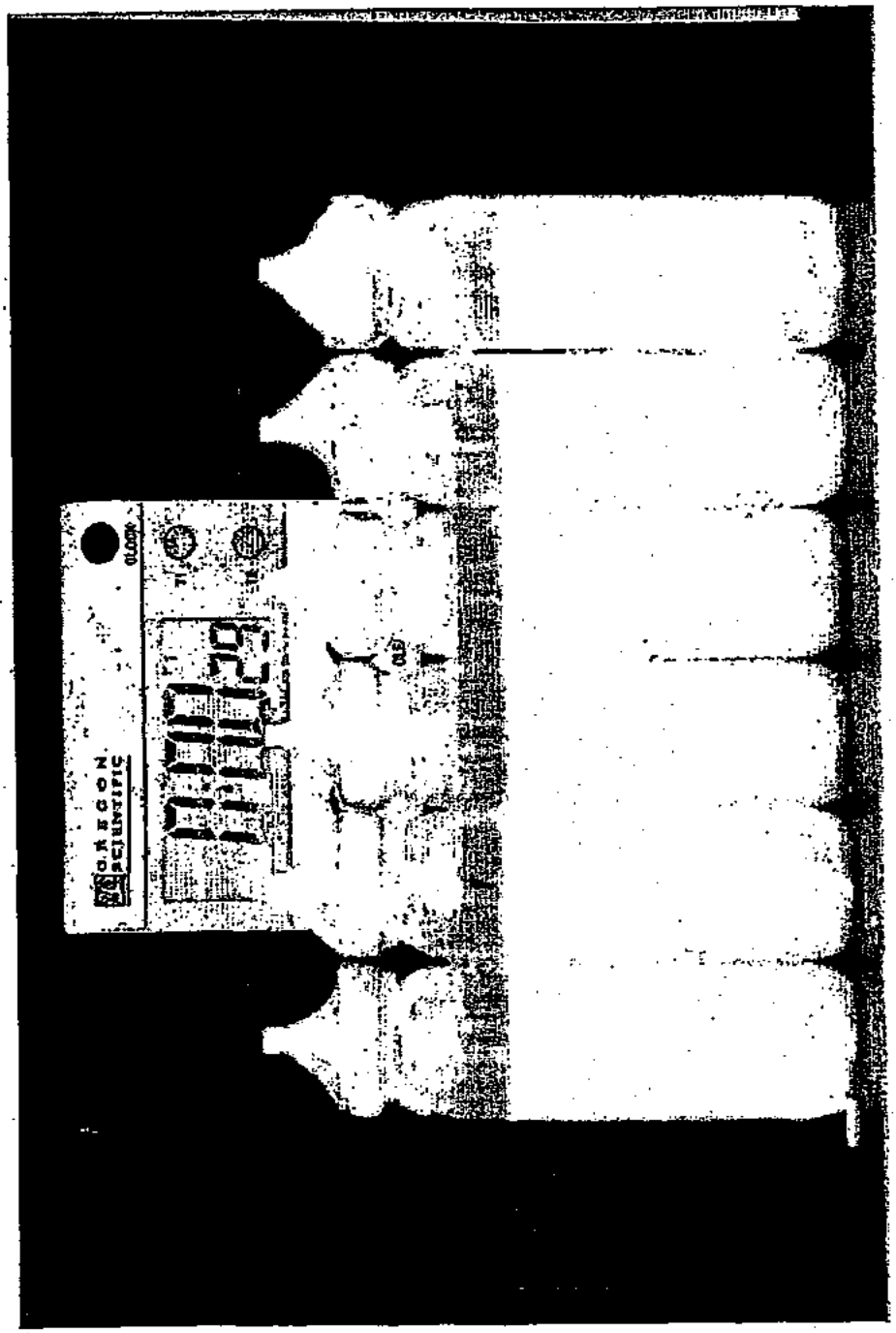


Fig 14/16

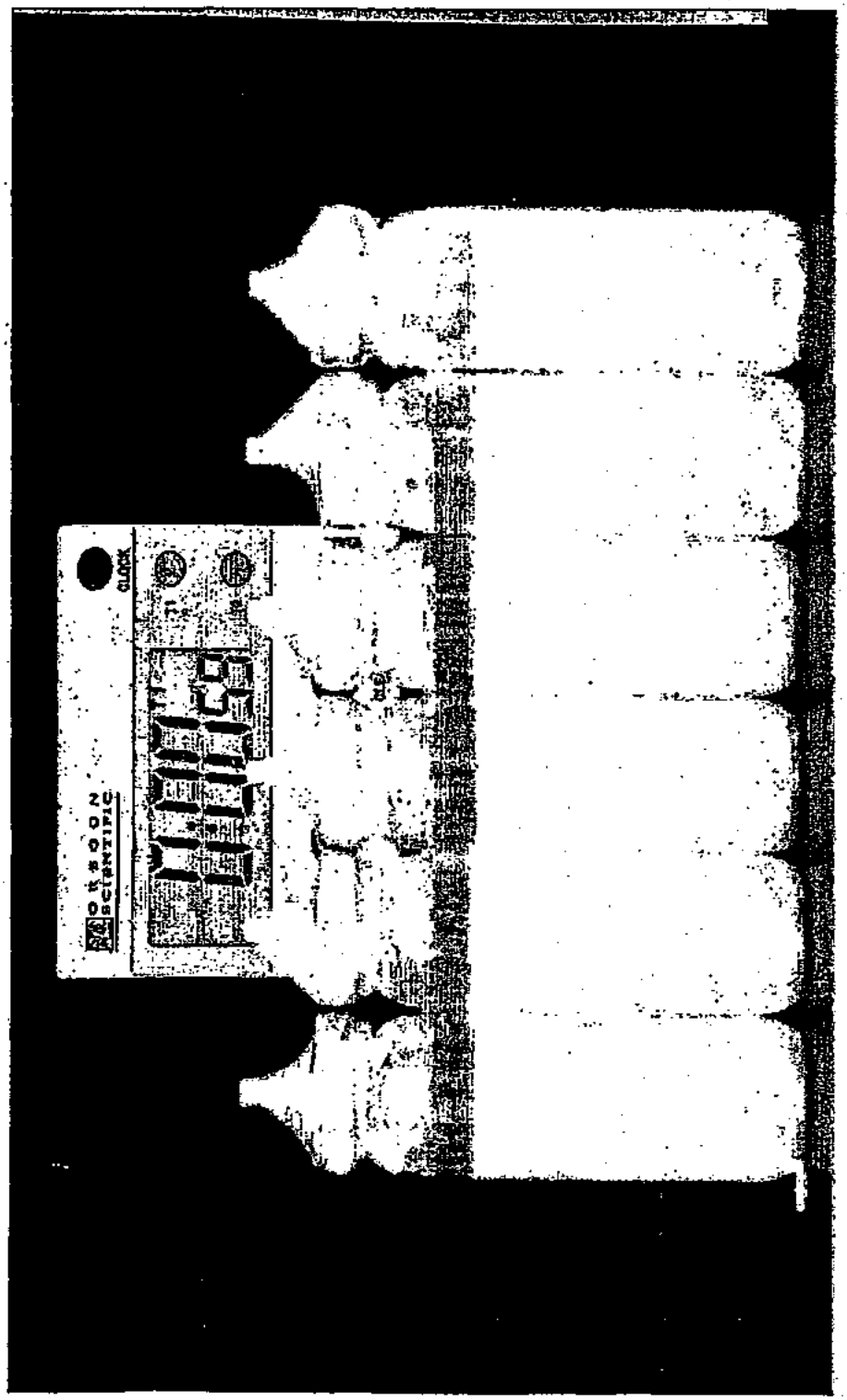


Fig. 15/16

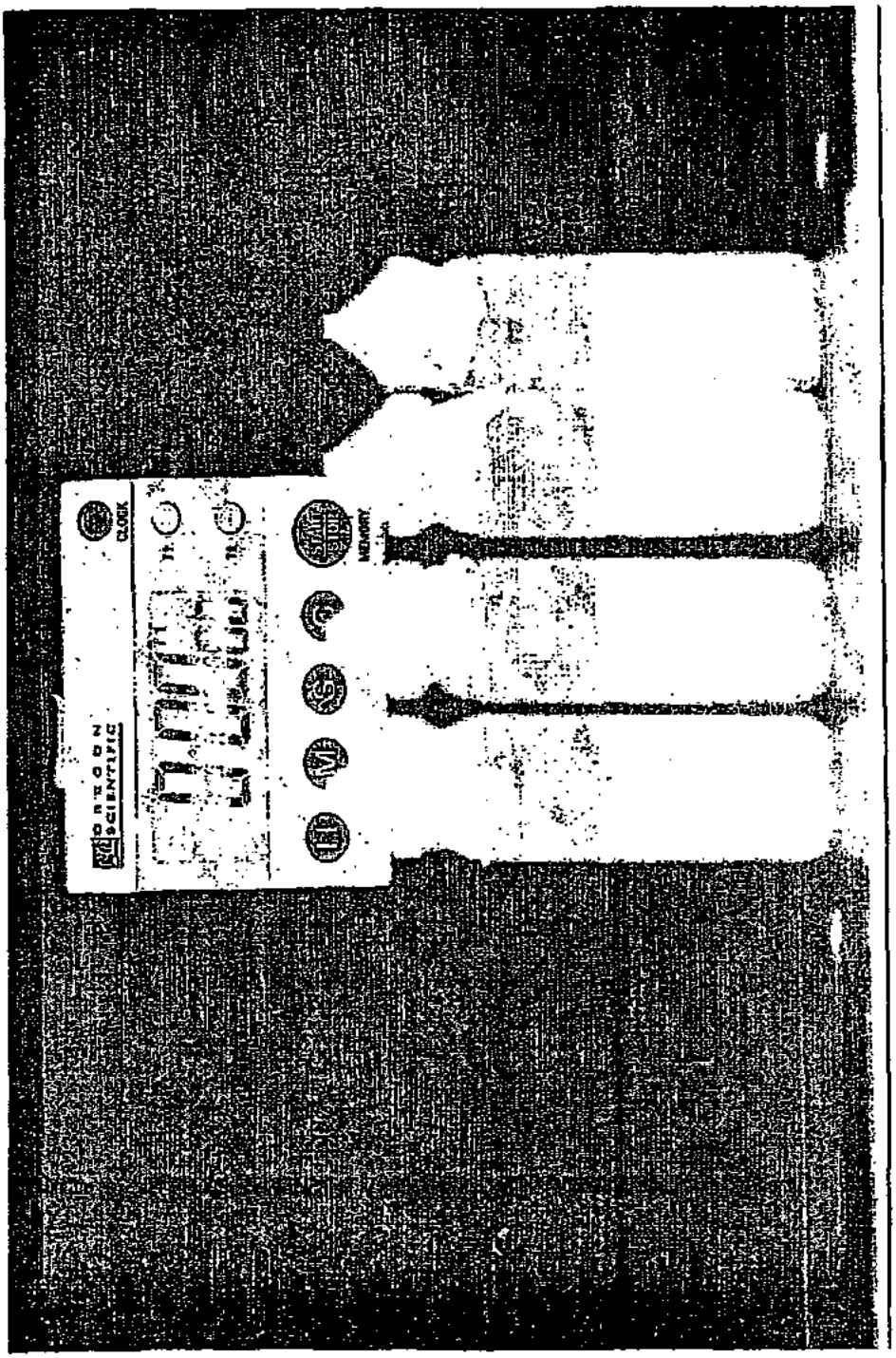
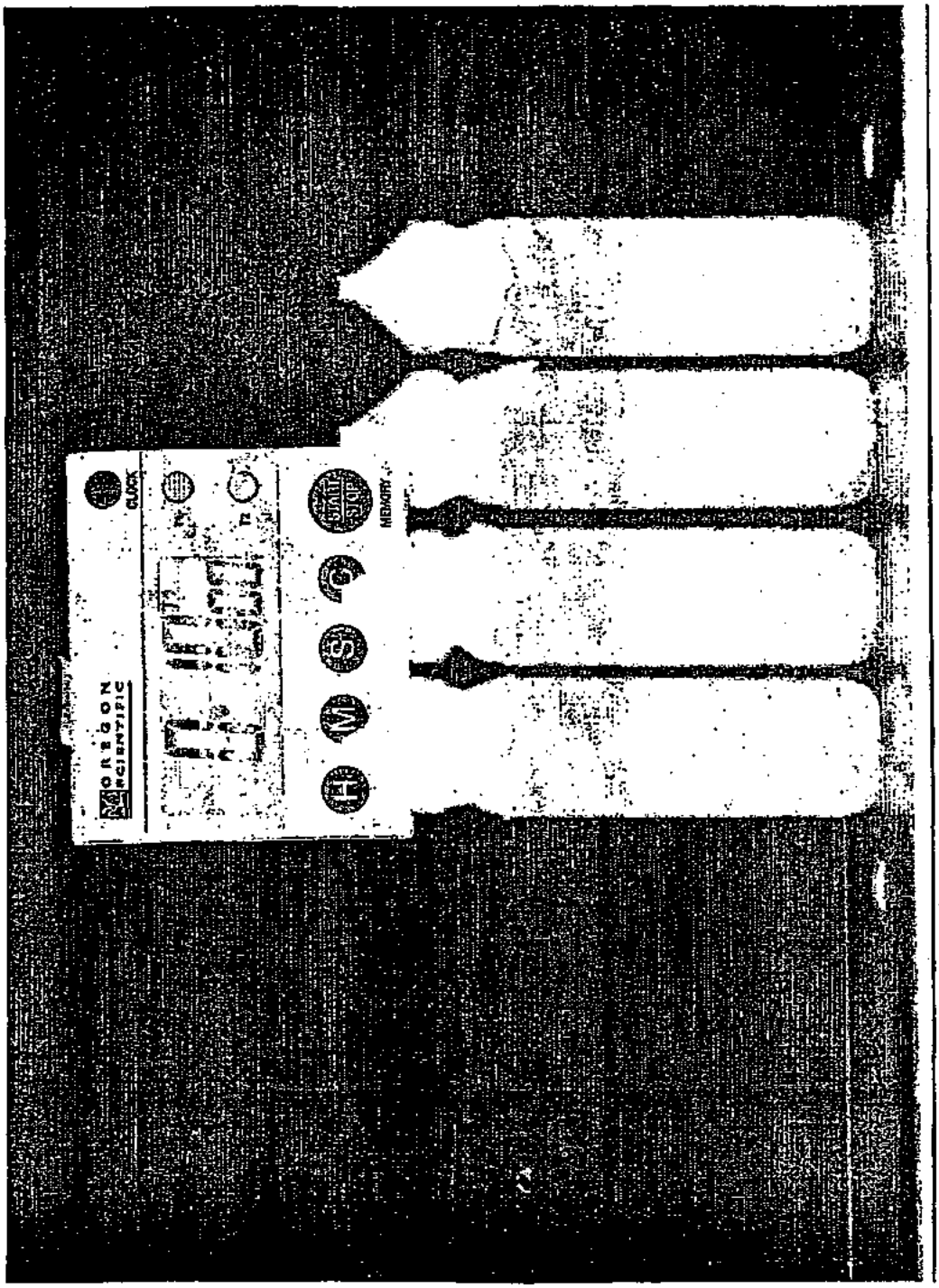


Fig. 16/16



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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 03/063842 A1

(54) Title: COMPOSITION FOR INHALATION

(57) Abstract: The invention relates to a formulation comprising formoterol and budesonide for use in the treatment of respiratory diseases. The composition further contains HFA 227, PVP and PEG, preferably PVP K25 and PEG 1000.

Composition for inhalation

Field of the invention

The present invention relates to a formulation comprising formoterol and budesonide for use in the treatment of inflammatory conditions/disorders, especially respiratory diseases such as asthma, COPD and rhinitis.

Background of the invention

Stability is one of the most important factors which determines whether a compound or a mixture of compounds can be developed into a therapeutically useful pharmaceutical product.

Combinations of formoterol and budesonide are known in the art, see for example WO 93/11773 discloses such a combination that is now marketed as Symbicort® in a dry powder inhaler. There are a variety of other inhalers by which a respiratory product can be administered, such as pressurised metered dose inhalers (pMDI's). Formulations for pMDI's may require certain excipients as disclosed in WO 93/05765.

It has now been found that certain HFA formulations comprising formoterol and budesonide together with polyvinylpyrrolidone (PVP) and polyethylene glycol (PEG) exhibit excellent physical suspension stability.

Description of the invention

In accordance with the present invention, there is provided a pharmaceutical composition comprising formoterol, budesonide, HFA 227, PVP and PEG characterised in that the PVP is present from about 0.0005 to about 0.03 %w/w and the PEG is present from about 0.05 to about 0.35% w/w.

Preferably the PVP is present in an amount of 0.001 % w/w. Preferably the PVP is PVP K25.

Preferably the PEG is present in an amount of 0.3 % w/w. Preferably the PEG is PEG 1000.

Preferably the concentrations of formoterol/budesonide are such that the formulation delivers formoterol/budesonide at 4.5/40 mcg, 4.5/80 mcg, 4.5/160 mcg or 4.5/320mcg per actuation.

The formoterol can be in the form of a mixture of enantiomers. Preferably the formoterol is in the form of a single enantiomer, preferably the R, R enantiomer. The formoterol can be in the form of the free base, salt or solvate, or a solvate of a salt, preferably the formoterol is in the form of its fumarate dihydrate salt. Other suitable physiologically salts that can be used include chloride, bromide, sulphate, phosphate, maleate, tartrate, citrate, benzoate, 4-methoxybenzoate, 2- or 4-hydroxybenzoate, 4-chlorobenzoate, p-toluenesulphonate, benzenesulphonate, ascorbate, acetate, succinate, lactate, glutarate, gluconate, tricaballate, hydroxynapaphthalenecarboxylate or oleate.
Preferably the second active ingredient is budesonide, including epimers, esters, salts and solvates thereof. More preferably the second active ingredient is budesonide or an epimer thereof, such as the 22R-epimer of budesonide.

The pharmaceutical compositions according to the invention can be used for the treatment or prophylaxis of a respiratory disorder, in particular the treatment or prophylaxis of asthma, rhinitis or COPD.
In a further aspect the invention provides a method of treating a respiratory disorder, in particular asthma, rhinitis or COPD, in a mammal, which comprises administering to a patient a pharmaceutical composition as herein defined.

The compositions of the invention can be inhaled from any suitable MDI device. Doses will be dependent on the severity of the disease and the type of patient, but are preferably 4.5/80 mcg or 4.5/160 mcg per actuation as defined above.

The concentration of PVP (0.001%w/w) used in this formulation has been found to give consistently stable formulations over the required dose range, incorporating a wide range of concentrations of the active components, and at a much lower concentration than indicated in the prior art.

The invention is illustrated by the following examples.

Experimental section

Two methods can be used to evaluate physical suspension stability: Optical suspension characterisation (OSCAR), and TURBISCAN. Both methods are used to semi-quantify sedimentation/creaming rates. OSCAR measurements are performed using the PET bottles directly. For TURBISCAN analysis, the suspensions are transferred to custom designed pressure cells for measurement of light transmittance and backscattering.

METHODOLOGY

OSCAR

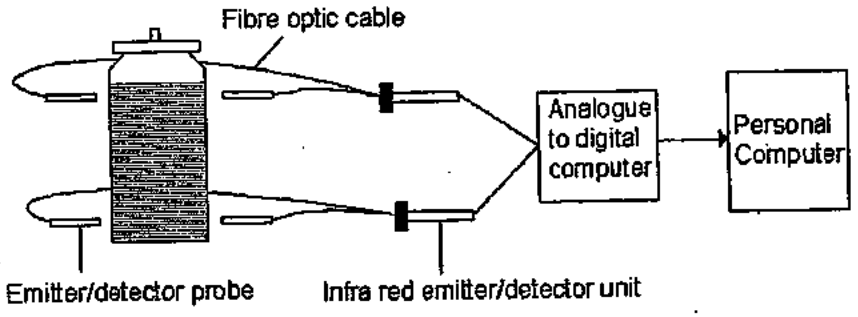
Optical Suspension Characterisation (OSCAR) equipment is custom designed for the rapid and reproducible semi-quantification of metered dose inhaler suspension characteristics.

The OSCAR equipment utilises changes in light transmission with time, to characterise a pre-agitated suspension formulation (a schematic diagram of the equipment is shown in Figure 1). The equipment consists of a twin headed test assembly. The head on the left side of the equipment is used with dilute suspensions and the right for concentrated suspensions. The selector switch mounted between the two test heads is used to alternate concentration choice. The output from the selected test head is directed to the equipment mounted voltage display and to the computer for data logging. The analogue signals from photodetectors are digitised and the values collected in data files, these are then processed using a suitable software package. There are two equipment mounted voltage displays, one each for the upper and lower photodetectors. The upper and lower photodetectors are height adjustable and a position readout display is provided to indicate the set height for each test run.

The Reagecon Turbidity standards (2500-4000 NTU) are used to calibrate the sensitivity of the OSCAR equipment. In this case, the 3000 NTU turbidity calibration standard is used as a standard calibration check. However any of the turbidity standards can be used to adjust the sensitivity of the probes to a specific voltage appropriate to the formulation.

Samples for test on the OSCAR equipment are presented in PET bottles crimped with non-metering valves.

Figure 1: Schematic for OSCAR set-up



For background information and prior art for this method refer to papers from Drug Delivery to the Lungs IX, 1997, Method Development of the OSCAR technique for the characterization of metered dose inhaler formulations, Authors N. Govind, P. Lambert And Drug delivery to the Lungs VI, 1995, A Rapid Technique for Characterisation of the Suspension Dynamics of metered Dose Inhaler Formulations, Author, PA Jinks (3M Healthcare Ltd)

TURBISCAN

Turbiscan MA 2000 is a concentrated dispersion and emulsion stability and instability analyser, or a vertical scan macroscopic analyser. It consists of a reading head moving along a flat-bottomed, 5ml cylindrical glass cell, which takes readings of transmitted and backscattered light every 40 μm on a maximum sample height of 80mm. The scan can be repeated with a programmable frequency to obtain a macroscopic fingerprint of the sample.

The reading head uses a pulsed near infrared light source (wavelength = 850 nm) and two synchronous detectors:

Transmission detector: Picks up light transmitted through the solution in the tube, at 0°

Backscattering detector: Receives the light back scattered by the product at 135°.

The profile obtained characterises the samples homogenieity, concentration and mean particle diameter. It allows for quantification of the physical processes the sample is

undergoing. As well as detecting destabilisation, Turbiscan allows comparison of, for example, the sedimentaion rate of different suspensions.

Turbiscan may be used in several modes, eg transmitted or backscattering modes. Turbiscan has been used here in these examples to measure the transmitted light as a funtion of time

Dispersion instability is the result of two physical processes: a) particle size increases as a result of the formation of aggregates, due to flocculation b) particle migration resulting in creaming or sedimentation. When a product is stable (ie no flocculation, creaming or sedimentation), the transmitted and backscattered light will remain constant i.e. scans of these will show a constant level profile. If the product undergoes changes in particle size, variations in the transmitted/ backscattered light show as change in the direction of the scan from horizontal or steady state profile.

For pressurised systems a cell capable of handling pressurised samples is required. Such a cell was used for the evaluations of these HFA formulations. The scans were performed in the AUTO mode.

The % transmission averages shown in the figure (see later) were taken from a zone around the middle of the suspension sample.

INITIAL EVALUATION

For the initial evaluation, only OSCAR was used.

Formulations containing formoterol fumarate dihydrate, budesonide, 0.001% w/w PVP K25 and either 0.1 % w/w or 0.3% PEG 1000 in HFA-227 were prepared in polyethylene terephlate (PET) bottles crimped with a continuous valve. For all formulations, the formoterol fumurate dihydrate concentration remained constant at 0.09mg/ml (equivalent to 4.5 mcg formoterol fumurate dihydrate per actuation) and the budesonide concentration varied between approximately 1mg/ml to 8 mg/ml (equivalent to 40 mcg to 320 mcg per actuation).

Early OSCAR data for Symbicort pMDI formulations

Budesonide dose ex-actuator	Formoterol dose ex-actuator	PVP K25 concentration (% w/w)	Time seconds	Transmittance (mV) Lower sensor	
				PEG concn %w/w	
				0.1	0.3
40 µg	4.5 µg	0.001	30 seconds		257
			60 seconds		264
80 µg	4.5 µg	0.001	30 seconds	202	
			60 seconds	240	
		0.002	30 seconds	184	
			60 seconds	185	
160 µg	4.5 µg	0.001	30 seconds	208	114
			60 seconds	304	191
		0.002	30 seconds	248	
			60 seconds	327	
320 µg	4.5 µg	0.001	30 seconds		475
			60 seconds		570
		0.002	30 seconds		930
			60 seconds		1443

OSCAR analysis of these formulations gave relatively low light transmittance values at the lower sensor, which is indicative of stable suspensions with low flocculation characteristics. Early indications were that the 0.001% w/w PVP with 0.3% PEG 1000 would give the best suspension.

FURTHER EVALUATION: various concentrations of PVP K25 with a constant PEG 1000 concentration of 0.3% w/w.

OSCAR, Turbiscan and photographic methods were used to evaluate the formulations. OSCAR and Turbiscan techniques have been described earlier. Samples with varying concentrations of PVP were analysed to determine suspension stability over time.

PHOTOGRAPHIC ANALYSIS

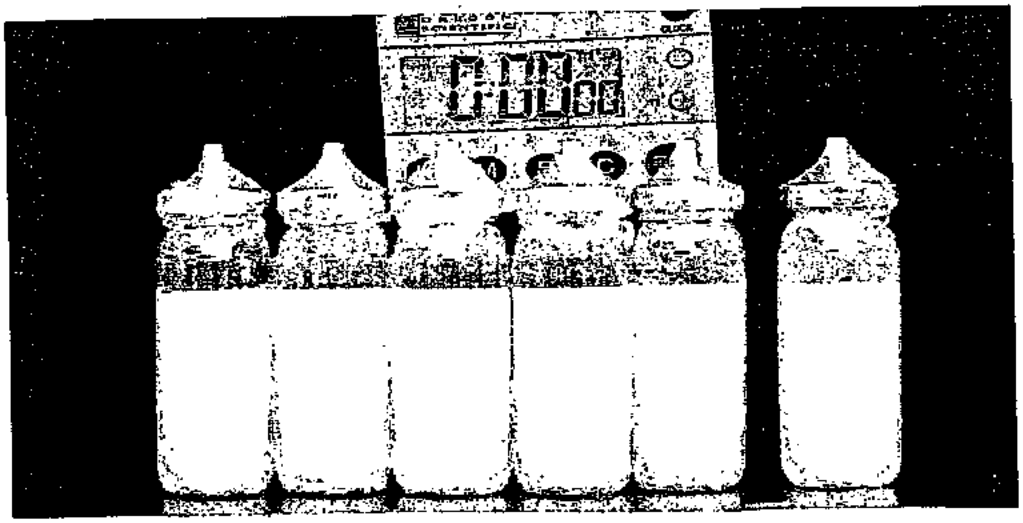
For the photographic analysis , samples were prepared in PET bottles and photographed digitally over time, using a black background. These photographs (some of which are shown here) show the behaviour of the suspension over time and allow easy comparison of the effectiveness of the various concentrations of PVP. The concentration of PVP varied from 0.0001 to 0.05 % w/w. From left to right on the photographs the concentration of PVP is as follows:

0.0001 far left	0.0005	0.001	0.01	0.03	0.05 far right

DIGITAL PHOTOGRAPHY OF FORMULATIONS SHOWING DEGREE OF DISPERSION OVER TIME

Budesonide 160µg/shot, Formoterol 4.5µg/shot with various PVP K25 concentrations and 0.3% PEG 1000 at 0, 15, 30, and 60 seconds standing time.

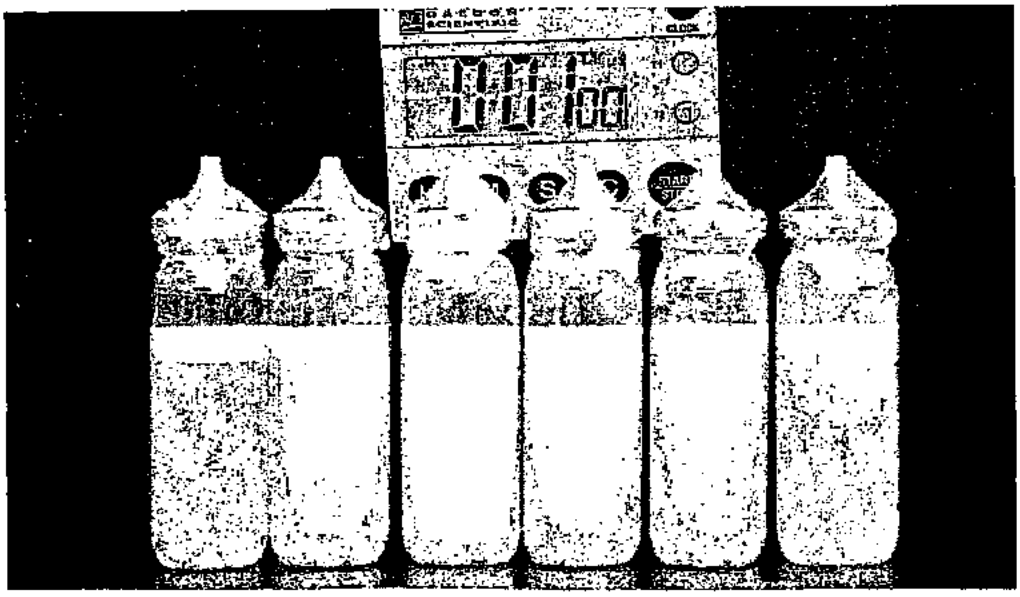
0 Seconds



0.0001 0.0005 0.001 0.01 0.03 0.05 %w/w PVP

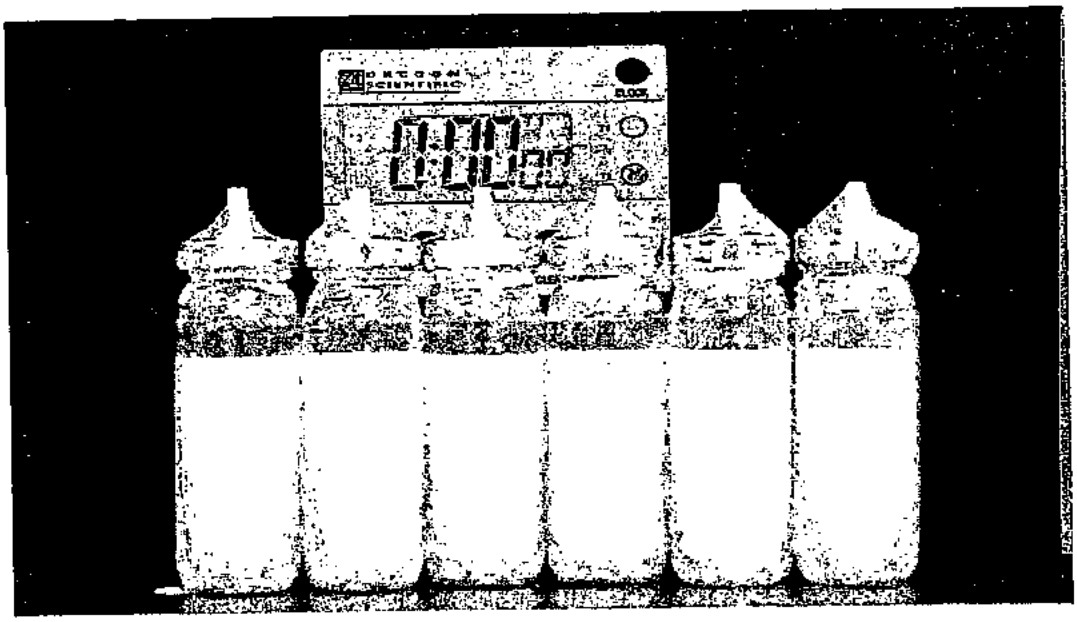
30 Seconds

60 Seconds

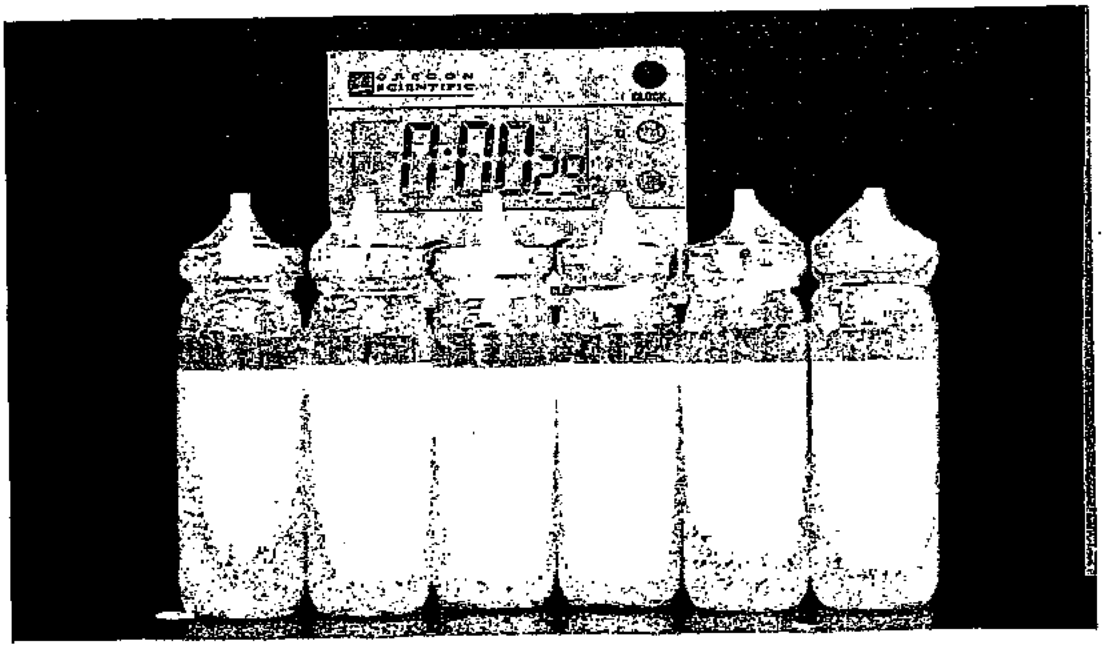


Budesonide 80µg/shot, Formoterol 4.5µg/shot with various PVP K25 concentrations and 0.3% PEG 1000 at 0, 30, and 60 seconds standing time.

0 Seconds



30 Seconds



60 Seconds

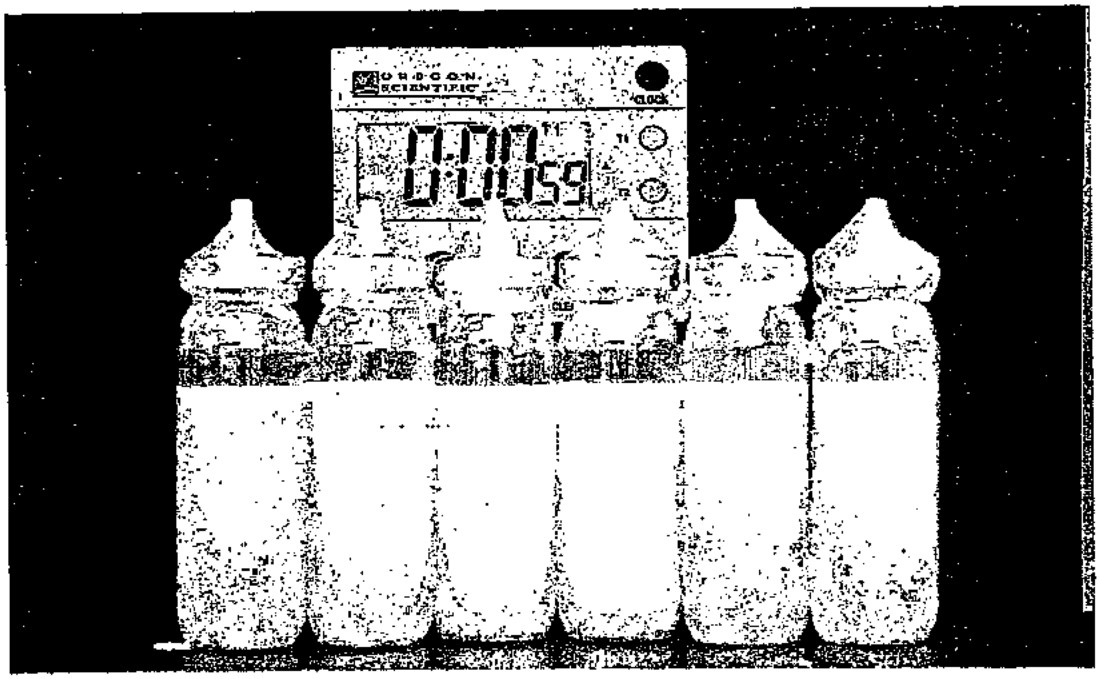


TABLE OF DEGREEE OF DISPERSION OF SUSPENSIONS OVER TIME: (ALL SAMPLES)

Photographs were taken of all doses (320µg/4.5µg to 40µg/4.5µg) at 0, 15, 30, 60, 90 seconds, and 2, 5 and 10 minutes. As this produced too many photographs to reproduce here, a chart has been constructed to give a reprentation of the degree of dispersion over time.

If the sample was fully suspended, the sample was rated 0 e.g. at 0 minutes they were fully dispersed. From there, the samples have been rated in increments of 1-5 at 20% intervals to express the degree of dispersion i.e. 0 was fully suspended and 5 fully creamed. This allows some comparison across the whole dose range and PVP concentration range used.

(Note concentration of Formoterol is 4.5µg/shot in all the samples)

(Samples are all fully dispersed at 0 seconds and therefore all have a score of 0)

Fully dispersed – 0	
More than 80% dispersed ie less than 20% clear liquid present	1
More than 60% dispersed ie less than 40% clear liquid present	2
Less than 40% dispersed ie more than 60% clear liquid present	3
Less than 20% dispersed ie more than 80% clear liquid present	4
Fully creamed	5

TABLE OF DEGREEE OF DISPERSION OF SUSPENSIONS OVER TIME: ALL SAMPLES

Dose	Time	PVP concentration (% w/w)					
µg/shot Budesonide	Sec/mins	0.0001	0.0005	0.001	0.01	0.03	0.05
320	15	2	1	**0-1**	**0-1**	**0-1**	**0-1**
	30	3	3	2	**1-2**	2	2
	60	4	4	3-4	2	3	3-4
	90	4	5	5	3	5	5
	2	5	5	4-5	4-5	5	5
	5	5	5	5	5	5	5
	10	5	5	5	5	5	5
160	15	3	2	**0-1**	**0-1**	2	2
	30	3	2	1	1	2	2
	60	5	4	1	2	4	5
	90	5	5	1	2	5	5
	2	5	5	1	2	5	5
	5	5	5	2	4	5	5
	10	5	5	2	4	5	5
80	15	2	1	0	0	1	1
	30	3	2	1	1	2	2
	60	4	2	1	1-2	3	3
	90	5	3	1-2	1-2	4	3
	2	5	3-4	1	1	5	4
	5	5	4	2	2	5	5
	10	5	5	3	3	5	5
40	15	1	1	0	0	1	2
	30	2	1	1	2	2	3
	60	1-2	1	1	2	2	3
	90	1-2	1-2	1-2	2	2-3	4
	2	2	2	2	3	4	5
	5	3	2	2	3	4	5
	10	4-5	3	2	4	5	5

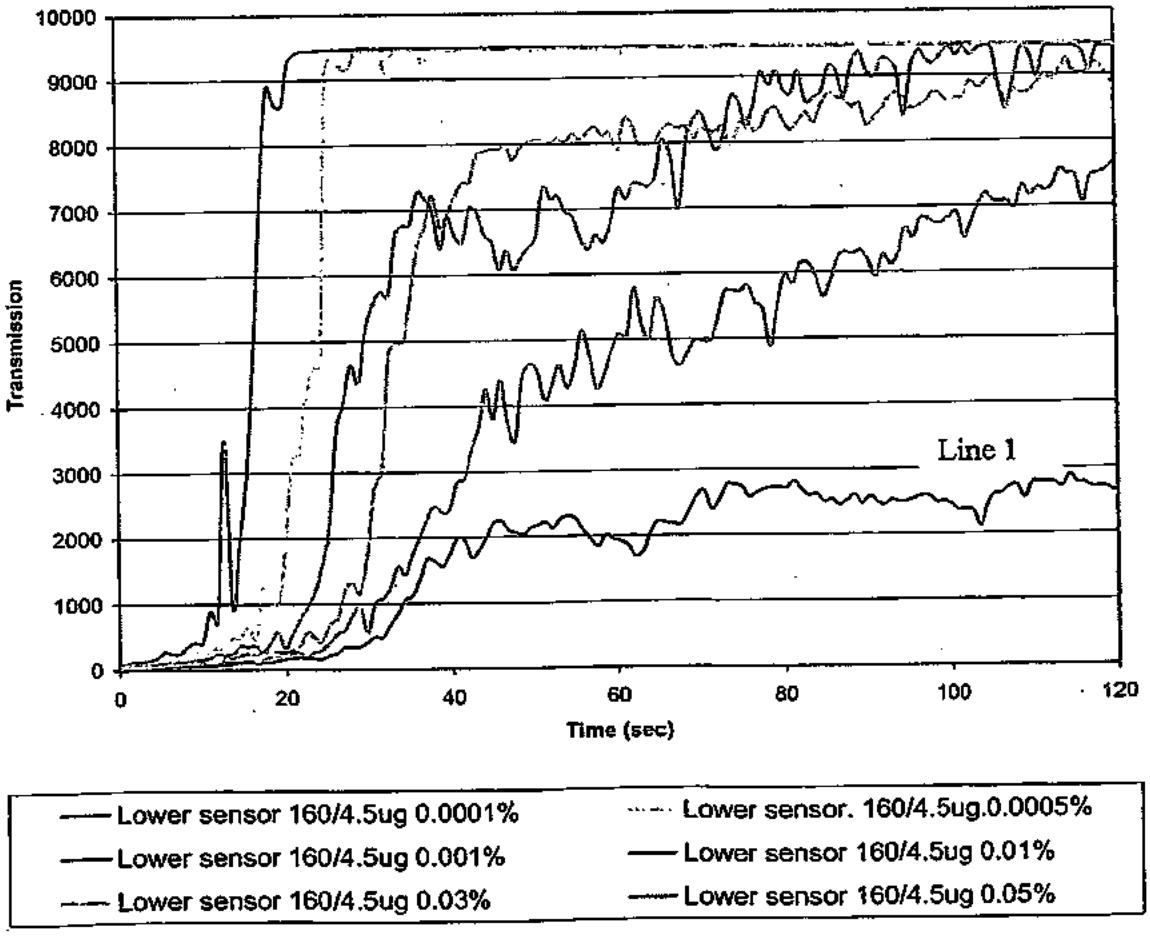
Suspensions considered excellent are highlighted in bold.

It can be seen that the formulations with 0.001% w/w PVP gave the best suspension stability overall.

OSCAR DATA (Graphs of light transmission versus time)

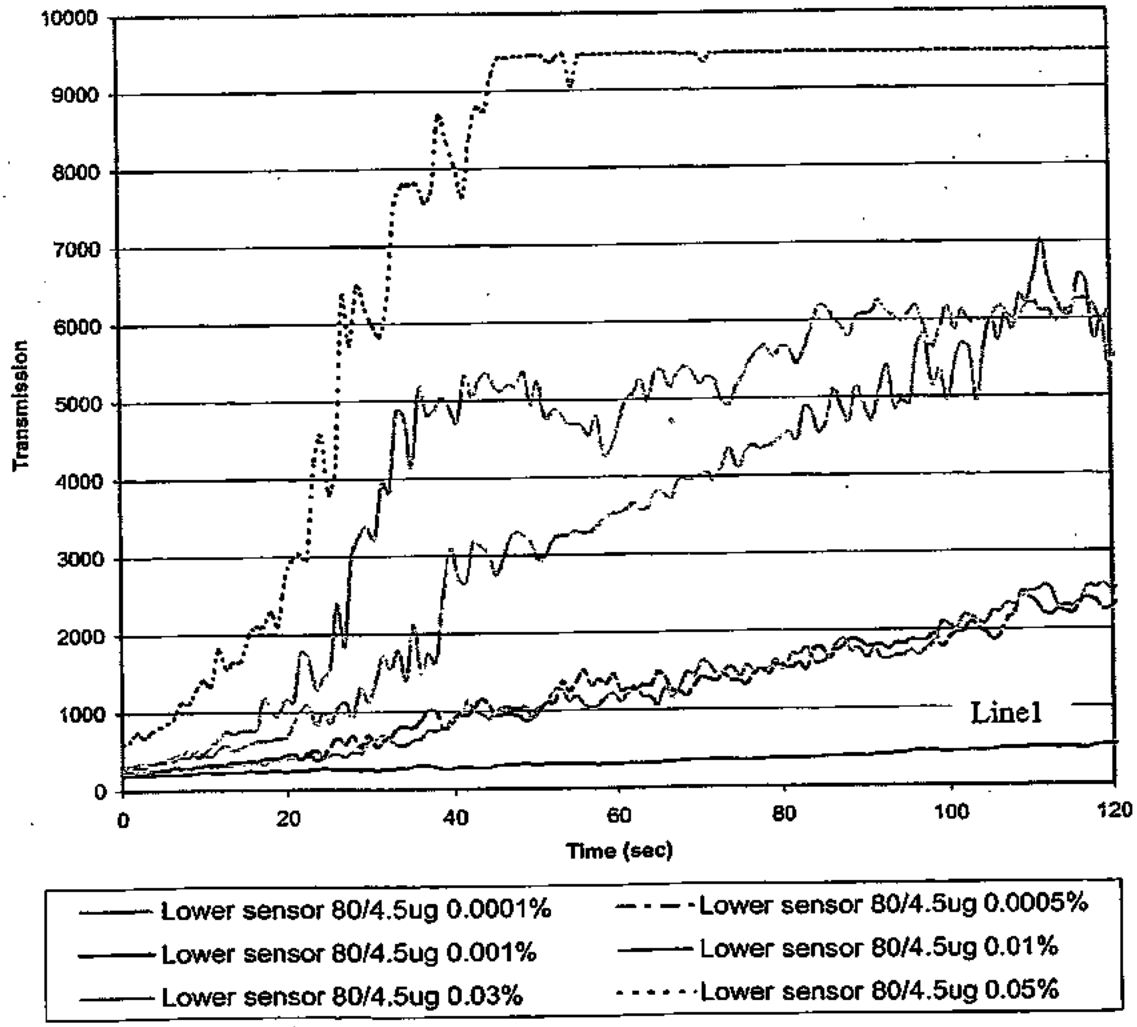
Figure 2 shows the average OSCAR transmission readings (lower sensor only) for various concentrations of PVP K25. A low transmission reading indicates that the suspension is dispersed preventing light being transmitted. Hence, it can be seen that the lowest line is the most stable formulation. This is the 0.001% PVP sample.

Figure 2: Averages of OSCAR data for formulation containing 160/4.5ug Budesonide/Formoterol. 0.3% w/w PEG 1000. 0.0001% - 0.05% w/w PVP K25.



In Figure 3, the bottom line, again with low transmission readings, clearly shows that the formulation containing 0.001% PVP is the most stable.

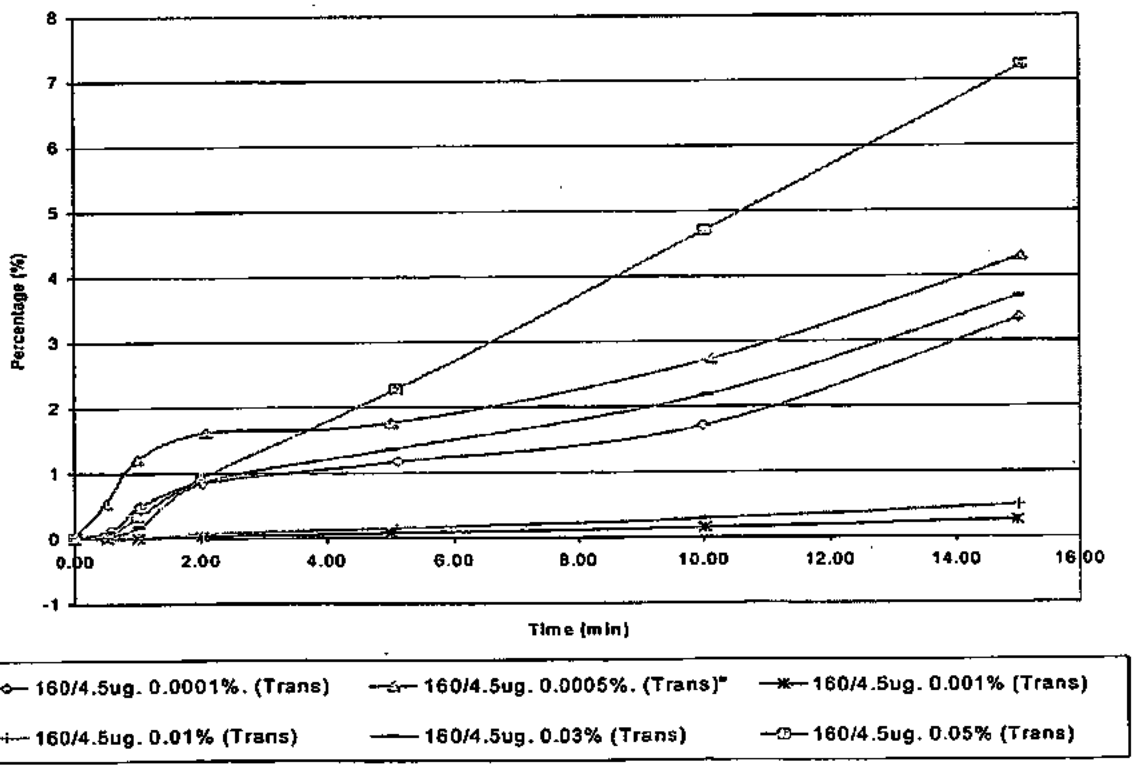
Figure 3: Averages of OSCAR data for formulation containing 80/4.5ug Budesonide/Formoterol. 0.3% w/w PEG 1000. 0.0001% - 0.05% w/w PVP K25, in HFA 227.



TURBISCAN DATA(Graphs of percentage (%) light transmission versus time)

Data from the Turbiscan can be intepretated in a similar vein to the OSCAR data in that a low percentage (%) transmission indicates the suspension is dispersed . The % transmission averages quoted here were taken from a zone around the middle of the suspension sample. In Figure 4 the most stable formulation is the lowest line with the lowest % transmission, i.e. the bold black line with 0.001%w/w PVP

Figure 4: Averages of Turbiscan data for formulation containing 160/4.5ug Budesonide/Formoterol. 0.3% w/w PEG 1000. 0.0001% - 0.05% w/w PVP K25, in HFA 227.



Figures 5 and 6 show that the suspension with 0.001% w/w PVP is the most stable (bottom bold line) with the lowest % transmission.

5

Figure 5: Averages of Turbiscan data for formulation containing 80/4.5ug Budesonide/Formoterol. 0.3% w/w PEG 1000. 0.0001% - 0.05% w/w PVP K25, in HFA 227.

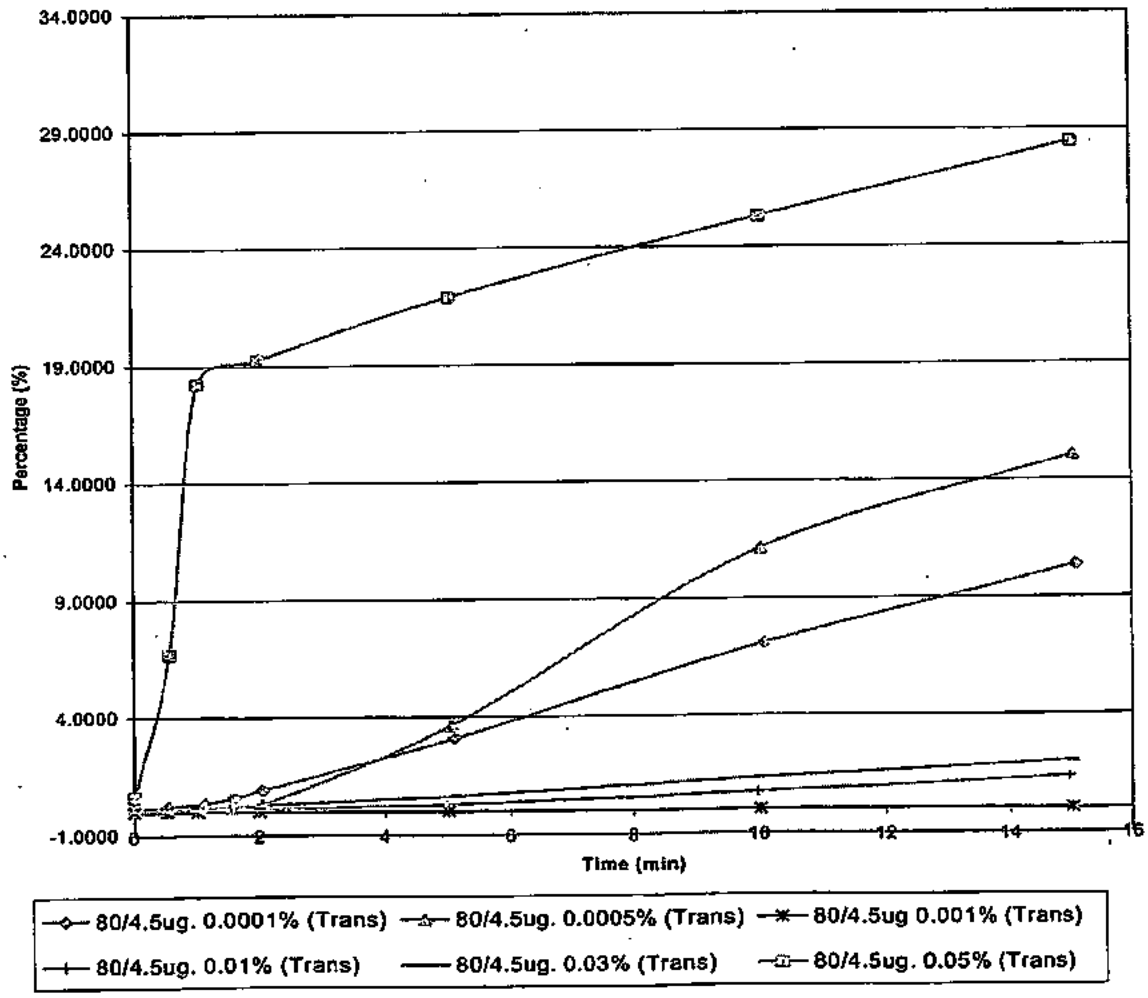
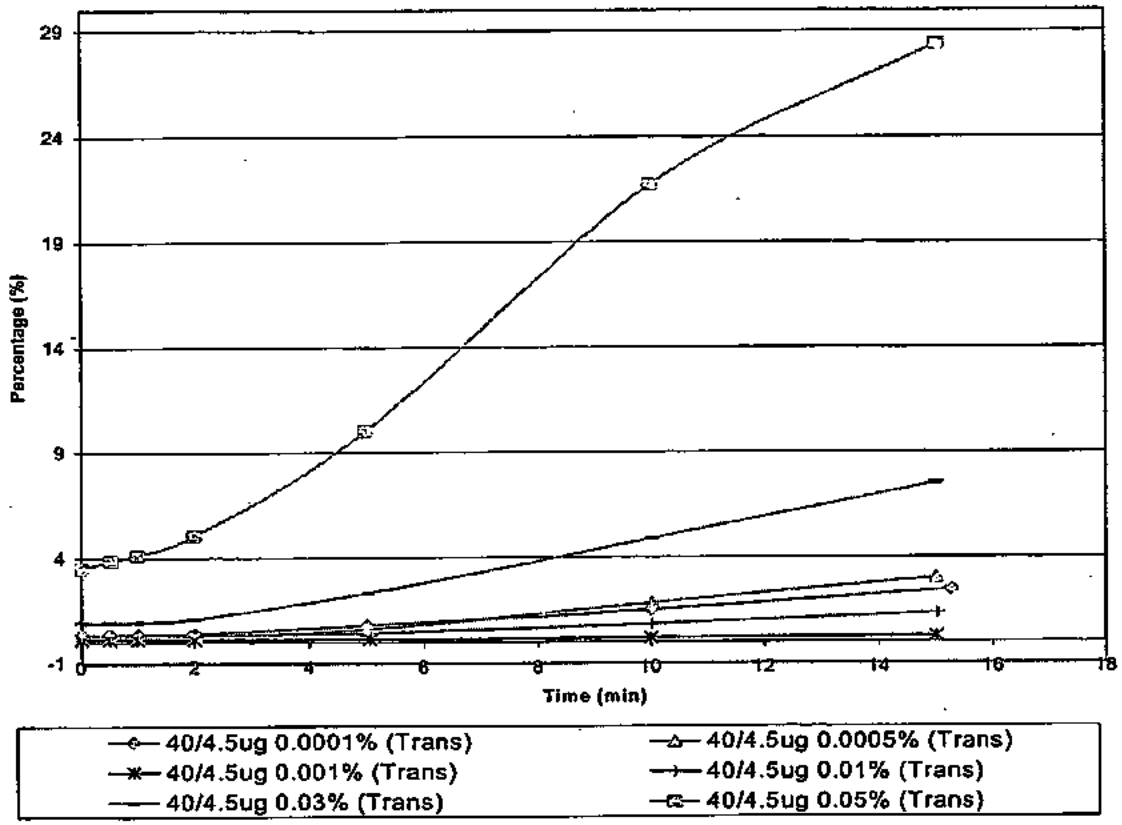


Figure 6: Averages of Turbiscan data for formulation containing 40/4.5ug Budesonide/Formoterol. 0.3% w/w PEG 1000. 0.0001% - 0.05% w/w PVP K25, in HFA 227.



FURTHER EVALUATION: Determination of the optimum PEG 1000 concentration.

For this evaluation, photography, turbiscan and force to fire data (valve performance) was used to determine the optimum PEG concentration.

METHODOLOGY - Force to fire (return force at 0.5mm stem return)

Force to fire testing was performed using the Lloyd LRX testing machine. The pMDI unit to be tested was placed valve down in a can holder on the lower platform of the unit. The upper crosshead was then moved to just above the base of the can. Can actuations were performed using a standard protocol. During measurement, force data is captured by

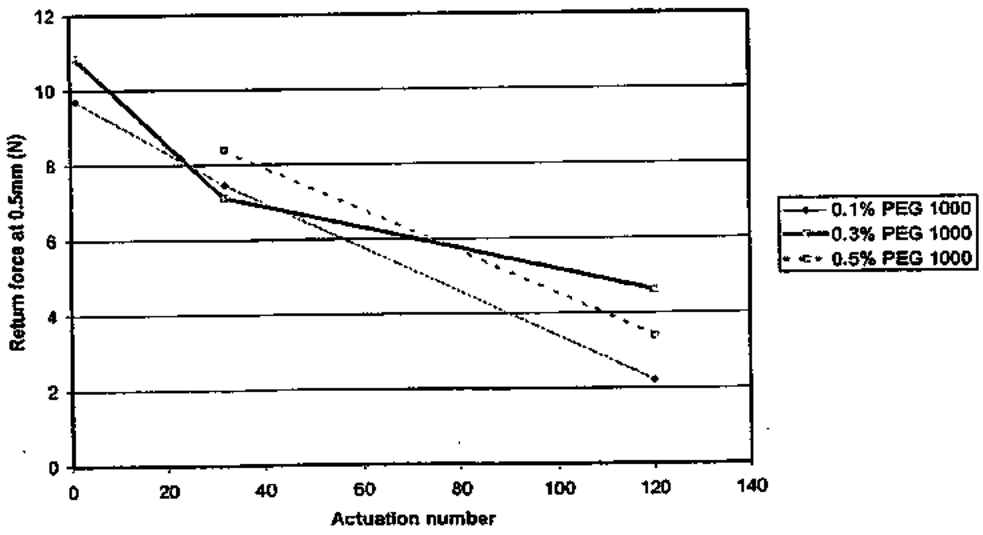
means of the load cell located at the top of the upper crosshead. This program was designed to output the return force at 0.5mm stem return as this is the point at which the metering chamber is considered to refill.

A low return force is indicative of high friction and potential sticking problems. It also suggests there may be a problem with low actuation weights as the propellant enters the metering chamber more slowly and has time to vaporise. Force to fire testing was performed at preset actuations.

DATA

FORCE TO FIRE DATA

Graph 1 Effect of PEG 1000 concentration on stem return force for the 4.5/160 µg formoterol/budesonide formulation

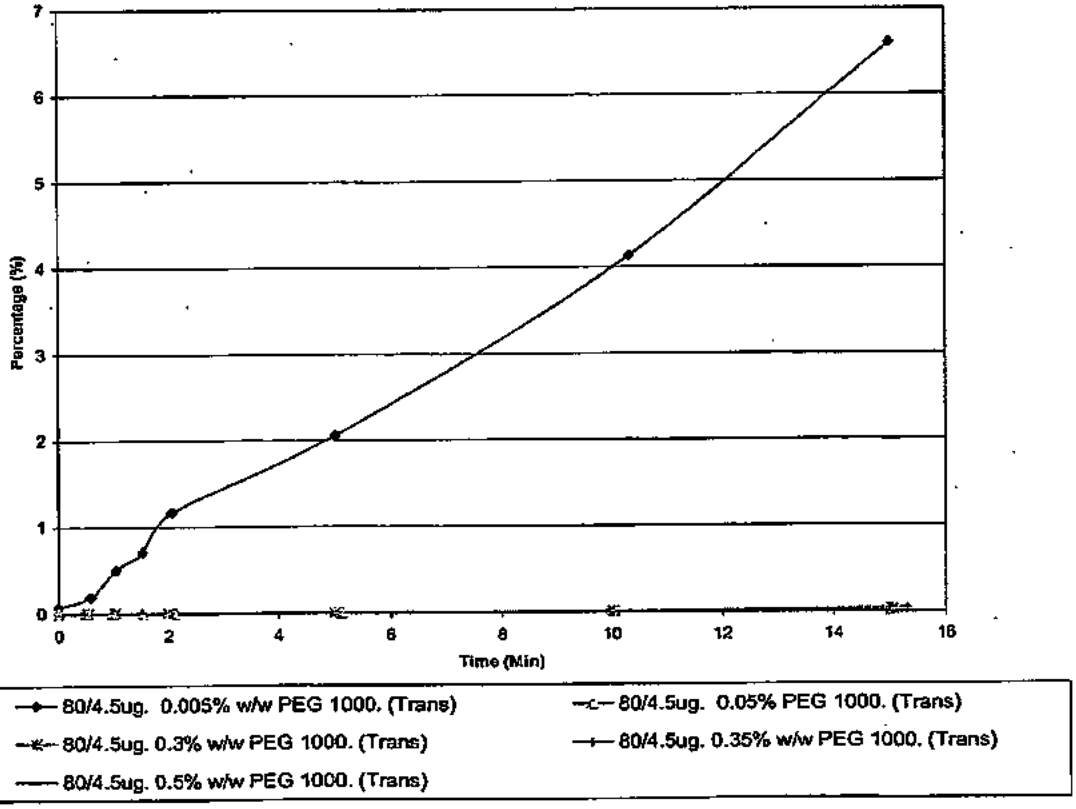


The above graph shows that at 120 actuations, the return force is greater for the 0.3% w/w PEG 1000 concentration than for the other concentrations of 0.5% and 0.1%. In general, the higher the return force the lesser the chance of the valve stem sticking. The above data shows that in this case 0.3% would be preferred.

TURBISCAN DATA

The Turbiscan data (figure 7) shows that there is little difference between the stability of suspensions made with varying levels of PEG 1000 except for the 0.005% w/w level which was unsatisfactory.

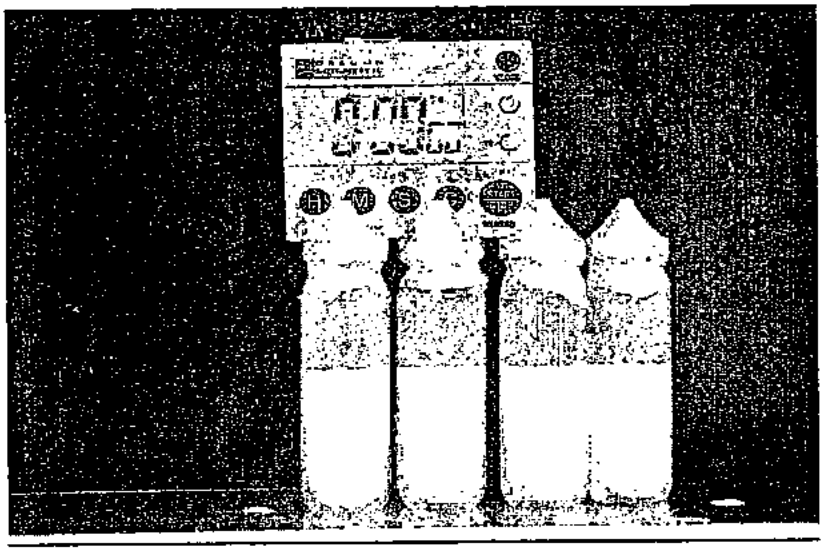
Figure 7:Averages of Turbiscan data for formulation containing 80/4.5ug Budesnoide/Formoterol. 0.001% w/w PVP K25. 0.005% - 0.5% w/w PEG 1000, in HFA 227.



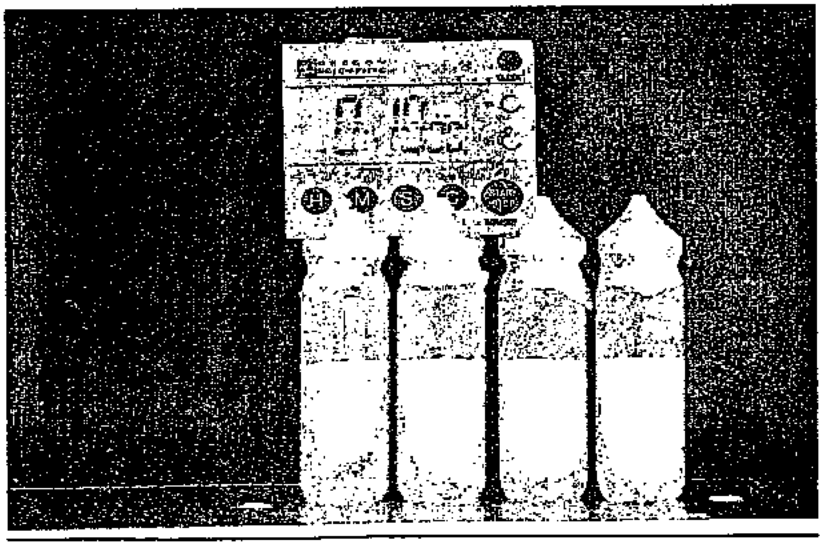
PHOTOGRAPHIC ANALYSIS

Digital photographs of suspensions containing Budesonide, Formoterol, HFA 227, 0.001%w/w PVP and varying levels of PEG 1000 show little variation in suspension stability over time (0 seconds to 10 minutes) except for the 0.005% w/w PEG level (in agreement with the Turbiscan data). Two photographs are shown below for examples.

Budesonide 80µg/shot, Formoterol 4.5µg/shot with 0.001% PVP K25 and various concentrations of PEG 1000 at 0 (1) and 10 minutes (2) standing time



PEG concn = left – right 0.005, 0.05, 0.35 and 0.5 % w/w



PRODUCT PERFORMANCE DATA

In addition to the above, product performance data for formulations containing formoterol fumurate dihydrate/budesonide at the following strengths, 4.5/80 mcg per actuation and

4.5/160 mcg per actuation, with 0.001% PVP K25 and either 0.1% or 0.3% PEG 1000 were stable for up to 12 months at 25°C/60% RH.

Product performance data for Symbicort formulations containing 0.001% PVP K25 and 0.1% PEG 1000 in HFA-227

Product strength (µg) (FFD/budesonide)	Fine particle fraction (% cumulative undersize for 4.7 µm cut-off)			
	Drug	Initial	25°C/60% RH 6 months	25°C/60% RH 12 months
4.5/80	Budesonide	51.3	52.8	62.0
	FFD	55.4	53.5	59.7
4.5/160	Budesonide	50.0	48.8	47.0
	FFD	54.2	52.1	51.3

Product performance data for Symbicort formulations containing 0.001% PVP K25 and 0.3% PEG 1000 in HFA-227

Product strength (µg) (FFD/budesonide)	Fine particle fraction (% cumulative undersize for 4.7 µm cut-off)			
	Drug	Initial	25°C/60% RH 6 months	25°C/60% RH 12 months
4.5/80	Budesonide	55.8	50.6	51.3
	FFD	64.2	57.6	58.7
4.5/160	Budesonide	48.7	50.2	52.3
	FFD	55.6	59.1	61.2

Claims.

1. A pharmaceutical composition comprising formoterol, budesonide, HFA 227, PVP and PEG.

2. A formulation according to claim 1 characterised in that the PVP is present from about 0.0005 to about 0.05 %w/w and the PEG is present from about 0.05 to about 0.35% w/w.
3. A pharmaceutical composition according to claim 1 or 2 in which the PVP is PVP K25.
4. A pharmaceutical composition according to claim 1 to 3 in which the PVP is present in an amount of 0.001% w/w.
5. A pharmaceutical composition according to any one of claims 1 to 4 in which the PEG is PEG 1000.
6. A pharmaceutical composition according to any one of claims 1 to 5 in which the PEG is present in an amount of 0.3% w/w.
7. A pharmaceutical composition according to any one of claims 1 to 6 in which formoterol is in the form of its fumarate dihydrate salt
8. A pharmaceutical composition according to any one of claims 1 to 7 in which the formoterol is in the form of the single R, R-enantiomer.
9. A pharmaceutical composition according to any one of claims 1 to 8 in which the second active ingredient is the 22R-epimer of budesonide.
10. A pharmaceutical composition according to any one of claims 1 to 9 for use for the treatment or prophylaxis of a respiratory disorder.
11. A pharmaceutical composition according to any one of claims 1 to 9 for use for the treatment or prophylaxis of asthma, rhinitis or COPD.
12. A method of treating a respiratory disorder in a mammal which comprises administering to a patient a pharmaceutical composition according to any one of claims 1 to 9.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 03/00156

A. CLASSIFICATION OF SUBJECT MATTER

IPC7: A61K 9/72, A61K 31/573, A61K 31/167, A61P 11/06, A61P 11/08
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC7: A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

WPI DATA, EPO-INTERNAL, PAJ, CA DATA, EMBASE, MEDLINE, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	EP 0534731 A1 (FISONS PLC), 31 March 1993 (31.03.93), page 2, lines 16-28 and 48-49, page 3, lines 25-31 and page 14, line 51 - page 15, line 55	1-12
Y	US 6004537 A (FRANK E. BLONDINO ET AL), 21 December 1999 (21.12.99), abstract, column 3, lines 30-41 and claim 9	1-12
A	WO 0178693 A2 (CHIESI FARMACEUTICI S.P.A.), 25 October 2001 (25.10.01)	1-12

[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
25 April 2003	29 -04- 2003
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer Ingrid Eklund/EÖ Telephone No. +46 8 782 25 00

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 03/00156

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 9821175 A1 (SEPRACOR, INC.), 22 May 1998 (22.05.98) --	1-12
A	WO 0203958 A1 (ASTRAZENECA AB), 17 January 2002 (17.01.02) --	1-12

Form PCT/ISA/210 (continuation of second sheet) (July 1998)

INTERNATIONAL SEARCH REPORT

Information on pat[redacted]mily members

29/03/03

International [redacted]plication No.
PCT/SE 03/00156

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0534731 A1	31/03/93	AT 132739 T	15/01/96
		AU 654397 B	03/11/94
		AU 2647192 A	27/04/93
		BG 61752 B	29/05/98
		BG 98681 A	28/02/95
		BR 1100446 A	18/04/00
		BR 9206549 A	17/10/95
		CA 2119932 A	01/04/93
		CN 1050285 B	15/03/00
		CN 1071832 A	12/05/93
		CZ 282506 B	16/07/97
		CZ 9400695 A	15/11/95
		DE 69207606 D,T	27/06/96
		DK 605578 T	25/03/96
		EP 0605578 A,B	13/07/94
		SE 0605578 T3	
		ES 2082507 T	16/03/96
		FI 110407 B	00/00/00
		FI 941388 A	25/03/94
		GB 9120396 D	00/00/00
		GR 3019098 T	31/05/96
		GR 3032103 T	31/03/00
		HK 1005564 A	00/00/00
		HU 67480 A	28/04/95
		HU 210818 B	28/08/95
		HU 9400853 D	00/00/00
		IL 103238 A	31/07/95
		JP 3142136 B	07/03/01
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		GB 9203212 D	00/00/00
US 6004537 A	21/12/99	AU 2194900 A	03/07/00
		BR 9916829 A	23/10/01
		CA 2355932 A	22/06/00
		CZ 20012216 A	17/04/02
		EP 1140059 A	10/10/01
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		JP 2002532418 T	02/10/02
		PL 348809 A	17/06/02
		WO 0035441 A	22/06/00

INTERNATIONAL SEARCH REPORT

International Application No.
PCT/S[redacted]/00156

Box I **Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)**

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 12
because they relate to subject matter not required to be searched by this Authority, namely:

see next sheet

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II ***Observations where unity of invention is lacking (Continuation of item 2 of first sheet)***

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

Claim 12 relates to a method of treatment of the human or animal body by surgery or by therapy/a diagnostic method practised on the human or animal body/Rule 39.1(iv). Nevertheless, a search has been executed for this claim. The search has been based on the alleged effects of the compound/composition.

INTERNATIONAL [redacted]RCH REPORT
Information on pate[redacted]ily members

29/03/03

Internation[redacted]lication No.
PCT/SE 03/00156

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 0178693 A2	25/10/01	AU 4858101 A	30/10/01
		AU 4859501 A	30/10/01
		AU 4860101 A	30/10/01
		AU 5834301 A	30/10/01
		AU 6926101 A	08/01/02
		BR 0110139 A	31/12/02
		BR 0110141 A	28/01/03
		EP 1274406 A	15/01/03
		EP 1276472 A	22/01/03
		EP 1276473 A	22/01/03
		EP 1276474 A	22/01/03
		GB 0109431 D	00/00/00
		GB 0109432 D	00/00/00
		GB 2363987 A	16/01/02
		GB 2363988 A	16/01/02
		NO 20024971 A	17/12/02
		NO 20024973 A	16/12/02
		NO 20024980 A	17/12/02
		WO 0178694 A	25/10/01
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		WO 0178696 A	25/10/01
		WO 0200197 A	03/01/02
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		AU 722859 B	10/08/00
		AU 5175598 A	03/06/98
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		DK 938467 T	07/10/02
		EP 0938467 A,B	01/09/99
		SE 0938467 T3	
		ES 2178015 T	16/12/02
		JP 2001503772 T	21/03/01
		PT 938467 T	29/11/02
		US 6040344 A	21/03/00
		US 6268533 B	31/07/01
WO 0203958 A1	17/01/02	AU 7286601 A	21/01/02
		GB 0016876 D	00/00/00
		NO 20030133 D	00/00/00

PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

PCT

To:

Global Intellectual Property
AstraZeneca AB
151 85 Södertälje

- 4 MAY 2004

NOTIFICATION OF TRANSMITTAL OF INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Rule 71.1)

Date of mailing *(day/month/year)*	30-04-2004
Applicant's or agent's file reference: 100629-1 WO	IMPORTANT NOTIFICATION

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/SE2003/000156	29-01-2003	01-02-2002

Applicant
AstraZeneca AB
et al

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. REMINDER

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in som Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

Name and mailing address of the IPEA/	Authorized officer
Patent- och registreringsverket Box 5055 S-102 42 STOCKHOLM Facsimile No. 08-667 72 88 Telex 17978 PATOREG-S	Rakel Falk Telephone No. 08-782 25 00

Form PCT/IPEA/416 (July 1992)

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY
(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION See Form PCT/IPEA/416	
100629-1 WO		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/SE 2003/000156	29.01.2003	01.02.2002
International Patent Classification (IPC) or national classification and IPC		
A61K 9/72, A61K 31/573, A61K 31/167, A61P 11/06, A61P 11/08		
Applicant		
AstraZeneca AB et al		

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 5 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:

   a. ☐ *(sent to the applicant and to the International Bureau)* a total of _____ sheets, as follows:

   ☐ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).

   ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.

   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s))

   _____, containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

☒	Box No. I	Basis of the report
☐	Box No. II	Priority
☒	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☐	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☐	Box No. VIII	Certain observations on the international application

Date of submission of the demand	Date of completion of this report
12.08.2003	27.04.2004
Name and mailing address of the IPEA/SE Patent- och registreringsverket Box 5055 S-102 42 STOCKHOLM Facsimile No. +46 8 667 72 88	Authorized officer Solveig Gustavsson/EÖ Telephone No. +46 8 782 25 00

Form PCT/IPEA/409 (cover sheet) (January 2004)

INTERNATIONAL PRELIMI[redacted] REPORT ON PATENTABILITY

Internati[redacted]pplication No.
PCT/SE 2003/000156

Box No. I Basis of the report

1. With regard to the language, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

☐ This report is based on a translation from the original language into the following language _____, which is the language of a translation furnished for the purposes of:

☐ international search (under Rules 12.3 and 23.1(b))
☐ publication of the international application (under Rule 12.4)
☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the elements of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report):*

☒ the international application as originally filed/furnished

☐ the description:

pages _____ as originally filed/furnished
pages* _____ received by this Authority on _____
pages* _____ received by this Authority on _____

☐ the claims:

pages _____ as originally filed/furnished
pages* _____ as amended (together with any statement) under Article 19
pages* _____ received by this Authority on _____
pages* _____ received by this Authority on _____

☐ the drawings:

pages _____ as originally filed/furnished
pages* _____ received by this Authority on _____
pages* _____ received by this Authority on _____

☐ a sequence listing and/or any related table(s) – see Supplemental Box Relating to Sequence Listing.

3. ☐ The amendments have resulted in the cancellation of:

☐ the description, pages _____
☐ the claims, Nos. _____
☐ the drawings, sheets/figs _____
☐ the sequence listing *(specify)*: _____
☐ any table(s) related to the sequence listing *(specify)*: _____

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).

☐ the description, pages _____
☐ the claims, Nos. _____
☐ the drawings, sheets/figs _____
☐ the sequence listing *(specify)*: _____
☐ any table(s) related to the sequence listing *(specify)*: _____

* *If item 4 applies, some or all of those sheets may be marked "superseded."*

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/SE 2003/000156

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application

☒ claims Nos. 10-12

because:

☒ the said international application, or the said claims Nos. 10-12 relate to the following subject matter which does not require an international preliminary examination *(specify)*:

See PCT Rule 67.1.(iv).: Methods for treatment of the human or animal body by surgery or therapy, as well as diagnostic methods.

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. _____ are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. _____ are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for said claims Nos. _____

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form
- ☐ has not been furnished
- ☐ does not comply with the standard

the computer readable form
- ☐ has not been furnished
- ☐ does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in the Annex C-*bis* of the Administrative Instructions.

☐ See Supplemental Box for further details.

INTERNATIONAL PRELIMI[redacted]Y REPORT ON PATENTABILITY

Internat[redacted]pplication No.
PCT/SE 2003/000156

Box No. V **Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

Novelty (N)	Claims	1-9	YES
	Claims		NO
Inventive step (IS)	Claims		YES
	Claims	1-9	NO
Industrial applicability (IA)	Claims	1-9	YES
	Claims		NO

2. Citations and explanations (Rule 70.7)

The opinion is based on the international search report. The following documents are considered relevant:

A. US6004537 A1
B. EP0534731 A1
C. WO0203958 A1
D. WO9821175 A1
E. WO0178693 A2

Document A pertains to a solution aerosol formulation adapted for use in a pressurized aerosol container. The formulation contains budesonide, formoterol and at least one flouroalkane propellant, and a cosolvent. One of the preferred fluoroalkanes is HFA 227.

Document B shows a pressurized aerosol composition comprising a liquefied hydrofluoroalkane, a powdered medicament and a polymer. The problem solved by document B is that of stabilization of medicament compositions by adding polymers. The preferred polymer is PVP, and other excipients that may be present in the formulation include lubricants, particularly polyethylene glycol. Different K-values of the PVP:s are evaluated. Active substances include drugs for use in the prophylactic or remedial treatment of reversible obstructive airway diseases, e.g. inhaled steroids, such as budesonide, and bronchodilators, e.g. formoterol, and combinations of two or more of these agents.

Control 3 of document C shows a composition that contains formoterol fumarate dihydrate, PEG 1000, PVP K25, HFA 227 and HFA 134a.

.../...

Supplemental Box

In case the space in any of the preceding boxes is not sufficient.
Continuation of: Box V

Documents D-E are considered to represent the state of the art. In document D, a method for the preparation of isomers of formoterol is disclosed, and document E, example 11, shows a dry powder mixture of budesonide and formoterol.

Document A is considered to represent the closest prior art. The difference between document A and the present application is the presence of stabilizing compounds in the formulations. Thus, the problem to be solved by the application is that of adding PVP and PEG to a composition for use in a pressurized aerosol container, in order to stabilize the composition.

A person skilled in the art who is presented with this problem, would realize that a similar problem is solved in document B, by the addition of a stabilizing polymer (PVP) and a lubricant, eg. PEG. Different K-values of PVP are discussed in document B, as is the molecular weight of PEG. Thus, a person skilled in the art would arrive at the solution according to the present application, i.e. the addition of PVP and PEG to a composition according to document A, would stabilize the composition in question.

Therefore, claims 1-9 lack the requirement of inventive step.

Even without the knowledge of document B, a person skilled in the art would arrive at the solution according to the present application by the use of the information in document C, where the combination of formoterol, PEG 1000 and PVP K25 for use in a pressurized aerosol container is disclosed.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 03/00156

A. CLASSIFICATION OF SUBJECT MATTER

IPC7: A61K 9/72, A61K 31/573, A61K 31/167, A61P 11/06, A61P 11/08
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC7: A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

WPI DATA, EPO-INTERNAL, PAJ, CA DATA, EMBASE, MEDLINE, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	EP 0534731 A1 (FISONS PLC), 31 March 1993 (31.03.93), page 2, lines 16-28 and 48-49, page 3, lines 25-31 and page 14, line 51 - page 15, line 55	1-12
	--	
Y	US 6004537 A (FRANK E. BLONDINO ET AL), 21 December 1999 (21.12.99), abstract, column 3, lines 30-41 and claim 9	1-12
	--	
A	WO 0178693 A2 (CHIESI FARMACEUTICI S.P.A.), 25 October 2001 (25.10.01)	1-12
	--	

[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
25 April 2003	29 -04- 2003
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer Ingrid Eklund/EÖ Telephone No. +46 8 782 25 00

Form PCT/ISA/210 (second sheet) (July 1998)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 03/00156

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

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INTERNATIONAL SEARCH REPORT

Information on patent family members

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		NZ 244439 A	26/01/94
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		PL 348809 A	17/06/02
		WO 0035441 A	22/06/00

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE03/00156

Box I **Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)**

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because they relate to subject matter not required to be searched by this Authority, namely:

see next sheet

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

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2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

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4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE03/00156

Claim 12 relates to a method of treatment of the human or animal body by surgery or by therapy/a diagnostic method practised on the human or animal body/Rule 39.1(iv). Nevertheless, a search has been executed for this claim. The search has been based on the alleged effects of the compound/composition.

INTERNATIONAL SEARCH REPORT

Information on patent family members

29/03/03

International application No.
PCT/SE 03/00156

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 0178693 A2	25/10/01	AU 4858101 A	30/10/01
		AU 4859501 A	30/10/01
		AU 4860101 A	30/10/01
		AU 5834301 A	30/10/01
		AU 6926101 A	08/01/02
		BR 0110139 A	31/12/02
		BR 0110141 A	28/01/03
		EP 1274406 A	15/01/03
		EP 1276472 A	22/01/03
		EP 1276473 A	22/01/03
		EP 1276474 A	22/01/03
		GB 0109431 D	00/00/00
		GB 0109432 D	00/00/00
		GB 2363987 A	16/01/02
		GB 2363988 A	16/01/02
		NO 20024971 A	17/12/02
		NO 20024973 A	16/12/02
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PATENT APPLICATION FEE DETERMINATION RECORD
Effective October 1, 2003

Application or Docket Number
10/502685

CLAIMS AS FILED - PART I

	(Column 1)	(Column 2)
TOTAL CLAIMS		
FOR	NUMBER FILED	NUMBER EXTRA
TOTAL CHARGEABLE CLAIMS	12 minus 20=	* —
INDEPENDENT CLAIMS	1 minus 3 =	* —
MULTIPLE DEPENDENT CLAIM PRESENT	— ☐	

* If the difference in column 1 is less than zero, enter "0" in column 2

SMALL ENTITY TYPE ☐		OR	OTHER THAN SMALL ENTITY	
RATE	FEE		RATE	FEE
BASIC FEE		OR	BASIC FEE	1080
XS 9=		OR	XS18=	
X43=		OR	X86=	
+145=		OR	+290=	
TOTAL		OR	TOTAL	1080

CLAIMS AS AMENDED - PART II

7-27-04

AMENDMENT A

	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA
Total	* 12	Minus	** 20	= —
Independent	* 1	Minus	*** 3	= —
FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM ☐				

SMALL ENTITY		OR	OTHER THAN SMALL ENTITY	
RATE	ADDITIONAL FEE		RATE	ADDITIONAL FEE
XS 9=		OR	XS18=	
X43=		OR	X86=	
+145=		OR	+290=	
TOTAL ADDIT. FEE		OR	TOTAL ADDIT. FEE	

AMENDMENT B

	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA
Total	*	Minus	**	=
Independent	*	Minus	***	=
FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM ☐				

RATE	ADDITIONAL FEE		RATE	ADDITIONAL FEE
XS 9=		OR	XS18=	
X43=		OR	X86=	
+145=		OR	+290=	
TOTAL ADDIT. FEE		OR	TOTAL ADDIT. FEE	

AMENDMENT C

	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA
Total	*	Minus	**	=
Independent	*	Minus	***	=
FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM ☐				

RATE	ADDITIONAL FEE		RATE	ADDITIONAL FEE
XS 9=		OR	XS18=	
X43=		OR	X86=	
+145=		OR	+290=	
TOTAL ADDIT. FEE		OR	TOTAL ADDIT. FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20."
*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3."
The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.

PTO/SB/07 (08-03)
Approved for use through 7/31/2006, OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
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MULTIPLE DEPENDENT CLAIM FEE CALCULATION SHEET

Substitute for Form PTO-1360
(For use with Form PTO/SB/06)

Application Number	Filing Date
10/502,635	
Applicant(s)	

May be used for additional claims or amendments

CLAIMS	~~AS FILED~~ 7-27-04		AFTER FIRST AMENDMENT		AFTER SECOND AMENDMENT	
	Indep	Depend	Indep	Depend	Indep	Depend
1	1					
2		1				
3		1				
4		1				
5		1				
6		1				
7		1				
8		1				
9		1				
10		1				
11		1				
12		1				
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42						
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44						
45						
46						
47						
48						
49						
50						
Total Indep	1					
Total Depend	11					
Total Claims	12					

	Indep	Depend	Indep	Depend	Indep	Depend
51						
52						
53						
54						
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61						
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95						
96						
97						
98						
99						
100						
Total Indep						
Total Depend						
Total Claims						