2021–1729

UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

ASTRAZENECA AB, ASTRAZENECA PHARMACEUTICALS LP,

Plaintiffs-Appellees

v.

MYLAN PHARMACEUTICALS INC., KINDEVA DRUG DELIVERY L.P.,

Defendants-Appellants

Appeal from the United States District Court for the Northern District of West Virginia, Case Nos. 1:18-cv-00193, 1:19-cv-00203, Judge Irene M. Keeley

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NON-CONFIDENTIAL OPENING BRIEF OF APPELLANTS MYLAN PHARMACEUTICALS INC. AND KINDEVA DRUG DELIVERY L.P.

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April 6, 2021

CLAIM 13 OF THE '328 PATENT

13. A pharmaceutical composition comprising formoterol fumarate dihydrate, budesonide, HFA227, PVP K25, and PEG-1000, wherein

the formoterol fumarate dihydrate is present at a concentration of 0.09 mg/ml,

the budesonide is present at a concentration of 2 mg/ml,

the PVP K25 is present at a concentration of 0.001% w/w, and

the PEG-1000 is present at a concentration of 0.3% w/w.

Appx146 (formatting added).

UNITED STATES COURT OF APPEALS
FOR THE FEDERAL CIRCUIT

CERTIFICATE OF INTEREST

Case Number 2021-1729

Short Case Caption Astrazeneca AB v. Mylan Pharmaceuticals Inc.

Filing Party/Entity Mylan Pharmaceuticals Inc.; Kindeva Drug Delivery L.P

Instructions: Complete each section of the form. In answering items 2 and 3, be specific as to which represented entities the answers apply; lack of specificity may result in non-compliance. **Please enter only one item per box; attach additional pages as needed and check the relevant box**. Counsel must immediately file an amended Certificate of Interest if information changes. Fed. Cir. R. 47.4(b).

I certify the following information and any attached sheets are accurate and complete to the best of my knowledge.

Date: 03/24/2021

Signature: /s/Shannon M. Bloodworth

Name: Shannon M. Bloodworth

1. Represented Entities. Fed. Cir. R. 47.4(a)(1).	**2. Real Party in Interest.** Fed. Cir. R. 47.4(a)(2).	**3. Parent Corporations and Stockholders.** Fed. Cir. R. 47.4(a)(3).
Provide the full names of all entities represented by undersigned counsel in this case.	Provide the full names of all real parties in interest for the entities. Do not list the real parties if they are the same as the entities. ☑ None/Not Applicable	Provide the full names of all parent corporations for the entities and all publicly held companies that own 10% or more stock in the entities. ☐ None/Not Applicable
Mylan Pharmaceuticals Inc.		Mylan Inc.; Viatris Inc.*
Kindeva Drug Delivery L.P.		Kindeva Midco L.P; Kindeva GP II LLC; 3M Company
		* Mylan Pharmaceuticals Inc. is wholly owned by Mylan Inc. Mylan Inc. is wholly owned by Viatris Inc., a publicly-held company. No publicly-held company owns 10% or more of Viatris Inc.'s stock.

☐ Additional pages attached

4. Legal Representatives. List all law firms, partners, and associates that (a) appeared for the entities in the originating court or agency or (b) are expected to appear in this court for the entities. Do not include those who have already entered an appearance in this court. Fed. Cir. R. 47.4(a)(4).

☐ None/Not Applicable ☐ Additional pages attached

Gordon H. Copland (Steptoe & Johnson PLLC)	William J. O'Brien (Steptoe & Johnson LLP)	Brandon M. White (Perkins Coie LLP)
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5. Related Cases. Provide the case titles and numbers of any case known to be pending in this court or any other court or agency that will directly affect or be directly affected by this court's decision in the pending appeal. Do not include the originating case number(s) for this case. Fed. Cir. R. 47.4(a)(5). See also Fed. Cir. R. 47.5(b).

☑ None/Not Applicable ☐ Additional pages attached

6. Organizational Victims and Bankruptcy Cases. Provide any information required under Fed. R. App. P. 26.1(b) (organizational victims in criminal cases) and 26.1(c) (bankruptcy case debtors and trustees). Fed. Cir. R. 47.4(a)(6).

☑ None/Not Applicable ☐ Additional pages attached

Confidential Material Omitted

The material omitted on pages 1, 19, 20, 21, 27, and 45 indicates the concentration of PVP in Appellants' ANDA product.

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TABLE OF ABBREVIATIONS AND CONVENTIONS

’137 patent	U.S. Patent No. 8,575,137
’239 patent	U.S. Patent No. 8,143,239
’328 patent	U.S. Patent No. 7,759,328
ANDA	Abbreviated New Drug Application
AstraZeneca	Appellees AstraZeneca AB and AstraZeneca Pharmaceuticals LP, collectively
CFC	chlorofluorocarbon
DPI	dry-powder inhaler
HFA	hydrofluoroalkane
HFA-134a	1,1,1,2-tetrafluoroethane
HFA-227	1,1,1,2,3,3,3-heptafluoropropane
Mylan	Appellants Mylan Pharmaceuticals Inc. and Kindeva Drug Delivery L.P., collectively
Mistry	Published Spanish Patent Application No. ES 2064244 (Appx18601)
OSCAR	optical suspension characterization
patents-in-suit	the ’137, ’239, and ’328 patents
PEG	polyethylene glycol
pMDI	pressurized metered-dose inhaler
POSA	person of ordinary skill in the art
PTO	United States Patent and Trademark Office
PVP	polyvinylpyrrolidone
Rogueda	International Publication No. WO 02/03958 A1 (Appx18504)
(*xx*:*yy-zz*)	column or page *xx*, lines *yy-zz*

RELATED CASES

No other appeals regarding the district court case or the patents at issue in this appeal (U.S. Patents 7,759,328; 8,143,239; and 8,575,137) have been before this or any other appellate court. Appellants Mylan Pharmaceuticals Inc. and Kindeva Drug Delivery L.P. and their counsel are unaware of any cases pending in this or any other court that will directly affect or be directly affected by this Court's decision in this case.

Confidential Material Omitted

INTRODUCTION

AstraZeneca reformulated Symbicort®—a known, two-drug asthma treatment—from one established inhaler format to another more favored in the U.S. market. It patented that reformulation by citing data and convincing the examiner that compositions with the excipient PVP at 0.001% achieved unique and unexpected stability compared to compositions with other concentrations of PVP, including 0.0005%. Indeed, the specification makes clear that 0.0005% PVP was one of the *worst*-performing concentrations tested. Despite the inventors' focus on 0.001% PVP throughout the specification and during prosecution, and the specification's sharp distinction between 0.001% and 0.0005% PVP, the district court construed the critical limitation requiring "0.001%" PVP to cover concentrations from 0.0005% to 0.0014%, thereby nullifying the differences highlighted by the patentees. Under that flawed construction, Mylan was forced to stipulate to infringement by ANDA products that contain percentage PVP.

The district court's construction was wrong. Intrinsic evidence is paramount when construing patent claims, and the inventors repeatedly touted 0.001% PVP for its stabilizing effects compared to other concentrations. The district court understood the significance of data showing enhanced stability at 0.001% PVP: it separately held that those results were unexpected and rendered the claims non-obvious. Yet the court's construction subsumed numerous other PVP concentrations into

"0.001%," including at least one (0.0005% PVP) described in the specification as producing distinctly inferior results. The district court made no effort to square its claim construction with the intrinsic evidence, and the two cannot be reconciled.

After the infringement stipulation, the district court conducted a bench trial on validity and held the claims non-obvious. That ruling was equally flawed. The court recognized that POSAs were motivated to reformulate the existing Symbicort® product as a chlorofluorocarbon-free pressurized inhaler, and that the choice of necessary and available excipients was limited. The court focused on two references. The first, Mistry, taught various excipients, including those in the claims, for use in CFC-free pressurized inhalers and further taught excipient concentration ranges encompassing those in the claimed formulations. The second, Rogueda, described an inhaler formulation that included the same excipients at the same percentages recited in the claims. Rogueda's formulation also included one of the two drugs in Symbicort®. Had that formulation included the other drug—one that Rogueda expressly mentioned among suitable active ingredients—Rogueda would have anticipated.

The district court dismissed Mistry based on attorney argument that the finite numbers of relevant prior-art excipients (two propellants, eight lubricants, and eight stabilizers) presented more than 2.5 million possible formulations. To conjure up so many combinations, AstraZeneca multiplied the numbers of relevant excipients and then multiplied again by 20,000, supposedly the number of possible discrete

concentrations for the lubricant and stabilizer within prior-art concentration ranges. The prospect of millions of combinations convinced the district court that Mistry taught too many possibilities to be helpful. But this Court's precedent has not treated prior-art ranges as profuse distinct embodiments, and the district court erred by casting that precedent aside.

The district court compounded its error by concluding that Rogueda taught away from its nearly anticipating formulation. The district court agreed that Rogueda did not disparage that composition. The court instead found teaching away based on data that supposedly "cut against" the formulation stability POSAs were seeking. But the most relevant data in Rogueda showed that the formulation Mylan cited was stable during the critical seconds after shaking the inhaler.

Finally, the district court concluded its obviousness analysis by determining that the claimed 0.001% PVP concentration demonstrated unexpected results that established non-obviousness. That was error for several reasons, foremost because the alleged unexpected results at 0.001% were not commensurate with the claims, which the district court had broadened to include formulations that demonstrated *inferior*, not superior, results.

Because the district court erred by expanding the scope of AstraZeneca's claims through a flawed construction, this Court should reverse that construction and the resulting infringement judgment. This Court should also reverse the non-

obviousness ruling or at least vacate and remand for further reconsideration under the correct law and without reliance on clearly erroneous fact-findings.

JURISDICTION

The district court had jurisdiction over this patent-infringement case under 28 U.S.C. § 1338(a). This Court has jurisdiction under 28 U.S.C. § 1295(a)(1) because the district court issued an amended final judgment on March 8, 2021, that resolved all pending claims, Appx2-3, and Mylan filed a timely notice of appeal the next day, Appx10726-10727.

STATEMENT OF ISSUES

1. Each asserted claim requires a composition containing 0.001% polyvinylpyrrolidone (PVP). The common specification of the patents-in-suit presents data comparing composition stability at different PVP concentrations and asserts that 0.001% PVP provided "the best" and "most stable" compositions compared to other values—including 0.0005%, which gave poor stability results. To overcome prior-art rejections during prosecution, the inventors narrowed their claims to require 0.001% PVP and emphasized unexpectedly superior properties of that specific value. Did the district court err by construing "0.001%" PVP to encompass concentrations from 0.0005% to 0.0014% based on a presumed plain meaning?

2. Skilled artisans were undisputedly motivated to design a pressurized metered-dose inhaler (pMDI) version of Symbicort®, and the need to avoid

chlorofluorocarbons (CFCs) would have led them to choose one of only two available propellants. The parties' dispute was whether the choice of propellant and two common excipients at known concentrations would have been obvious. The prior art included Mistry, which taught the claimed propellant and excipients at concentration ranges encompassing those in the claims. It also included Rogueda, which specifically taught a composition including the *precise* propellant, excipients, and excipient concentrations claimed by AstraZeneca. Did the district court err by relying on a misleading demonstrative showing millions of theoretical possibilities to conclude that Mistry failed to demonstrate obviousness and by concluding that Rogueda taught away even though Rogueda did not disparage a nearly anticipating formulation?

STATEMENT OF THE CASE

This appeal concerns the proper construction and validity of claims from three related patents: U.S. Patents 7,759,328; 8,143,239; and 8,575,137.

A. The patents-in-suit claim compositions for administering a known combination of formoterol and budesonide using a metered-dose inhaler

All three AstraZeneca patents share the same specification, inventors, and priority date. The asserted claims recite an established drug combination, formoterol and budesonide, formulated with known excipients, HFA-227, PVP K25, and PEG-1000.

1. The ’328, ’239, and ’137 patents describe optimized inhaler formulations

The patents-in-suit describe the invention as “a formulation comprising formoterol and budesonide for use in the treatment of respiratory diseases.” Appx126 (Abstract).[1] Formoterol is a bronchodilator, and budesonide is an anti-inflammatory corticosteroid. Both drugs were known and had long been used together for treating asthma and other respiratory conditions by the patents’ 2002 priority date. Appx143 (1:25-28) (citing published co-formulation); Appx18500-18502 (Abstract, 2:29-60, 3:50-55) (similar).

The claimed pMDI formulations contain three additional, inactive ingredients: a propellant (HFA-227) and two polymeric excipients (polyethylene glycol (PEG) and PVP). Appx143 (1:25-45). HFA-227 was one of only two known hydrofluoroalkane (HFA) propellants suitable for replacing CFCs to avoid ozone depletion. Appx9-10. PEG operates primarily as a lubricant to keep the inhaler’s valve from sticking during use, and the patents identify PEG-1000 (PEG with an average molecular weight of 1000 g/mol) as preferred. Appx143 (1:49-51), Appx145-146 (6:61-7:24). PVP is a suspension agent that keeps drugs suspended in a formulation. Appx143 (2:17-21); Appx9915 (447:17-19). The patents identify PVP K25 (named

[1] For simplicity, this brief cites the specification of the ’328 patent.

for its nominal viscosity or K-value) as the preferred grade of PVP. Appx143 (1:46-48).

HFA-227, PEG, and PVP had all been used in prior-art pMDI formulations. *E.g.*, Appx18603-18605 (Mistry) (2:17-37, 3:21-28, 4:13-21).

a. The specification emphasizes formulation stability associated with 0.001% PVP

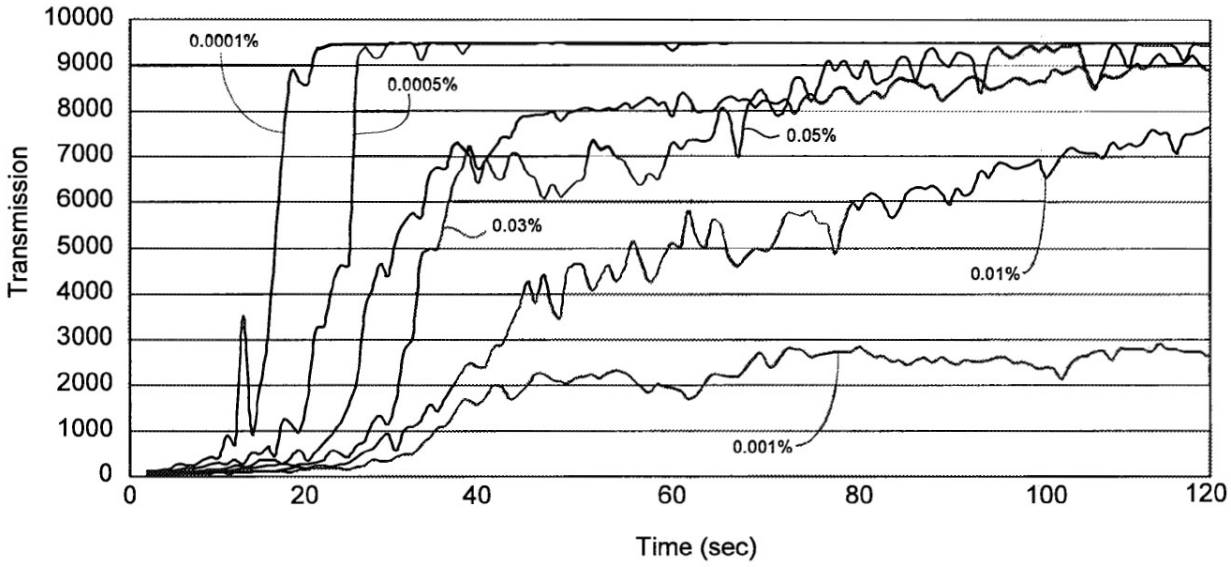
Throughout the specification, the inventors touted using 0.001%[2] PVP to achieve formulation stability as a key feature of the invention. The specification singles out formulation stability as "one of the most important factors" that dictates whether a particular formulation can become "a therapeutically useful pharmaceutical product." Appx143 (1:21-24, 1:32-35). In the context of a pMDI, stability refers to how evenly dispersed the active ingredients remain within the formulation over time. Appx144 (4:4-14).

In their specification, the inventors presented data to demonstrate the stability of formoterol/budesonide pMDI formulations with different PVP concentrations. Those data came from optical suspension characterization (OSCAR) testing, Turbiscan testing, and visual observation of the formulations. In OSCAR testing, a sample is shaken to disperse the formulation and then monitored for light transmittance

[2] All concentrations in this brief are expressed as percentages by weight ("w/w").

over time. Lower transmittance indicates that the ingredients remain dispersed. Appx144-145 (3:9-45, 6:34-38), Appx127-129 (Figs. 1-3). Turbiscan testing similarly involves serial measurements of light transmission through a formulation. Appx144-145 (3:47-4:3, 6:43-51). A third test involves shaking a sample and photographing it at intervals to assess the degree of dispersion over time. Appx145 (5:5-6:27).

The inventors concluded that formulations containing 0.001% PVP gave "consistently stable formulations over the required dose range," Appx143 (2:17-21), and in each test proved "the best" and "the most stable" compared to other tested PVP concentrations, Appx145 (6:30-54). For example, Figure 2 shows OSCAR readings for several otherwise identical formulations containing 0.0001%, 0.0005%, 0.001%, 0.01%, 0.03%, or 0.05% PVP K25:



Appx128 (Fig. 2); *see also* Appx129 (Fig. 3). Samples with 0.001% PVP showed the lowest light transmission over an extended period, and the inventors therefore concluded that those formulations were the most stable. Appx145 (6:33-42).

Turbiscan results similarly showed lower levels of light transmission at 0.001% PVP than at any other tested concentration:

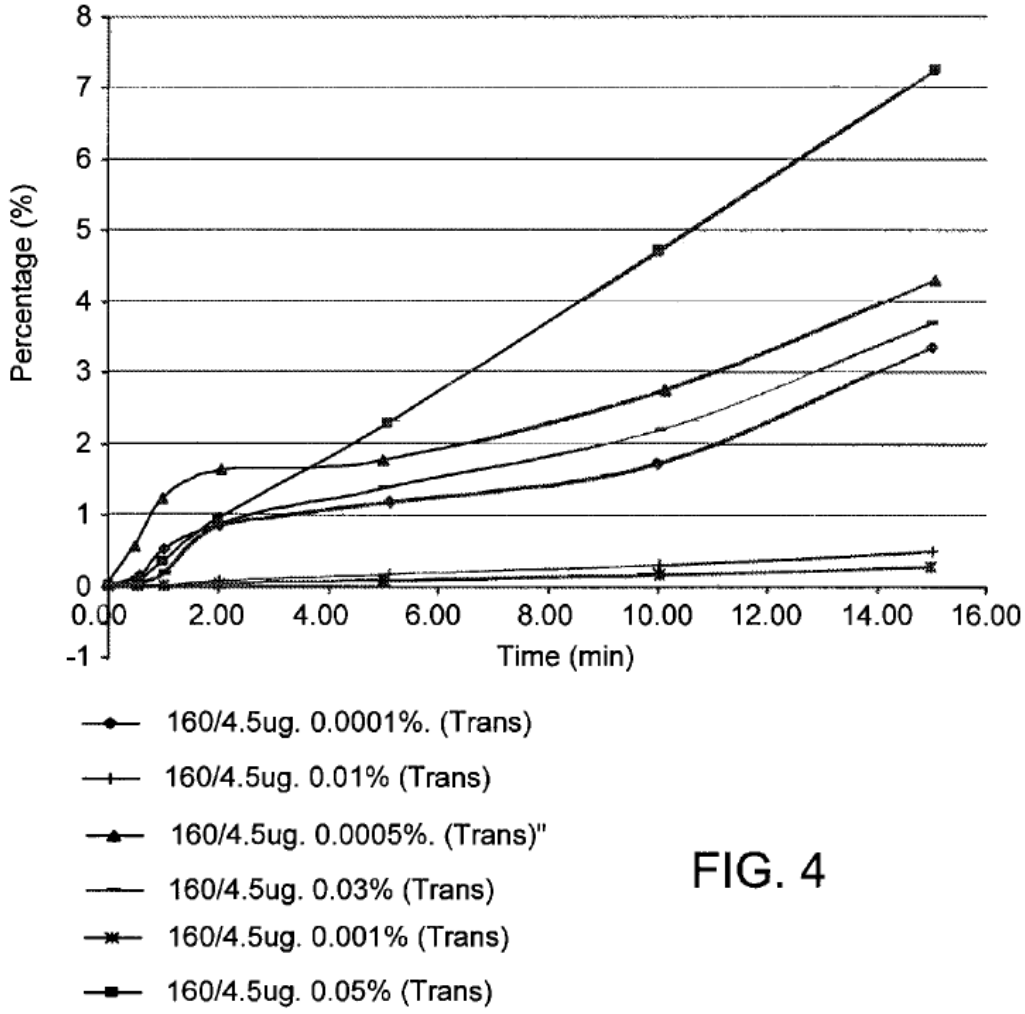


FIG. 4

Appx130 (Fig. 4); *see also* Appx131-132 (Figs. 5-6). Here too, the inventors concluded that 0.001% PVP provided the greatest prolonged formulation stability with the lowest light-transmission readings. Appx145 (6:43-54). The inventors'

qualitative photographic assessments led to the same conclusion: "formulations with 0.001% PVP gave the best suspension stability overall." Appx145 (5:28-6:31), Appx135-140 (Figs. 9-14).[3]

b. The corresponding claims require formulations containing 0.001% PVP

Reflecting those empirical conclusions, the asserted claims of the patents-in-suit require 0.001% PVP. For example, independent claim 13 the '328 patent recites:

> 13. A pharmaceutical composition comprising formoterol fumarate dihydrate, budesonide, HFA227, PVP K25, and PEG-1000, wherein
>
> the formoterol fumarate dihydrate is present at a concentration of 0.09 mg/ml,
>
> the budesonide is present at a concentration of 2 mg/ml,
>
> the PVP K25 is present at a concentration of 0.001% w/w, and
>
> the PEG-1000 is present at a concentration of 0.3% w/w.

Appx146 (formatting added). Claim 14 is similar. Appx146-147. Claims 8 and 9 recite methods for treating a respiratory disorder by administering those compositions. Appx146.

The asserted claims of the '239 and '137 patents are similar. In the '239 patent, claims 12 and 13 recite pMDIs containing suspensions with the same

[3] Parallel experiments revealed "little difference" in stability with varying concentrations of PEG. Appx146 (7:27-42), Appx133-134 (Figs. 7, 8), Appx141-142 (Figs. 15, 16).

ingredients listed above, where the drugs are in particulate form and a single puff of the inhaler delivers 80 µg or 160 µg of budesonide (2 or 4 mg/ml in the formulation, respectively).[4] Appx172. Claims 18 and 19 recite methods of administration using the same pMDIs. *Id.* In the '137 patent, claims 10 and 19 recite a pharmaceutical suspension and related method of treatment using formoterol fumarate dihydrate, 1-8 mg/ml budesonide, HFA-227, 0.3% PEG-1000, and 0.001% PVP K25. Appx123-124.

2. The 0.001% PVP limitation was critical to allowance

a. During prosecution of the '328 patent, the applicants narrowed their claims to require 0.001% PVP and relied on their stability data

The application that became the '328 patent—the earliest of the three patents-in-suit—entered U.S. prosecution in July 2004. Appx15879-15880. At first, the claims were not limited to 0.001% PVP. Original independent claim 1 permitted an unbounded amount of PVP, and claim 2 recited a broad concentration range spanning from "about 0.0005 to about 0.05% w/w":

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

[4] The inventors noted that budesonide concentrations of 1-8 mg/ml correspond to 40-320 µg delivered per actuation. Appx144 (4:28-34).

> 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.

Appx15919.

The examiner rejected all pending claims on obviousness grounds. Appx16197-16206. The examiner concluded that two prior-art references would have rendered the claims obvious because the first, Meade, taught pharmaceutical compositions containing the claimed components, while the second, Weers, taught using formoterol and budesonide for treating respiratory disorders, and a POSA would have been motivated to determine an optimum amount of PVP within the claimed 0.0005% to 0.05% range. Appx16204-16206.

In response, the applicants amended the claims and limited the PVP concentration to 0.001%:

> 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.

Appx16213-16214. The applicants argued that "neither Meade nor Weers disclose[d] a pharmaceutical composition containing PVP at a concentration of 0.001% w/w." Appx16221. The applicants also told the examiner they had "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." Appx16222

(citing specification). Based on "the amendment to claim 1" and the "surprising discovery that the specified low concentration of PVP" yielded superior suspension stability, the applicants requested withdrawal of the obviousness rejection. Appx16223.

The examiner maintained the rejection. He acknowledged that the cited references did not specifically disclose 0.001% PVP but, relying on the law governing ranges, called on the applicants to "show the criticality of 0.001% w/w PVP versus the invention where PVP concentration is slightly greater or less than 0.001 % w/w PVP." Appx16306-16307.

The applicants then filed a request for continuing examination, submitted an inventor declaration, and amended the claims to specify amounts of budesonide paired with several different PVP concentrations, including 0.0001%, 0.0005%, 0.001%, and 0.01% PVP. Appx16318-16321, Appx16330-16337. The applicants argued that certain PVP concentrations yielded better stability over time when paired with different budesonide concentrations. Appx16325-16327. According to the applicants, the prior art did not suggest that the amount of PVP would govern suspension stability at the recited budesonide concentrations, and their data generally showed "the best results overall were obtained using 0.001% PVP." Appx16327-16328.

The examiner again rejected the claims for obviousness over Meade and Weers. Appx16444-16448. The examiner noted that the amended claims were "much broader than what are being interpreted as unexpected results." Appx16447-16448. In turn, applicants again narrowed the claims to specify 0.001% PVP, along with recited amounts of formoterol, budesonide, and PEG. Appx16455-16457. The examiner then allowed the claims, noting that the "claimed invention is specific to chemical components and amounts thereof." Appx16478-16479. The '328 patent issued in July 2010.

b. The '239 and '137 continuation patents followed with minimal prosecution

The application for the '239 patent was filed as a continuation in May 2010. A preliminary amendment introduced claims reciting compositions with 0.001% PVP or 0.001% to 0.01% PVP. Appx17000-17001. The examiner issued obviousness rejections over Meade and Weers and obviousness-type double patenting rejections over the '328 patent. Appx17083-17087. After an interview, the applicants filed a terminal disclaimer and amended the claims to recite formoterol and budesonide as particles. Appx17104-17111. A notice of allowance followed on November 16, 2011, Appx17114, and the '239 patent issued in March 2012.

The application for the '137 patent followed as another continuation, and the applicants presented claims reciting PVP in concentrations of 0.001% or from 0.001% to 0.01%. Appx17415-17421. The examiner initially rejected all claims for

obviousness-type double patenting over the '328 and '239 claims and rejected certain method-of-treatment claims as indefinite for failing to specify the target indications. Appx17488-17491. The claims were allowed after the applicants filed a terminal disclaimer and amended the method claims to recite "treating a respiratory disorder." Appx17511-17519; Appx17524. The '137 patent issued in November 2013.

B. The prior art described formulations combining formoterol with budesonide for respiratory administration and described metered-dose inhalers containing the claimed excipients

Long before the February 2002 priority date, prior art promoted inhaled combinations of budesonide and formoterol for treating asthma. Prior art also described using HFA-227 together with PVP and PEG, including in the precise grades and concentrations claimed in the patents-in-suit, to produce inhaled formulations for treating respiratory disorders.

1. The preexisting Symbicort® Turbuhaler provided a co-formulation of formoterol with budesonide as a dry-powder inhaler

Since at least 1993, AstraZeneca had marketed a budesonide/formoterol co-formulation called the Symbicort® Turbuhaler. Appx143 (1:25-28). That formulation, however, was a dry-powder inhaler (DPI), and DPIs were known to have certain drawbacks. To be effective, DPIs require users to take a deep, fast breath, which is challenging for young children, the elderly, and patients with neurological

impairments. Appx11. Pressurized metered dose inhalers (pMDIs) avoid those problems, and asthma patients had long used pMDIs as an alternative delivery format. Appx12. Patients in the large and lucrative U.S. market also preferred pMDIs over DPIs. Appx36-37.

Given the well-known disadvantages of DPIs, both parties' experts agreed that by the 2002 priority date there was a specific need for a budesonide/formoterol combination in a pMDI suspension format and that POSAs would have been "highly motivated" to pursue one for the treatment of respiratory disorders. Appx10314 (846:10-20); Appx10309-10311 (841:19-843:10). Thus, as the district court found, a POSA would have been motivated to adapt Symbicort's co-formulation for the pMDI format. Appx36-37.

2. Mistry described CFC-free pMDI formulations suitable for drugs including formoterol and budesonide

Mistry described polymers that worked in HFA propellants to stabilize pMDI suspension formulations. Appx18601-18627. Mistry disclosed polymeric excipients that were particularly advantageous due to their solubility in HFA propellants. Appx18602 ("We have now found, surprisingly, that certain polymers are both soluble in aerosol propellants and are able to stabilize pharmaceutical compositions."). Among the drugs Mistry described as compatible with the preferred propellant and excipients were budesonide, formoterol, "and combinations of two or more of said agents." Appx18606. AstraZeneca listed the U.S. version of the Mistry patent,

Appx18493, in the FDA's Orange Book as covering both marketed strengths of its Symbicort® pMDI product, Appx15626.

Mistry recognized concerns about the ozone-layer-depleting properties of traditional CFC propellants and the need to find replacement propellants suitable for use in inhaled medical products. Appx18602. Mistry disclosed particularly preferred compositions using HFA-227, PVP (as the surfactant used to stabilize the compositions), and PEG (as a valve lubricant). Appx18603-18605. Mistry taught preferred PVP K-values of 15-120, a range encompassing the PVP K25 grade claimed in the patents-in-suit. Appx18603. Mistry also disclosed a preferred PVP concentration range of 0.001%-1%, which includes the claimed 0.001% concentration. Appx18604. Mistry further taught that PEG grades preferably have molecular weights from 400-2000 and are used at concentrations preferably between 0.1-2%. Appx18604-18605. Mistry's preferred PEG grade and concentration ranges encompass the claimed PEG grade (1000) and concentration (0.3%). Mistry also described various short-term and long-term physical, chemical, and dose-stability tests conducted on its many example formulations. Appx18608-18610 (tests), Appx18614-18623 (examples).

3. Rogueda described control pMDI formulations containing HFA-227, PEG-1000, and PVP K25

Rogueda disclosed pMDI formulations "comprising a drug, an aerosol propellant, a polar fluorinated molecule and an excipient soluble in the polar fluorinated

molecule." Appx18505. Among the drugs Rogueda identified as suitable for use in such pMDIs were "budesonide, formoterol fumarate dihydrate" and the combination product "Symbicort™ (budesonide and formoterol)." Appx18505-18506.

Rogueda identified HFA-134a and HFA-227 as preferred propellants and PEG-1000 and PVP K25 as suitable excipients, with suitable concentrations of each ranging from 0.001% to 1%. Appx18506, Appx18511-18512, Appx18514. Rogueda compared novel formulations containing polar fluorinated molecules against control suspensions. Control 9 contained budesonide in HFA-227 with PVP K25 at 0.001% and PEG-1000 at 0.3%. Appx16-17; Appx18523, Appx18529. Control 3 contained formoterol fumarate dihydrate with PVP K25 at 0.001% and PEG-1000 at 0.1%, in a mixture of HFA-227 and HFA-134a. Appx16-17; Appx18523, Appx18528-18529. In stability testing, Rogueda's control formulations did not fully cream (have active ingredients float out of suspension) until about 30 minutes after shaking. Appx18532. By contrast, other controls "with no added stabilisers" (e.g., with no PVP) took only "a few seconds to a few minutes to be fully destabilised." Appx18532. The following chart compares Rogueda's Control 9 and Control 3 to the formulations AstraZeneca claimed in the patents-in-suit:

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CLAIMED FORMULATIONS	ROGUEDA CONTROL 9	ROGUEDA CONTROL 3
budesonide and formoterol (fumarate dihydrate)	budesonide	formoterol (fumarate dihydrate)
0.001% PVP K25	0.001% PVP K25	0.001% PVP K25
0.3% PEG-1000	0.3% PEG-1000	0.1% PEG-1000
HFA-227	HFA-227	HFA-227 and HFA-134a

C. AstraZeneca accused Mylan's ANDA products of infringing the patents-in-suit

In October 2018, AstraZeneca filed suit, asserting that Mylan's Abbreviated New Drug Application (ANDA) infringed the '328, '239, and '137 patents. Appx300. Mylan counterclaimed for declaratory judgments of non-infringement and invalidity. Appx8032-8043.[5]

1. Mylan's ANDA products contain percentage PVP

Mylan's ANDA seeks FDA approval for inhalation aerosol products with budesonide and formoterol fumarate dihydrate in two strengths (160/4.5 μg and 80/4.5 μg). Mylan's ANDA products are generic versions of AstraZeneca's

[5] The suit was filed in the District of Delaware and later transferred to the Northern District of West Virginia. Appx14072, Appx14097. Before trial, Kindeva Drug Delivery L.P. was substituted for original co-defendant 3M Corp. Appx9250-9253. AstraZeneca dismissed its claims regarding a fourth patent in a pre-trial stipulation. Appx8772-8777.

Symbicort® pMDI products. But unlike the Symbicort® products, which use a PVP K25 concentration of 0.001%, Mylan's ANDA products have a PVP K25 concentration of percentage. Appx5028.

2. AstraZeneca's asserted claims all require 0.001% PVP

Shortly before trial, AstraZeneca narrowed the asserted claims to '328 patent claims 9, 10, 13 and 14; '239 patent claims 12, 13, 18 and 19; and '137 patent claims 10 and 19. Appx9303. Every asserted claim requires a pharmaceutical composition or treatment with a pharmaceutical composition containing budesonide, formoterol fumarate dihydrate, 0.001% PVP K25, and 0.3% PEG-1000 in HFA-227.

3. After the district court construed "0.001%" PVP to include percentage PVP, Mylan stipulated to infringement but reserved its right to dispute claim construction

During pretrial proceedings, the parties disputed the meaning of "0.001%" PVP as required by every asserted claim. The issue was critical because the proposed ANDA products contain only percentage PVP. Appx5028. AstraZeneca urged that "0.001%" should be construed to have one significant digit and cover all PVP concentrations from 0.0005% to 0.0014% due to mathematical rounding. Appx7383-7385; Appx7892 (27:4-20). Mylan countered that the intrinsic evidence contradicted AstraZeneca's construction because the specification and prosecution history highlighted the criticality of 0.001% PVP and distinguished values that would fall within AstraZeneca's broad reading of that specific term. Appx6804-6806. Mylan con-

strued "0.001%" PVP more narrowly to mean that precise number with only minor variations, from 0.00095% to 0.00105%. Appx6804.

The district court adopted AstraZeneca's construction. Appx52-68. The court concluded that the "plain and ordinary meaning" of "0.001%" is a number expressed with one significant digit, subject to rounding and thus including all PVP concentrations from 0.0005% to 0.0014%. Appx68, Appx63. The court read the claims and specification as supporting that construction because they used 0.001% written "with a single significant digit." Appx64-65. The court acknowledged that during prosecution the inventors had specifically limited the claims to 0.001% PVP to distinguish prior art. Appx66-67. But it held that Mylan fell short of establishing "clear and unmistakable disavowal" to overcome what it viewed as the term's ordinary and customary meaning. Appx67.

Because the ANDA products' percentage PVP concentration fell between 0.0005% and 0.0014%, the parties stipulated that those products infringed under the district court's construction. Appx8772-8777. But Mylan reserved its right to dispute that construction and renew its noninfringement defense under any modified construction. Appx8774.

4. After a trial, the district court concluded that the claims were not obvious over the prior art

During the ensuing bench trial on validity, Mylan asserted obviousness combinations including (1) Mistry and the Symbicort DPI, and (2) Mistry, the Symbicort

DPI, and Rogueda. Appx9703-9706 (246:2-249:24).[6]

The district court ruled that the asserted claims would not have been obvious over the prior art. Appx4-48. The district court first noted the parties' agreement that a POSA would have been motivated to adapt Symbicort® from the existing DPI format to a pMDI. Appx36. That motivation, the court explained, came from the "preference for pMDIs in the American market" and the "shift away from CFC propellants." Appx36-37. As to the choice of suspension or solution, the court noted that a suspension "most resembles a DPI because the drug particles remain in a solid state." Appx38. The court added that keeping the same particle size used in the Symbicort® DPI "would likely not have been a choice available to a POSA." Appx38-39.

As for the non-CFC propellant, the district court cited two options, HFA-227 and HFA-134a, but noted that "every FDA-approved HFA pMDI product used HFA 134a, not HFA 227." Appx39 (citation omitted). Those propellants had different densities, which would cause active ingredients to either cream (in HFA-227), or sediment (in HFA-134a). *Id.* Creaming, the court explained, could cause adherence to the interior wall of the container at the gas-liquid interface. Appx39. Foreshadowing its later teaching-away determination, the court concluded that because Rogueda

[6] The Symbicort® Turbuhaler DPI formulation was established as prior art through published studies of the product. Appx18572-18583 (McGavin).

identified the adhesion issue in connection with its Controls 3 and 9, "HFA 227 likely would have been a fatal choice." *Id.*

a. The court concluded that Mistry posed 2,560,000 options—too many to render any of them obvious

The court considered whether Mistry's teachings rendered the claimed invention obvious. Appx40-42. The court viewed the question as an issue of numbers. It read Mistry as disclosing finite numbers of excipient polymers and valve lubricants. Appx40. And it acknowledged Mylan's evidence that "fewer than ten pharmaceutical grades of PVP and PEG, respectively, were commercially available at the priority date (including PVP K25 and PEG-1000)." Appx40. But it credited AstraZeneca's evidence regarding the need for "extensive experimentation," Appx41, and AstraZeneca's argument that testing the various combinations "would have taken an 'eternity,'" *id.* (citation omitted). In particular, an AstraZeneca demonstrative exhibit that the court attached to its opinion, Appx50, calculated that there were 2,560,000 potential formulations. *Id.* Based on that number, the district court concluded that Mistry did not render the claims obvious:

> Here, the number of possible combinations disclosed by Mistry alone is in the millions. Therefore, at the priority date a POSA would not have been motivated to select the specific formulations claimed by the patents-in-suit.

Appx41-42.

b. The court concluded that Rogueda taught away even though Rogueda did not disparage its nearly anticipating control formulations

The district court further concluded that Rogueda taught away from the claimed invention. Appx42-44. The court recognized that Rogueda's control formulations were close to the claimed formulations. Appx43. In particular, Rogueda's Control 9 contained budesonide, HFA 227, PVP K25 at 0.001% and PEG-1000 at 0.3%, Appx43; Appx18529, while Control 3 contained formoterol with a blend of HFA-227 and HFA-134a, PVP K25 at 0.001% and PEG-1000 at 0.1%, Appx43; Appx18528-18529. The district court acknowledged that Rogueda "did not necessarily disparage" those controls. Appx44. But the court concluded that data in Rogueda "cut against" a POSA's goal because they showed evidence of particle adhesion and aggregation. *Id.* Based on that evidence, the court held that Rogueda taught away from the claimed invention. Because of that teaching away, the court also concluded that a POSA would not have had a reasonable expectation of success in creating the claimed invention. Appx46.

c. The court concluded that unexpected results of "an embodiment" within the claims rendered the claims non-obvious

The court further held that unexpected results supported non-obviousness, noting that "AstraZeneca[ ] succeeded in its patent prosecution when it demonstrated the superior stability of its formulation with 0.001% w/w PVP K25." Appx47.

Although that stability was not superior during the critical first seconds after a patient shakes the inhaler, the court pointed to testimony by AstraZeneca's expert that the data showing stability beyond that period would not be irrelevant. *Id*. Despite recognizing that its own construction was broader than the 0.001% embodiment, the court ruled that "because *an* embodiment within the scope of the claims had unexpected properties, the claims are valid and not obvious." *Id.* (emphasis added).

The district court's amended final judgment included an order under 35 U.S.C. § 271(e)(4)(A) prohibiting final approval of Mylan's ANDA until expiration of the patents-in-suit. Appx2-3.

SUMMARY OF ARGUMENT

1. The district court erred in construing the claim limitation requiring "0.001%" PVP to encompass all PVP concentrations from 0.0005% to 0.0014%. In so doing, the court applied its own understanding of numerical rounding to derive a "plain and ordinary" meaning supported nowhere in the patents-in-suit. The resulting overbroad construction of "0.001%" PVP irreconcilably conflicts with the intrinsic record.

The patents' specification includes data assessing the stability of formulations containing different concentrations of PVP, from 0.0001% to 0.05%. The inventors reported that 0.001% PVP consistently provided "the best" and "the most stable" formulations, whereas 0.0005% PVP yielded some of the *least* stable formulations.

The district court's construction contradicts the specification by nevertheless treating 0.001% and 0.0005% PVP as one and the same.

The prosecution history confirms the error in the district court's construction. During prosecution, the applicants repeatedly responded to rejections over prior art by amending broad claims to replace PVP concentration ranges with limitations narrowed specifically to 0.001% PVP. In so doing, the applicants emphasized the criticality of 0.001% PVP for improving formulation stability and asserted that formulations with 0.001% PVP exhibited unexpectedly superior results compared to other tested values, including 0.0005%. The district court's broad reading of "0.001%" PVP as encompassing all PVP concentrations from 0.0005% to 0.0014% contradicts the clear guidance from the intrinsic record.

As this Court has often warned, patent claims should not be read in a vacuum; rather, they must be construed as they would be understood by skilled artisans when read in view of the specification and prosecution history. The district court's construction turns that settled approach on its head by adopting a perceived plain meaning for "0.001%" divorced from the patents-in-suit and reducing the intrinsic record to a postscript in its analysis. This Court has rejected similar blind reliance on numerical rounding to expand claim scope when the resulting construction would contradict intrinsic evidence demanding greater precision. The same principles apply here, and the district court's construction should be overturned.

Mylan's proposed construction properly limits "0.001%" PVP to that specific value with only minor variation of 0.00095% to 0.00104%, consistent with the precision dictated by the specification and prosecution history. The inventors made clear that 0.001% (specifically) yielded the most stable formulations, and they distinguished other formulations that included PVP measured with precision to four decimal places, including 0.0005%. Moreover, the specification taught that small differences in PVP concentration—e.g., between 0.001% and 0.0005%—produced substantial differences in formulation stability. Mylan's construction stays true to the intrinsic record and reflects a level of precision consistent with the teachings of the patents and the inventors' statements during prosecution.

Because the district court erred in construing "0.001%" PVP, the stipulated infringement ruling regarding Mylan's ANDA formulation containing percentage PVP should be reversed or at least vacated for reconsideration under the correct construction.

2. The district court also erred in concluding that AstraZeneca's claims were non-obvious. Everyone agreed that skilled artisans were motivated to reformulate Symbicort® into a pMDI, and the court agreed that a POSA would have sought to do so with the same active ingredients. The issues were which propellant and excipients to use and at what concentrations. The claims all require HFA-227 as the propellant, with excipients PVP K25 at a concentration of 0.001% and PEG-1000 at 0.3%.

Mistry described pMDI formulations that replaced disfavored CFC propellants with one of two non-CFC propellants. Of the two, Mistry preferred the one claimed here, HFA-227. Mistry also recognized the need to consider which excipients could be used with its preferred non-CFC propellant. For the stabilizer, Mistry preferred PVP with a K-value between 15-120 and a concentration range of 0.001%-1%. For the other excipient, the valve lubricant, Mistry especially preferred the claimed lubricant PEG, at a molecular weight between 400-2000, and a concentration of 0.1-2%. Mistry thus taught the claimed propellant as preferred, and it provided concentration ranges for the additional two excipients that encompass those claimed. Under this Court's law on the obviousness of ranges, overlap between ranges in a claimed composition and those in the prior art creates a presumption of obviousness. Mistry easily established that presumption.

The district court erred by relying instead on a demonstrative exhibit—not testimony or other evidence—that Mistry taught millions of possible formulations. But AstraZeneca concocted that number by converting modest ranges into 20,000 discrete options. There is no precedent or logic for that approach. The district court erred in relying on that inflated number rather than on established precedent regarding the obviousness of ranges.

The district court erroneously considered Mistry in isolation due to another reversable error: it concluded that Rogueda, a nearly anticipating reference, taught

away from AstraZeneca's claims. As with precedent on prior-art ranges, the district court disregarded precedent on teaching away. Under that precedent, a reference teaches away only when it criticizes, discredits, or otherwise discourages a claimed solution. Rogueda did none of that.

The court accepted that Rogueda did not disparage its control formulations, including Control 9, which exactly matched AstraZeneca's claimed propellant, excipients, and excipient concentrations. The district court nevertheless concluded that Rogueda implicitly taught away by presenting data that "cut against" the claims. That was error. Rogueda presented different types of data, and its data about the length of time the control suspension remained stable after shaking showed stability over a period of *minutes*. The experts agreed that the period within about 20 *seconds* after shaking was what mattered. Rogueda's most relevant data thus did not "cut against" using the control formulations, they showed that those formulations satisfied skilled artisans' primary objective: stability after shaking. Indeed, satisfying that objective was why AstraZeneca's claims were allowed in the first place.

The district court's teaching-away ruling relied on data about adhesion of the formulation to the inside of the can and aggregation of particles within the suspension. But can adhesion was a known issue with a known solution: Teflon coating. As a matter of law, recognizing a drawback with a known solution does not amount to teaching away. The court's reliance on the aggregation data was similarly flawed.

Rogueda observed that aggregation may have some effect on performance, but that comment fell well short of a teaching away.

Finally, the district court erred in assessing secondary considerations. The court concluded that AstraZeneca's alleged unexpected results at 0.001% PVP established non-obviousness. That was error for several reasons. Secondary considerations must be commensurate in scope with the claims, and the evidence of unexpected results here applied only to the 0.001% embodiment. Because the court's construction also covers the inferior 0.0005% embodiment, the cited evidence of non-obviousness was not commensurate with the claims. Moreover, to be probative of non-obviousness, unexpected results must demonstrate a difference in kind rather than degree. The results here merely demonstrated that the *degree* of stability may be improved. Finally, the district court erred when it concluded that the mere existence of unexpected results meant the claims were not obvious. Unexpected-results evidence is not dispositive standing alone; it must be weighed against the affirmative obviousness evidence. The district court failed to perform that weighing.

The non-obviousness ruling should be reversed, or at least vacated and remanded for reconsideration under the correct law and free from clearly erroneous fact-findings.

ARGUMENT

I. Standard of Review

Claim construction is a question of law that may include subsidiary fact-findings. *Teva Pharms. USA, Inc. v. Sandoz, Inc.*, 574 U.S. 318, 331-33 (2015). When, as here, district courts interpret claim terms using intrinsic evidence alone, this Court reviews claim construction *de novo*. *Allergan Sales, LLC v. Sandoz, Inc.*, 935 F.3d 1370, 1373 (Fed. Cir. 2019).

Whether a claimed invention would have been obvious under 35 U.S.C. § 103 is a legal conclusion based on underlying facts. *Graham v. John Deere Co. of Kan. City*, 383 U.S. 1, 17 (1966). That legal conclusion is reviewed without deference, and the district court's factual determinations are reviewed for clear error. *Kao Corp. v. Unilever U.S., Inc.*, 441 F.3d 963, 968 (Fed. Cir. 2006). A factual finding is clearly erroneous when the reviewing court is left with definite and firm conviction that a mistake has been made, even despite some supporting evidence. *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1359 (Fed. Cir. 2007). Obviousness must be established with facts supported by clear and convincing evidence. *Apotex USA, Inc. v. Merck & Co.*, 254 F.3d 1031, 1036 (Fed. Cir. 2001).

II. The district court misconstrued the "0.001%" PVP limitation by relying on a presumed plain meaning that contradicts the intrinsic record

The asserted claims require PVP at a specific concentration, 0.001%. The patents' specifications and prosecution histories emphasize the advantages of that

particular concentration. The inventors repeatedly singled out 0.001% PVP as providing "the best" and "the most stable" formulations. They cited data showing that even small variations above or below 0.001% PVP substantially compromised formulation stability. And when confronted with rejections, they repeatedly narrowed claims reciting PVP concentration ranges to cover 0.001% specifically.

Yet the district court adopted a much broader construction for the term. The court construed "0.001%" based solely on a presumed ordinary meaning—expanded by rounding from the next decimal place—not supported anywhere in the intrinsic record. The district court's reading swept so broadly that it encompassed formulations that the inventors—both in the specification and during prosecution— *contrasted* with those containing 0.001% PVP and identified as particularly *unstable*. The district court's expansive interpretation fundamentally conflicts with the intrinsic record and cannot be reconciled with bedrock principles of claim construction. This Court should correct the district court's error and reverse the judgment of infringement or at least vacate and remand for reconsideration under the correct construction.

A. The intrinsic record precludes the "plain and ordinary meaning" adopted by the district court

The district court construed "0.001%" to cover all PVP concentrations from 0.0005% to 0.0014% based on "rules of rounding" as applied to values with one significant digit. Appx63-64, Appx68. The court identified no basis for that

construction other than a "plain and ordinary meaning" for the disputed term. *See id.* But the district court cited no evidence to establish an ordinary meaning of "0.001%" PVP in the claims, and no such ordinary meaning exists.[7]

Turning to the specification and prosecution histories, the district court emphasized that those sources used the term "0.001%" with "a single significant digit." Appx64-67. But merely repeating a term does not explain its meaning. The district court's construction rests entirely on a presumed ordinary meaning wholly divorced from the intrinsic record.

Claims are "not construed in the abstract"; instead, a claim term must be given "the meaning it would have to persons in the field of the invention, when read and understood in light of the entire specification and prosecution history." *Fenner Invs., Ltd. v. Cellco P'ship*, 778 F.3d 1320, 1322-23 (Fed. Cir. 2015). Claim construction "requires a determination as to how a person of ordinary skill in the art would understand a claim term 'in the context of the entire patent, including the

[7] The district court suggested the parties *agreed* that a POSA "would interpret the specification to convey that the '0.001%' term is subject to rounding according to the number of significant digits." Appx63. But Mylan did not agree. Indeed, that was the central issue in dispute: AstraZeneca treated the claimed "0.001%" PVP concentration as 0.001 rounded to one significant digit, and Mylan explained why that reading was wrong. As described below, Mylan argued instead for a construction allowing only for minor variations from 0.001% (0.00095% to 0.00105%) to account for measurement imprecision. Appx6804-6806; Appx7707-7708; Appx7907-7909 (42:15-44:14); Appx63.

specification.'" *Trs. of Columbia Univ. v. Symantec Corp.*, 811 F.3d 1359, 1362 (Fed. Cir. 2016) (quoting *Phillips v. AWH Corp.*, 415 F.3d 1303, 1313 (Fed. Cir. 2005) (en banc)). The specification is "'always highly relevant to the claim construction analysis," and "it is the single best guide to the meaning of a disputed term.'" *Phillips*, 415 F.3d at 1315 (quoting *Vitronics Corp. v. Conceptronic, Inc.*, 90 F.3d 1576, 1582 (Fed. Cir. 1996)).

1. The district court's construction expands the claims to cover a PVP concentration that the specification described as producing *unstable* formulations

The asserted patents tout formulation stability as "one of the most important factors" when developing a pharmaceutical product. Appx143 (1:21-24). The patents provide data from several assays comparing the relative stabilities of pMDI formulations with different PVP concentrations, including 0.0001%, 0.0005%, 0.001%, 0.01%, 0.03%, and 0.05%. Appx145 (5:5-6:54), Appx128-132, Appx135-140 (Figs. 2-6, 9-14). Under the district court's claim construction, "0.001%" would encompass two of those values: 0.001% and 0.0005%. Appx68, Appx63 (construing "0.001%" to include PVP concentrations from 0.0005% to 0.0014%); Appx7892 (27:4-15) (AstraZeneca confirming same). Yet the applicants emphasized that over the course of several minutes 0.001% formulations consistently outperformed every other PVP concentration tested, including—and often *especially*—0.0005%.

For example, Figure 2 shows OSCAR test results for a panel of formulations that varied by PVP concentration, including 0.001% (blue) and 0.0005% (red):

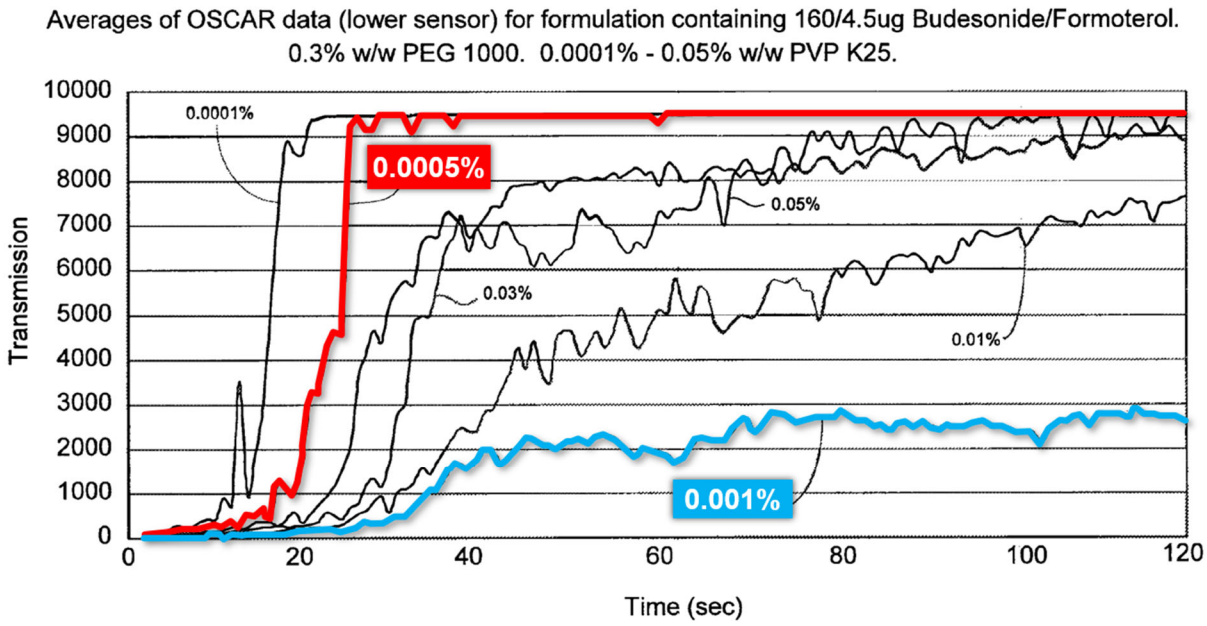
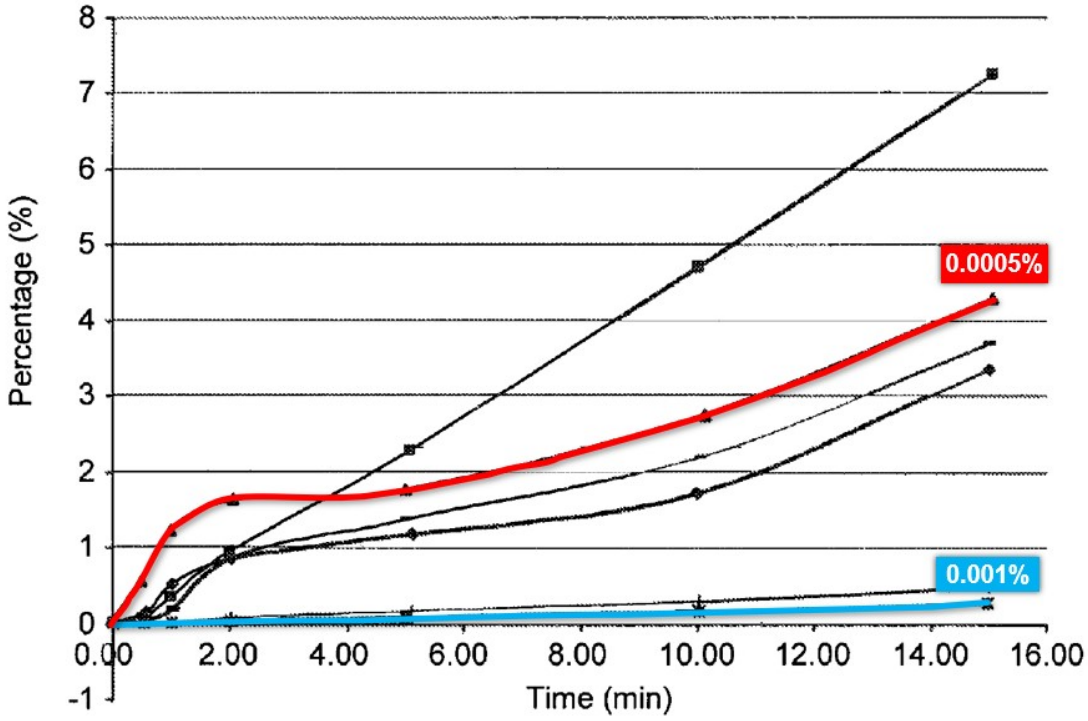


FIG. 2

Appx128 (Fig. 2) (annotated); *see* Appx7706. In OSCAR testing, lower light transmission indicates better suspension stability. Appx143-144 (2:66-3:45). The sustained lower light transmission at 0.001% PVP (blue) over time indicates much better stability compared to the transmittance observed at 0.0005% PVP (red). Appx145 (6:30-39).

The specification reported similar results from Turbiscan stability testing, with much lower sustained percentage of light transmission for formulations containing 0.001% PVP (blue) compared to those with 0.0005% PVP (red) over the full fifteen minutes, as illustrated by Figure 4:



Appx130 (Fig. 4) (annotated); Appx144-145 (3:47-4:21, 6:43-54).

As shown above, formulations with 0.001% PVP were "the most stable" and provided "the best suspension stability overall." Appx145 (6:30-54). In contrast, 0.0005% PVP repeatedly ranked among the *worst* options for formulation stability. Appx128-132 (Figs. 2-6); *see also* Appx16330-16337 (similar data provided by inventor declaration during prosecution). The specification thus distinguishes formulations with 0.001% PVP as *superior* to all other tested values, including—and often especially—0.0005%. Moreover, it shows that moving from 0.001% to 0.0005% PVP had pronounced adverse effects on formulation stability over time, which the specification emphasizes as a key determinant of useful pMDI formulations. In so

doing, the specification makes clear that those PVP concentrations are not interchangeable and cannot be equated with one another. Yet the district court's construction treats them the same, erasing the specification's clear distinction between 0.001% and 0.0005% PVP.

The district court ignored this key intrinsic evidence. Mylan made the point repeatedly, even submitting an annotated figure from the specification to highlight the gulf between 0.001% and 0.0005% PVP in terms of functional stability, as reported by the inventors. Appx7705-7707; Appx6804-6805; Appx7903-7904 (38:21-39:21). Yet nowhere in its claim construction analysis did the district court acknowledge, much less grapple with, the fundamental distinction that the inventors drew between 0.001% and 0.0005% PVP. *See* Appx64-65.

2. During prosecution, the inventors relied on results specific to 0.001% PVP and amended the claims to excise claim scope that the district court's construction would restore

The prosecution history further undermines the district court's broad construction of "0.001%" PVP. For example, during prosecution of the earliest asserted patent (the '328), the applicants originally pursued claims reciting the PVP concentration as a range extending "from about 0.0005% to about 0.05% w/w." Appx15919-15920 (claim 2). When faced with prior-art rejections, the applicants amended the claims to limit the recited amount of PVP to "0.001%," distinguished the cited art as failing to teach that concentration, and relied on the "surprising discovery" 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." Appx16213, Appx16221-16223; *see also* Appx143 (2:17-21) (distinguishing 0.001% PVP as providing "stable formulations … at a much lower concentration than indicated in the prior art"). The applicants' amendments specifically removed other PVP concentrations, *including* the 0.0005% value added back under the district court's construction.

Later during prosecution, the applicants tried to reintroduce claims reciting a broader range of PVP concentrations. Appx16319-16321 (e.g., claims 1, 23). But the examiner again rejected those claims as "much broader than what are being interpreted as unexpected results." Appx16445-16448. And the applicants again acquiesced by narrowing the claims to recite 0.001% PVP specifically. Appx16455-16457. In allowing those claims, the examiner noted they were "specific to chemical components *and the amounts thereof*." Appx16478-16479 (emphasis added).

In short, the applicants repeatedly narrowed broader ranges to claim formulations limited to 0.001% PVP, and they distinguished other possibilities as less effective. Here too, the district court's broad interpretation of "0.001%" contradicts the intrinsic evidence.

3. Precedent underscores the district court's error in disregarding the intrinsic record

As shown above, the specification and file history rule out the district court's construction. Both drew a sharp distinction between 0.001% PVP and other possible

PVP concentrations, including 0.0005%, for purposes of stability. The inventors plainly considered the degree of stability "to be material to patentability." *Allergan Sales*, 935 F.3d at 1375-76 (applying limiting construction to account for properties emphasized in the specification and during prosecution); Appx143 (1:21-24, 2:17-21) (emphasizing formulation stability). And throughout the intrinsic record, the inventors highlighted the stabilizing effects of 0.001% PVP specifically.

Nevertheless, the district court's construction expands the claims a full 50% above and 50% below that recited 0.001% value. Moreover, the district court's construction of "0.001%" PVP as encompassing 0.0005% to 0.0014% results in the asserted claims covering 0.0005% PVP, which the patents themselves report as among the *least stable* of numerous tested concentrations. A construction so at odds with the intrinsic record cannot be correct.

Viskase Corp. v. American National Can Co., 261 F.3d 1316, 1320-22 (Fed. Cir. 2001), addressed a similar issue and rejected the district court's rounding approach. The disputed limitation there required that the density of polyethylenes used in the claimed thermoplastic films be "below about 0.91 g/cm^3." *Id.* at 1320. The district court construed "0.91 g/cm^3" to include densities from 0.905 to 0.914 g/cm^3 because numbers in that range would round to 0.91 g/cm^3. *Id.* But the defendant explained that broadening construction could not be reconciled with the specification and prosecution history. In particular, the specification had identified 0.91 g/cm^3

as a dividing line for polyethylenes with different densities, and that teaching would have made little sense if 0.91 g/cm^3 included values up to 0.914 g/cm^3. *Id.* at 1321. During prosecution, the inventors had also distinguished a reference that described polymers with a density range of 0.910 to 0.940 g/cm^3, *id.*, and the inventors reported density values for other polymers with precision to three decimal places elsewhere in the specification, *id.* at 1322.

This Court reversed the district court's construction and "conclude[d] that a [POSA], reading the first family specifications and prosecution histories, would not view 'below about 0.91' as extending to an upper limit of 0.914." *Id.* at 1322. Accordingly, the Court construed "below about 0.91 g/cm^3" to mean "below about 0.910 g/cm^3." *Id.* The Court further held that even considering the use of "about" in the disputed term "about 0.91 g/cm^3," the claims could not cover products with a density of 0.912 g/cm^3 in view of the intrinsic record. *Id.*

This Court should reach the same result here. As in *Viskase*, the district court's construction was premised solely on a mathematical assumption about rounding decimal values. In *Viskase*, that disconnected approach did not fit the context of the patents-in-suit because the resulting construction would have covered polymers that, according to the patents' specifications and file histories, lacked a key property. The district court's construction of "0.001%" here likewise overextends the claims to cover PVP concentrations that were described and distinguished, both in the

specification and during prosecution, as lacking the formulation stability associated with 0.001% PVP. In this case as in *Viskase*, the intrinsic record calls for greater precision than the district court's simple rounding approach. The claims should be construed accordingly.

This Court has definitively rejected an approach to claim construction "in which the specification should be consulted only after a determination is made, whether based on a dictionary, treatise, or other source, as to the ordinary meaning or meanings of the claim term in dispute." *Phillips*, 415 F.3d at 1320. Here, the district court began by settling on a purported plain meaning based on rounding and then turned to the specification and prosecution history only to assess whether those resources sufficed to overcome its stated view. *See* Appx66-68. That approach impermissibly limited the role of the intrinsic record to "serving as a check" on the district court's presupposed ordinary meaning. *Phillips*, 415 F.3d at 1320. Not only was that analysis incorrect, but the district court reached the wrong conclusion even affording the specification and file history such limited consideration. Those resources unequivocally show that the supposed ordinary meaning fails when applied to the patents at issue. The district court's overbroad construction should be reversed.

B. Mylan's construction correctly reflects the intrinsic record's consistent focus on 0.001% PVP as critical for achieving formulation stability

Unlike the district court's construction, Mylan's proposed construction for "0.001%" PVP comports with the asserted patents' specification and the prosecution record. Mylan argued that "0.001%" should be construed to mean that precise concentration with only minor variations. Appx6804; Appx7708 (alternatively stated as "0.0010 w/w PVP"); Appx7909 (44:7-14); Appx63. The claims recite 0.001% as a specific PVP concentration, and the intrinsic record—through the inventors' experimental data, claim amendments, and repeated substantive assertions—consistently highlighted the importance and singular effects of that particular value. Only Mylan's construction is commensurate with those preeminent guides to claim meaning.

Mylan's construction encompasses values varying at most from 0.00095 to 0.00104%, in keeping with the precision dictated by the specification and prosecution history. Time after time, the inventors emphasized the unique properties of 0.001% PVP. Appx16222-16223 (describing 0.001% as "the best" and relying on "superior qualities" of "*the specified* low concentration of PVP" (emphasis added)); Appx16326 (discussing the "criticality," "superior results," and "best suspension stability" of 0.001% PVP, while distinguishing "formulations with higher or lower concentrations"); Appx143 (2:17-21) (stating that the 0.001% concentration of PVP

"has been found to give consistently stable formulations"), Appx145 (6:30-54) (describing 0.001% PVP as "the best" and "the most stable"). In addition, the specification showed that the inventors varied PVP concentrations in their experimental formulations with precision out to four decimal places. For example, the PVP concentrations tested in the specification included 0.0001% and 0.0005% PVP. Appx128-132 (Figs. 2-6), Appx145 (5:10-18). Mylan's construction thus reflects the appropriate level of precision.

Importantly, the specification taught that those small differences *matter*. The inventors asserted that 0.001% PVP provided improved formulation stability over extended periods as compared to all other tested PVP concentrations, including 0.0005%. Reducing the PVP concentration by just 0.0005%—from 0.001% to 0.0005%—often meant the difference between the most stable and one of the most *un*stable formulations. *E.g.*, Appx128 (Fig. 2), Appx145 (6:34-39). The asserted claims thus recite 0.001% specifically—without reciting a range and without using words of approximation, both of which the inventors knew well how to do. *See* Appx143 (1:43-44) ("from about 0.0005 to about 0.03%"); Appx15919 (original claim 2); Appx16319 (amended claim 1); Appx123 ('137 claim 1); *see also Takeda Pharm. Co. v. Zydus Pharms. USA, Inc.*, 743 F.3d 1359, 1364-1365 (Fed. Cir. 2014) (limiting claim to recited numerical value where "the inventors knew how to express ambiguity in claim language when they so desired").

As noted, the district court's construction extends from 0.0005% to 0.0014% PVP, a 50% expansion above and below the claimed 0.001% PVP concentration. That overbroad interpretation covers formulations that the inventors reported as unstable, conflicts with the level of precision used to describe PVP concentrations in the specification, substantially undermines narrowing amendments made during prosecution, and negates a central theme throughout the intrinsic record: the criticality of 0.001% PVP. Mylan's construction avoids each of those problems.

The district court mistakenly concluded that Mylan had to establish "clear and unmistakable disavowal" of a construction encompassing 0.0005% to 0.0014% PVP. Appx67. But as Mylan pointed out, Appx7902-7903 (37:23-38:12), Appx7907-7909 (42:9-44:14), its construction for "0.001%" PVP does not depend on disavowal or disclaimer. That numerical term has no single, unambiguous plain meaning. And Mylan's analysis—rooted in teachings from the specification and prosecution history—demonstrated that its construction is the correct one in the first instance, consistent with "those sources available to the public that show what a person of skill in the art would have understood disputed claim language to mean." *Phillips*, 415 F.3d at 1314 (citation omitted); *see also Personalized Media Commc'ns, LLC v. Apple Inc.*, 952 F.3d 1336, 1345-46 (Fed. Cir. 2020) (rejecting analysis that "effectively require[ed] the prosecution history evidence to rise to the level of a disclaimer in order to inform the meaning of the disputed claim term").

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Mylan's construction best represents the "meaning that matters in claim construction," that is, "the meaning in the context of the patent." *Ruckus Wireless, Inc. v. Innovative Wireless Soln's, LLC*, 824 F.3d 999, 1003 (Fed. Cir. 2016) (quoting *Columbia Univ.,* 811 F.3d at 1363). It should therefore be adopted.

C. The district court's infringement ruling should be reversed, or at least vacated, under the correct construction of "0.001%" PVP

Given the district court's construction of "0.001%" PVP as encompassing 0.0005% to 0.0014% PVP, Mylan stipulated that its ANDA product containing percentage PVP infringed. Appx8772-8774. If that construction is overturned, the judgment of infringement should be reversed because Mylan's ANDA product would not and could not satisfy the critical requirement for "0.001%" PVP recited in every asserted claim. At a minimum, the Court should vacate for the district court to reconsider infringement under the correct construction.

III. The district court's obviousness analysis was legally flawed and based on clearly erroneous findings

The district court agreed, and AstraZeneca did not dispute, that a POSA would have been motivated to pursue a pMDI version of the Symbicort® DPI. Appx36. The district court's analysis accepted the premise that the motivation to pursue a Symbicort® pMDI would have included a desire to use the same active ingredients. Appx37; *see also* Appx10314 (846:14-18); Appx9919 (451:4-8). And the court recognized at least one reason why a POSA would have pursued a pMDI suspension

formulation. Appx38. While the court noted that using the same size particles as in the Symbicort® DPI "would likely not have been a choice available to a POSA," Appx38-39, it did not doubt the obviousness of using a suspension.

Instead, the district court's obviousness analysis came down to the choice of propellant, HFA-227 rather than HFA-134a, and the additional claimed excipients, PVP K25 and PEG-1000 at concentrations of 0.001% and 0.3%, respectively. The district court erred in three critical respects when analyzing those limitations and AstraZeneca's assertion of unexpected results. First, the court disregarded well-established case law regarding the obviousness of values claimed within prior-art ranges. The court instead relied on a lawyer-created demonstrative exhibit that dissected small numerical ranges from the prior art into tiny increments to suggest that a POSA faced millions of distinct possibilities—an approach that departs from how this Court has considered range teachings. Second, the district court eliminated the closest prior art by finding that Rogueda taught away, even while acknowledging that "Rogueda did *not* necessarily disparage" its nearly anticipatory teachings. Appx44 (emphasis added). Third, after having construed "0.001%" PVP to encompass PVP concentrations that AstraZeneca's own patents associate with inferior results, the district court nevertheless found unexpected results because the claims include *a* superior embodiment within their expanded scope. That legally flawed approach to unexpected results cannot sustain the non-obviousness judgment.

A. Mistry rendered the claims obvious under this Court's law on overlapping ranges

1. The district court's decision turned on the obviousness of selecting the claimed compositions from among Mistry's disclosed ranges

Mylan asserted obviousness based on the motivation to reformulate Symbicort® as a pMDI, Appx33, and each combination included Mistry, which taught improved pMDI compositions replacing CFCs with HFA propellants, Appx18602-18603. The district court's decision centered on whether a POSA seeking to make Symbicort® in a pMDI suspension would have found it obvious, based on Mistry's teachings, to use HFA-227 with PVP K25 and PEG-1000 at the recited concentrations. Appx41-42.

Mistry recognized the difficulty of finding excipients that were both soluble in the HFA propellant and capable of stabilizing a formulation. Appx18602. But Mistry offered solutions to that problem and explained that the resulting compositions could be used with "any medicinal product that may be administered conventionally to the lungs and/or to the nose by inhalation of a pressurized aerosol formulation." Appx18606. That specifically included budesonide, formoterol, and "combinations of two or more of said agents." *Id.* As for the propellant, Mistry identified two of "particular interest," HFA-134a and HFA-227, with HFA-227 "particularly

preferred." Appx18605.[8] As an excipient, Mistry "particularly preferred" PVP with K-values of 15 to 120. Appx18603. And it "especially" preferred PVP concentrations of "0.001 to 1% w/w." Appx18604. Finally, Mistry taught adding a valve lubricant, and it referred "especially" to PEG with molecular weights of "preferably 400 to 2000" and at preferred concentrations of 0.1 to 2%. Appx18604-18605.

Mistry was therefore highly relevant to the asserted claims, which recite:

- HFA-227 (Mistry's particularly preferred propellant);
- PVP (Mistry's preferred stabilizer), with a K-value within Mistry's preferred range and at a concentration at the lower point in Mistry's preferred range; and
- PEG (Mistry's "especially" preferred lubricant), with a molecular weight in Mistry's preferred range and at the concentration specifically mentioned in Mistry.

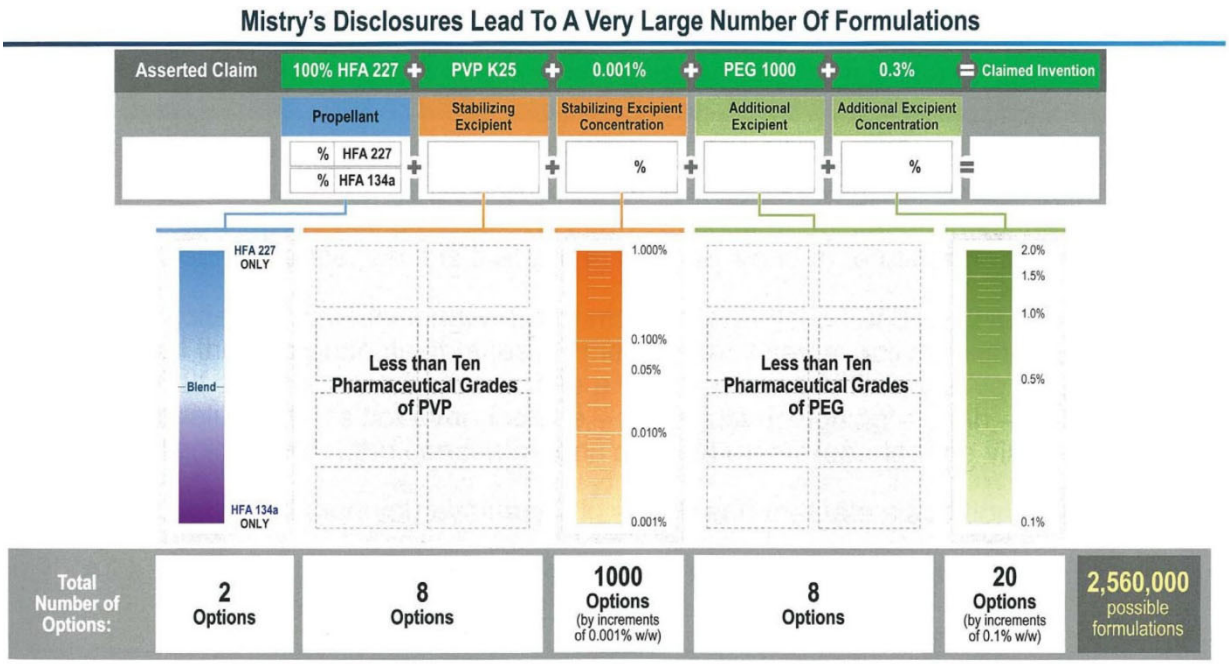
[8] The district court suggested that HFA-227 was disfavored because "every FDA-approved HFA pMDI product used HFA 134a, not HFA 227." Appx39. The court did not say whether that observation factored into its non-obviousness determination, but to the extent it considered lack of regulatory approval relevant, it erred. A POSA's knowledge and motivations are not limited to FDA-approved art. *See Bayer Pharma AG v. Watson Labs., Inc.*, 874 F.3d 1316, 1326 (Fed. Cir. 2017) ("[T]he motivation to combine inquiry for drug formulations is not limited to what already has or could gain FDA approval" and "a lack of FDA approval cannot negate an otherwise apparent motivation to formulate a product."). Moreover, HFA-227 had been used in prior-art commercial pMDI products. Appx18638-18641; Appx18568-18569 (Intal Forte).

Mistry's teachings fit comfortably within this Court's precedent regarding the obviousness of claims with specific values in known ranges. "[I]t is not inventive to discover the optimum or workable ranges by routine experimentation," and overlap between concentration ranges in a claimed composition and those in the prior art "creates a presumption of obviousness." *E.I. DuPont de Nemours & Co. v. Synvina C.V.*, 904 F.3d 996, 1006 (Fed. Cir. 2018); *see also Iron Grip Barbell Co. v. USA Sports, Inc.*, 392 F.3d 1317, 1322 (Fed. Cir. 2004).

Despite that established precedent and Mistry's highly relevant disclosures, the district court dismissed Mistry on grounds that "the number of possible combinations disclosed by Mistry alone is in the millions" and "[t]herefore, at the priority date a POSA would not have been motivated to select the specific formulation claimed …." Appx41-42. Relying on AstraZeneca's demonstrative exhibit, Appx50, the district court apparently discounted Mistry in the belief that established law on the obviousness of ranges did not apply due to the number of distinct formulations shown on that exhibit.

2. The district court erred when it based its decision on AstraZeneca's misleading demonstrative exhibit

AstraZeneca's demonstrative converted a routine teaching of a finite number of options with modest ranges into an algebraic equation that produced a bloated number of possible formulations and effectively obscured the disclosure of overlapping prior-art ranges in the first place:



Appx50.

Converting prior-art concentration ranges into a specific number of unique options makes little sense. Whatever granularity the advocate selects for chopping up a prior-art range will dictate the number of resulting options. AstraZeneca's demonstrative converts a PVP K25 concentration range of 0.001%-1.000% into 1,000 different options, and it converts the PEG-1000 concentration range of 0.1%-2.0% into 20 different options. But Mistry's ranges were not framed as distinct, quantized options. No expert in this case testified that POSAs would consider Mistry's teachings that way. The innumeracy of converting bounded ranges into an astronomical number of distinct teachings was misleading attorney argument.

Precedent confirms the legal error in AstraZeneca's demonstrative. In *In re Peterson*, 315 F.3d 1325 (Fed. Cir. 2003), this Court affirmed the *prima facie*

obviousness of a superalloy with boron and carbon and nine constituent metals at specific concentrations in view of a prior art reference, Shah, that taught the claimed constituent metals (and boron and carbon) at concentrations that encompassed the ranges claimed:

	Claim 5	Shah
Rhenium	about 1–3%	0– 7%
Chromium	about 14%	3–18%
Cobalt	about 9.5%	0–20%
Tungsten	about 3.8%	0–18%
Tantalum	about 2%	0–15%
Molybdenum	about 1.5%	0– 4%
Carbon	about 0.05%	at least 0.002%
Boron	about 0.004%	at least 0.002%
Aluminum	about 3–4.8%	3– 8%
Titanium	about 4.8% to about 3%	0– 5%
Nickel	balance	balance

Id. at 1329. This Court concluded that Shah's overlapping ranges rendered Peterson's claim "*prima facie* obvious." *Id.* at 1330. This Court did not consider Shah to have taught eight options for rhenium (0%, 1%, 2%, etc.), sixteen options for chromium (3%, 4%, etc.), or thousands of options for each of carbon and boron (.002%, .003%, etc.). If AstraZeneca's logic were applied to Shah's teachings (even excluding carbon and boron), the result would have been about 147,000,000 options. Multiplying in the additional options for boron and carbon would send that number skyrocketing even higher. But this Court did not approach the prior art that way. Instead, this Court concluded that Shah's overlapping ranges rendered Peterson's claim presumptively obvious, absent evidence that, e.g., the claimed alloy showed unexpected

results over the broader prior art range. *Id.* at 1330; *see also Valeant Pharms. Int'l, Inc. v. Mylan Pharms. Inc.*, 955 F.3d 25, 34 (Fed. Cir. 2020) (rejecting the district court's analysis that a pH range of 3-4 included a mathematically infinite number of possibilities and concluding that the claims were prima facie obvious even if one looked at the range as 100 different points).

The district court erred by disregarding settled obviousness law addressing prior-art ranges and instead likening the facts to *Genetics Institute, LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291, 1306-07 (Fed. Cir. 2011). Appx36. But *Genetics Institute* was different. That case was not simply about selecting a narrower range from a broader known range. The invention was cloned human Factor VIII protein, essential for blood clotting. 655 F.3d at 1294. Cloning was critical for creating a protein source other than from human blood, but cloning Factor VIII was difficult because the protein is especially large. *Id.* at 1295. Both parties had discovered a smaller recombinant protein that mimicked the biological activity of Factor VIII. The dispute arose from an interference proceeding, and the issues before the Court included whether Genetics' claims rendered Novartis's claims obvious. Genetics' claimed protein was smaller than Novartis's, but it did not permit substitution in the portions remaining from the original cloned version. *Id.* at 1303. Novartis's claimed protein was large, but it permitted some substitution.

This Court characterized the distinction between the two claims as "structural differences between the proteins." *Id.* at 1304. It also noted that the goal in the field was to make smaller proteins, not larger ones. This Court thus concluded that Genetics' smaller and structurally distinct protein did not render obvious Novartis's larger protein. *Id.* at 1304-05. The dissent in *Genetics Institute* argued for applying the range analysis from *Peterson*. *Id.* at 1313-14 (Dyk, J., dissenting). The majority disagreed because the two inventions "differ[ed] in terms of the size of the permitted amino acid deletions, the location of those deletions, and the degree of allowable amino acid substitutions." *Id.* at 1306. It also noted that "there was no motivation to optimize for some value within the range." *Id.*

Contrary to the district court's suggestion, nothing in *Genetics Institute* casts doubt on the principle that the "normal desire of scientists or artisans to improve upon what is already generally known provides the motivation to determine where in a disclosed set of percentage ranges is the optimum combination of percentages." *Peterson*, 315 F.3d at 1330. And the structural differences that drove the result in *Genetics Institute* are absent here. Mistry was directed to the same thing AstraZeneca's patents were seeking: HFA-based pMDI formulations with suitable excipients. And AstraZeneca did not identify any important structural differences in the propellants and excipients. The issue was simply one of choosing concentrations from among overlapping ranges of known excipients.

Because the district court's rejection of Mistry turned on its erroneous reliance on AstraZeneca's demonstrative, and because Mistry's teachings demonstrate obviousness under this Court's precedent on prior-art ranges, AstraZeneca needed to demonstrate that its claimed values were critical, "'generally by showing that the claimed range achieves unexpected results relative to the prior art range.'" *Peterson*, 315 F.3d at 1330 (quoting *In re Geisler*, 116 F.3d 1465, 1469-70 (Fed. Cir. 1997)). Although AstraZeneca argued that 0.001% PVP demonstrated such results to secure its patents, it cannot do that under the district court's broad construction of "0.001%." That construction, asserted for infringement purposes, created a claimed range of equivalent PVP concentrations from 0.0005% to 0.0014%.

Mistry taught a PVP range of 0.001% to 1%. Appx18604. Figure 2 of AstraZeneca's patents shows that the claimed compositions cannot be differentiated functionally from Mistry:

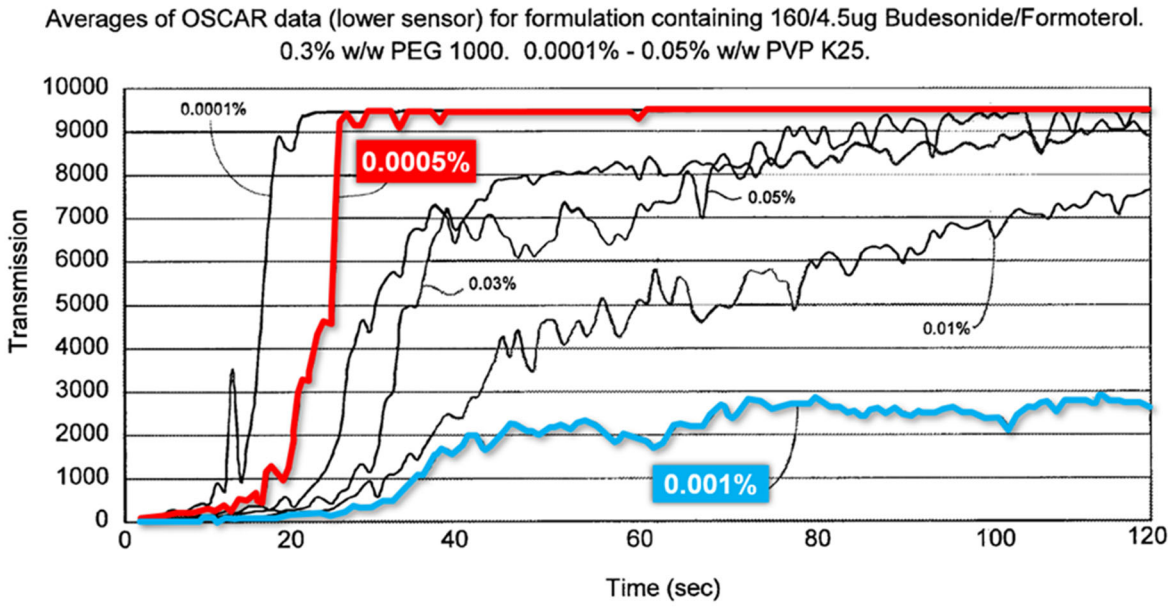


FIG. 2

Appx128 (Fig. 2) (annotated). In Figure 2, every PVP concentration above the construed 0.0005%-0.0014% range showed stability superior to the results at 0.0005% and inferior to the results at 0.001%. Thus, 0.01%, 0.03%, and 0.05% PVP—all within Mistry's disclosed range—exhibited stabilities indistinguishable from the claimed formulations under the district court's construction, with stabilities falling between those for 0.001% and 0.0005% PVP. Having successfully advocated a broad construction for infringement purposes, AstraZeneca must live with the consequences of that construction when it comes to obviousness.

B. The district court's conclusion that Rogueda taught away was legally and factually erroneous

The district court made another critical error by concluding that Rogueda taught away from the claimed invention even though Rogueda disclosed

compositions that nearly anticipated the claims. Appx44. Only by discounting Rogueda could the district court find that a POSA would have lacked clues pointing to the claimed combination. Appx45 (citing *Leo Pharm. Prods., Ltd. v. Rea*, 726 F.3d 1346, 1357 (Fed. Cir. 2013)); Appx41 (relying on testimony from AstraZeneca's expert that by his own admission concerned only Mistry's teachings). The court's finding that there was no reasonable expectation of success was likewise premised solely on teaching away. Appx46 (referring to can adhesion in Rogueda as the reason why a POSA would not have expected success with the claimed formulation). And the court's finding of an "unexpected superior property" of the claimed invention expressly relied on a comparison "to Rogueda Control 9, which, as a whole, teaches away from the claims." Appx47. In short, teaching away was central to all aspects of the district court's obviousness analysis. That ruling was both legally and factually erroneous and provides an independent basis for reversal or vacatur.

A prior-art reference teaches away only when it "criticizes, discredits, or otherwise discourages the solution claimed." *In re Brandt*, 886 F.3d 1171, 1178 (Fed. Cir. 2018) (alterations omitted) (quoting *In re Fulton*, 391 F.3d 1195, 1201 (Fed. Cir. 2004)). This Court has often articulated "teaching away" in terms of a prior-art reference that would have affirmatively led a skilled artisan away from the claimed invention. *See, e.g.*, *Meiresonne v. Google, Inc.*, 849 F.3d 1379, 1382 (Fed. Cir. 2017) (citing *Galderma Labs., L.P. v. Tolmar, Inc.*, 737 F.3d 731, 738 (Fed. Cir.

2013)). As a matter of law, merely expressing a preference for one solution over another, or even identifying a problem with a prior-art solution, does *not* amount to a teaching away. *See id.* Nor does a reference teach away if it discourages a path not required by the claims or pursued by its inventors. *MeadWestVaco Corp. v. Rexam Beauty & Closures, Inc.*, 731 F.3d 1258, 1264-65 (Fed. Cir. 2013) (reversing teaching-away determination when the art taught away from use in a fragrance product and the claims were not limited to a fragrance product).

1. Rogueda did not expressly teach away from any path

The district court recognized that "[i]t may be true that Rogueda did not necessarily disparage the formulations in Controls 3 and 9 …." Appx44. That observation undermines the court's conclusion that Rogueda taught away. Even assuming Rogueda's data demonstrated a preference for other formulations, or implicitly suggested that its control formulations had drawbacks, neither assumption could establish teaching away under this Court's law. *See Galderma*, 737 F.3d at 738-39 (recognizing increased side effects with a higher drug dosage did not teach away from the higher dose).

2. Rogueda's control data did not teach away from the claimed formulations

Despite recognizing that Rogueda did not disparage Controls 3 or 9, the district court concluded that Rogueda taught away based on testimony about Rogueda's

data. But just as Rogueda's *text* did not disparage its control formulations, Rogueda's *data* did not teach away either.

The district court concluded that Rogueda's control data "cut against the very goal a POSA would have been trying to achieve—a stable product with a consistent dose." Appx44. But in drawing that conclusion, the court did not mention Rogueda's teachings about how long the active ingredients remained suspended in the controls after agitation—even though stability was the focus of AstraZeneca's patents. Instead, the court focused on Rogueda's data about *can adhesion* and *particle aggregation*, Appx43-44, issues that were not significant concerns in the patents. The district court erred by ignoring what mattered and by relying on what did not.

a. AstraZeneca's patents are directed to suspensions with improved stability after shaking

The parties agreed that to achieve consistent dosing, formulation stability is needed for less than 20 seconds after agitation (shaking of the canister). Mylan's expert testified stability after shaking should be on "the order of 15 seconds." Appx9686 (229:6-12). AstraZeneca's expert agreed about the significance of suspension stability during those first 15 seconds. Appx10236-10238 (768:25-770:12); Appx10251-10252 (783:22-784:19) (agreeing that all formulations shown in Fig. 2 of the patents (Appx128) were stable during the first 15 seconds). Dr. Govind, one of the inventors on AstraZeneca's patents, agreed that a goal of a POSA was suspension stability after shaking, and that "between 10 and 20 seconds" of stability

sufficed. Appx9947 (479:7-19). The district court agreed that patients typically actuate a pMDI within about "twenty seconds" of shaking. Appx13 (discussing the testimony of AstraZeneca expert Dr. Panettieri).

Like AstraZeneca's patents, Rogueda relied on visual inspection and OSCAR data to detect stability. Appx18532 (28:4-12). For its HFA-227 formulations, Rogueda monitored creaming (ingredients rising up out of suspension). *Id.* Based on visual inspection, Rogueda explained that the control samples with stabilizers "on average creamed within half an hour after shaking." Appx18532 (28:20-23, 29-30). In OSCAR testing, controls with stabilizers creamed "within a few minutes," while those *without* stabilizers creamed much faster—in "a few seconds to a few minutes." Appx18532 (28:14-15). Referring to the controls *with* stabilizers, Mylan's expert, Dr. Pritchard, explained that "[h]alf an hour is an extremely long time in the life of that suspension. And so the skilled artisan would look at that and believe they had a stable formulation." Appx9674 (217:8-14). AstraZeneca's expert, Dr. Young, agreed that Rogueda described its control samples as creaming within a few minutes rather than a few seconds. Appx10248 (780:2-7). Although Dr. Young testified that creaming is "more complex," he did not disagree with Dr. Pritchard that, based only on Rogueda's OSCAR and visual inspection data, Rogueda's controls were stable during the critical seconds after shaking.

Simply put, Rogueda did not disparage its control formulations, and the reported data did not show instability in those controls during the critical period after shaking. Contrary to the district court's finding that Rogueda's "data cut against the very goal a POSA would have been trying to achieve," Appx44, there was no evidence that Rogueda's control formulations lacked stability in the relevant timeframe.

b. Can adhesion and particle aggregation were not the focus of AstraZeneca's patents, and they were at most minor issues for which known solutions existed

Instead of evaluating instability data, the district court relied on expert testimony that "formulations with budesonide or formoterol and PVP K25 and PEG-1000 adhered to the test cans at the gas-liquid interface and had particle aggregation." Appx43-44 (citing Appx18531-18532, Appx18534-18536 (Rogueda)). But neither of those issues was tied to post-shaking stability, the objective of AstraZeneca's patents, and neither was a significant concern.

Can adhesion was a known issue in the field, and one for which POSAs had a ready solution: a non-stick internal surface. Appx9684-9685 (227:24-228:7) (Dr. Pritchard explaining the use and availability of Teflon-coated cans). AstraZeneca's Dr. Govind agreed that POSAs were aware of Teflon-coating to avoid adhesion, Appx9943 (475:2-14), and AstraZeneca's Dr. Young agreed that the choice of can

would be a matter of routine optimization, Appx10270-10271 (802:22-803:1).[9] As a matter of law, a problem does not teach away from a claimed invention when a POSA would have recognized a solution in the prior art. *See Optivus Tech., Inc. v. Ion Beam Applications S.A.*, 469 F.3d 978, 989-90 (Fed. Cir. 2006) (no teaching away where the prior art did not discourage a POSA from solving a problem present in the prior art).

AstraZeneca's claims are directed to pharmaceutical compositions and treatment methods that do not require or prohibit any type of can or internal coating. AstraZeneca's experts did not dispute that POSAs would have recognized the benefits of using a coated can to reduce adhesion. Because AstraZeneca's claims would cover the known solution of a coated can, the district court erred when it concluded that Rogueda's data referencing adhesion taught away from the claimed invention. *See Santarus, Inc. v. Par Pharm., Inc.*, 694 F.3d 1344, 1355 (Fed. Cir. 2012) (reference that taught away from formulating a drug in a tablet, capsule, or granule did not teach away from broad claims that encompassed a powdered formula).

The district court also erred to the extent it relied on Rogueda's particle-aggregation data. Rogueda did not identify a failure of its control formulations.

[9] AstraZeneca has not asserted that its claimed formulation avoids the adhesion problem. Instead, AstraZeneca used the known solution: a non-stick coating. Appx9942-9947 (Tr.474:3-479:6) (Dr. Govind's testimony about the decision to use non-stick coating).

Rogueda at most referred to "some effect on the performance of the pMDI …." Appx18534. As for how a POSA might view the aggregation data, AstraZeneca's expert was uncertain about the conditions under which the aggregation data were collected. Appx10163-10164 (695:22-696:1) (Dr. Young testifying that the "likelihood" is that Rogueda's aggregation test was done under agitation). Regardless of Dr. Young's uncertainty, AstraZeneca's own patents suggest that aggregation occurs after the post-shaking period a POSA would be concerned with. The patents discuss aggregation/flocculation as a cause of the suspension instability tested with Turbiscan and OSCAR. Appx144 (4:4-14, 4:58-60).[10] As Dr. Pritchard explained, light transmission measured by OSCAR occurs when a suspension "starts to cream, to float towards the top, or to start to flocculate." Appx9686 (229:22-23). When discussing the OSCAR data in Figure 3, Dr. Govind also associated flocculation with instability measured by light transmission. Appx10037 (569:2-6) (explaining that greater light transmission in OSCAR shows "the destabilizing effect or the flocculation"). Because creaming took *minutes*—not seconds—to occur in Rogueda's Control 9, whatever Rogueda's data show about the particles upon aggregation, and thus after creaming, does not undercut the observed stability during the seconds after

[10] "Flocculation," "aggregation," and "agglomeration" refer to the tendency of suspended particles to form loose clumps or "flocs." *See* Appx10140-10141 (672:17-673:1), Appx10158 (690:5-12) (Dr. Young); Appx9563-9564 (112:22-113:2) (Dr. Pritchard); Appx9992 (524:8-18) (Dr. Govind).

shaking. The data in Rogueda were like the evidence of increased side effects in *Galderma*: they may have indicated a tradeoff to consider, but they did not teach away from the claimed invention. *Galderma*, 737 F.3d at 738-39; Appx9563-9564 (112:23-113:18); Appx9684 (227:5-18). Teaching away requires more.

If this Court concludes that the district court erred in its teaching-away determination with respect to adhesion or aggregation, or both, the district court's obviousness conclusion should be vacated. Evidence of possible issues with prior art must be weighed alongside affirmative evidence of obviousness. *See Ecolochem, Inc. v. S. Cal. Edison Co.*, 227 F.3d 1361, 1380 (Fed. Cir. 2000) (weighing evidence of skepticism and teaching away and affirming judgment of obviousness). Furthermore, evidence suggesting benefits of additional prior-art solutions does not alone resolve the obviousness inquiry. *In re Gurley*, 27 F.3d 551, 553 (Fed. Cir. 1994) (explaining that an "obvious composition does not become patentable simply because it has been described as somewhat inferior to some other product for the same use").

C. The district court's unexpected-results analysis was flawed and cannot cure its deficient consideration of the prior art

The district court's unexpected-results analysis spanned just two sentences:

> [A] POSA would understand the [claimed] formulation's stability after fifteen seconds to be an unexpected superior property when compared to Rogueda Control 9, which, as a whole, teaches away from the claims. [Appx10223-10226 (755:21-758:1).] Accordingly, because an embodiment

> within the scope of the claims had unexpected properties, the claims are valid and not obvious.

Appx47.

On its face, that analysis depended on the district court's flawed conclusion that Rogueda taught away and cannot stand for that reason alone. But it also contains at least three *additional* legal errors. First, the observed duration of stability was at most a difference in *degree* when compared to the prior art and therefore not significantly probative of non-obviousness. Second, that difference in degree applied only to *one* formulation within the scope of the claims and thus was not commensurate in scope with the claimed invention. And third, the mere *existence* of an unexpected result did not render AstraZeneca's claims non-obvious.

1. Any unexpected result was at most a difference in degree, not in kind

When an improvement results merely in a difference in *degree* rather than in *kind*, those results are unlikely to establish non-obviousness, even if unexpected. As this Court has explained, "[u]nexpected results that are probative of nonobviousness are those that are 'different in kind and not merely in degree from the results of the prior art.'" *Galderma*, 737 F.3d at 739 (quoting *Iron Grip*, 392 F.3d at 1322). Thus, when assessing whether unexpected results overcome a challenger's evidence on the first three *Graham* factors, a decisionmaker must evaluate both the significance and kind of the unexpected results. *Bristol-Myers Squibb Co. v. Teva Pharms. USA, Inc.*,

752 F.3d 967, 977 (Fed. Cir. 2014) ("While a 'marked superiority' in an expected property may be enough in some circumstances to render a compound patentable, a 'mere difference in degree' is insufficient." (quoting *In re Papesch*, 315 F.2d 381, 392 (CCPA 1963))).

As an unexpected result, AstraZeneca pointed to evidence that "the 0.001% embodiment of the claims tested in the patent showed superior stability over the entire time period measured." Appx10507 (citing the '328 patent, Appx128-131, Appx145). But those data did not show a different kind of stability, just that—at most—the 0.001% embodiment demonstrated a higher *degree* of stability *after* the critical first seconds after shaking. AstraZeneca's expert testified that the extended duration of stability beyond 15 seconds after shaking would not have been "irrelevant to a POSA." Appx47. But the law requires more to establish unexpected results. A difference in kind poses a bar much higher than "not irrelevant." The claimed formulations' reported stability beyond the typical timeframe for administration hardly amounts to a difference in kind, and the district court did not find otherwise. Without such a finding, AstraZeneca's asserted unexpected results are not probative of non-obviousness. *Galderma*, 737 F.3d at 739.

2. The unexpected result at 0.001% PVP was not commensurate with the scope of the claims

The district court's unexpected-results analysis also fails as a matter of law because the asserted improvement in degree was associated with only one

embodiment within the claims. *See* Appx47 ("[B]ecause *an* embodiment within the scope of the claims has unexpected properties, the claims are valid and not obvious." (emphasis added)). "It is the established rule that objective evidence of non-obviousness must be commensurate in scope with the claims which the evidence is offered to support." *Allergan, Inc. v. Apotex Inc.*, 754 F.3d 952, 965 (Fed. Cir. 2014) (quotation marks omitted) (collecting cases). And here, the district court construed the "0.001%" PVP limitation to reach far beyond just 0.001%.

This error was particularly acute because the asserted unexpected result was presented as an improvement relative to *another embodiment construed to fall within the scope of the same claims*. Under the district court's construction, the claims cover formulations with both 0.001% *and* 0.0005% PVP. The asserted unexpected result was thus an improvement of one claimed embodiment over another claimed embodiment. The district court's answer to this problem was that "[e]vidence of unexpected properties need only be 'reasonably commensurate with the scope of the claims.'" Appx47 (citing *In re Kao*, 639 F.3d 1057, 1069 (Fed. Cir. 2011)). While "reasonably commensurate" suggests some flexibility, it does not go so far as the district court stretched it. As this Court explained in *Kao*, it is not necessary to test *every* claimed embodiment for the unexpected result. 639 F.3d at 1068. It is enough if there is an adequate basis "to support the conclusion that other embodiments falling within the claim will behave in the same manner." *Id.* But here we know that the 0.0005% PVP

embodiment that the district court also deemed within the scope of the claims *lacked* whatever superior results were associated with 0.001%. *E.g.*, Appx128 (Fig. 2). *Kao*'s flexibility does not extend to claims covering embodiments that lack the unexpected result; it simply alleviates the need to prove all embodiments will behave in the same way if there is a basis for concluding as much.

3. The mere presence of an unexpected result does not resolve the obviousness inquiry

Finally, even if AstraZeneca's unexpected-results evidence demonstrated a difference in kind, and even if those results were commensurate with its claims, the district court still erred because it assumed that the mere presence of unexpected results resolves the obviousness inquiry. According to the district court, "because an embodiment within the scope of the claims had unexpected properties, the claims are valid and not obvious." Appx47. That conclusion does not follow. Secondary considerations are evidence to be weighed alongside affirmative evidence of obviousness; they do not alone resolve the question. *See Bristol-Myers*, 752 F.3d at 977 ("While secondary considerations must be taken into account, they do not necessarily control the obviousness determination.").

Having already concluded that the claims were non-obvious, the district court may have felt it unnecessary to weigh the strength of the secondary considerations evidence. But that cursory assessment of unexpected results—even if not flawed for the reasons explained above—cannot cure the errors it made regarding Mistry and

Rogueda. Nor could unexpected results about stability *beyond* the critical 15-20 seconds after shaking outweigh Mylan's affirmative evidence of obviousness. If this Court does not reverse the obviousness judgment, it should at a minimum vacate and remand for reconsideration by the district court.

CONCLUSION

This Court should reverse the district court's overbroad construction of "0.001%" PVP and vacate the associated judgments of noninfringement and non-obviousness. Even if this Court affirms the district court's claim construction, it should reverse or vacate the district court's judgment that the asserted claims were not invalid for obviousness over the prior art.

Respectfully submitted,

PERKINS COIE LLP

by /s/Shannon M. Bloodworth

Shannon M. Bloodworth

Counsel for Appellants Mylan Pharmaceuticals Inc. and Kindeva Drug Delivery L.P.

ADDENDA

UNITED STATES DISTRICT COURT

for the

Northern District of West Virginia

AstraZeneca AB,Astrazeneca Pharmaceuticals LP

Plaintiff(s)

v.

Civil Action No. 1:18cv193, 1:19cv203

Mylan Pharmaceuticals Inc. Kindeva Drug Deliver

Defendant(s)

JUDGMENT IN A CIVIL ACTION

The court has ordered that:

☐ Judgment award ☐ Judgment costs ☒ Other

other: Court determines that Mylan has failed to carry its burden of proving obviousness by clear and convincing evidence. Court Orders in favor of Plaintiffs, AstraZeneca AB and AstraZeneca Pharmaceuticals LP.

This action was:

☐ tried by jury ☐ tried by judge ☒ decided by judge

decided by Judge Irene M. Keeley

Date: March 2, 2021

CLERK OF COURT

Cheryl Dean Riley

/s/ J. Musgrave Deputy Clerk

Signature of Clerk or Deputy Clerk

IN THE UNITED STATES DISTRICT COURT
FOR THE NORTHERN DISTRICT OF WEST VIRGINIA
AT CLARKSBURG

ASTRAZENECA AB and ASTRAZENECA PHARMACEUTICALS LP, Plaintiffs, v. MYLAN PHARMACEUTICALS INC. and KINDEVA DRUG DELIVERY, L.P., Defendants.	Civil Action No. 1:18-cv-00193-IMK
ASTRAZENECA AB and ASTRAZENECA PHARMACEUTICALS LP, Plaintiffs, v. MYLAN PHARMACEUTICALS INC. and KINDEVA DRUG DELIVERY, L.P., Defendants.	Civil Action No. 1:19-cv-00203-IMK

AMENDED FINAL JUDGMENT

For the reasons set forth in the Court's Memorandum Opinion and Order Making Findings of Fact and Granting Judgment in Favor of the Plaintiffs, Dkt. No. 431, IT IS HEREBY ORDERED THAT:

1. The product that is the subject of Defendants' Abbreviated New Drug Application ("ANDA") No. 211699 infringes Claims 9, 10, 13, and 14 of U.S. Patent No. 7,759,328, Claims 12, 13, 18, and 19 of U.S. Patent No. 8,143,239, and Claims 10 and 19 of U.S. Patent No. 8,575,137, and those claims have not been proven invalid or unenforceable.

2. Pursuant to 35 U.S.C. § 271(e)(4)(A), the effective date of any final approval of ANDA No. 211699 shall be a date that is not earlier than the latest date of expiration of U.S. Patent Nos. 7,759,328, 8,143,239, and 8,575,137, including any extensions or additional periods of exclusivity.

3. Judgment is entered in favor of Plaintiffs and against Defendants.

Date: March 8, 2021

Irene M. Keeley

HON. IRENE M. KEELEY
UNITED STATES DISTRICT JUDGE

IN THE UNITED STATES DISTRICT COURT
FOR THE NORTHERN DISTRICT OF WEST VIRGINIA

ASTRAZENECA AB and
ASTRAZENECA PHARMACEUTICALS LP,

Plaintiffs,

v. **CIVIL ACTION NO. 1:18CV193**
(Judge Keeley)

MYLAN PHARMACEUTICALS INC. and
KINDEVA DRUG DELIVERY L.P.,

Defendants.

c/w 1:19CV203

MEMORANDUM OPINION AND ORDER MAKING FINDINGS OF FACT AND GRANTING JUDGMENT IN FAVOR OF THE PLAINTIFFS, ASTRAZENECA AB AND ASTRAZENECA PHARMACEUTICALS LP

I. BACKGROUND

In this patent infringement action, the plaintiffs, AstraZeneca AB and AstraZeneca Pharmaceuticals LP (collectively, "AstraZeneca"), and the defendants, Mylan Pharmaceuticals Inc. and Kindeva Drug Delivery L.P.[1] (collectively, "Mylan"), dispute whether claims 9, 10, 13, and 14 of United States Patent No. 7,759,328 ("the '328 Patent"); claims 12, 13, 18, and 19 of United States Patent No. 8,143,239 ("the '239 Patent"); and claims 10 and 19 of United States Patent No. 8,575,137 ("the '137 Patent") (collectively, "the asserted claims" or the "patents-in-suit") are

[1] Although AstraZeneca originally included 3M Company as a defendant in this action, the parties stipulated to its dismissal because all activities related to the generic Symbicort® program under review by the FDA as ANDA No. 211699 were transferred from 3M to Kindeva (Dkt. No. 386).

valid and enforceable (Dkt. Nos. 285 at 4, 5; 286 at 4, 5; 390).[2] The asserted claims are associated with Symbicort®, AstraZeneca's New Drug Application ("NDA") product approved by the FDA as a treatment for asthma in patients six years of age and older, and as a maintenance treatment in patients with chronic obstructive pulmonary disease (Dkt. Nos. 285 at 3, 4; 286 at 3, 4). Mylan has filed an Abbreviated New Drug Application ("ANDA") seeking to engage in the commercial manufacture, use, or sale of generic versions of the two dosage forms of Symbicort®, prior to the expiration of the patents-in-suit.

The Drug Price Competition and Patent Term Restoration Act of 1984, Pub. L. No. 98-417, 98 Stat. 1585, otherwise known as the "Hatch-Waxman Act", seeks to encourage "pioneering research and development of new drugs," as well as the "production of low-cost, generic copies of those drugs." Eli Lilly & Co. v. Teva. Pharm. USA, Inc., 557 F.3d 1346, 1348 (Fed. Cir. 2009). To that end, a manufacturer may obtain Food and Drug Administration ("FDA") approval to market a generic drug by making a certification that each patent listed in the FDA's Approved Drug Products with

[2] All docket and page numbers refer to the numbers assigned by the Court's electronic docket. Unless indicated otherwise, all docket numbers refer to Case No. 1:18CV193.

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Therapeutic Equivalence Evaluations ("the Orange Book") as covering the NDA drug are "invalid or will not be infringed by the manufacture, use, or sale of the new generic drug for which the ANDA is submitted" ("paragraph IV certification"). Id. (citing 21 U.S.C. § 355(j)(2)(A)(vii)(IV)). Upon receiving a paragraph IV certification, a patentee may sue the applicant for patent infringement within 45 days, thus delaying FDA approval of the ANDA. Id. (citing 21 U.S.C. § 355(j)(5)(B)(iii)).

In this case, in which AstraZeneca has sued Mylan under the Hatch-Waxman Act for infringement of the patents-in-suit, the Court is tasked with deciding whether the asserted claims of AstraZeneca's patents are invalid as obvious under 35 U.S.C. § 113.[3] As discussed below, the Court **CONCLUDES** that

[3] Initially, four patents associated with Symbicort® were at issue in this case. These include U.S. Patent Nos. 7,759,328; 8,143,239; 8,575,137; and 7,967,011 (the "'011 patent) (Dkt. No. 1; Case No. 1:19CV203, Dkt. No. 1). On November 12, 2019, AstraZeneca amended its complaint to add infringement claims for U.S. Patent No. 10,166,247 (the "'247 patent") (Dkt. No. 89), and deleted its previous claims related to the '011 Patent from the amended complaint.

Thereafter, on September 21, 2020, the parties stipulated to the dismissal of all claims, counterclaims, and defenses regarding the '247 patent (Dkt. No. 349). Mylan also stipulated that their generic product infringed the ten asserted claims at issue and that AstraZeneca's product, Symbicort®, embodied the claims. Id.

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Mylan has failed to demonstrate by clear and convincing evidence that the asserted claims of the patents-in-suit are invalid for obviousness.

II. FINDINGS OF FACT

A. The Parties, Jurisdiction, and Venue

AstraZeneca AB is a corporation organized under the laws of Sweden, with its principal place of business at S-151 85 Södertälje, Sweden. AstraZeneca Pharmaceuticals LP is a limited partnership organized under the laws of the State of Delaware, with its principal place of business at 1800 Concord Pike, Wilmington, Delaware 19803. Mylan Pharmaceuticals Inc. is a company organized under the laws of the State of West Virginia with its principal place of business at 781 Chestnut Ridge Road, Morgantown, West Virginia 26505. Kindeva Drug Delivery L.P. is a company organized under the laws of the State of Delaware, with a place of business at 42 Water Street, Building 75, St. Paul, Minnesota 55170. The Court has subject matter and personal jurisdiction, and venue is proper.

Thus, based on the parties' various stipulations, the only remaining issue at trial was whether the asserted claims are invalid as obvious under § 113.

B. Factual and Procedural Background

Because the asserted claims of the patents-in-suit recite a specific method for treating asthma and COPD, the Court begins its analysis with a brief discussion of these respiratory disorders, as well as a review of the development of the Symbicort® pMDI and the relevant prosecution history of AstraZeneca's patent applications related to Symbicort®.

1. Asthma and COPD

a. Asthma

Asthma "is a reversible inflammatory condition of the lungs." (Trial Trans. 356:12-14). The reversibility of asthma is important as compared to other respiratory conditions, like COPD, where the changes may be fixed. Id. at 356:14-16. Any inflammation in the lungs can interfere with the exchange of carbon dioxide for oxygen. Id. at 356:17-21. This interference can lead to hypoxia (oxygen starvation), and death if not addressed. Id. at 356:19-23. An individual suffering an asthma attack will cough, wheeze, and experience shortness of breath. Id. at 356:14-25, 357:1-2. Medications that control asthma symptoms target the actual site of the inflammation. Id. at 357:3-11.

Of chief concern in an asthma attack is the airway obstruction

caused by this inflammation, which may be triggered by the patient's environment, allergies, or acute illness. Id. at 357:18-358:1. Mylan's expert, Dr. Ulus Atasoy, analogized escalating lung inflammation in an asthma attack to a small snowball rolling down a hill, growing in intensity before potentially leading to severe asthma attack or death. Id. at 358:1-3. According to Dr. Atasoy, targeting this inflammation in the lungs results in a better chance of controlling the attack. Id. at 358:4-8. Inhaled corticosteroids ("ICS") are used to reduce the inflammation in the lungs and the swelling and tightening of the airways. Id. at 358:9-11. Long-acting beta agonists ("LABAs") are used to open the airways. Id. at 358:11-13.

b. COPD

Unlike asthma, chronic obstructive pulmonary disease ("COPD") is a fixed inflammatory condition of the lungs (Trial Trans. 356:13-16). Except for Symbicort®, no other ICS LABA pMDIs indicated for COPD are available in the United States. Id. at 836:5-7.

2. Development of Symbicort®

a. Montreal Protocol

The first pressurized metered dose inhalers launched in the

1950s used chlorofluorocarbon ("CFC")-based propellants (Dkt. No. 415 at 10). In 1989, however, the Montreal Protocol recognized CFCs as harmful to the environment. As a consequence, these types of propellants were phased out of production (DTX 1017, JTX 2403).

In connection with that phase out, two consortia from several pharmaceutical companies were formed to generate safety data on the two hydrofluoroalkane ("HFA") propellants identified as suitable for product use: HFA 134a and HFA 227 (JTX 2403.0048-49). The International Pharmaceutical Aerosols Consortium for Toxicology I ("IPACT I") was formed in August 1990 to examine HFA 134a. Id.; see also DTX 1017.60. The International Pharmaceutical Aerosols Consortium for Toxicology II ("IPACT II") was formed in February 1991 to study HFA 227. Id. As a result of those studies, in July 1994, regulatory authorities approved the IPACT I toxicology data for HFA 134a as suitable for pMDI use. Later, in September 1995, the IPACT II data for HFA 227 was approved. Id.

b. Delivery of Respiratory Drugs

Several delivery systems are available to administer inhaled medications. These include nebulizers, dry powder inhalers ("DPI"), and pressurized metered dose inhalers ("pMDI"). Each of these systems has a different method for transporting inhalable

medications into a patient's lungs.

Nebulizers use pressurized air with a solution to breathe the medication into the lungs (Trial Trans. 359:8-11). Nebulizers are not portable and require regular cleaning. Id. at 105:18-20. Before the advent of metered dose inhalers and DPIs, these respiration treatments were the only maintenance treatment available, and they proved challenging for young asthmatics. Id. at 359:14-18. Nebulizers are now typically used only in hospital settings to administer emergency treatments for asthma attacks. Id. at 359:11-13.

DPIs are breath-actuated and introduce a specific amount of dry powder formulation into a patient's lungs. Id. at 360:5-9. In order to use DPIs, the patient must take a deep, fast breath. Id. at 360:10-11. But individuals experiencing a respiratory attack may not be able to produce such a breath. Id. at 360:11-13. Further, because treatment with a DPI depends on the respiratory force a patient generates, use of this kind of inhaler is challenging for young children, elderly individuals, and those with neurological impairments. Id. at 101:10-12; 360:13-16. If the patient cannot generate an adequate breath, the medicine will not be delivered to the lower airways. Id. at 832:8-11.

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PMDIs contain gas which is liquified under pressure. Id. at 106:21-22. Mylan's formulation expert, Dr. John Pritchard, testified that using a pMDI is like operating a consumer aerosol; the patient presses a button on the can, "and the spray comes out." Id. at 106:22-24. In contrast to a consumer aerosol, however, pMDIs have a metering valve, which controls the dose the patient receives. Id. at 106:25, 107:1-5.

According to Dr. Pritchard, newly diagnosed asthma patients are given Albuterol, a rescue medication,[4] in a pMDI format. Id. at 107:6-10. This is because the pMDI does not require a deep breath for an adequate dose. Id. at 107:8-11. The liquified gas held under pressure does all the work needed to get the medication into the patient's lungs. Id. Dr. Pritchard believes that providing all newly diagnosed patients with an Albuterol pMDI rescue inhaler means that patients are familiar with these types of devices and need not learn how to use DPIs. Id. at 107:11-13.

When patients use pMDIs, the inhaler is typically shaken

[4] A rescue medication is different from a controller, or maintenance, therapy (Trial Trans. 830:13-15). A controller therapy is taken every day to manage a patient's symptoms. Id. Symbicort® maintains its effect for twenty-four (24) hours when used twice per day. Id. at 834:22-25.

before being placed into the mouth and actuated. Id. at 832:14-16. According to Dr. Reynold Panettieri, AstraZeneca's expert clinician, it typically takes a patient about twenty seconds to actuate a pMDI after shaking it. Id. at 832:19-21. The optimal use of the inhaler also depends on a patient's ability to coordinate actuating the inhaler and taking a breath. Id. at 832:22-833:3. Patients who are very young, very old, or cognitively impaired may experience some delay between shaking the inhaler and taking a breath. Id. Dr. Panettieri testified that it is critically important to the effective treatment of patients with asthma and COPD to deliver a consistent and reproducible dose of an inhaled drug into the patient's lower airways. Id. at 833:10-17.

3. Prior Art

a. Mistry

Mistry is the lead inventor on related foreign and United States patents and patent applications titled "Pressurized aerosol compositions" and directed primarily to polymers that work in HFA propellants to stabilize pMDI suspension formulations. (JTX 2381.0001-2).

The invention claimed in Mistry is:

a pressurized aerosol composition . . . that comprises a

> liquefied hydrofluoroalkane, a medicinal product in powder form dispersible therein and a polymer soluble in the liquefied hydrofluoroalkane, wherein the polymer includes repeating structural unites, the units being selected from units that contain an amide and units that contain an ester of a carboxylic acid.

Id. at pp. 2-3.

Relevant to the patents-in-suit, Mistry disclosed polymers soluble in HFA propellants. Id. at p. 2 ("We have now found, surprisingly, that certain polymers are both soluble in aerosol propellants and are able to stabilize pharmaceutical compositions."). Mistry also disclosed preferred hydrofluoroalkanes of HFA 134a, HFA152a, and HFA 227. Id. at p. 5. Of these, compositions including HFA 227 were particularly preferred. Id.

Mistry particularly preferred a polymer containing 1-ethylene-pyrrolidin-2-one, i.e., polyvinylpyrrolidone ("PVP"). Id. at p. 3. Mistry found that a "wide variety of molecular weights" provided acceptable suspensions. Id. PVP is usually characterized by its K value, "where K is determined from measurements of viscosity using the Fikentscher equation." Id. Mistry particularly preferred polymers with K values from 10 to 150, with a specific preference for 15 to 120. Id. "The particular K values and ranges that may be mentioned include 10-14, 15-18, 29-32, 88-100 and 115-125." Id.

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Mistry also disclosed polymers containing a carboxylic acid ester and repeating structural units such as polyvinyl acetate and copolymers of vinyl acetate and vinylpyrrolidone. Id. at pp. 3-4. It also included acrylic acid/methacrylate copolymers. Id. at p. 4. "The amount of polymer in the composition will depend on the active ingredient that is 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, preferably 0.0001 to 5% w/w and especially 0.001 to 1% w/w." Id.

Lubricants disclosed by Mistry include polyethoxylated compounds, "especially polyethylene glycol with an average molecular weight from 200 to 3000," with 400 to 2000 being preferred. Id. Mistry also disclosed polysorbates, alkyl aryl polyether alcohols, and lubricating excipients like fully halogenated chlorofluorocarbons of high molecular weight and medium-chain fatty acids. Id. A concentration from 0.01 to 4% w/w was preferred, with the most preferable being between 0.1 to 2% w/w. Id. at 4-5.

Mistry contemplated numerous medicaments that may be dispersed in a propellant mixture, including drugs such as sodium cromoglycate, nedocromil sodium, inhaled steroids like budesonide,

bronchodilators like salbutamol, reproterol, and formoterol, anticholinergics, and combinations of two or more agents. Id. at 6. Mistry listed sodium cromoglycate and salbutamol as an example of a combination of two agents. Id.

b. Rogueda

Rogueda disclosed a number of medicines, excipients, and lubricants that could be included in pMDIs (JTX-2001.0170). Particularly relevant to the claims in this case, Rogueda used a series of control samples to compare directly to novel formulations. Id. at p. 180. Two of these samples included ingredients relevant to the claims at issue:

- Control 3: Formoterol Fumarate Dihydrate with PEG 1000 and PVP K25 in a HFA 227 and 134a mix.
- Control 9: Budesonide with PEG 1000 and PVP K25 in HFA 227.

Id. at p. 189.

Control 3 included the following concentrations of ingredients:

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

Id. at p. 195. Control 9 included the following concentrations of ingredients:

Budesonide: 0.259% w/w
PEG 1000: 0.3% w/w
PVP K25: 0.001% w/w
HFA 227: to 100% w/w

Id.

Rogueda found that samples prepared with HFA 134a were on average better than the ones prepared with HFA 227 due, primarily, to the differences in the chemicals' densities. Id. at 197. The budesonide examples, when compared with controls 7, 8, and 9, demonstrated a drastic reduction in the amount of drug adhesion to the wall of the can. Id. The formoterol fumarate dihydrate examples 3, 4, 8, and 11, when compared with controls 1, 2, and 3, showed similar drastic improvement over respective control samples. Id.

c. Intal and Tilade

Intal and Tilade are mast cell stabilizer pMDI products intended to treat asthma and were approved by regulatory authorities[5] prior to the priority date (Dkt. No. 415 at 10, Trial

[5] Although marketed and sold in markets outside of the United States, Intal and Tilade were not approved by the FDA at the priority date (Trial Trans. at 700:4-7).

Trans. at 700:13-14). Each product contains PVP, PEG, and an active ingredient suspended in propellant HFA 227. JTX 2376, JTX 2383. However, both Intal and Tilade use different grades of PVP and PEG from those used in the Symbicort® pMDI formulation (Dkt. No. 415 at 11, 12). Additionally, both products use significantly higher doses of their active ingredients than those used in the claimed formulation (Trial Trans. at 700:14-18).

4. Brief Summary of Prosecution History of Patents-In-Suit

The Patent and Trademark Office ("PTO") issued the patents-in-suit after considering, inter alia, Mistry and Rogueda and concluding that the claims were not obvious (JTX 2023.0002, 2001.0825, JTX2003.0328, JTX2005.0333). The PTO, however, rejected claims 1-12 of the '328 patent as unpatentable over Meade et al and Weers et al. (JTX 2001.0327). "Meade teaches that the formoterol can exist in the form of formoterol fumarate . . . [and] that propellant gas such as HFA-227, co-solvent such as polyethylene glycol (PEG), and surfactants such as polyvinylpyrrolidone (PVP) can be added [to] the composition." Id. The PTO also noted that Meade did not teach "(1) an exemplified pharmaceutical composition comprising budesonide, 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; [and] (3) the instant amounts of PVP and PEG." Id.

Weers taught that drugs such as budesonide and formoterol were administered to patients to treat respiratory disorders. Id. at pp. 327-28. According to the PTO, 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." Id. at p. 328.

The patent applicants, Drs. Nayna Govind and Maria Marlow (the "Applicants"), contended before the PTO that the claims were not obvious in light of the teachings of Meade and Weers. Id. at p. 344. They stressed that neither Meade nor Weers disclosed a pharmaceutical composition containing PVP at a concentration of 0.001% w/w, id., stating they had "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.'" Id. at p. 345 (quoting Specification at page 2).

The PTO ultimately rejected claims 1-3, 5-9, and 12 as obvious over Meade. Id. at p. 429. Claims 13 to 15 were added to this

rejection, and the Examiner concluded that the Applicants had not shown the criticality of the invention comprising 0.001% w/w PVP. Id. at p. 430.

On July 27, 2007, the Applicants appealed to the Board of Patent Appeals and Inferences from the final rejection of claims 1-3, 5-9, and 12-15. Id. at p. 434. After additional amendments and rejections, the Board Examiner allowed the claims because the "results provided in the specification on pages 7-9 for the stability of the instant composition overcomes any obviousness type rejection. . . . The claimed invention is specific to chemical components and amounts thereof." Id. at p. 602.

5. Inter Partes Review

On July 24, 2017, the PTO adjudicated a petition for inter partes review of claims 1-15 of the '328 patent. Id. at p. 888. Pursuant to the "reasonable likelihood" standard of 35 U.S.C. § 314(a), the Patent Trial and Appeal Board ("PTAB") concluded that the petitioner had not established a reasonable likelihood that it would prevail in showing the unpatentability of "claims 1 and 4-15 over the combined teachings of Mistry, Rogueda, and Carling because each of those claims requires a pharmaceutical composition comprising formoterol fumarate dihydrate at a concentration of 0.09

mg/ml in combination with specific values and concentrations and/or weight percentages of budesonide, PVP K25, and PEG 1000." Id. at pp. 907-908.

6. The Asserted Claims

a. The '328 Patent

The '328 Patent, filed on January 29, 2003, is titled "Composition for Inhalation," and lists Drs. Govind and Marlow as inventors (JTX 2023). The patent lists AstraZeneca AB as the assignee. The relevant claims of the patent are as follows:

1. A pharmaceutical composition comprising formoterol fumarate dihydrate, budesonide, 1,1,1,2,3,3,3-heptafluoropropane (HFA 227), PVP K25 (polyvinyl pyrrolidone with a nominal K-value of 25), and PEG-1000 (polyethylene glycol with an average molecular weight of 1,000), wherein the formoterol fumarate dihydrate is present at a concentration of 0.009 mg/ml, the budesonide is present at a concentration in the range of 1 mg/ml to 8 mg/ml, the PVP K25 is present at a concentration of 0.001% w/w, and the PEG-1000 is present at a concentration of 0.3% w/w.

...

4. A method of treating symptoms of a respiratory disorder, comprising administering to a patient the pharmaceutical

composition according to claim **1**, wherein the respiratory disorder is asthma, rhinitis, or chronic obstructive pulmonary disease (COPD).

...

9. The method of claim **4**, wherein the concentration of budesonide is 2 mg/ml.

10. The method of claim **4**, wherein the concentration of budesonide is 4 mg/ml.

...

13. A pharmaceutical composition comprising formoterol fumarate dihydrate, budesonide, HFA 227, PVP K25, and PEG-1000, wherein the formoterol fumarate dihydrate is present at a concentration of 0.09 mg/ml, the budesonide is present at a concentration of 2 mg/ml, the PVP K25 is present at a concentration of 0.001% w/w, and the PEG-1000 is present at a concentration of 0.3% w/w.

14. A pharmaceutical composition comprising formoterol fumarate dihydrate, budesonide, HFA227, PVP K25, and PEG-1000, wherein the formoterol fumarate dihydrate is present at a concentration of 0.09 mg/ml, the budesonide is present at a concentration of 4 mg/ml, the PVP K25 is present at a concentration

of 0.001% w/w, and the PEG-1000 is present at a concentration of 0.3% w/w.

AstraZeneca has alleged that Mylan's ANDA product will infringe claims 9, 10, 13, and 14.

b. The '239 Patent

The '239 Patent, filed on May 28, 2010, is titled "Composition for Inhalation," and lists Drs. Govind and Marlow as inventors (JTX 2024). The patent lists AstraZeneca AB as the assignee. The relevant claims of the patent are as follows:

10. A pressurized metered dose inhaler containing a suspension composition comprising formoterol fumarate dihydrate in the form of particles; budesonide in the form of particles; 1,1,1,2,3,3,3-heptafluoropropane (HFA 227); PVP K25 (polyvinyl pyrrolidone with a nominal K-value of 25); and PEG-1000 (polyethylene glycol with an average molecular weight of 1,000); wherein the budesonide is present at a concentration in the range of 1 mg/ml to 8 mg/ml; the PVP K25 is present at a concentration of 0.001% w/w; and the PEG-1000 is present at a concentration of 0.3% w/w, and wherein an actuation of the inhaler delivers 4.5 µg formoterol fumarate dihydrate and 40 to 320 µg budesonide.

...

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12. The inhaler of claim **10**, wherein an actuation of the inhaler delivers 80 µg budesonide.

13. The inhaler of claim **10**, wherein an actuation of the inhaler delivers 160 µg budesonide.

...

16. A method of administering an inhalable composition to a patient, the method comprising

> providing a pressurized metered dose inhaler containing a suspension composition comprising formoterol fumarate dihydrate in the form of particles, budesonide in the form of particles, HFA 227, PVP K25, and PEG-1000, wherein the budesonide is present at a concentration in the range of 1 mg/ml to 8 mg/ml; the PVP K25 is present at a concentration of 0.001% w/w; and the PEG-1000 is present at a concentration of 0.3% w/w, and wherein an actuation of the inhaler delivers 4.5 µg formoterol fumarate dihydrate and 40 to 320 µg budesonide; and

causing the patient to inhale the composition from the inhaler.

...

18. The method of claim **16**, wherein an actuation of the inhaler delivers 80 µg budesonide.

19. The method of claim **16**, wherein an actuation of the inhaler delivers 160 µg budesonide.

AstraZeneca has alleged that Mylan's ANDA product will infringe claims 12, 13, 18, and 19.

c. The '137 Patent

The '137 Patent, filed on March 5, 2012, is titled "Composition for Inhalation," and lists Drs. Govind and Marlow as inventors (JTX 2021). The patent lists AstraZeneca AB as the assignee. The relevant claims of the patent are as follows:

9. A pharmaceutical suspension composition comprising formoterol fumarate dihydrate, budesonide, HFA 227, PVP K25, and PEG-1000, wherein the budesonide is present at a concentration in the range of 1 mg/ml to 8 mg/ml and the PVP K24 is present at a concentration of 0.001 w/w.

10. The pharmaceutical suspension composition of claim **9**, wherein the PEG-1000 is present at a concentration of 0.3% w/w.

...

19. A method of treating a respiratory disorder, the method comprising administering the pharmaceutical suspension composition of claim **10** to a patient identified as in need of treatment with the composition.

AstraZeneca has alleged that Mylan's ANDA product will infringe claims 10 and 19.

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7. Claim Construction

On August 12, 2020, the Court construed the claim term "0.001%," which appears in several claims in the patents-in-suit, to have its ordinary and plain meaning (Dkt. No. 317). AstraZeneca argued that "0.001%" should be construed to have its plain meaning, which is "0.001%, expressed using one significant digit." (Dkt. No. 292 at 5). Mylan contended that "0.001%" meant "that precise number, with only minor variations" because AstraZeneca abandoned its proposed construction of "0.001%" during prosecution of the patents-in-suit (Dkt. No. 288 at 4). After reviewing the claim language, the patent specifications, and the prosecution history, the Court determined that AstraZeneca's proposed construction was consistent with the claim language and specification of the patents-in-suit.

Additionally, while the parties were briefing competing interpretations of the term "pharmaceutical composition," AstraZeneca agreed to adopt Mylan's proposed construction of a "suspension for therapeutic administration," rather than "a suspension that is suitable for therapeutic administration." (Dkt. No. 320).

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III. CONCLUSIONS OF LAW

A. Applicable Legal Standards

1. Burden of Proof

Each of the asserted claims is presumed to be valid. See 35 U.S.C. § 282; Microsoft Corp. v. I4i Ltd. P'ship, 564 U.S. 91, 94, 131 S.Ct. 2238, 2243 (2011); Novo Nordisk A/S v. Caraco Pharm. Labs., Ltd., 719 F.3d 1346, 1352 (Fed. Cir. 2013). Mylan thus bears the burden of proving invalidity by clear and convincing evidence. See 35 U.S.C. § 282 ("The burden of establishing invalidity of a patent or any claim thereof shall rest on the party asserting such invalidity."); Microsoft Corp., 564 U.S. at 102, 131 S.Ct. at 2246 ("[A] defendant raising an invalidity defense [bears] a heavy burden of persuasion, requiring proof of the defense by clear and convincing evidence." (citation omitted) (internal quotation marks omitted)). "Clear and convincing evidence places in the fact finder 'an abiding conviction that the truth of [the] factual contentions are highly probable.'" Procter & Gamble Co. v. Teva Pharm. USA, Inc., 566 F.3d 989, 994 (Fed. Cir. 2009) (quoting Colorado v. New Mexico, 467 U.S. 310, 316, 104 S.Ct. 2433 (1984)).

"The burden of proof never shifts to the patentee to prove validity." Pfizer, Inc. v. Apotex, Inc., 480 F.3d 1348, 1359 (Fed.

Cir. 2007). But, when determining whether Mylan has met its burden of proof, the Court must consider all of the evidence presented at trial, including the testimony and evidence offered by AstraZeneca. See id. at 1360.

2. Obviousness

A patent will not issue or may be invalidated if the subject matter of the patent is obvious.

> A patent may not be obtained . . . 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.

35 U.S.C. § 103 (hereafter, "Section 103"). Obviousness is a question of law, which depends on several underlying factual inquiries. Richardson-Vicks Inc. v. Upjohn Co., 122 F.3d 1476, 1479 (Fed. Cir. 1997).

> Under § 103, the scope and content of the prior art are to be determined; differences between the prior art and the claims at issue are to be ascertained; and the level of ordinary skill in the pertinent art resolved. Against this background, the obviousness or nonobviousness of the subject matter is determined. Such secondary considerations as commercial success, long felt but unsolved needs, failure of others, etc. might be utilized to give light to the circumstances surrounding the origin of the subject matter sought to be patented.

KSR Int'l Co. v. Teleflex Inc., 550 U.S. 398, 406, 127 S.Ct. 1727

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(2007) (quoting Graham v. John Deere Co., 383 U.S. 1, 17-18, 86 S. Ct. 684 (1966)). "[W]hile an analysis of any teaching, suggestion, or motivation to combine known elements is useful to an obviousness analysis, the overall obviousness inquiry must be expansive and flexible." In re Cyclobenzaprine Hydrochloride Extended-Release Capsule Patent Litigation, 676 F.3d 1063, 1069 (Fed. Cir. 2012) (citing KSR, 550 U.S. at 415, 419, 127 S.Ct. 1727).

"To render a claim obvious, prior art cannot be 'vague' and must collectively, although not explicitly, guide an artisan of ordinary skill toward a particular solution." Unigene Labs., Inc. v. Apotex, Inc., 655 F.3d 1352, 1361 (Fed. Cir. 2011) (citing Bayer Schering Pharm. AG v. Barr Labs., Inc., 575 F.3d 1341, 1347 (Fed. Cir. 2009)). "[M]ost inventions that are obvious were also obvious to try," and a "combination is only obvious to try if a person of ordinary skill has a 'good reason to pursue the known options.'" Unigene, citing KSR, 550 U.S. at 421. "When a field is unreduced by direction of the prior art,' and when prior art gives 'no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful, an invention is not obvious to try.'" Unigene, quoting Bayer Schering, 575 F.3d at 1347 (additional citations omitted).

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B. Defining the Level of Ordinary Skill in the Art

Determining who constitutes a person of ordinary skill in the art ("POSA") is a factual question involving a two-step inquiry to determine (1) what exactly is that "relevant art" at issue, and (2) who qualifies as a "person of ordinary skill" in that art. Seed Research Equip. Solutions, LLC v. Gary W. Clem, Inc., No. 09-01282-EFM-KGG 2011 WL 5024351, at *3 (D. Kan. Oct. 20, 2011) (citing Arachnid, Inc. v. Merit Indus., Inc., 201 F. Supp. 2d 833, 888 (N.D. Ill. 2002).

Regarding patents, "art" is defined as "[a] field of useful endeavor." Art, Black's Law Dictionary (11th ed. 2019) And "relevant art" is the "[a]rt to which one can reasonably be expected to look for a solution to the problem that a patented device tries to solve." Id. "The relevant art is defined by the nature of the problem confronting the would-be inventor." Ryko Mfg. Co. v. Nu-Star, Inc., 950 F.2d 714, 716 (Fed. Cir. 1991) (internal quotation omitted). "Factors that may be considered in determining level of ordinary skill in the art include: (1) the educational level of the inventor; (2) types of problems encountered in the art; (3) prior art solutions to those problems; (4) rapidity with which innovations are made; (5) sophistication of the technology;

and (6) educational level of active workers in the field." Daiichi Sankyo Co., Ltd. v. Apotex, Inc., 501 F.3d 1254, 1256 (Fed. Cir. 2007) (citation omitted). These factors are illustrative, not exhaustive. Id.

In this case, the parties agree that, for the formulation claim, a POSA at the priority date would have been a person with at least (1) an advanced degree, such as a master's degree or Ph.D., in a pharmaceutical science, such as a formulation science; (2) several years of experience in the field of aerosol pharmaceutical development; and (3) the ability to collaborate with others, such as colleagues with expertise in related areas (i.e., physicians specializing in treating respiratory diseases) (Dkt. No. 415 at 7). AstraZeneca asserts that a POSA would also be trained in chemistry (Dkt. No. 417 at 7). Mylan's expert, Dr. Pritchard, explained that a POSA would be able to consult with colleagues having expertise in chemistry if and when necessary (Trial Trans. 95:15-24, 154:4-20; 156:18-157:6; see also id. at 340:15-341:16).

The parties also offered slightly different definitions of the level of ordinary skill in the art required for the method of treatment claim. According to Dr. Atasoy, a POSA for the method of treatment would have a medical degree and at least several years of

experience with patients, such as those with asthma and COPD. Id. at 361:12-20. A POSA may collaborate with other colleagues, including experts in the field of aerosol pharmaceutical developments. Id. at 361:20-22. According to Dr. Panettieri, a POSA would have a medical degree with several years of experience in treating respiratory diseases such as COPD and asthma, id. at 837:11-13, and may collaborate with others, including a scientist with experience in the development of inhaled pharmaceutical products. Id. at 837:14-16.

These slight differences in the parties' proposed definitions would not impact the opinion of either the formulator or method of treatment expert. Id. at 118:1-18, 362:1-4, 599:4-18, and 837:20-22. Therefore, the Court determines that a formulator POSA would have an advanced degree such as a master's degree or Ph.D. in a pharmaceutical science, several years of experience in the field of aerosol pharmaceutical development, and the ability to collaborate with others, including experts in the field of chemistry or chemical engineering. A method of treatment POSA would have a medical degree and at least several years of experience treating patients with respiratory problems, such as asthma or COPD, and may collaborate with other colleagues, including expert formulators in

the field of aerosol pharmaceutical products.

C. The Parties' Contentions

Mylan contends that the patents-in-suit are invalid as obvious because the claimed formulations would have been an obvious pMDI reformulation of the Symbicort® Turbuhaler DPI ("Symbicort® DPI"). According to Mylan, a POSA would have been motivated to reformulate the Symbicort® DPI as a pMDI while maintaining its proven dosing and efficacy. Further, with only two pMDI formats available, a suspension would have been both obvious and preferred. HFA 227 would have been the preferred non-CFC propellant of the two readily available options, and a POSA would have selected PVP and PEG as excipients based on the prior art. Finally, a POSA would have optimized excipient grades and concentrations through routine testing with a reasonable expectation of success.

AstraZeneca asserts that Mylan has not met its burden to prove obviousness by clear and convincing evidence. It argues that the prior art on which Mylan relies teaches away and would not have motivated a POSA to make the claimed combination. It also contends that Mylan failed to show it would have been obvious to select and combine the elements of the claimed invention because a POSA would not have been motivated to make a suspension, to use HFA 227, PVP

K25, or PEG-1000, and would not have arrived at the claimed formulation by routine optimization or otherwise. AstraZeneca further argues that a POSA would not have had a reasonable expectation of success, and that the claimed invention exhibits unexpected properties.

The Court will address each of the parties' arguments in turn.

D. The Asserted Claims are Valid and Not Obvious

The patents-in-suit claim a new formulation to deliver budesonide and formoterol fumarate dihydrate. Therefore, the claimed invention is obvious if a person of ordinary skill would have selected and combined the prior art references to reach the claimed composition or formula. Eli Lilly and Co. v. Zenith Goldline Pharm., 471 F.3d 1369, 1380 (Fed. Cir. 2006) ("[T]o establish a prima facie case of obviousness based on a combination of elements in the prior art, the law requires a motivation to select the references and to combine them in the particular claimed manner to reach the claimed invention.").

1. Motivation to Select

As the party bearing the burden of proof, Mylan must show a "reason that would have prompted [a POSA] to combine the elements in the way the claimed new invention does," with a reasonable

expectation of success in solving a known problem. KSR, 550 U.S. at 418; Orexo AB v. Actavis Elizabeth LLC, 903 F.3d 1265, 1271 (Fed. Cir. 2018). "The obviousness inquiry does not merely ask whether a skilled artisan could combine the references, but instead asks whether 'they would have been motivated to do so.'" Adidas AG v. Nike, Inc., 963 F.3d 1355, 1359 (Fed. Cir. 2020) (quoting InTouch Techs., Inc. v. VGO Commc'ns, Inc., 751 F.3d 1327, 1352 (Fed. Cir. 2014)). "Fundamental differences between the references are central to th[e] motivation to combine inquiry." Adidas AG, 751 F.3d at 1359.

A skilled artisan's motivation to make a particular combination includes "whether he would select particular references in order to combine their elements." WBIP, LLC v. Kohler Co., 829 F.3d 1317, 1337 (Fed. Cir. 2016). "The inventor's own path itself never leads to a conclusion of obviousness. . . . What matters is the path that [a POSA] would have followed, as evidenced by the pertinent prior art." Otsuka Pharm. Co., Ltd. v. Sandoz, Inc., 678 F.3d 1280, 1296 (Fed. Cir. 2012).

"A prima facie case of obviousness typically exists when the ranges of a claimed composition overlap the ranges disclosed in the prior art." In re Peterson, 315 F.3d 1325, 1329 (Fed. Cir. 2003).

An overlap provides sufficient motivation to optimize the ranges. Id. at 1330 ("The normal desire of scientists or artisans to improve upon what is already generally known provides the motivation to determine where in a disclosed set of . . . ranges is the optimum combination.").

Broad ranges disclosed in prior art may preclude a finding of obviousness. See Genetics Inst., LLC v. Novartis Vaccines and Diagnostics, Inc., 655 F.3d 1291, 1306-07 (Fed. Cir. 2011) ("[T]he facts here present a case where the 'disclosed range is so broad as to encompass a very large[6] number of possible distinct compositions' thus 'requir[ing] nonobvious invention,' not a case, as in Peterson, where prior art 'ranges that are not especially broad invite routine experimentation to discover optimum values.").

Here, the parties do not dispute that a POSA would have been motivated to adapt Symbicort® from a DPI to a PMDI (Trial Trans. 101:10-12, 367:1-5, 842:1-9). The preference for pMDIs in the American market, coupled with the shift away from CFC propellants

[6] The patent at issue contained "68,000 truncated variants of a protein made up of 2,332 amino acids, and the allegedly interfering inventions differ[ed] in terms of the size of the permitted amino acid deletions, the location of those deletions, and the degree of allowable amino acid substitutions." Id.

following the Montreal Protocol, would have motivated a POSA to try to create a pMDI with an ICS and LABA. Id. at 101:10-102:2, 451:4-13, 360:2-7, 842:15-23. But given the dearth of prior art that taught towards a formulation with all of the claimed components of the claims at issue, it is unclear what would have prompted (or even enabled) a POSA at the priority date to select and combine all the elements of the claimed invention.

First, a POSA would have had to select both budesonide and formoterol as the active ingredients in the claimed formulation. Mylan argues that these were the active ingredients in the Symbicort® DPI already on the market. As established at trial, however, the formulation of a dry powder inhaler differs significantly from a pMDI. Therefore, even if a POSA had been motivated to use both budesonide and formoterol, a POSA's work would have just begun. Indeed, a POSA would have confronted additional choices concerning the concentrations of these medicaments in the formulation, whether to pursue a solution or a suspension, which grades of excipient and/or valve lubricant to use and in what concentrations, and which propellant or propellants to use. All of these choices, and the unpredictable ways each adjustment could impact the overall formulation, created an

insurmountable hurdle for a POSA.[7]

Second, to adapt the Symbicort® DPI to a pMDI, a POSA would have had to choose whether to pursue a solution or suspension formulation. A suspension formula most resembles a DPI because the drug particles remain in a solid state rather than dissolving into a smaller form and size, as they would in a solution. See, e.g., Trial Trans. 110:12-14, 141:1-8, 142:9-19, 143:18-147:23.

One of the "most important goals" of a formulator POSA would be to guarantee dose uniformity through the life of the device. Id. at 140:7-23, 611:23-25. Critically, particles from a DPI, designed to be used in a device that operates differently and to be co-blended with DPI-specific excipients, cannot be transferred wholesale to a pMDI propellant-based system. Id. at 622:6-25. Thus, the prior art did not teach using DPI particles in pMDIs, but instructed that the effective dose, based on particle size as emitted by the device, should match an existing CFC product (Dkt. No. 417 at 26). See also JTX 2353.0007, JTX 2392.0005, PTX 650.0006, Trial Trans. at 621:24-623:17. Keeping the same particle size used in the Symbicort® DPI therefore would likely not have

[7] See Attachment 1, "Choices Faced by the POSA", PDX-1.036.

been a choice available to a POSA using the prior art known at the priority date.

Next, a POSA would have had to know to use HFA 227 exclusively, rather than a blend of HFA 227 and HFA 134a, or just HFA 134a. Yet, as of the priority date, every FDA-approved HFA pMDI product used HFA 134a, not HFA 227 (JTX 2353.0013; Trial Trans. at 255:16-18, 653:14-16). Further, the density of budesonide and formoterol would cause these medicaments to sediment in HFA 134a but cream in HFA 227 (Dkt. No. 417 at 28). Formulations that cream, or float to the top of the liquid suspension, "can adhere substantially at the gas-liquid interface, preventing dose uniformity." Id. at 29; Trial Trans. at 657:16-658:19.

Critically, Controls 3 and 9 in the Rogueda prior art identified this issue. Unlike Rogueda's formulations using HFA 134a, the budesonide and formoterol formulations using HFA 227, PVP K25, and PEG-1000 adhered to the gas-liquid interface (JTX 2374.0028; Trial Trans. at 656:6-659:18). Therefore, if a POSA's primary concern was to duplicate the effective, proven, and consistent dosing in the Symbicort® DPI, the prior art at priority suggested that using HFA 227 likely would have been a fatal choice.

Finally, to arrive at the claimed formulation, a POSA would

have to use PVP K25 and PEG-1000 in specific concentrations. Although one of the prior art references at the time, Mistry, used six PVP grades within its most preferred ranges (17 PF, K29/32, K90, K120, C15, and C30), it did not use K25 (JTX 2381.0003, pp. 12-13; Trial Trans. at 311:12-312:5, 740:6-19). Thus, the long list of PEG grades and concentrations in Mistry would not have motivated a POSA to select PEG-1000 in a concentration of 0.3% w/w (JTX 2381.0015, Trial Trans. at 314:6-8, 732:5-6).

Given the "design space" in which a POSA found himself, Mylan argues a POSA would have undertaken "routine experimentation" and been guided by multiple references and his own knowledge that fewer than ten pharmaceutical grades of PVP and PEG, respectively, were commercially available at the priority date (including PVP K25 and PEG-1000) (Dkt. No. 418 at 18). It also contends that, from experience, a POSA would have understood that multiple grades would be screened at the same time during optimization. Id.

But this argument discounts the fact that Mistry disclosed twelve excipient polymers, with six different grades being "most preferred," and eleven lubricants—all of which would have required experimentation to determine the properties of each potential formulation. See Trial Trans. at 194:12-198:8. Moreover, a POSA

would have had to engage in extensive experimentation to arrive at the concentrations used in the patents-in-suit. See id. at 737:8-747:12 (Dr. Young opining that, without hindsight, and based on Mistry, a POSA would never have used PVP and PEG in the concentrations at issue here).

AstraZeneca argues that, had a POSA relied on Mistry's disclosures alone, the sheer number of potential formulations would have exceeded 2,560,000. See "Mistry's Disclosures Lead to a Very Large Number of Formulations," Attachment B. And, had a POSA considered other prior art references at the priority date, the number of possible combinations would have been even higher. Compare PDX-2.097, Attachment C, with id. Testing these formulations to determine whether or not the combination was viable would have taken an "eternity." Trial Trans: 746:22-747:12.

Mylan's argument amounts to simply experimenting in the "design space," and does not consider how different amounts of various ingredients could impact each other. See Allergan, Inc. v. Sandoz, Inc., 796 F.3d 1293, 1305 (Fed. Cir. 2015) ("[T]he record shows that the claimed amounts of the two different ingredients could and did materially and unpredictably alter the property of the claimed formulation."). Here, the number of possible

combinations disclosed by Mistry alone is in the millions. Therefore, at the priority date a POSA would not have been motivated to select the specific formulation claimed by the patents-in-suit.

2. Teaching Away

AstraZeneca argues that Rogueda's controls teach away from selecting formulations with budesonide, formoterol, HFA 227, PVP K25, and PEG-1000 because the combinations closest to the claimed formulation were unsuitable and left medication residue at the gas-liquid exchange barrier.

> "[W]here there is a range disclosed in the prior art, and the claimed invention falls within that range, a relevant inquiry is whether there would have been a motivation to select the claimed composition from the prior art ranges. In those circumstances, the burden of production falls upon th patentee to come forward with evidence that (1) the prior art taught away from the claimed invention; (2) there were new and unexpected results relative to the prior art; or (3) there are other pertinent secondary considerations."

Id. at 1304-05. A reference does not teach away if it "merely expresses a general preference for an alternative invention but does not criticize, discredit, or otherwise discourage investigation into the claimed invention." Meiresonne v. Google, Inc., 849 F.3d 1379, 1382 (Fed Cir. 2017). "A reference teaches

away when a person of ordinary skill, upon reading the reference, would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken in the claim." Id. "A reference that properly teaches away can preclude a determination that the reference renders a claim obvious." In re Moutett, 686 F.3d 1322, 1333 (Fed. Cir. 2012); see also Winner Intern. Royalty Corp. v. Wang, 202 F.3d 1340, 1349-50 (Fed. Cir. 2000).

Rogueda performed tests to compare his invention containing polar fluorinated molecules to several "control" formulations. Control 3 and Control 9 are relevant to the patents-in-suit because Control 3 contained formoterol, 0.001% w/w PVP K25, 0.1% w/w PEG-1000 in a density-matched blend of HFA 227 and HFA 134a, and Control 9 contained budesonide, 0.001% w/w PVP K25 and 0.3% w/w PEG-1000 in HFA 227. The claimed formulation at issue in this case contains budesonide, formoterol, 0.001% w/w PVP K25, 0.3% w/w PEG-1000, and HFA 227.

According to Mylan, Rogueda established that this formulation could be successfully created. The expert testimony at trial, however, established that formulations with budesonide or formoterol and PVP K25 and PEG-1000 adhered to the test cans at the

gas-liquid interface and had particle aggregation (JTX 2374 at pp. 27-28, 30-32; Trial Trans. at 680:1-686:21, 690:5-696:6). Based on this, AstraZeneca contends that a POSA would have expected that budesonide and formoterol formulations with PVP K25 and PEG-1000 would be unstable (Dkt. No. 417 at 13).

The experts at trial all agreed that dose uniformity and consistent dosing would be priorities for a POSA (Trial Trans. 262:13-268:15, 389:2-11, 601:13-25, 831:3-9). Therefore, the bare data in Rogueda, which was not even the focus of the testing at issue, does not support Mylan's argument that this prior art would have made the claimed invention obvious. It may be true that Rogueda did not necessarily disparage the formulations in Controls 3 and 9, but the data cut against the very goal a POSA would have been trying to achieve—a stable product with a consistent dose. Therefore, because a POSA would have been discouraged from incorporating the formulations in Controls 3 and 9, Rogueda teaches away and does not render the claims obvious.

3. Obvious to Select or Combine

"When there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the

known options within his or her technical grasp." KSR, 550 U.S. at 421. "If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense." Id.

Here, based on the prior art available at the priority date, there was no finite number of identified, predictable solutions. Rather, the prior art disclosed multiple grades of different excipients, different propellants, and various LABAs and inhaled corticosteroids that could be used. Therefore, without "clues pointing to the most promising combinations, an artisan could have spent years experimenting without success." Leo Pharm. Products, Ltd. v. Rea, 726 F.3d 1346, 1357 (Fed. Cir. 2013); Trial Trans. at 746:22-747:12. Consequently, even if the Court were to find Dr. Pritchard's "design space" argument persuasive, his proposed routine optimization would not have resulted in the claimed invention within a reasonable period of time. It therefore would not have been obvious to try based on the prior art available to a POSA at the priority date.

4. Reasonable Expectation of Success

The experts all agree that a POSA would have required a formulation having dose uniformity (Trial Trans. 262:13-268:15,

389:2-11, 601:13-25, 831:3-9). The expectation of success is assessed in view of this goal. See Institut Pasteur & Universite Pierre et Marie Curie v. Focarino, 738 F.3d 1337, 1346-47 (Fed. Cir. 2013). "[T]here can be little better evidence negating an expectation of success than actual reports of failure." See In re Cyclobenzaprine, 676 F.3d at 1081.

As the Court has discussed, the prior art taught that budesonide formulations with PVP K25 and PEG-1000 undesirably adhered to the device at the liquid-gas interface. Therefore, a POSA would not have had a reasonable expectation of success in creating a stable budesonide pMDI using HFA 227, PVP K25, and PEG-1000, much less when these ingredients were combined with formoterol.

5. Unexpected Properties

Because Mylan has failed to carry its burden of proving a motivation to select and combine the elements of the claims, Otsuka, 678 F.3d at 1296, the Court need not reach the issue of unexpected properties. Even so, Mylan's arguments on this issue are unavailing. Unexpected properties are present where "the claimed invention exhibits some superior property or advantage" that a POSA "would have found surprising or unexpected." Procter & Gamble v.

Teva Pharm., 566 F.3d 989, 994 (Fed. Cir. 2009). Evidence of unexpected properties need only be "reasonably commensurate with the scope of the claims." In re Huai-Hung Kao, 639 F.3d 1057, 1068 (Fed. Cir. 2011).

Here, AstraZeneca's succeeded in its patent prosecution when it demonstrated the superior stability of its formulation with 0.001% w/w PVP K25. Mylan stresses that all tested formulations of Symbicort® with varying concentrations of PVP K25 had the same stability over the first fifteen seconds after shaking. But as Dr. Young opined this would not render the rest of the data irrelevant to a POSA (Trial Trans. at 752:3-15, 758:16-759:22). Indeed, a POSA would understand the formulation's stability after fifteen seconds to be an unexpected superior property when compared to Rogueda Control 9, which, as a whole, teaches away from the claims. Id. at 755:21-758:1. Accordingly, because an embodiment within the scope of the claims had unexpected properties, the claims are valid and not obvious.

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MEMORANDUM OPINION AND ORDER MAKING FINDINGS OF FACT AND GRANTING JUDGMENT IN FAVOR OF THE PLAINTIFFS, ASTRAZENECA AB AND ASTRAZENECA PHARMACEUTICALS LP

IV. CONCLUSION

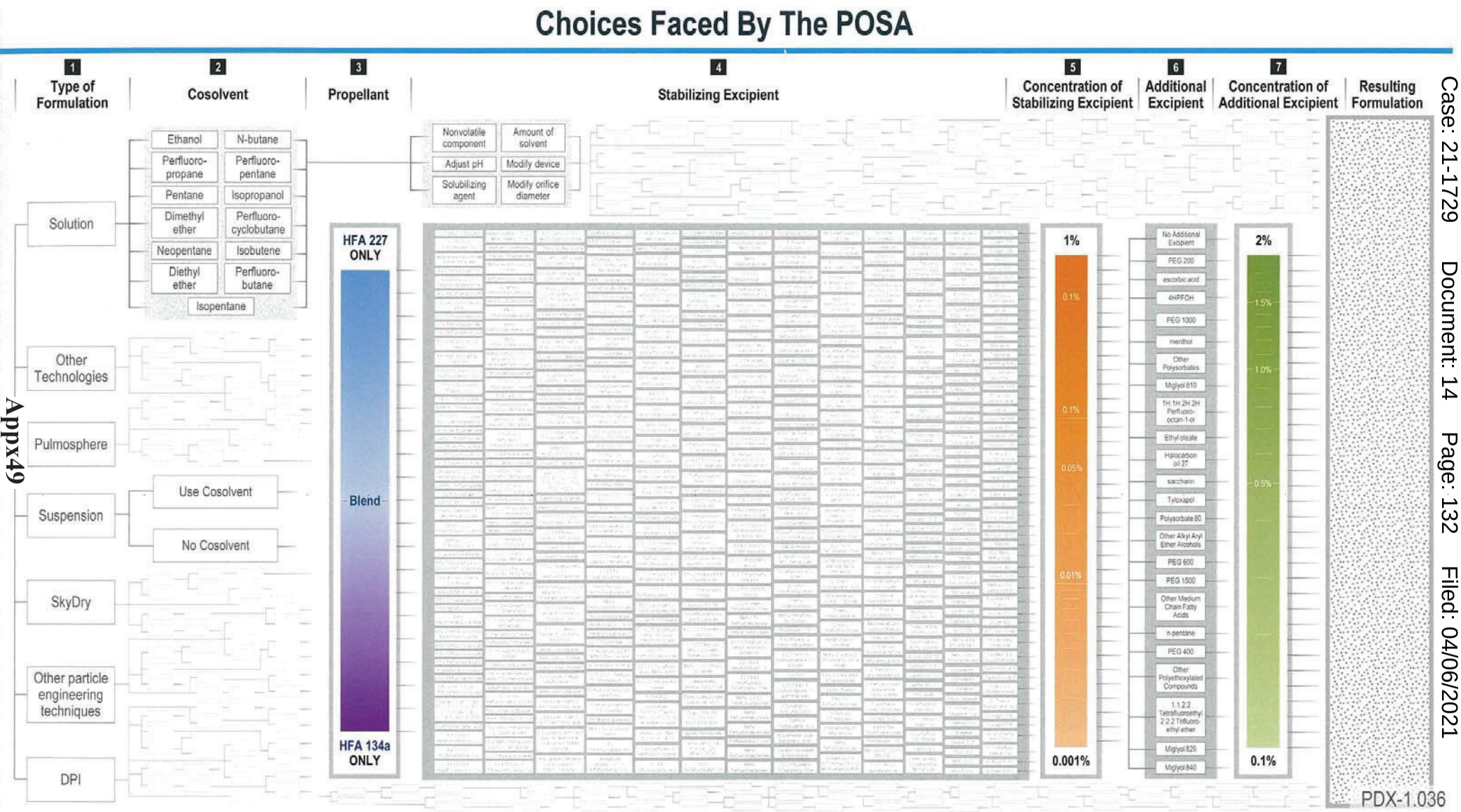
For the reasons discussed, the Court determines that Mylan has failed to carry its burden of proving obviousness by clear and convincing evidence.

It is so **ORDERED.**

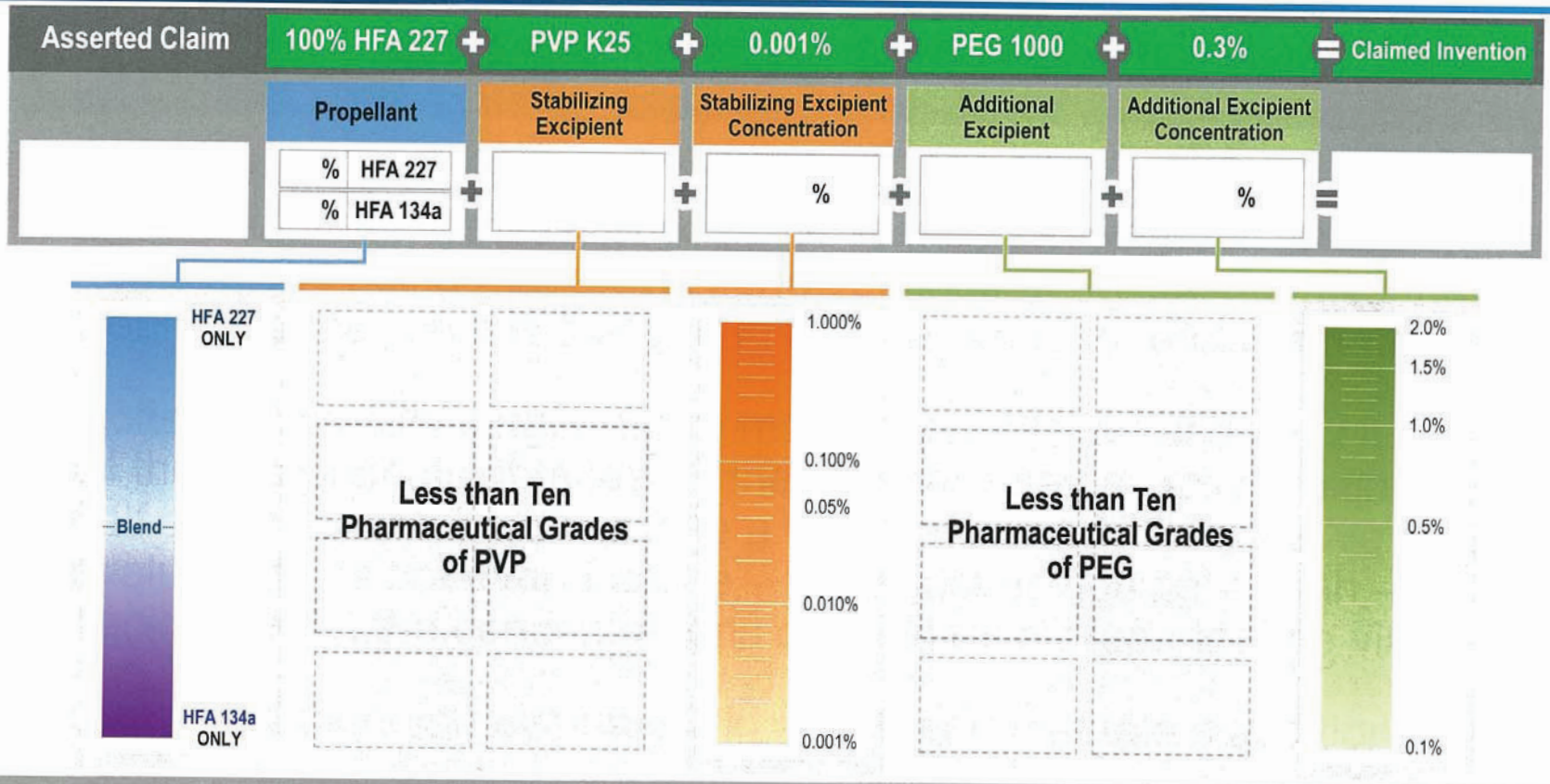
The Clerk is directed to enter separate judgment orders in favor of Plaintiffs, AstraZeneca AB and AstraZeneca Pharmaceuticals LP, in Civil Action Nos. 1:18cv193 and 1:19cv203, and to transmit copies of these orders to counsel of record.

DATED: March 2, 2021

/s/ Irene M. Keeley
IRENE M. KEELEY
UNITED STATES DISTRICT JUDGE



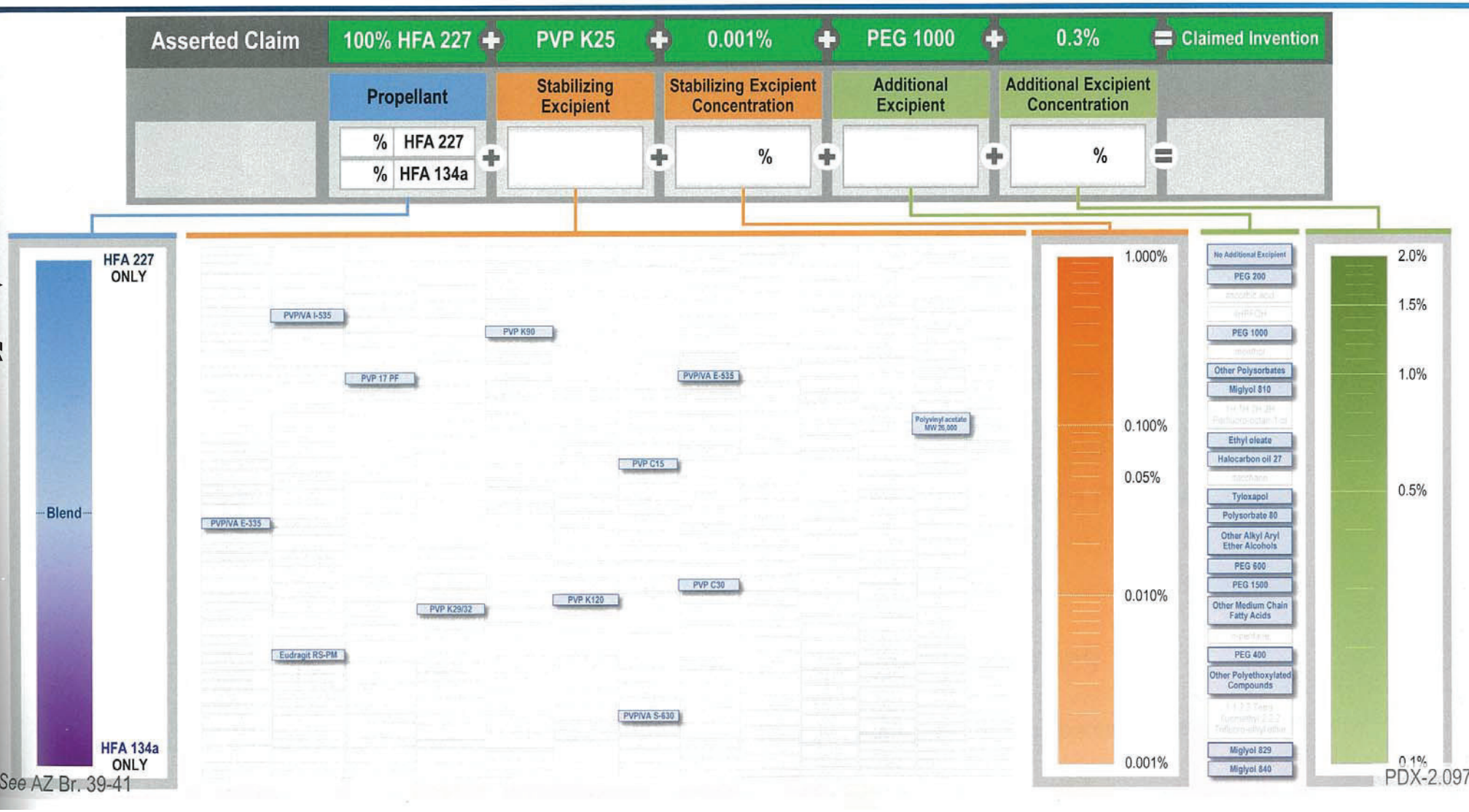
Mistry's Disclosures Lead To A Very Large Number Of Formulations



Total Number of Options:	2 Options	8 Options	1000 Options (by increments of 0.001% w/w)	8 Options	20 Options (by increments of 0.1% w/w)	2,560,000 possible formulations

See AZ Br. 39-41

The Rest Of The Prior Art Disclosed Even More Possible Options



See AZ Br. 39-41

PDX-2.097

IN THE UNITED STATES DISTRICT COURT
FOR THE NORTHERN DISTRICT OF WEST VIRGINIA

ASTRAZENECA AB and
ASTRAZENECA PHARMACEUTICALS LP,

Plaintiffs/Counter-Defendants,

v. **CIVIL ACTION NO. 1:18CV193**
(Judge Keeley)

MYLAN PHARMACEUTICALS INC., **c/w 1:19CV203**
3M COMPANY, and
KINDEVA DRUG DELIVERY, L.P.,

Defendants/Counter-Claimants.

MEMORANDUM OPINION AND ORDER ADOPTING
ASTRAZENECA'S PROPOSED CONSTRUCTION OF THE TERM "0.001%"

This patent infringement case involves four United States Patents issued to AstraZeneca AB and sold and distributed by AstraZeneca Pharmaceuticals LP (collectively, "AstraZeneca"). Specifically, the patents at issue are U.S. Patent Nos. 7,759,328 ("the '328 patent"), 8,143,239 ("the '239 patent"), 8,575,137 ("the '137 patent"), and the 10,166,247 ("the '247 patent) (collectively, "the patents-in-suit"). AstraZeneca uses the pharmaceutical compositions and methods described in these patents to produce Symbicort® (budesonide/formoterol fumarate dihydrate), a prescription drug approved for the treatment of asthma in patients 6 years of age and older and maintenance treatment in patients with chronic obstructive pulmonary disease ("COPD"), including bronchitis and emphysema.

Pending before the Court is the parties' proposed competing

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claim construction of the term "0.001%". The Court adopts AstraZeneca's proposed construction of the term "0.001%" for the reasons that follow.

I. BACKGROUND

According to AstraZeneca, 3M Company, through its 3M Drug Delivery Systems division, submitted Abbreviated New Drug Application ("ANDA") No. 211699 to the United States Food and Drug Administration ("FDA") under 21 U.S.C. § 355(j), in order to obtain approval to engage in the commercial manufacture, use or sale of budesonide and formoterol fumarate dihydrate inhalation aerosol, 80 mcg/4.5 mcg and 160 mcg/4.5mcg ("Mylan's ANDA Products") (Dkt. No. 285 at 5-6). On August 17, 2018, 3M transferred certain interests in ANDA No. 211699 to Mylan Pharmaceuticals Inc. Id. at 6. Thereafter, in a letter dated August 30, 2018, Mylan notified AstraZeneca that it had filed ANDA No. 211699 seeking approval to market Mylan's ANDA Products prior to the expiration of the patents listed in FDA's Approved Drug Products with Therapeutic Equivalence Evaluations for Symbicort. Id. In its letter, Mylan asserted that the '328, '239, and '137 patents are invalid, unenforceable, and not infringed by the commercial manufacture, use, or sale of Mylan's ANDA Products. Id.

In a second letter dated October 11, 2019, Mylan notified AstraZeneca that it had submitted a certification to the FDA to

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obtain approval to engage in the commercial manufacture, use, or sale of the product described in ANDA No. 211699 prior to the expiration of the '247 patent. Id. at 8. Mylan also asserted in its second letter that the '247 patent was invalid, unenforceable, and not infringed by the commercial manufacture, use, or sale of Mylan's ANDA Products. Id. Following receipt of Mylan's letters, AstraZeneca filed this patent infringement suit, which also seeks a declaration of infringement of the patents-in-suit (Dkt. No. 285).

II. LEGAL STANDARDS

The construction of patent claims is a matter of law governed by federal statutes and the decisions of the Supreme Court of the United States and the United States Court of Appeals for the Federal Circuit. See Markman v. Westview Instruments, Inc., 52 F.3d 967, 979 (Fed. Cir. 1995). When interpreting the meaning of a claim, a court may consider the context, the specification, and the prosecution histories as intrinsic evidence. Id. (quoting Unique Concepts, Inc. v. Brown, 939 F.2d 1558, 1561 (Fed. Cir. 1991)). "It is a bedrock principle of patent law that the claims of a patent define the invention to which the patentee is entitled the right to exclude." Phillips v. AWH Corp., 415 F.3d 1303, 1312 (Fed. Cir. 2005) (internal quotation marks omitted). The description of an

invention in the claims, therefore, limits the scope of the invention. Id. "[T]here is no magic formula or catechism for conducting claim construction." Id. at 1324. Instead, the Court is free to attach the appropriate weight to appropriate sources "in light of the statutes and policies that inform patent law." Id.

"[T]he words of a claim are generally given their ordinary and customary meaning [which is] the meaning that the term would have to a person of ordinary skill in the art in question at the time of the invention, i.e., as of the effective filing date of the patent application." Id. at 1312-13 (internal citations and quotation marks omitted). "[T]he ordinary meaning of a claim term is its meaning to the ordinary artisan after reading the entire patent." Id. at 1321 (internal quotation marks omitted).

When construing patent claims, then, a court must consider the context of the entire patent, including both asserted and unasserted claims. Id. at 1314. Because a patent will ordinarily use patent terms consistently, "the usage of a term in one claim can often illuminate the meaning of the same term in other claims." Id. Accordingly, "[d]ifferences among claims" can provide insight into "understanding the meaning of particular claim terms," and "the presence of a dependent claim that adds a particular limitation gives rise to a presumption that the limitation in

question is not present in the independent claim." Id. at 1314-15 (citing Liebel-Flarsheim Co. v. Medrad, Inc., 358 F.3d 898, 910 (Fed. Cir. 2004)).

Pursuant to 35 U.S.C. § 112, ¶ 1, an inventor must use the patent specification to describe the claimed invention in "full, clear, concise, and exact terms." The patent specification therefore "is always highly relevant to the claim construction analysis. Usually, it is dispositive; it is the single best guide to the meaning of a disputed term." Vitronics Corp. v. Conceptronic, Inc., 90 F.3d 1576, 1582 (Fed. Cir. 1996).

"[T]he specification may reveal a special definition given to a claim term by the patentee that differs from the meaning it would otherwise possess. In such cases, the inventor's lexicography governs." Phillips, 415 F.3d at 1316. "Even when the specification describes only a single embodiment, the claims of the patent will not be read restrictively unless the patentee has demonstrated a clear intention to limit the claim scope using words or expressions of manifest exclusion or restriction." Hill-Rom Servs., Inc. v. Stryker Corp., 755 F.3d 1367, 1372 (Fed. Cir. 2014) (quoting Liebel-Flarsheim, 358 F.3d at 906) (internal quotation marks omitted).

Nevertheless, a court may not import a limitation into the

claims from the specification. Phillips, 415 F.3d at 1323. The Federal Circuit has "repeatedly warned" against limiting the claims to the embodiments specifically described in the specification. Id. In other words, a court should not construe the patent claims as being limited to a single embodiment simply because the patent describes only one embodiment. Id. (citing Gemstar-TV Guide Int'l Inc. v. Int'l Trade Comm'n, 383 F.3d 1352, 1366 (Fed. Cir. 2004)).

A court "should also consider the patent's prosecution history, if it is in evidence." Markman, 52 F.3d at 980. The prosecution history, which is "intrinsic evidence," "consists of the complete record of the proceedings before the PTO [Patent and Trademark Office] and includes the prior art cited during the examination of the patent." Phillips, 415 F.3d at 1317. "[T]he prosecution history can often inform the meaning of the claim language by demonstrating how the inventor understood the invention and whether the inventor limited the invention in the course of prosecution, making the claim scope narrower than it would otherwise be." Id.

"The construction that stays true to the claim language and most naturally aligns with the patent's description of the invention will be, in the end, the correction construction." Renishaw PLC v. Marposs Societa' per Azionio, 158 F.3d 1243, 1250

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(Fed. Cir. 1998). It follows that "a claim interpretation that would exclude the inventor's device is rarely the correct interpretation." Osram GmbH v. Int'l Trade Comm'n, 505 F.3d 1351, 1358 (Fed. Cir. 2007) (quoting Modine Mfg. Co. v. U.S. Int'l Trade Comm'n, 75 F.3d 1545, 1550 (Fed. Cir. 1996)). It is with these legal principles in mind that the Court now turns to the construction of the disputed term among the asserted claims of the patents-in-suit.

III. ANALYSIS

The term "0.001%" appears in several claims in the patents-in-suit. AstraZeneca argues that "0.001%" should be construed by its plain meaning, "which is '0.001%, expressed using one significant digit.'" (Dkt. No. 292 at 5). Mylan contends that "0.001%" "means that precise number, with only minor variations" because AstraZeneca abandoned its proposed construction of "0.001%" during prosecution of the patents-in-suit (Dkt. No. 288 at 4).

A. The Claims

The Court begins its analysis by looking to the "actual words of the claim," Becton, Dickinson and Co. v. Tyco Healthcare Group, LP, 616 F.3d 1249, 1254 (Fed. Cir. 2010), as well as the context in which the disputed term appears. Phillips, 415 F.3d at 1314. Patent claims come in two general forms: independent and dependent. 35

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U.S.C. § 112(c). Independent claims do not refer to any other claim of the patent and are read separately to determine their scope. Inamin, Ltd. v. Magnetar Tech. Corp., 623 F. Supp.2d 1055, 1065 (C.D. Cal. 2009). Dependent claims, in contrast, refer to at least one other claim, include all of the limitations of the claim to which they refer, and specify a further limitation on that claim. 35 U.S.C. § 112(d); see also Monsanto Co. v. Syngenta Seeds, Inc., 503 F.3d 1352, 1357 (Fed. Cir. 2007).

1. The '328 Claims

Independent claim 1 reads:

> 1. A pharmaceutical composition comprising formoterol fumarate dihydrate, budesonide, 1,1,1,2,3,3,3-heptafluoropropane (HFA277), PVP K25 (polyvinyl pyrrolidone with a nominal K-value of 25), and PEG-1000 (polyethylene glycol with an average molecular weight of 1,000), wherein the formoterol fumarate dihydrate is present at a concentration of 0.09 mg/ml, the budesonide is present at a concentration in the range of 1 mg/ml to 8 mg/ml, the PVP K25 is present at a concentration of 0.001% w/w, and the PEG-1000 is present at a concentration of 0.3% w/w.

'328 patent, col. 8. Independent claim 12 reads:

> 12. A pharmaceutical composition comprising formoterol fumarate dihydrate, budesonide, HFA227, PVP K25, and PEG-1000, wherein the formoterol fumarate dihydrate is present at a concentration of 0.09 mg/ml, the budesonide is present at a concentration of 1 mg/ml, the PVP K25 is present at a concentration of 0.001% w/w, and the PEG-1000 is present at a concentration of 0.3% w/w.

Id. Independent claim 13 reads:

> 13. A pharmaceutical composition comprising formoterol fumarate dihydrate, budesonide, HFA227, PVP K25, and PEG-1000, wherein the formoterol fumarate dihydrate is present at a concentration of 0.09 mg/ml, the budesonide is present at a concentration of 2 mg/ml, the PVP K25 is present at a concentration of 0.001% w/w, and the PEG-1000 is present at a concentration of 0.3% w/w.

Id. Independent claim 14 reads:

> 14. A pharmaceutical composition comprising formoterol fumarate dihydrate, budesonide, HFA227, PVP K25, and PEG-1000, wherein the formoterol fumarate dihydrate is present at a concentration of 0.09 mg/ml, the budesonide is present at a concentration of 4 mg/ml, the PVP K25 is present at a concentration of 0.001% w/w, and the PEG-1000 is present at a concentration of 0.3% w/w.

Id. at cols. 8, 9. Independent claim 15 reads:

> 15. A pharmaceutical composition comprising formoterol fumarate dihydrate, budesonide, HFA227, PVP K25, and PEG-1000, wherein the formoterol fumarate dihydrate is present at a concentration of 0.09 mg/ml, the budesonide is present at a concentration of 8 mg/ml, the PVP K25 is present at a concentration of 0.001% w/w, and the PEG-1000 is present at a concentration of 0.3% w/w.

Id. at cols. 9, 10.

2. The '239 Claims

Independent claim 1 reads:

> 1. A pressurized metered dose inhaler containing a suspension composition comprising formoterol fumarate dihydrate in the form of particles; budesonide in the form of particles; 1,1,1,2,3,3,3-heptafluoropropane (HFA227); polyvinyl pyrrolidone (PVP); and polyethylene glycol (PEG), wherein the budesonide is present in the composition at a concentration in the range of 1 mg/ml to 8 mg/ml, the PVP is present at a concentration in the range of 0.001% to 0.01% w/w, and the PEG is present at a concentration in the range of 0.05 to 0.5% w/w, and

> wherein an actuation of the inhaler delivers 4.5 µg formoterol fumarate dihydrate and 40 to 320 µg budesonide.

'239 patent, cols. 8 and 9. Dependent claim 4 recites that the PVP is present in the composition at a concentration of 0.001% w/w. Id. at col. 9. Independent claim 10 reads:

> 10. A pressurized metered dose inhaler containing a suspension composition comprising formoterol fumarate dihydrate in the form of particles; budesonide in the form of particles; 1,1,1,2,3,3,3-heptafluoropropane (HFA227); PVP K25 (polyvinyl pyrrolidone with a nominal K-value of 25); and PEG-1000 (polyethylene glycol with an average molecular weight of 1,000), wherein the budesonide is present at a concentration in the range of 1 mg/ml to 8 mg/ml; the PVP K25 is present at a concentration of 0.001% w/w; and the PEG-1000 is present at a concentration of 0.3% w/w, and wherein an actuation of the inhaler delivers 4.5 µg formoterol fumarate dihydrate and 40 to 320 µg budesonide.

Id. Independent claim 16 reads:

> 16. A method of administering an inhalable composition to a patient, the method comprising providing a pressurized metered dose inhaler containing a suspension composition comprising formoterol fumarate dihydrate in the form of particles, budesonide in the form of particles, HFA227, PVP K25, and PEG-1000, wherein the budesonide is present at a concentration in the range of 1 mg/ml to 8 mg/ml; the PVP K25 is present at a concentration of 0.001% w/w; and the PEG-1000 is present at a concentration of 0.3% w/w , and wherein an actuation of the inhaler delivers 4.5 µg formoterol fumarate dihydrate and 40 to 320 µg budesonide; and causing the patient to inhale the composition from the inhaler.

Id. at cols. 9, 10. Independent claim 24 reads:

> 24. A method of administering an inhalable composition to a patient, the method comprising providing a pressurized

> metered dose inhaler containing a suspension composition comprising formoterol fumarate dihydrate in the form of particles; budesonide in the form of particles; HFA227; PVP; and PEG, wherein the budesonide is present in the composition at a concentration in the range of 1 mg/ml to 8 mg/ml, the PVP is present at a concentration in the range of 0.001% to 0.01% w/w, and the PEG is present at a concentration in the range of 0.05 to 0.5% w/w, and wherein an actuation of the inhaler delivers 4.5 µg formoterol fumarate dihydrate and 40 to 320 µg budesonide; and causing the patient to inhale the composition from the inhaler.

Id. at col. 10.

3. The '137 Claims

Independent claim 1 reads:

> 1. A pharmaceutical suspension composition comprising formoterol fumarate dihydrate; budesonide; 1,1,1,2,3,3,3-heptafluoropropane (HFA227); polyvinyl pyrrolidone (PVP); and polyethylene glycol (PEG), wherein the budesonide is present in the composition at a concentration in the range of 1 mg/ml to 8 mg/ml, the PVP is present at a concentration in the range of 0.001% to 0.01% w/w, and the PEG is present at a concentration in the range of 0.05 to 0.5% w/w.

'137 patent, col.8. Dependent claim 4 recites that the PVP is present in the composition at a concentration of 0.001% w/w. Id.

Independent claim 9 reads:

> 9. A pharmaceutical suspension composition comprising formoterol fumarate dihydrate, budesonide, HFA227, PVP K25, and PEG-1000, wherein the budesonide is present at a concentration in the range of 1 mg/ml to 8 mg/ml and the PVP K25 is present at a concentration of 0.001% w/w.

Id. Dependent claim 25 recites that the PVP is at a concentration of 0.001% w/w. Id. at col. 9.

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4. The '247 Claim

The only claim at issue regarding the '247 patent is dependent claim 4. Dependent claim 4 recites that "the pharmaceutical composition according to **claim 1**[1] in which the PVP is present in an amount of 0.001% w/w." '247 patent, col. 8 (emphasis in original).

B. The Claim Language

The center of the parties' dispute lies with how many significant digits are necessary to express the term "0.001%". Both parties agree that a person of ordinary skill in the art would interpret the specification to convey that the "0.001%" term is subject to rounding according to the number of significant digits. Thus, as advanced by AstraZeneca, the "0.001%" term would include a range from "0.0005%" to "0.0014%", based on the rules of rounding. Under Mylan's proposed construction, this range would include "0.00095" to "0.00105%". See, e.g., Noven Pharm., Inc. v. Actavis Labs. UT, Inc., C.A. No. 15-249-LPS, 2016 WL 3625541, at *3, 5 (D. Del. July 5, 2016) (construing "15 mg/cm^2" as its "[p]lain and ordinary meaning, i.e., '15 mg/cm^2' means 15 plus or minus at least .5, yielding a claimed range of greater than or

[1] Independent claim 1 reads, "A stable pharmaceutical composition comprising formoterol, budesonide or an epimer thereof, 1,1,1-2,3,3,3-heptafluoropropane (HFA227), polyvinyl pyrrolidone (PVP) and polyethylene glycol (PEG)." '247 patent, col. 8.

equal to 14.5 mg/cm^2 and less than 15.5 mg/cm^2").

The plain language of all of the relevant claims in the patents-in-suit states the term at issue as "0.001%." Mylan's proposed definition, which attempts to add a significant digit such that the claim term would be read as "0.0010%," conflicts with the plain language of the claim.

The task of the Court is to "define[] the claim with whatever specificity and precision is warranted by the language of the claim and the evidence bearing on the proper construction." PPG Indus. v. Guardian Indus. Corp., 156 F.3d 1351, 1355 (Fed. Cir. 1998). Here, neither the claim language nor prosecution history of the patents in suit indicates that AstraZeneca intended to include "0.001% expressed with two significant digits" in its claims. The Court is thus reluctant to follow Mylan's suggestion and rely on the prosecution history—where AstraZeneca never expressed "0.001%" or any of the other concentrations of PVP with more than one significant digit—to adopt a construction that might define the disputed term with greater specificity than warranted by the claim language.

C. The Specification

The Court turns to the patent specification in the patents-in-suit for guidance. Phillips, 415 F.3d at 1317. The specification

states that "[s]tability 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." '328 patent, col. 1:21-24; '239 patent, col. 1:25-28; '137 patent, col. 1:26-30; '247 patent, col. 1:12-15. The specification also teaches that the PVP is "preferably" present "in an amount of 0.001% w/w." '328 patent, col. 1:46; '239 patent, col. 1:49; '137 patent, col. 1:48; '247 patent, col. 1:48. The "0.001% w/w" concentration of PVP "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." '328 patent, col. 2:17-21; '239 patent, col. 2:22-26; '137 patent, col. 2:18-22; '247 patent, col. 2:11-15.

While the specification is often described as "'the single best guide to the meaning of a disputed term,'" Phillips, 415 F.3d at 1315 (quoting Vitronics, 90 F.3d at 1582), "the scope of patent protection" is defined by "[t]he claims, not specification embodiments." Kara Technology Inc. v. Stamps.com, Inc., 582 F.3d 1341, 1348 (Fed. Cir. 2009). After a careful review of the specification, it is clear that AstraZeneca used "0.001%" consistently with a single significant digit.

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D. The Prosecution History

Mylan's strongest argument relies on the prosecution history of the patents-in-suit. According to Mylan, its proposed construction is supported because, during the prosecution of the patents, AstraZeneca engaged in multiple rounds of patent argument and ultimately narrowed its original claim for PVP concentration to "0.001%." (Dkt. No. 288 at 6). Mylan argues that this adjustment establishes that AstraZeneca disclaimed all other concentrations of PVP, and that the patents-in-suit all claim a PVP concentration of precisely "0.001%". Id. In support of its argument, Mylan asserts that during prosecution AstraZeneca favorably distinguished its proposed invention from the prior art by demonstrating the criticality of 0.001% PVP to the stability of the pharmaceutical composition. Id. Mylan also points to AstraZeneca's limitation and argument that 0.001% PVP "suprising[ly]" provided the "best results" in terms of stability. Id.

AstraZeneca, however, contends that during prosecution it never disclaimed "0.001%" expressed with one significant digit (Dkt. No. 308 at 9). It insists there was no disavowal or disclaimer of the claim scope because expressing a preference for "0.001%" w/w PVP does not rise to the level of clear and unequivocal evidence that the claimed invention did not include

other embodiments of PVP, such as 0.0005%, that would be included in rounding "0.001%" to a single significant digit. Id. at 8. Importantly, AstraZeneca points out that it never expressed a PVP concentration in the invention with more than one significant digit during the prosecution history. Id. at 7.

In context, AstraZeneca's proposed construction is consistent with the claim language and specification of the patents-in-suit. See Phillips, 415 F.3d at 1317 ("Yet because the prosecution history represents an ongoing negotiation between the PTO and the applicant, rather than the final product of that negotiation, it often lacks the clarity of the specification and thus is less useful for claim construction purposes."). Undoubtedly, by adjusting its PVP preference, AstraZeneca was attempting to distinguish the prior art, which revealed stability in a range of 0.0025% w/w to 0.5% w/w PVP (Dkt. No. 288-3 at 26). But the evidence relied on by Mylan falls short of the "clear and unmistakable disavowal" needed to overcome "the heavy presumption that claim terms carry their full ordinary and customary meaning." Biogen Idec, Inc. v. GlaxoSmithKline LLC, 713 F.3d 1090, 1095 (Fed. Cir. 2013) (internal citations and quotation marks omitted). Therefore, because the ordinary and customary meaning of "0.001%" would be to read "0.001%" with one significant digit, the Court

declines to adopt Mylan's proposed construction based on the prosecution history of the patents-in-suit.

IV. CONCLUSION

The Court **ADOPTS** AstraZeneca's proposed construction and **CONSTRUES** the term "0.001%" consistent with its plain and ordinary meaning, that is, expressed with one significant digit.

It is so **ORDERED.**

The Clerk is directed to transmit copies of this Order to counsel of record.

DATED: August 12, 2020

/s/ Irene M. Keeley
IRENE M. KEELEY
UNITED STATES DISTRICT JUDGE

US008575137B2

(12) United States Patent
Govind et al.

(10) Patent No.: US 8,575,137 B2
(45) Date of Patent: *Nov. 5, 2013

(54) **COMPOSITION FOR INHALATION**

(75) Inventors: **Nayna Govind**, Loughborough (GB); **Maria Marlow**, Loughborough (GB)

(73) Assignee: **AstraZeneca AB**, Macclesfield (GB)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **13/411,939**

(22) Filed: **Mar. 5, 2012**

(65) **Prior Publication Data**

US 2012/0216802 A1 Aug. 30, 2012

Related U.S. Application Data

(63) Continuation of application No. 12/790,196, filed on May 28, 2010, now Pat. No. 8,143,239, and a continuation of application No. 10/502,685, filed as application No. PCT/SE03/00156 on Jan. 29, 2003, now Pat. No. 7,759,328.

(30) **Foreign Application Priority Data**

Feb. 1, 2002 (SE) 0200312

(51) **Int. Cl.**
A01N 45/00 (2006.01)
A61K 31/335 (2006.01)

(52) **U.S. Cl.**
USPC **514/167**; 514/463

(58) **Field of Classification Search**
None
See application file for complete search history.

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Primary Examiner — Alton Pryor
(74) *Attorney, Agent, or Firm* — Fish & Richardson P.C.

(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.

53 Claims, 16 Drawing Sheets

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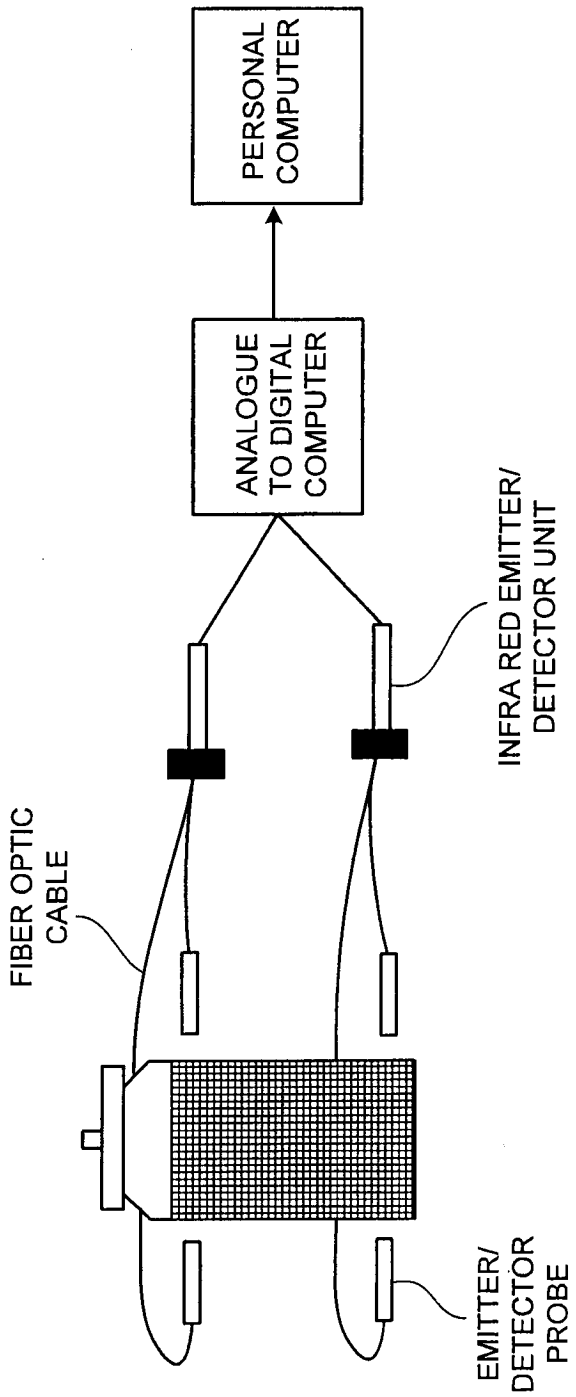


SCHEMATIC FOR OSCAR SET-UP

FIG. 1

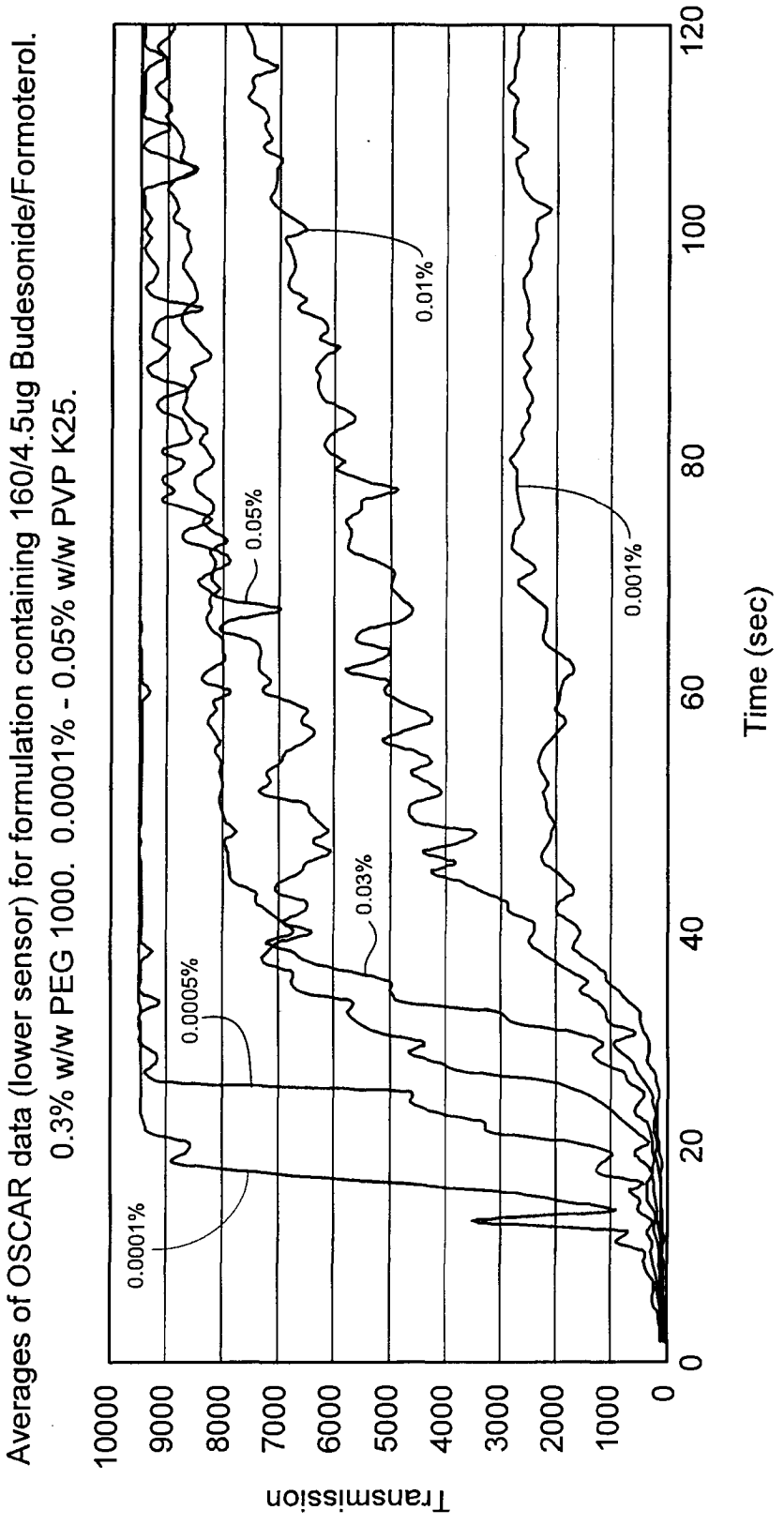


FIG. 2

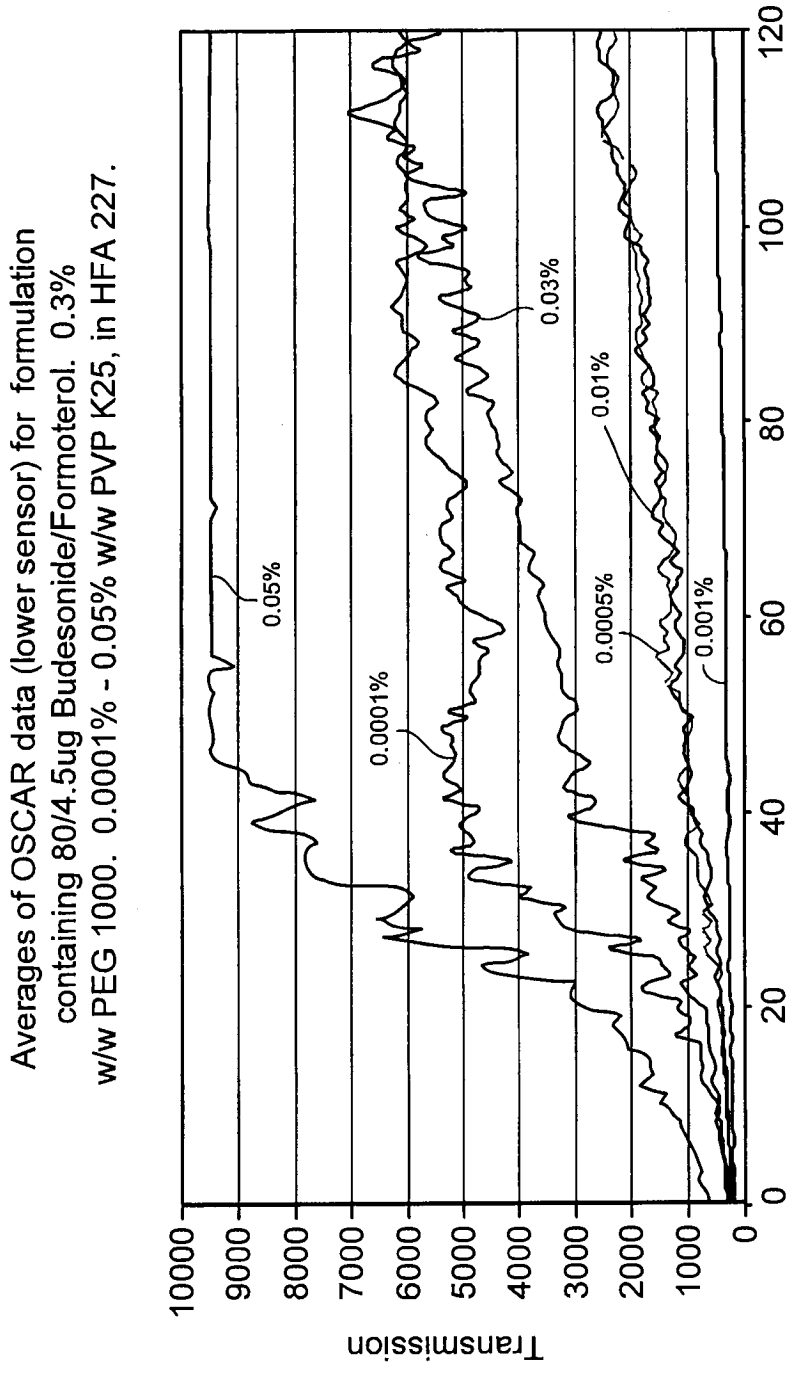


FIG. 3

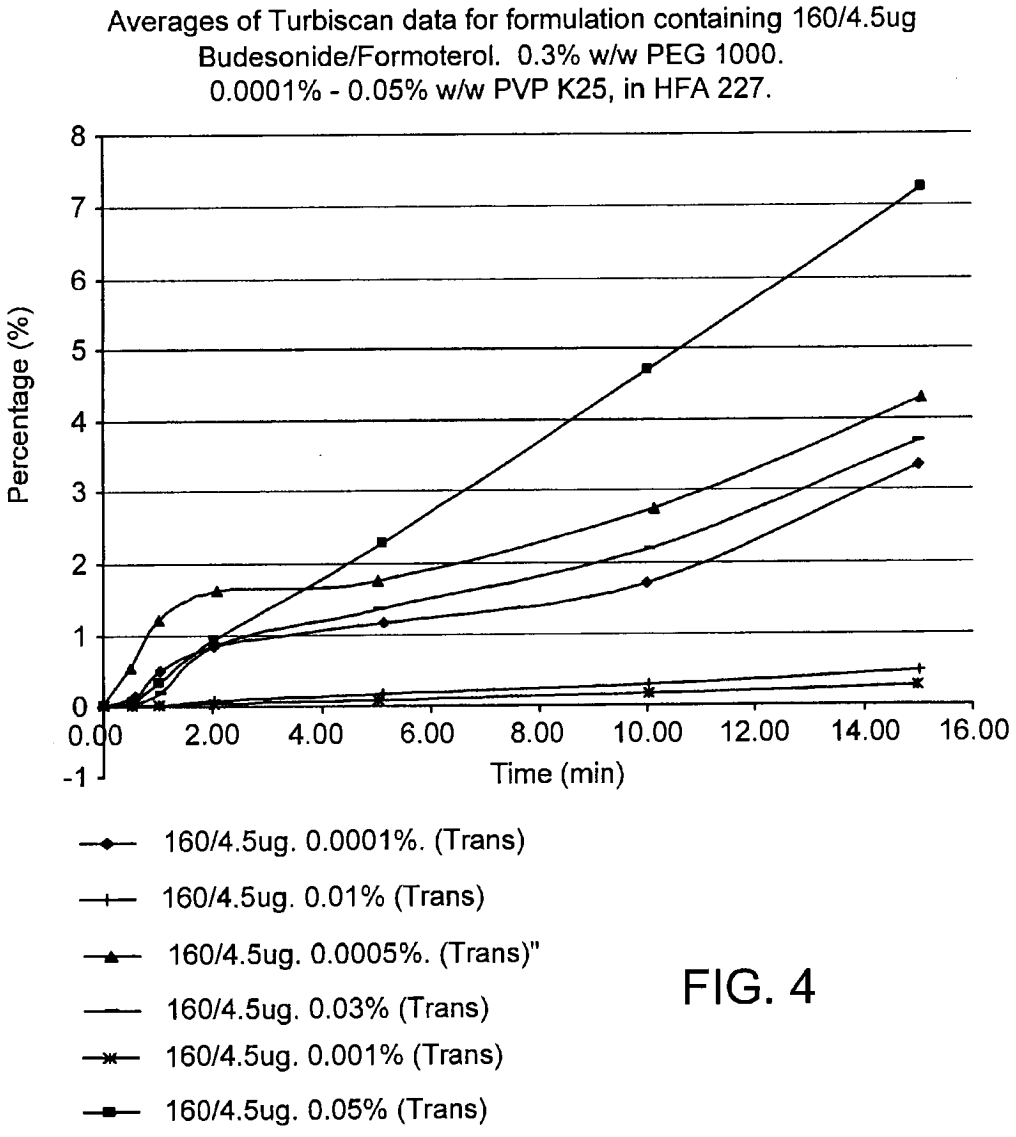


FIG. 4

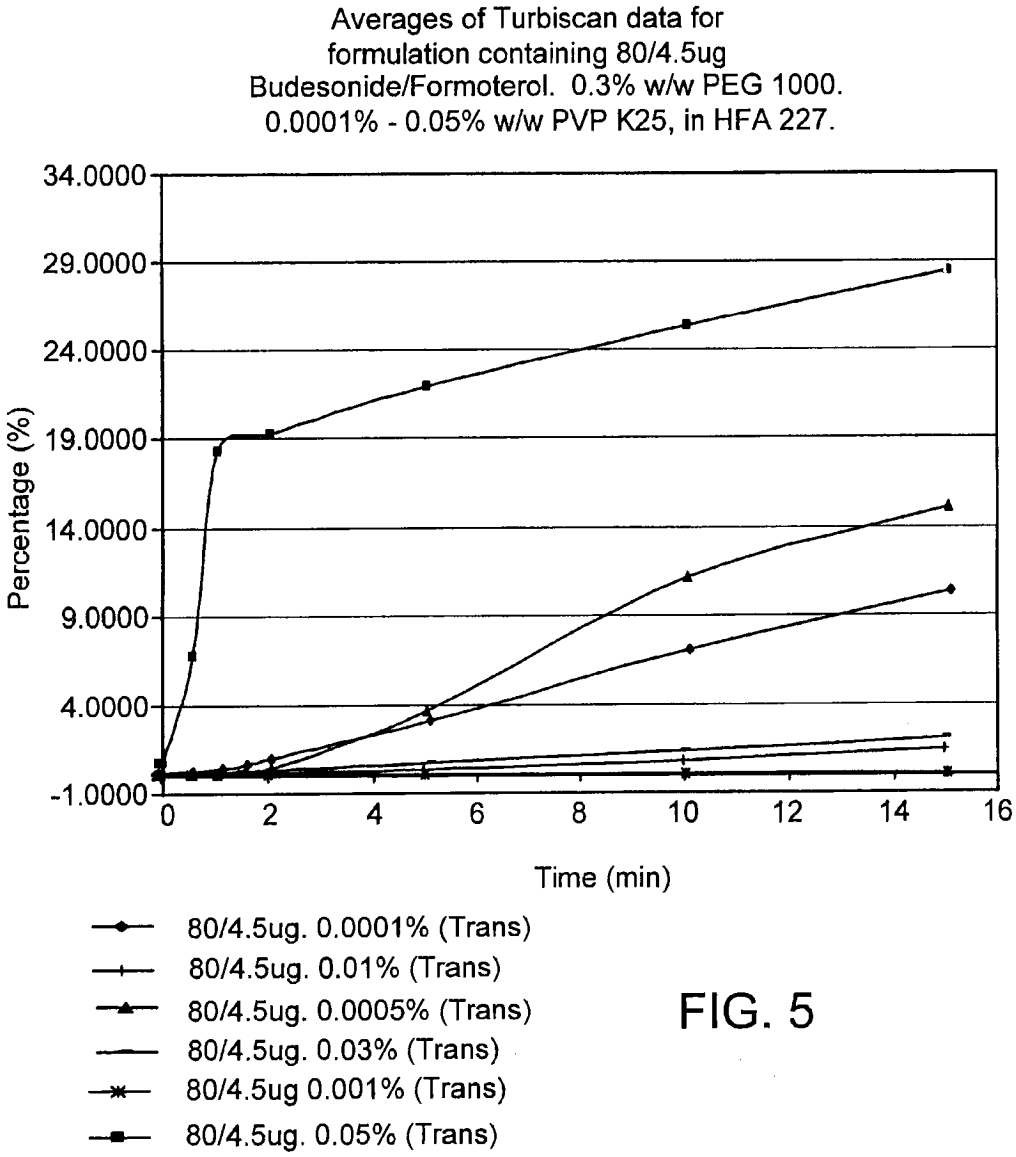


FIG. 5

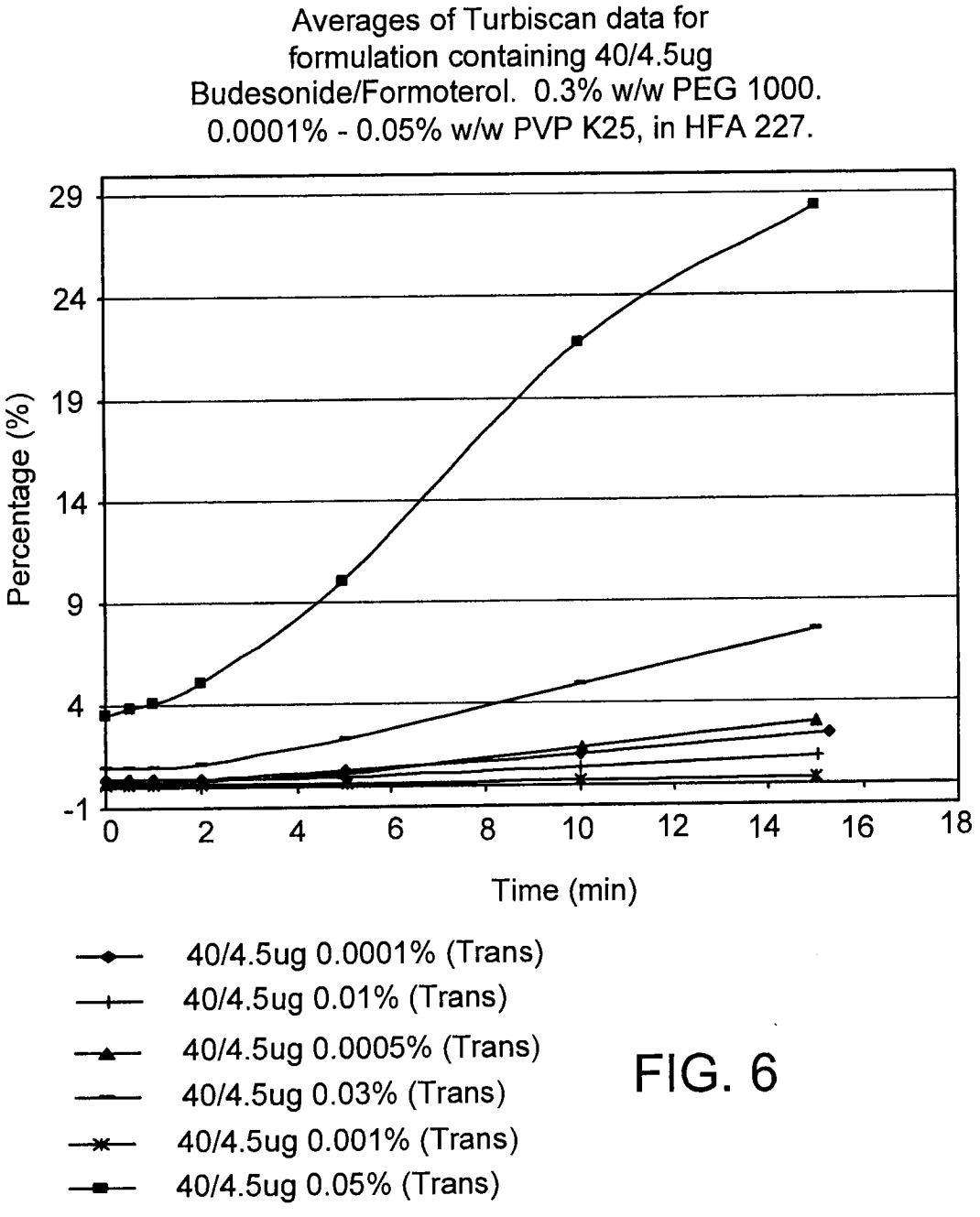


FIG. 6

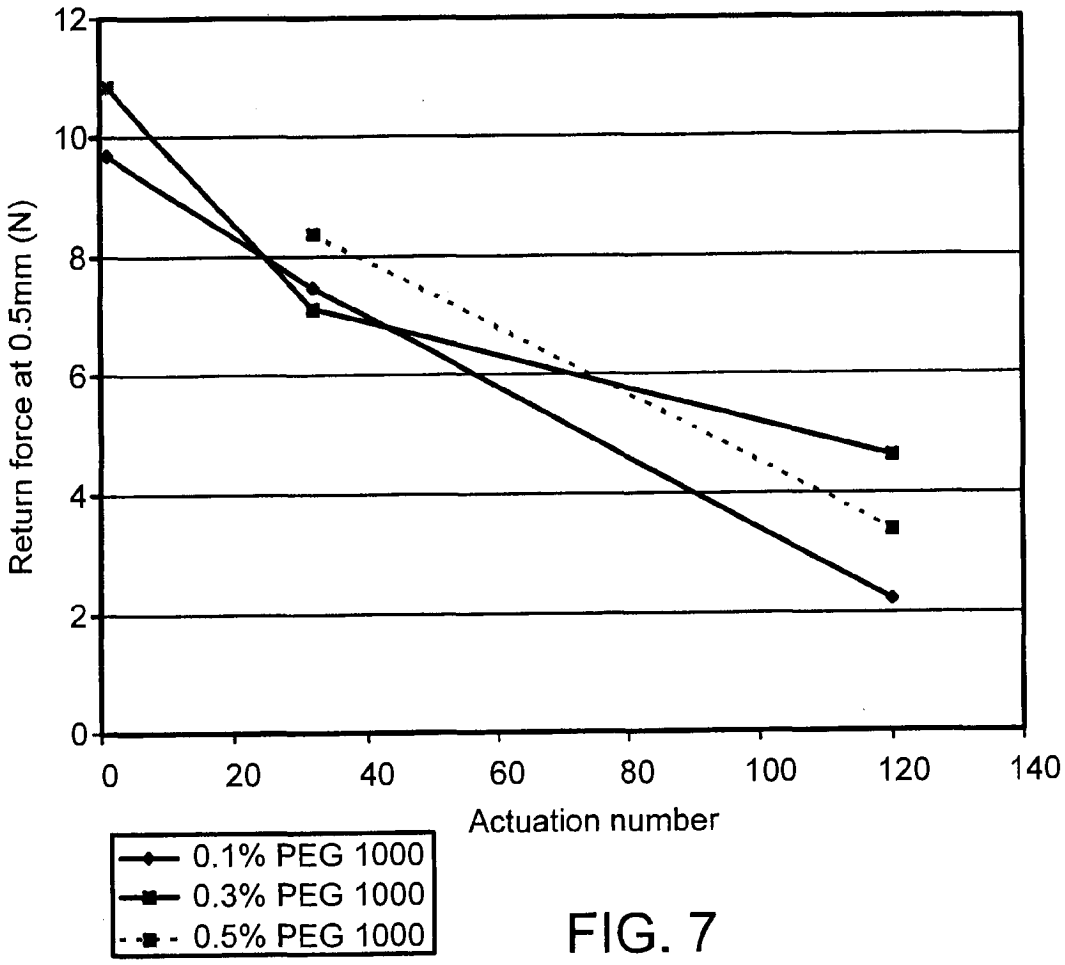


FIG. 7

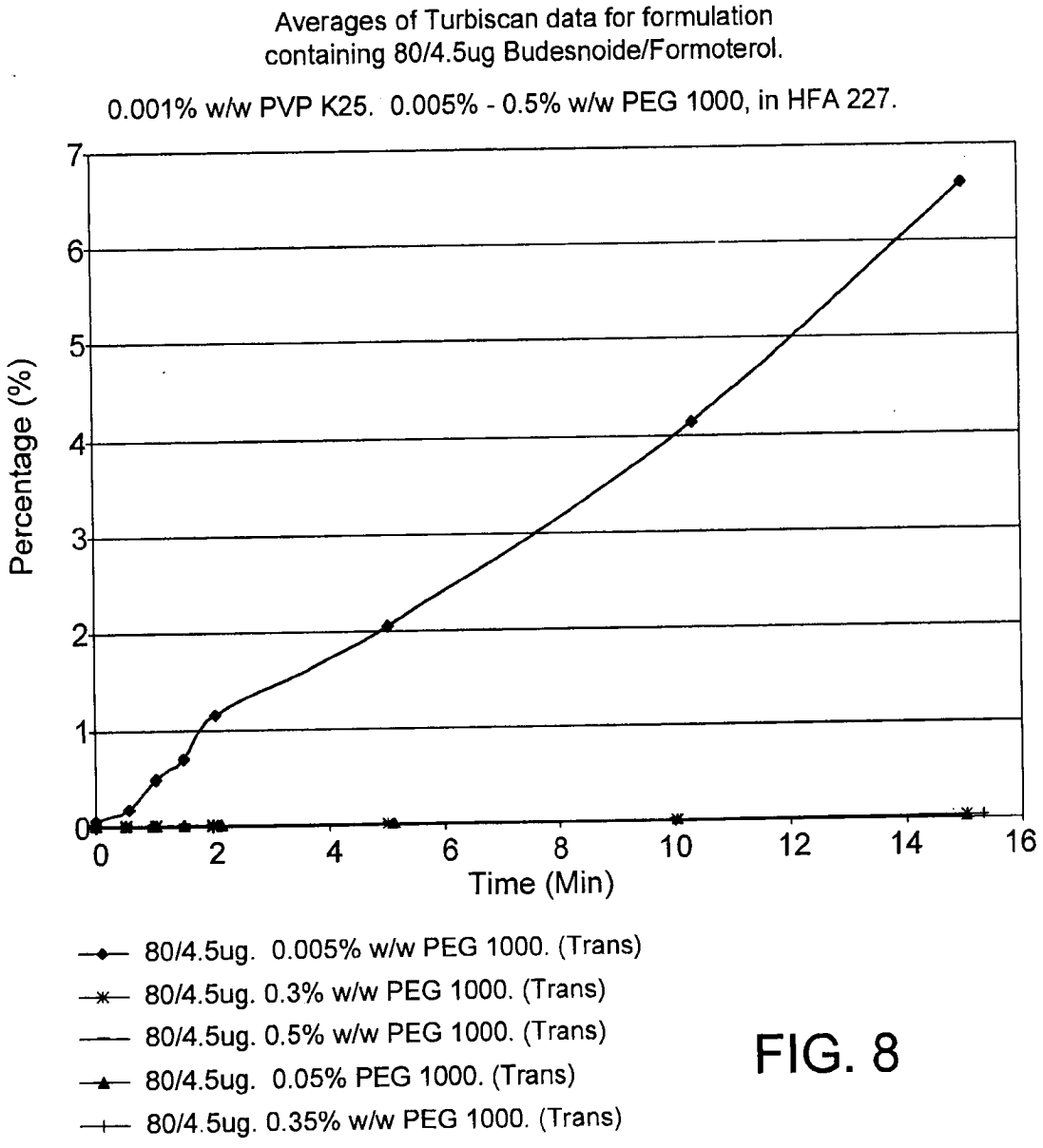


FIG. 8

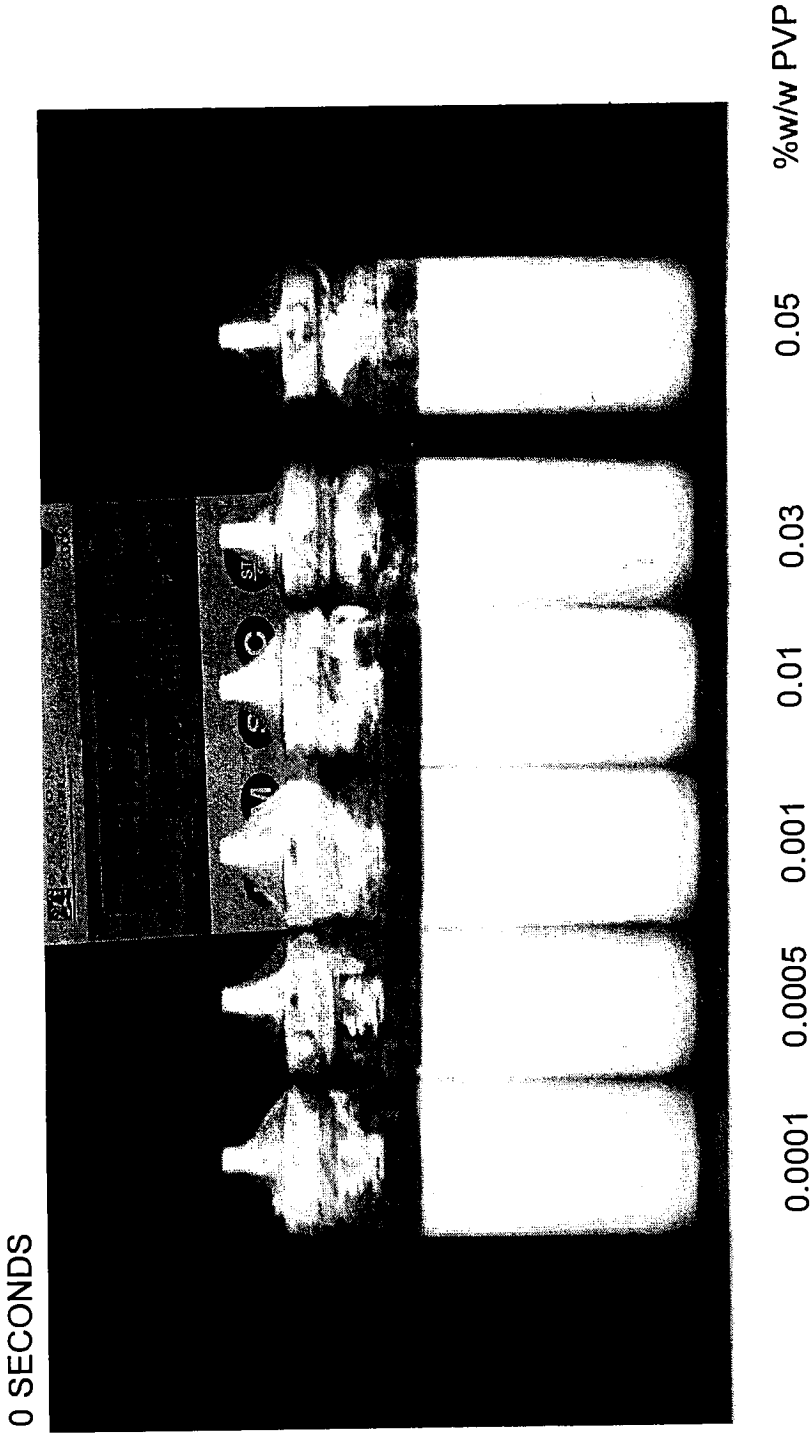


FIG. 9

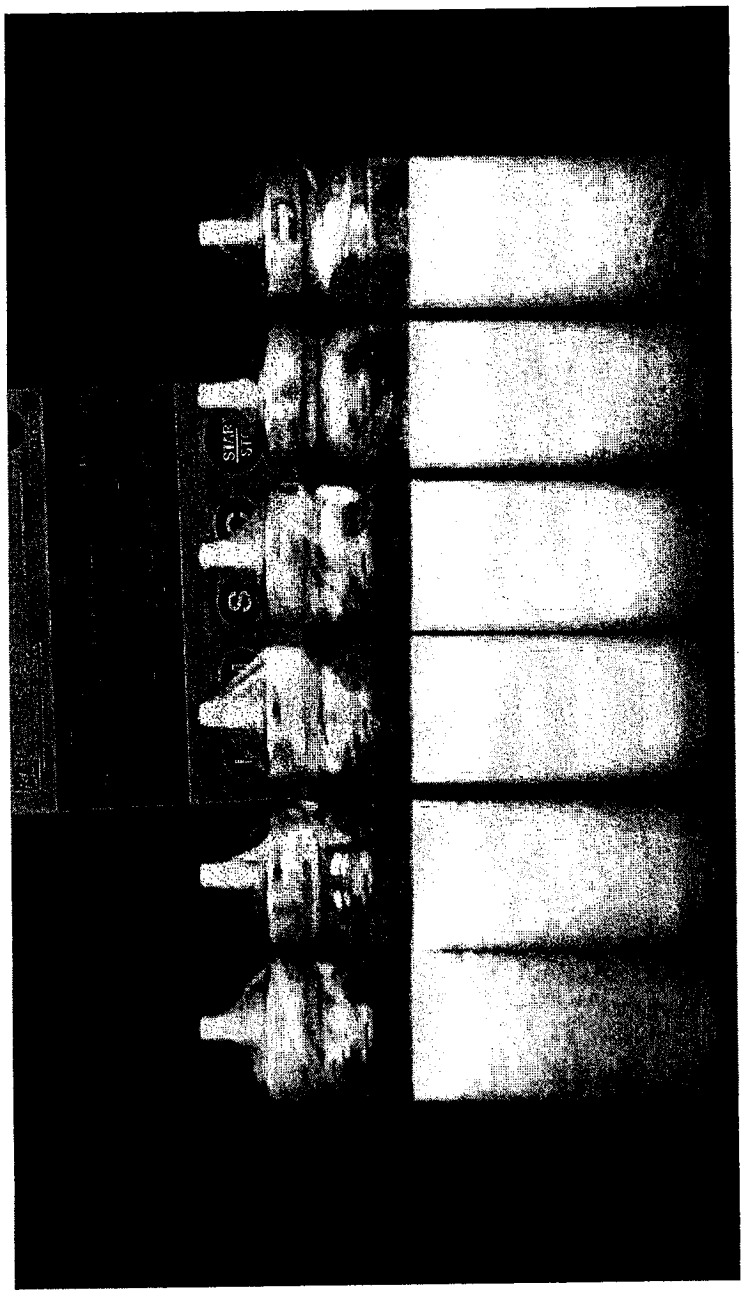


FIG. 10

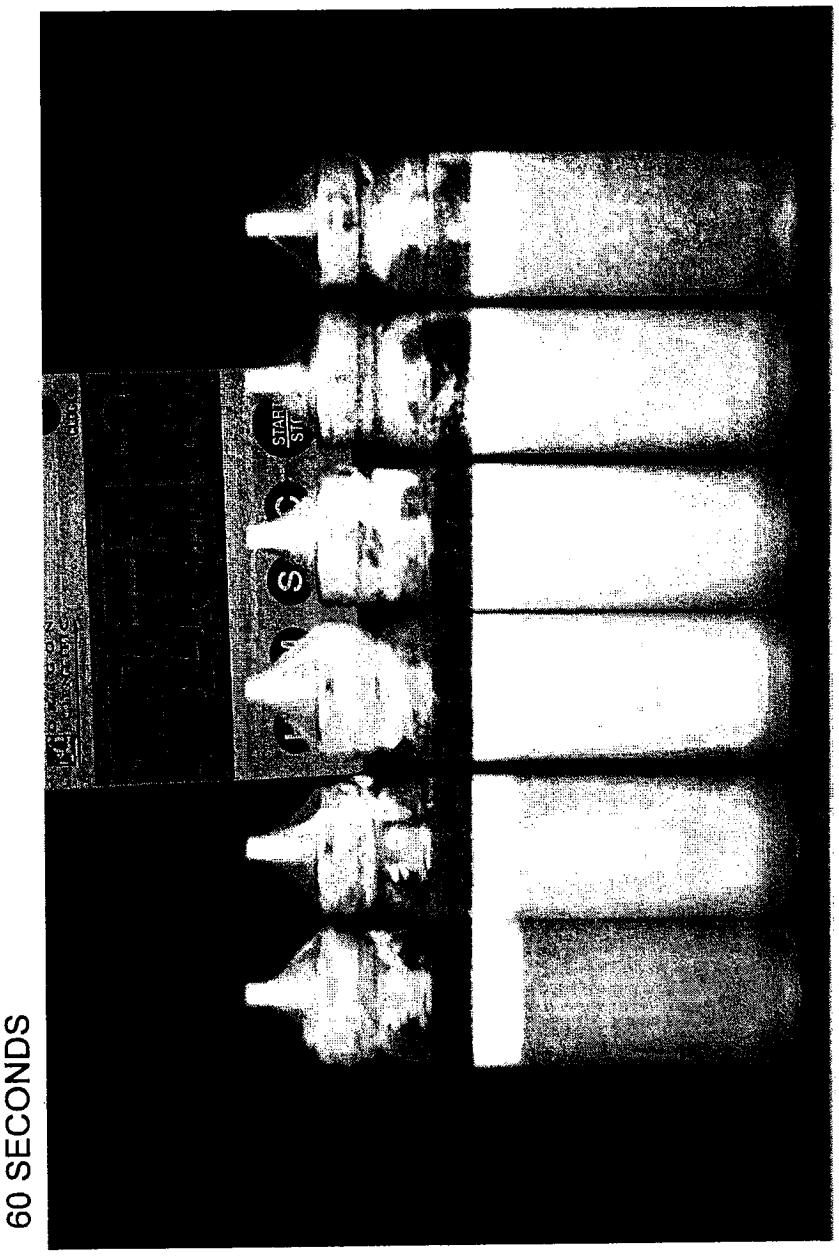


FIG. 11

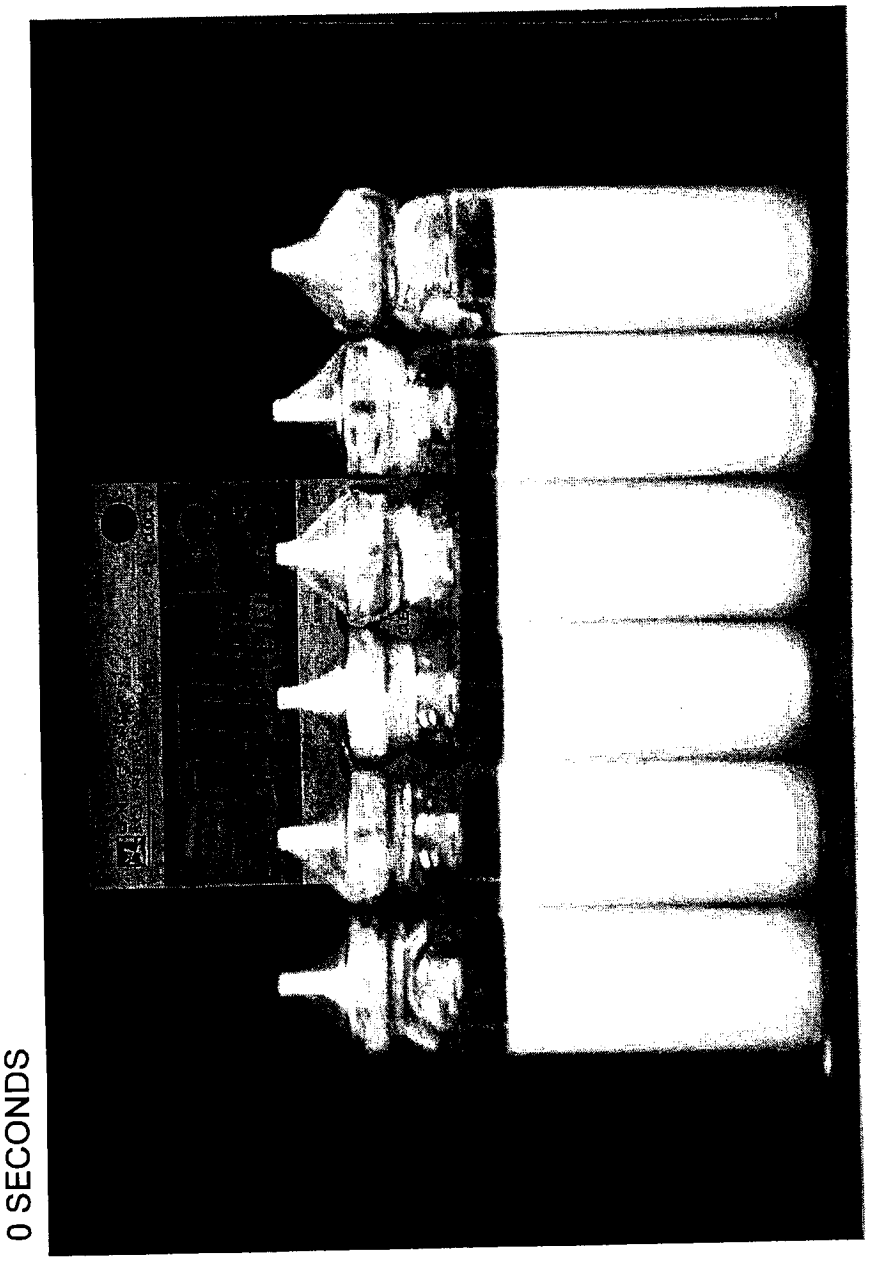


FIG. 12

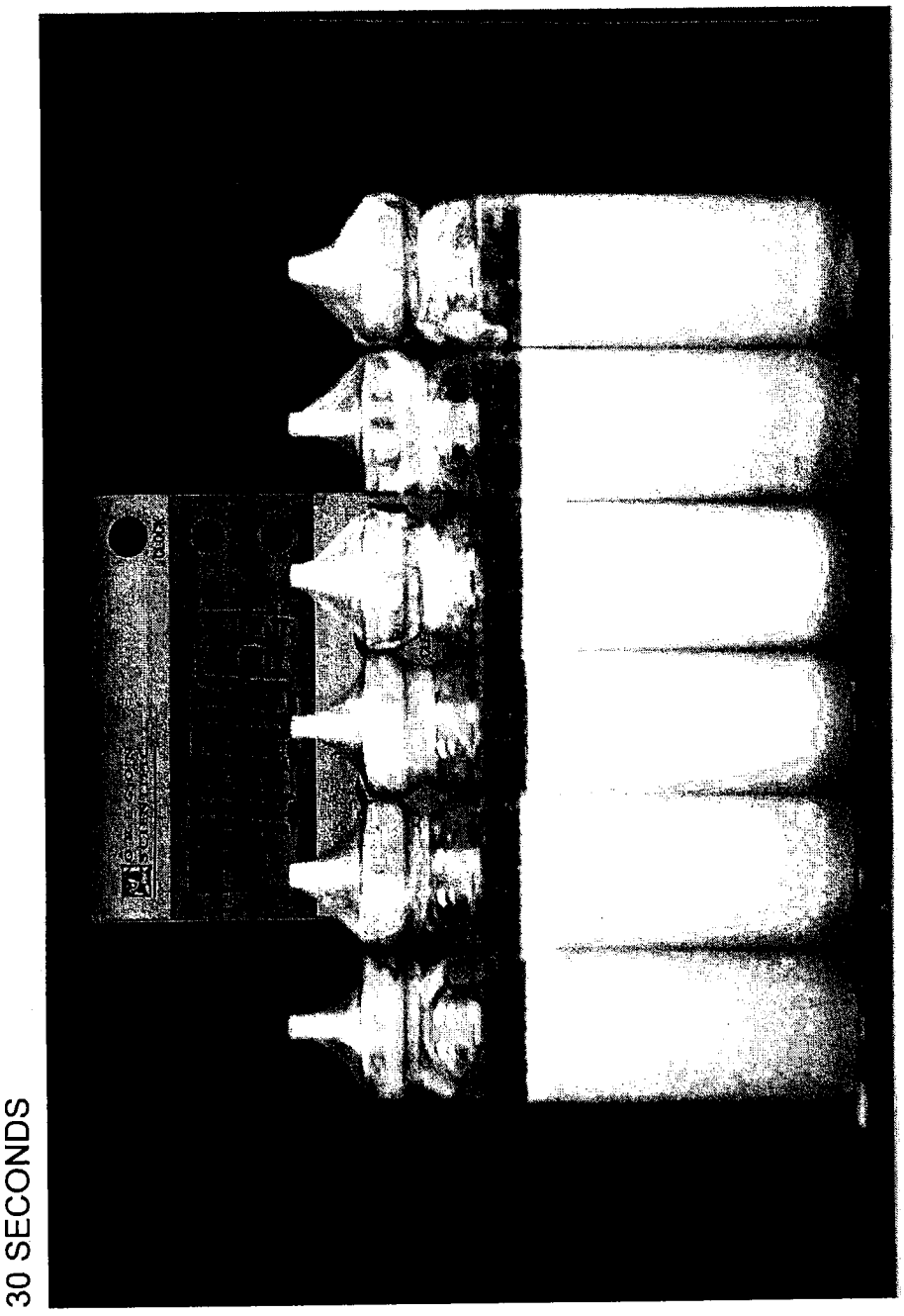


FIG.13

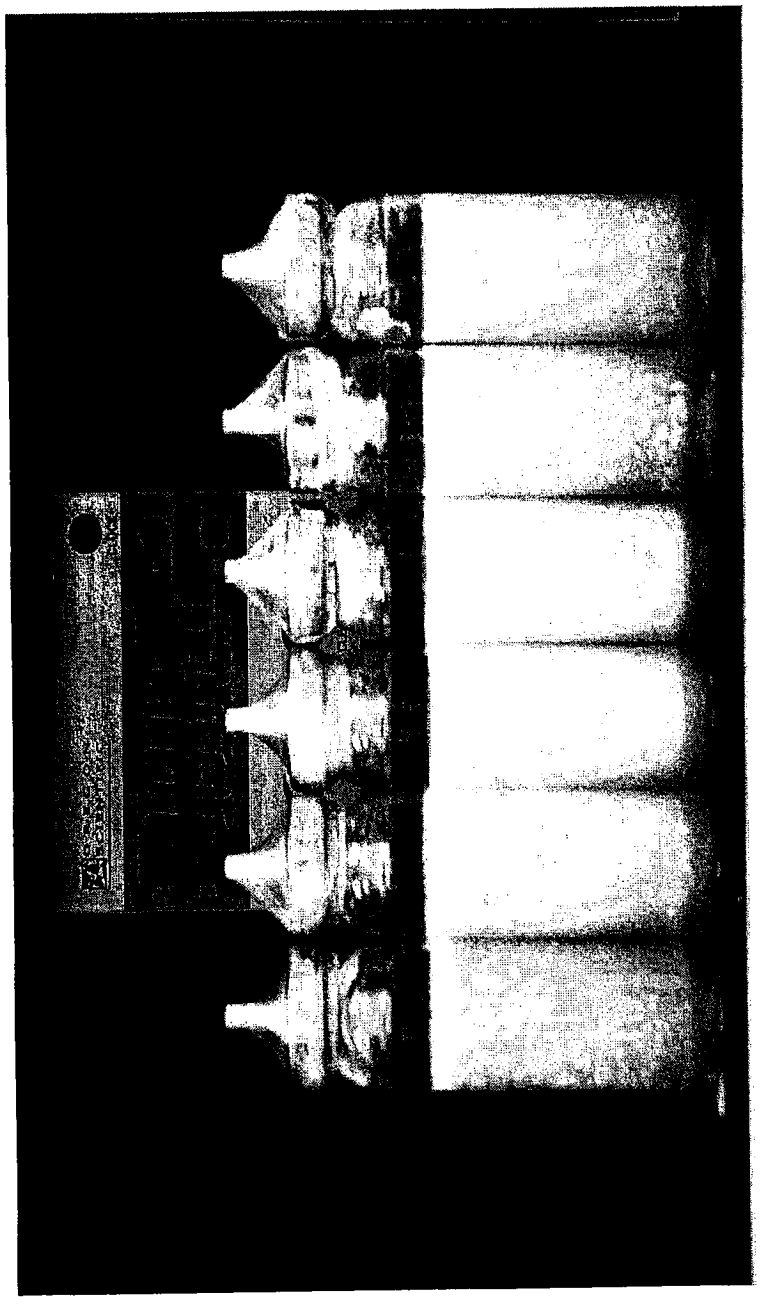
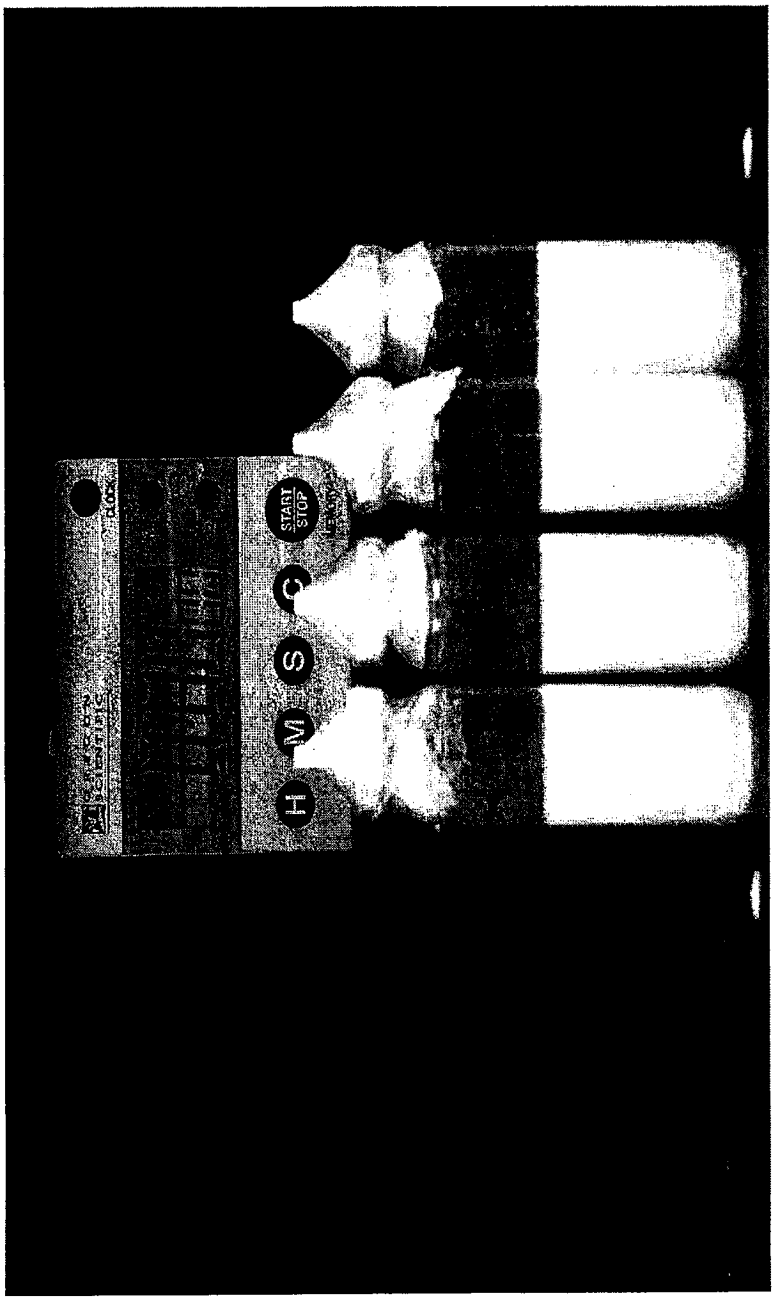


FIG. 14



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

FIG. 15

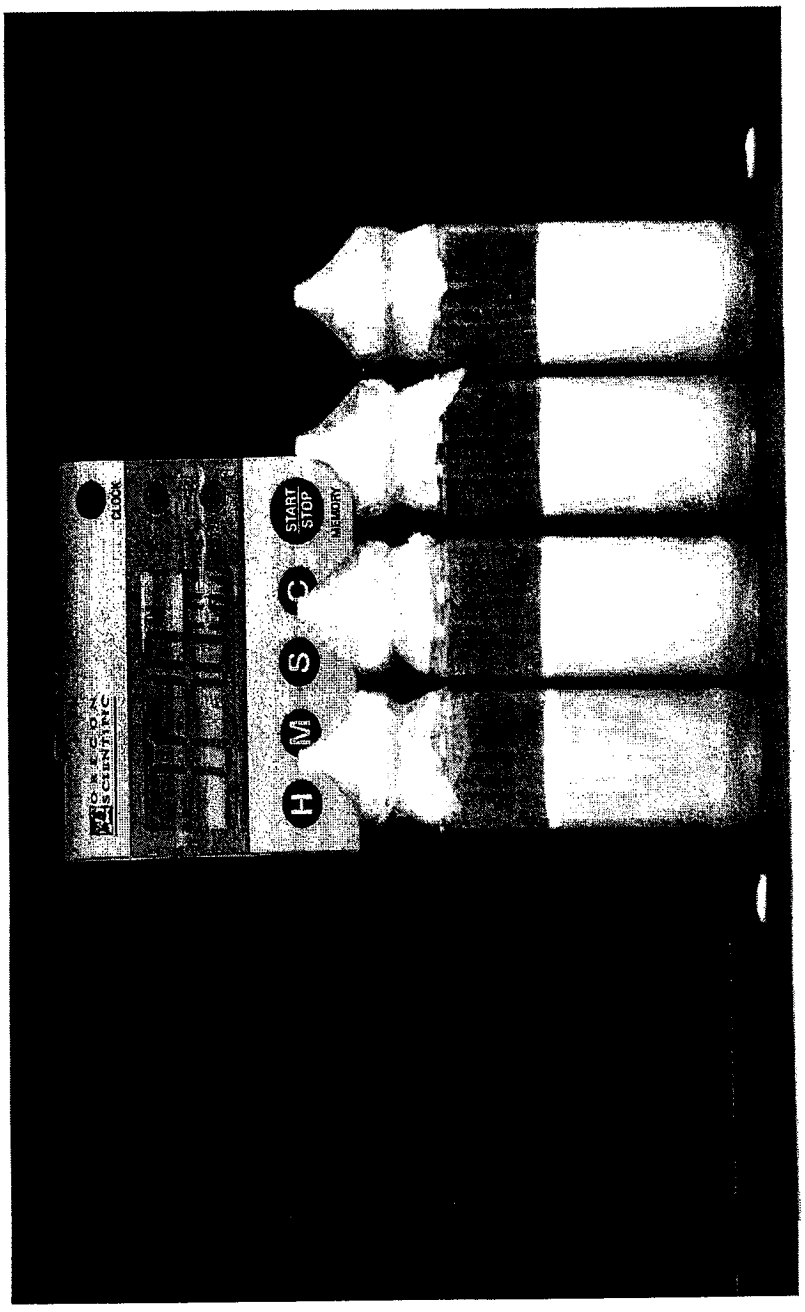


FIG. 16

COMPOSITION FOR INHALATION

CROSS-REFERENCE TO RELATED APPLICATIONS

This application is a continuation of U.S. application Ser. No. 12/790,196, filed May 28, 2010, which is a continuation of U.S. application Ser. No. 10/502,685, filed Jul. 27, 2004, now issued as U.S. Pat. No. 7,759,328, which is a national phase application under 35 U.S.C. §371 of PCT International Application No. PCT/SE2003/000156, filed Jan. 29, 2003, which claims priority to Swedish Application Serial No. 0200312-7, filed Feb. 1, 2002. The contents of these prior applications are incorporated herein by reference in their entirety.

TECHNICAL FIELD

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

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

In accordance with the present invention, there is provided a pharmaceutical composition comprising formoterol, budesonide, HFA 227 (1,1,1,2,3,3,3-heptafluoropropane), 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 (PVP having a nominal K-value of 25).

Preferably the PEG is present in an amount of 0.3% w/w. Preferably the PEG is PEG 1000 (PEG having an average molecular weight of 1000 Daltons).

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.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. **1** is a schematic drawing of an Optical Suspension Characterisation (OSCAR) set-up.

FIGS. **2-3** are graphs showing the averages of OSCAR data (lower sensor) for formulations in HFA 227 containing 4.5 μg formoterol; 0.3% w/w PEG 1000; 0.0001% -0.05% w/w PVP K25; and 160 μg budesonide (FIG. **2**) or 80 μg budesonide (FIG. **3**).

FIGS. **4-6** are graphs showing the averages of Turbiscan data for formulations in HFA 227 containing 4.5 μg formoterol; 0.3% w/w PEG 1000; 0.0001% -0.05% w/w PVP K25; and 160 μg budesonide (FIG. **4**), 80 μg budesonide (FIG. **5**), or 40 μg budesonide (FIG. **6**).

FIG. 7 is a graph showing the effect of PEG 1000 concentration on stem return force for formulations containing 4.5 μg formoterol; 160 μg budesonide; and 0.1%, 0.3%, or 0.5% w/w PEG 1000.

FIG. **8** is a graph showing the averages of Turbiscan data for formulations in HFA 227 containing 80 μg budesonide; 4.5 μg formoterol; 0.0001% PVP K25; and 0.005% - 0.5% w/w PEG 1000.

FIGS. **9-11** are a series of digital photographs, taken after standing times of 0 seconds (FIG. **9**), 30 seconds (FIG. **10**), and 60 seconds (FIG. **11**), of suspensions in HFA 227 containing budesonide (160 μg/actuation); formoterol (4.5 μg/actuation); 0.3% PEG 1000; and PVP K25 at 0.0001%, 0.0005%, 0.001%, 0.01%, 0.03%, and 0.05% w/w.

FIGS. **12-14** are a series of digital photographs, taken after standing times of 0 seconds (FIG. **12**), 30 seconds (FIG. **13**), and 60 seconds (FIG. **14**), of suspensions in HFA 227 containing budesonide (80 μg/actuation); formoterol (4.5 μg/actuation); 0.3% PEG 1000; and PVP K25 at 0.0001%, 0.0005%, 0.001%, 0.01%, 0.03%, and 0.05% w/w.

FIGS. **15-16** are digital photographs, taken after standing times of 0 minutes (FIG. **15**) and 10 minutes (FIG. **16**), of suspensions in HFA 227 containing budesonide (80 μg/actuation); formoterol (4.5 μg/actuation); 0.001% PVP K25; and PEG 1000 at 0.005, 0.05, 0.35, and 0.5% w/w.

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 FIG. 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, P A 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, 5 ml 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 homogeneity, 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 sedimentation rate of different suspensions.

Turbiscan may be used in several modes, e.g., transmitted or backscattering modes. Turbiscan has been used here in these examples to measure the transmitted light as a function 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; and b) particle migration resulting in creaming or sedimentation. When a product is stable (i.e., 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 terephthalate (PET) bottles crimped with a continuous valve. For all formulations, the formoterol fumarate dihydrate concentration remained constant at 0.09 mg/ml (equivalent to 4.5 mcg formoterol fumarate dihydrate per actuation) and the budesonide concentration varied between approximately 1 mg/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 tech-

niques 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

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

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

Table of Degree of Dispersion of Suspensions Over Time: (All Samples)

Photographs were taken of all doses (320 μg/4.5 μg to 40 μg/4.5 μg) 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 representation of the degree of dispersion over time.

If the sample was fully suspended, the sample was rated 0, i.e., 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 4.5 μg/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, i.e., less than 20% clear liquid present 1

More than 60% dispersed, i.e., less than 40% clear liquid present 2

Less than 40% dispersed, i.e., more than 60% clear liquid present 3

Less than 20% dispersed, i.e., more than 80% clear liquid present 4

Fully creamed 5

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

Dose μg/shot	Time	PVP concentration (% w/w)					
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

-continued

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

Dose μg/shot	Time	PVP concentration (% w/w)					
Budesonide	Sec/mins	0.0001	0.0005	0.001	0.01	0.03	0.05
	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)

FIG. **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 FIG. **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 interpreted 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 FIG. **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

FIGS. **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.

METHODOLOGY—Force to Fire (Return Force at 0.5 mm 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

FIG. **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 (FIG. **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).

FIGS. **15** and **16** show Budesonide 80 μg/shot, Formoterol 4.5 μg/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 fumarate 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)	Drug	Fine particle fraction (% cumulative undersize for 4.7 μm cut-off) 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)	Drug	Fine particle fraction (% cumulative undersize for 4.7 μm cut-off) 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

The invention claimed is:

1. A pharmaceutical suspension composition comprising formoterol fumarate dihydrate; budesonide; 1,1,1,2,3,3,3-heptafluoropropane (HFA227); polyvinyl pyrrolidone (PVP); and polyethylene glycol (PEG), wherein the budesonide is present in the composition at a concentration in the range of 1 mg/ml to 8 mg/ml, the PVP is present at a concentration in the range of 0.001% to 0.01% w/w, and the PEG is present at a concentration in the range of 0.05 to 0.5% w/w.

2. The pharmaceutical suspension composition of claim **1**, wherein the PEG is PEG 1000 (PEG with an average molecular weight of 1,000).

3. The pharmaceutical suspension composition of claim **1**, wherein the PVP is PVP K25 (PVP with a nominal K-value of 25).

4. The pharmaceutical suspension composition of claim **1**, wherein the PVP is present in the composition at a concentration of 0.001% w/w.

5. The pharmaceutical suspension composition of claim **4**, wherein the PVP is PVP K25.

6. The pharmaceutical suspension composition of claim **5**, wherein the PEG is PEG 1000.

7. The pharmaceutical suspension composition of claim **1**, wherein the budesonide is in the form of its 22R-epimer.

8. The pharmaceutical suspension composition of claim **1**, wherein the formoterol fumarate dihydrate is in the form of its R,R enantiomer.

9. A pharmaceutical suspension composition comprising formoterol fumarate dihydrate, budesonide, HFA227, PVP K25, and PEG-1000, wherein the budesonide is present at a concentration in the range of 1 mg/ml to 8 mg/ml and the PVP K25 is present at a concentration of 0.001% w/w.

10. The pharmaceutical suspension composition of claim **9**, wherein the PEG-1000 is present at a concentration of 0.3% w/w.

11. The pharmaceutical suspension composition of claim **9**, wherein the budesonide is in the form of its 22R-epimer.

12. The pharmaceutical suspension composition of claim **9**, wherein the formoterol fumarate dihydrate is in the form of its R,R enantiomer.

13. A method of treating a respiratory disorder, the method comprising administering the pharmaceutical suspension composition of claim **1** to a patient identified as in need of treatment with the composition.

14. The method of claim **13**, wherein the patient is suffering from asthma.

15. The method of claim **13**, wherein the patient is suffering from chronic obstructive pulmonary disease (COPD).

16. A method of treating a respiratory disorder, the method comprising administering the pharmaceutical suspension composition of claim **9** to a patient identified as in need of treatment with the composition.

17. The method of claim 16, wherein the patient is suffering from asthma.

18. The method of claim 16, wherein the patient is suffering from COPD.

19. A method of treating a respiratory disorder, the method comprising administering the pharmaceutical suspension composition of claim 10 to a patient identified as in need of treatment with the composition.

20. The method of claim 19, wherein the patient is suffering from asthma.

21. The method of claim 19, wherein the patient is suffering from COPD.

22. A pressurized metered dose inhaler containing the pharmaceutical suspension composition of claim 1.

23. The inhaler of claim 22, wherein the PEG is PEG 1000.

24. The inhaler of claim 22, wherein the PVP is PVP K25.

25. The inhaler of claim 22, wherein the PVP is present in the composition at a concentration of 0.001% w/w.

26. The inhaler of claim 25, wherein the PVP is PVP K25.

27. The inhaler of claim 26, wherein the PEG is PEG 1000.

28. A pressurized metered dose inhaler containing the pharmaceutical suspension composition of claim 9.

29. A pressurized metered dose inhaler containing the pharmaceutical suspension composition of claim 10.

30. A method of treating a respiratory disorder, the method comprising

providing the inhaler of claim 22 to a patient in identified need thereof; and

causing the patient to inhale the composition from the inhaler.

31. The method of claim 30, wherein the patient is suffering from asthma.

32. The method of claim 30, wherein the patient is suffering from COPD.

33. A method of treating a respiratory disorder, the method comprising

providing the inhaler of claim 22; and

instructing a patient in need thereof to inhale the composition from the inhaler.

34. The method of claim 33, wherein the patient is suffering from asthma.

35. The method of claim 33, wherein the patient is suffering from COPD.

36. A method of treating a respiratory disorder, the method comprising

providing the inhaler of claim 26 to a patient in identified need thereof; and

causing the patient to inhale the composition from the inhaler.

37. The method of claim 36, wherein the patient is suffering from asthma.

38. The method of claim 36, wherein the patient is suffering from COPD.

39. A method of treating a respiratory disorder, the method comprising

providing the inhaler of claim 26; and

instructing a patient in need thereof to inhale the composition from the inhaler.

40. The method of claim 39, wherein the patient is suffering from asthma.

41. The method of claim 39, wherein the patient is suffering from COPD.

42. A method of treating a respiratory disorder, the method comprising

providing the inhaler of claim 28 to a patient in identified need thereof; and

causing the patient to inhale the composition from the inhaler.

43. The method of claim 42, wherein the patient is suffering from asthma.

44. The method of claim 42, wherein the patient is suffering from COPD.

45. A method treating a respiratory disorder, the method comprising

providing the inhaler of claim 28; and

instructing a patient in need thereof to inhale the composition from the inhaler.

46. The method of claim 45, wherein the patient is suffering from asthma.

47. The method of claim 45, wherein the patient is suffering from COPD.

48. A method of treating a respiratory disorder, the method comprising

providing the inhaler of claim 29 to a patient in identified need thereof; and

causing the patient to inhale the composition from the inhaler.

49. The method of claim 48, wherein the patient is suffering from asthma.

50. The method of claim 48, wherein the patient is suffering from COPD.

51. A method treating a respiratory disorder, the method comprising

providing the inhaler of claim 29; and

instructing a patient in need thereof to inhale the composition from the inhaler.

52. The method of claim 51, wherein the patient is suffering from asthma.

53. The method of claim 51, wherein the patient is suffering from COPD.

* * * * *

US007759328B2

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

(10) **Patent No.: US 7,759,328 B2**
(45) **Date of Patent: Jul. 20, 2010**

(54) **COMPOSITION FOR INHALATION**

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(73) Assignee: **AstraZeneca AB**, Sodertalje (SE)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

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PCT Pub. Date: **Aug. 7, 2003**

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(30) **Foreign Application Priority Data**

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(51) **Int. Cl.**
A01N 45/00 (2006.01)
A61K 31/335 (2006.01)

(52) **U.S. Cl.** **514/167**; 514/463

(58) **Field of Classification Search** 424/45, 424/46, 489, 48

See application file for complete search history.

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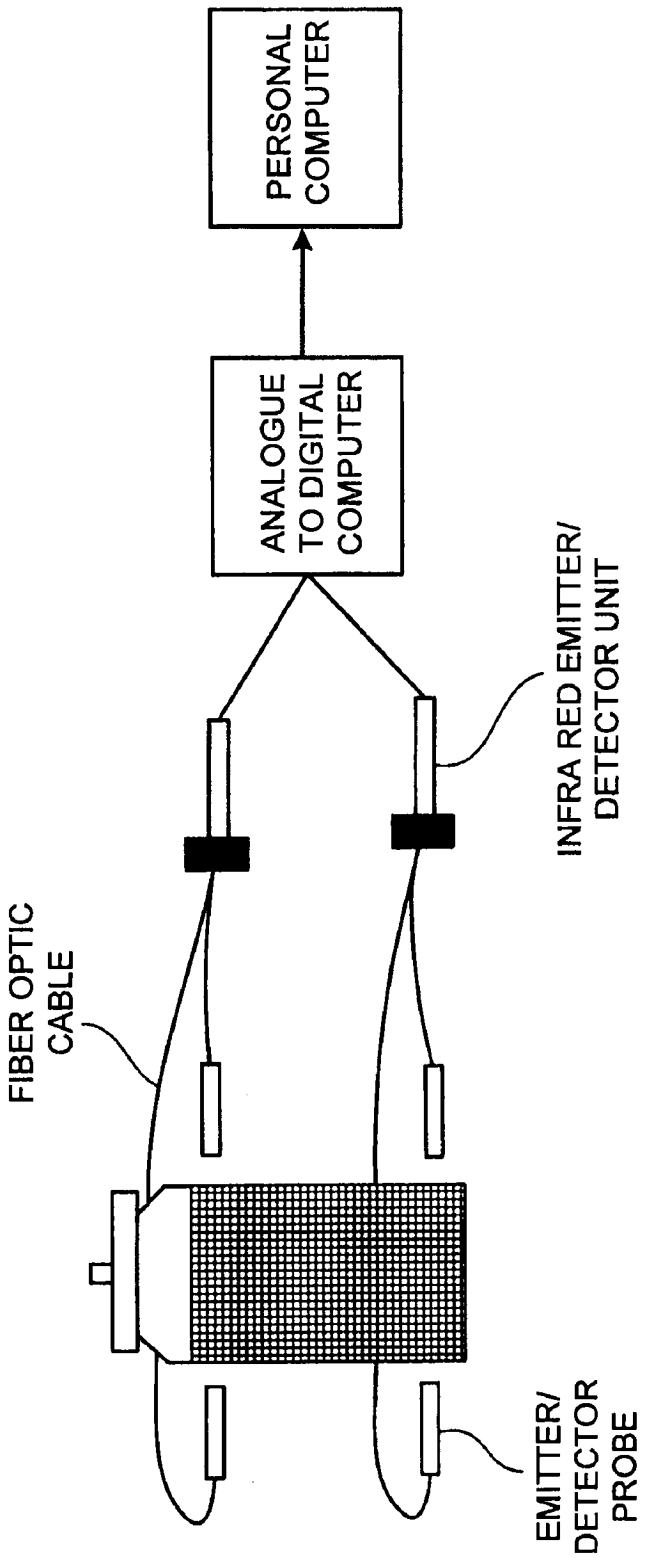
Primary Examiner—Alton N Pryor
(74) *Attorney, Agent, or Firm*—Fish & Richardson P.C.

(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.

15 Claims, 16 Drawing Sheets



SCHEMATIC FOR OSCAR SET-UP

FIG. 1

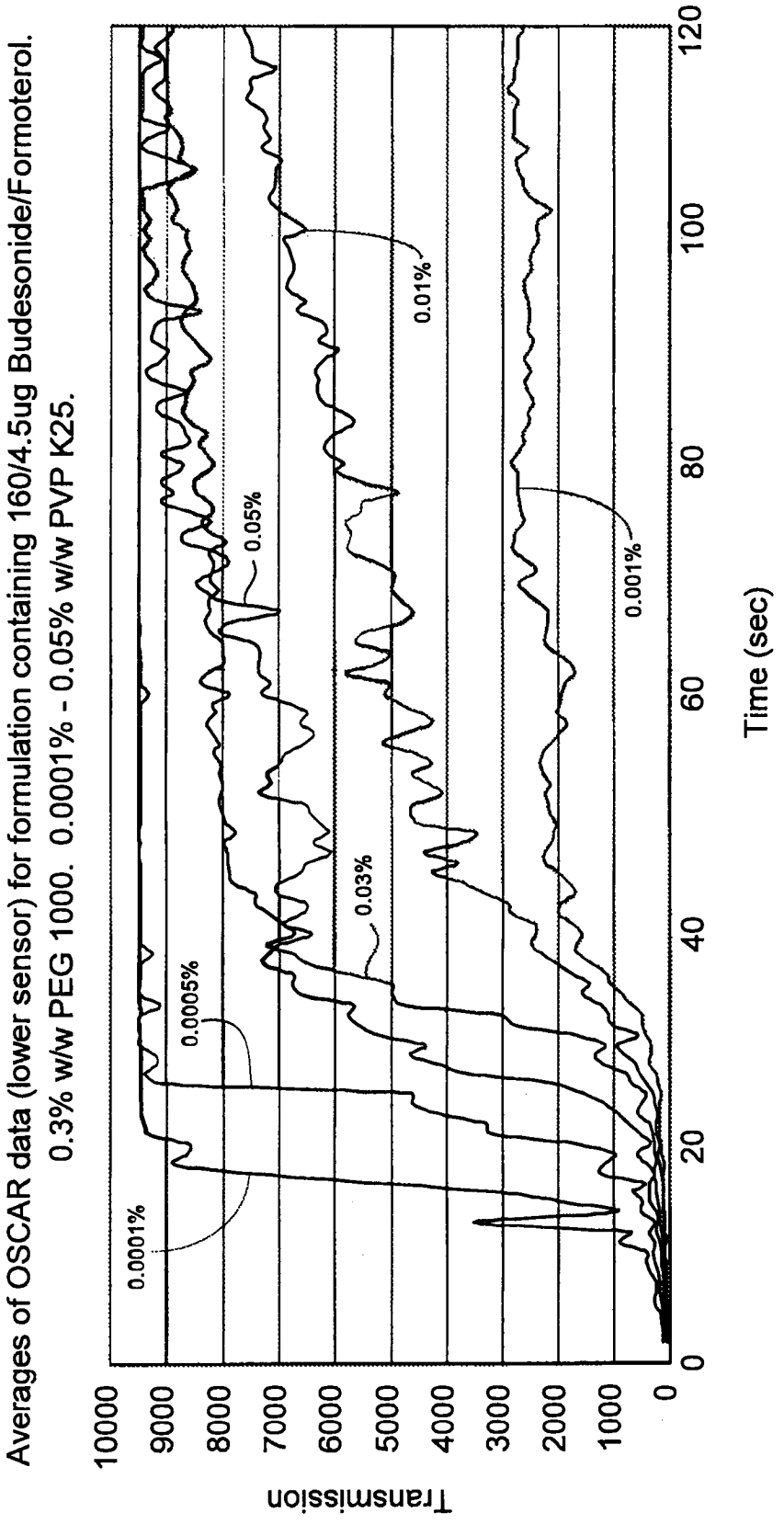


FIG. 2

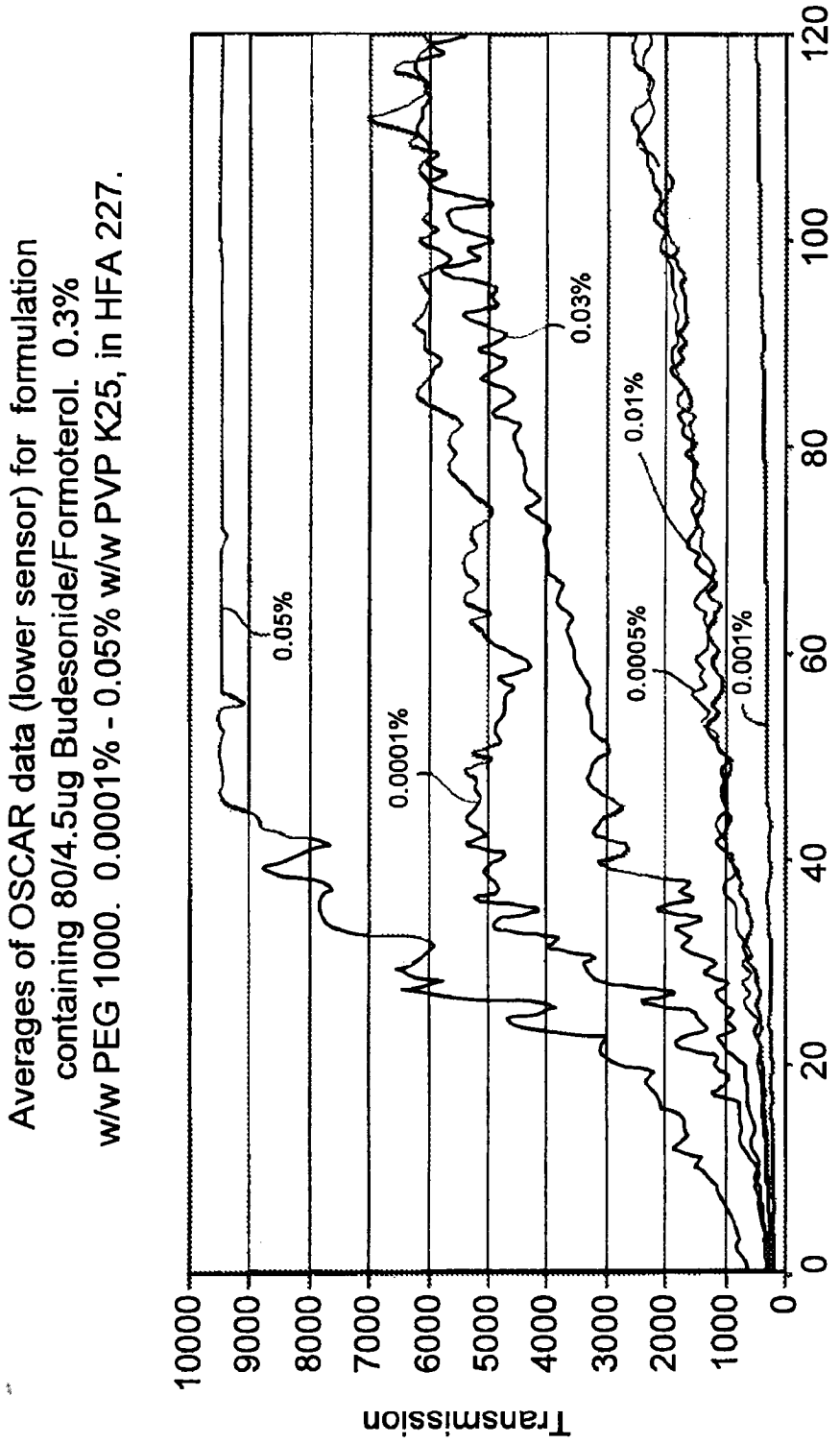


FIG. 3

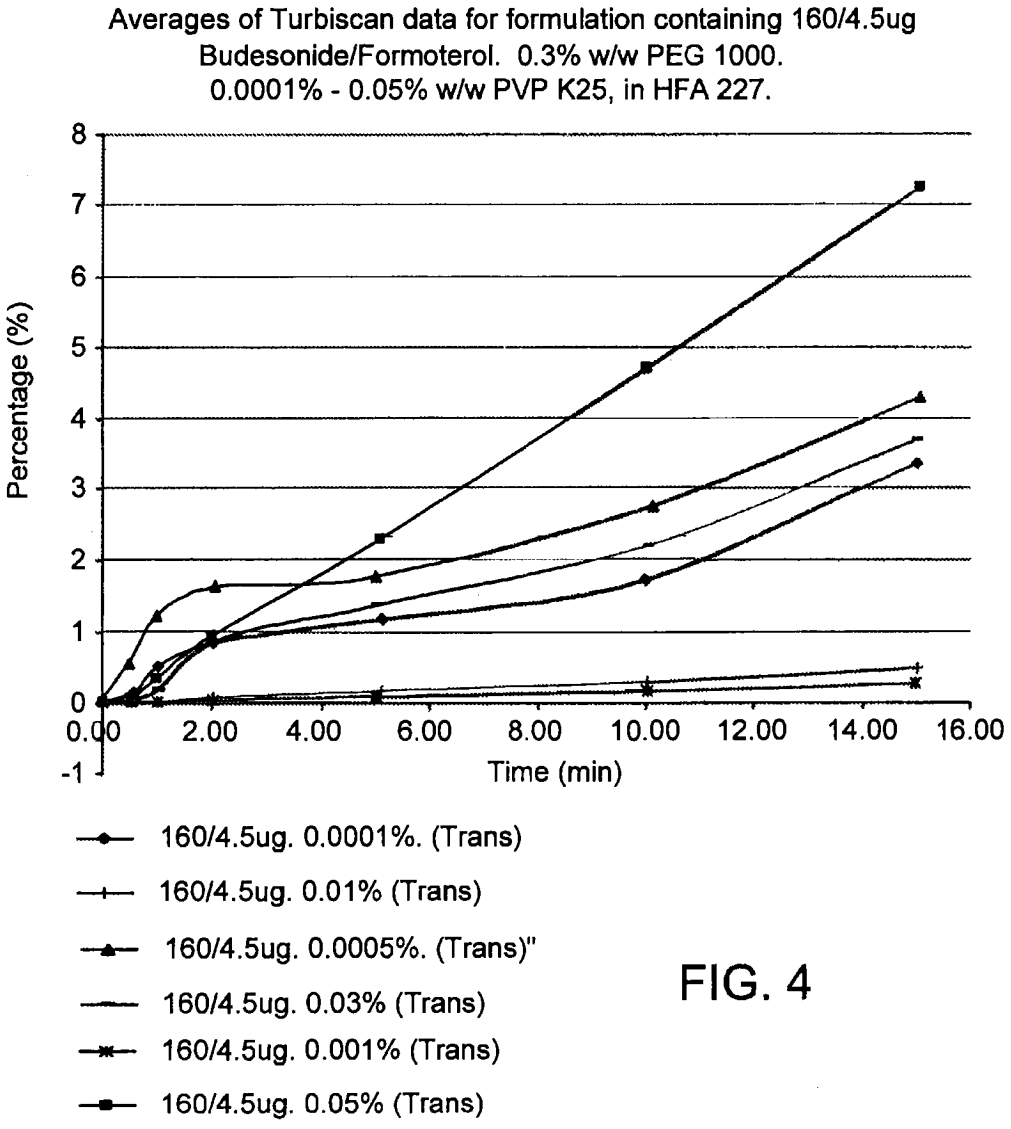


FIG. 4

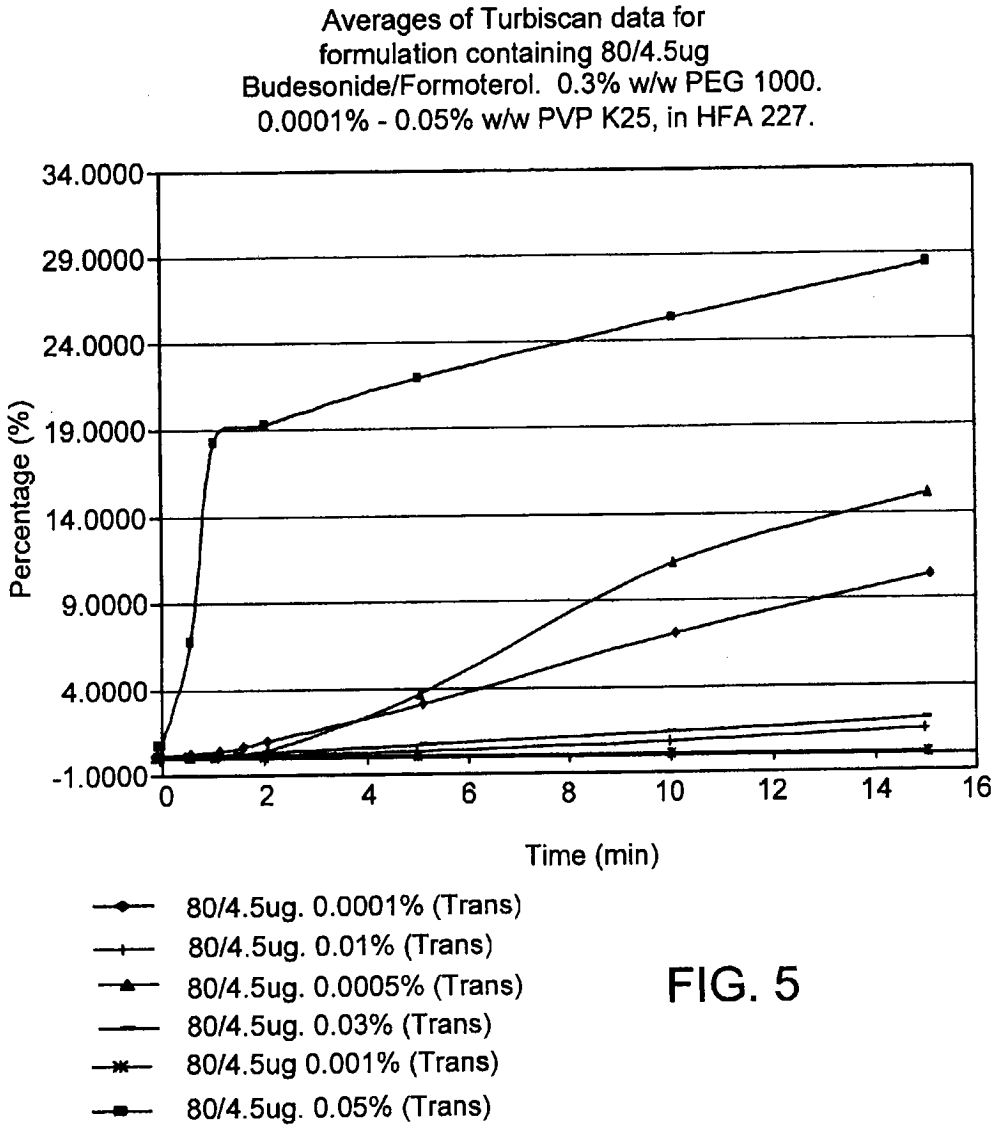


FIG. 5

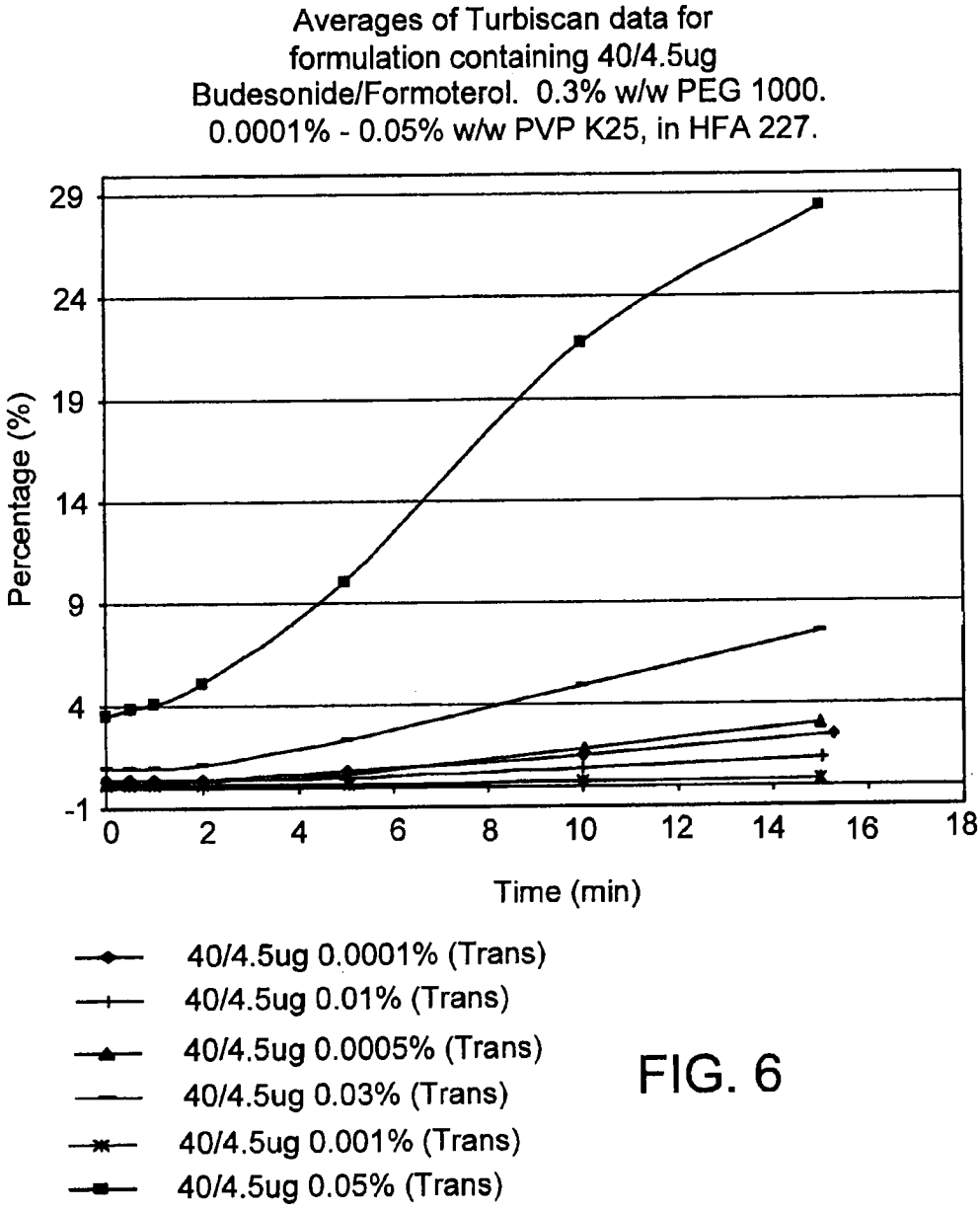


FIG. 6

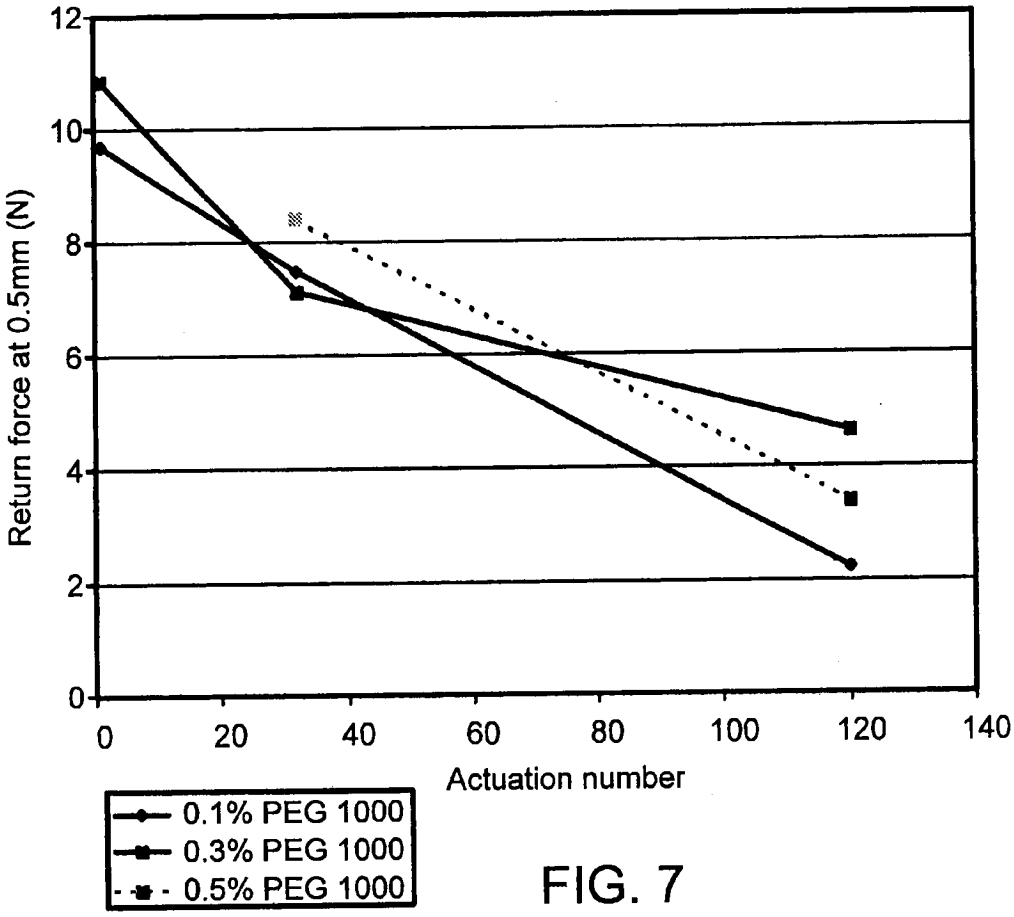


FIG. 7

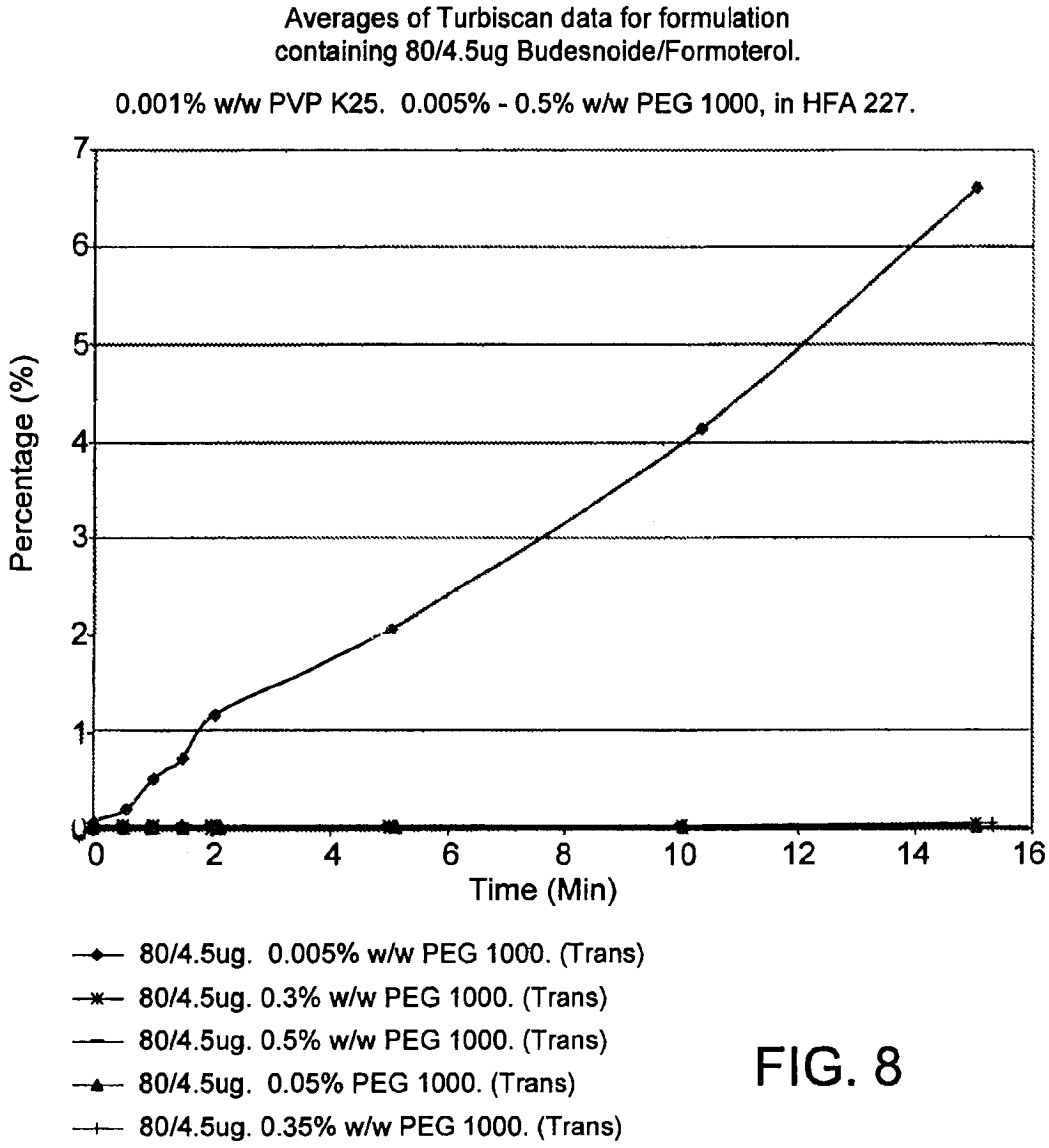


FIG. 8

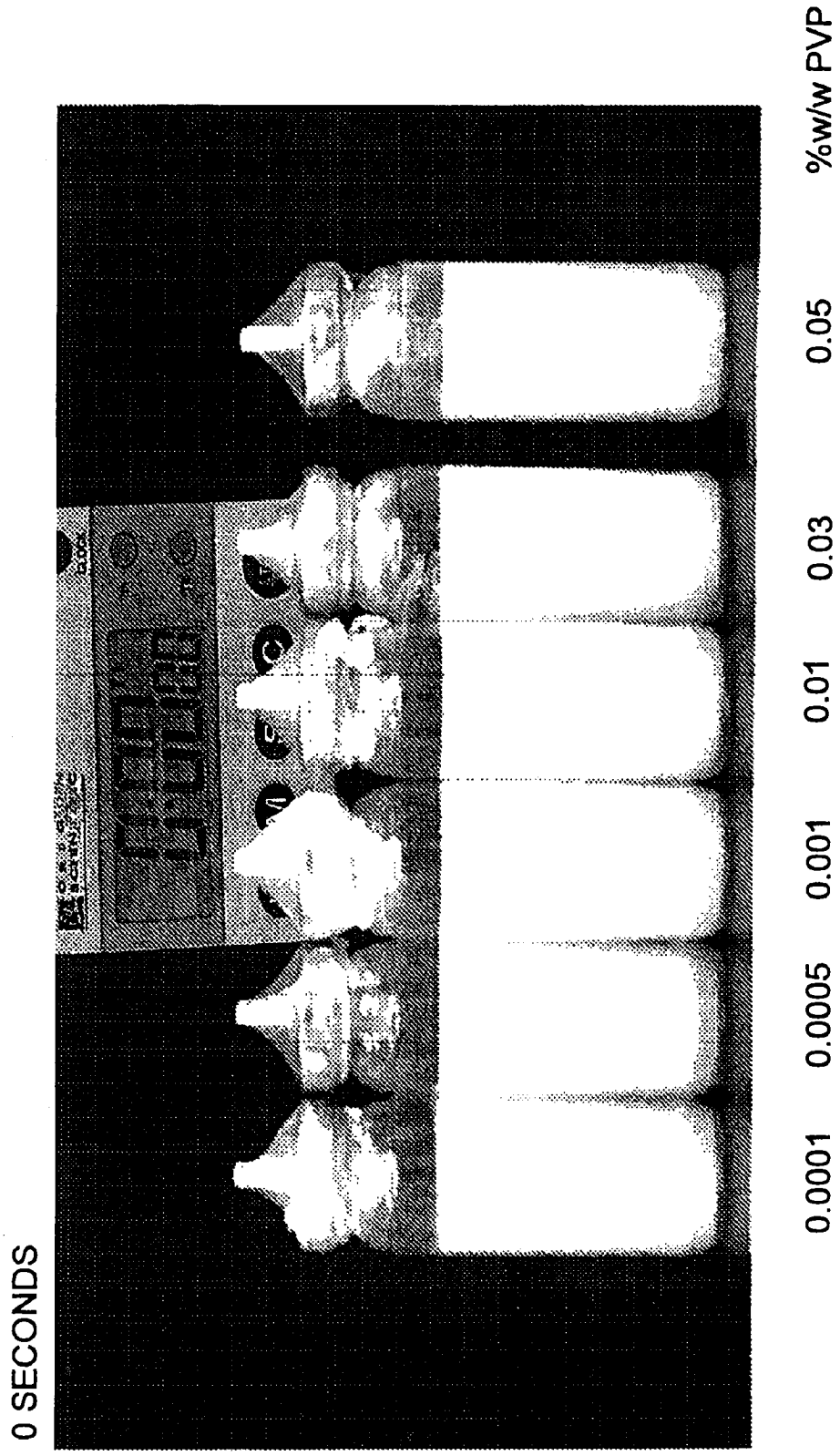


FIG. 9

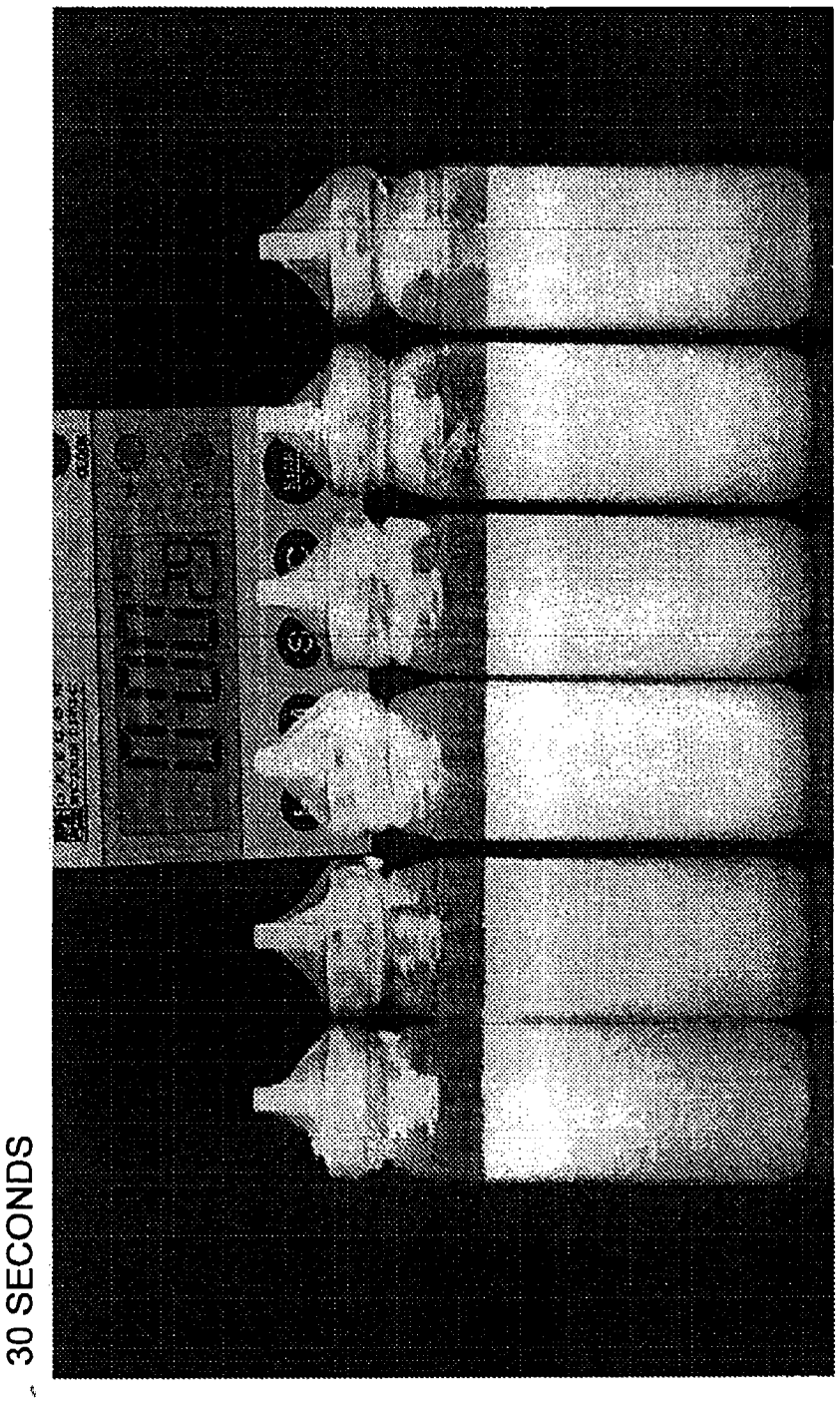


FIG. 10

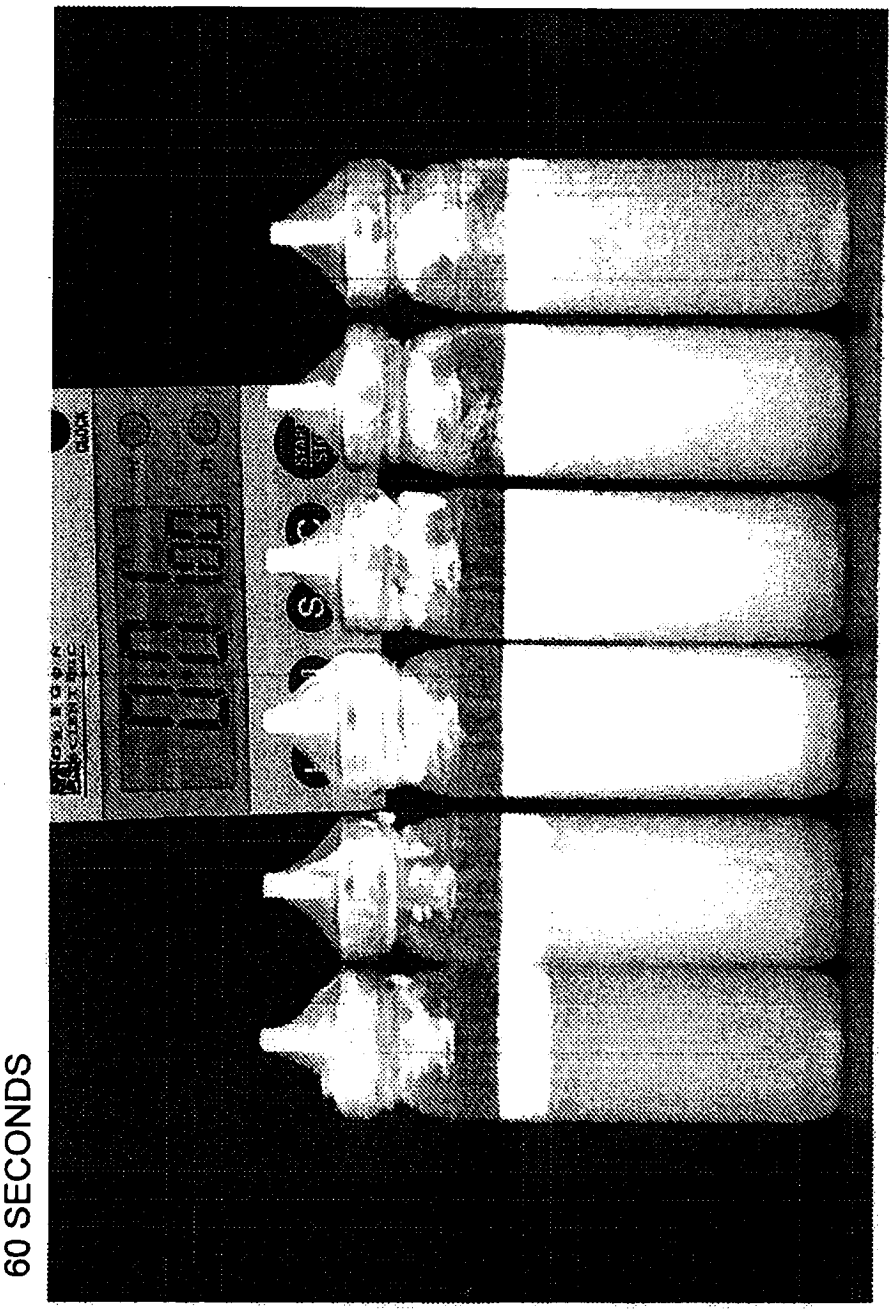


FIG. 11

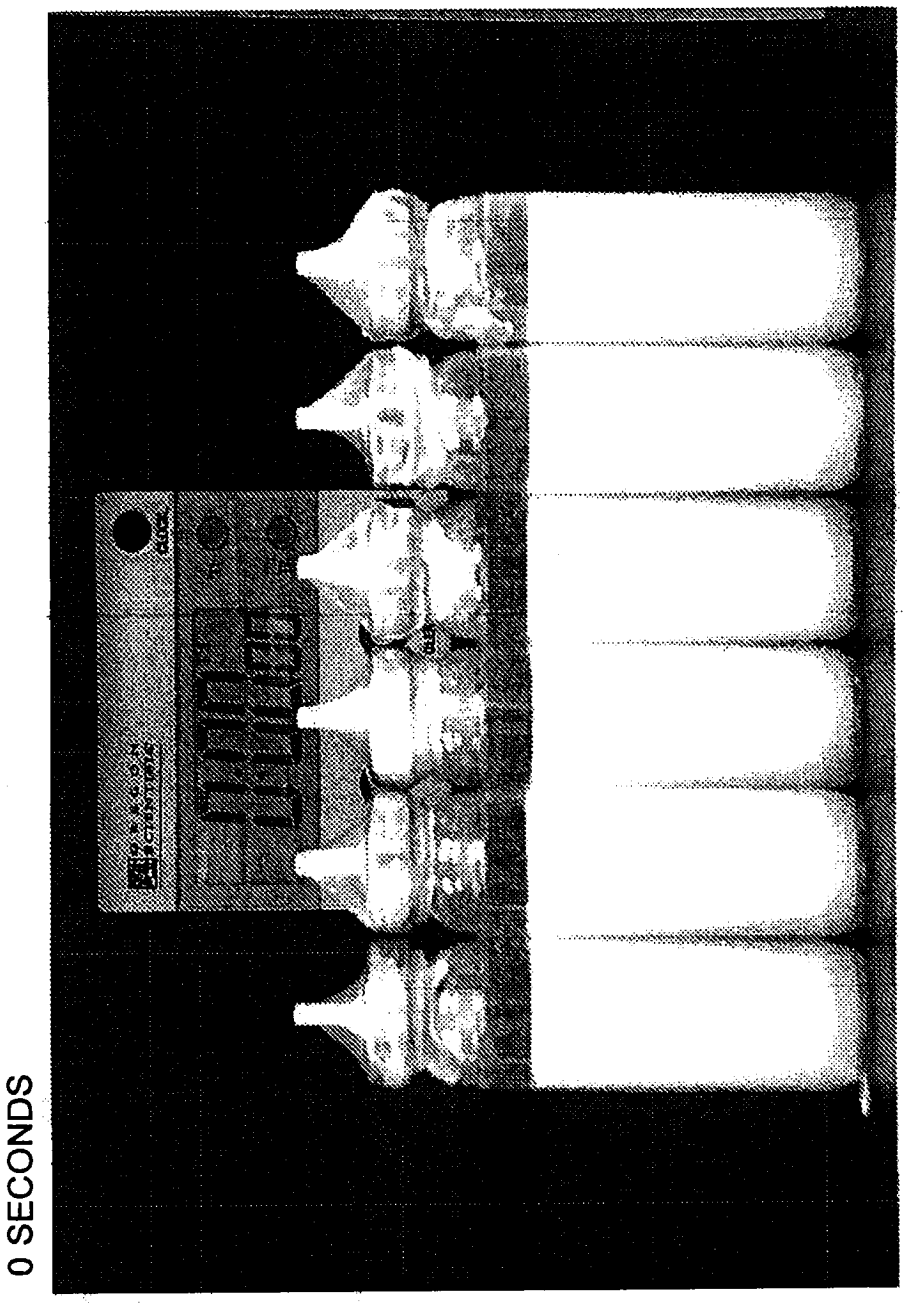


FIG. 12

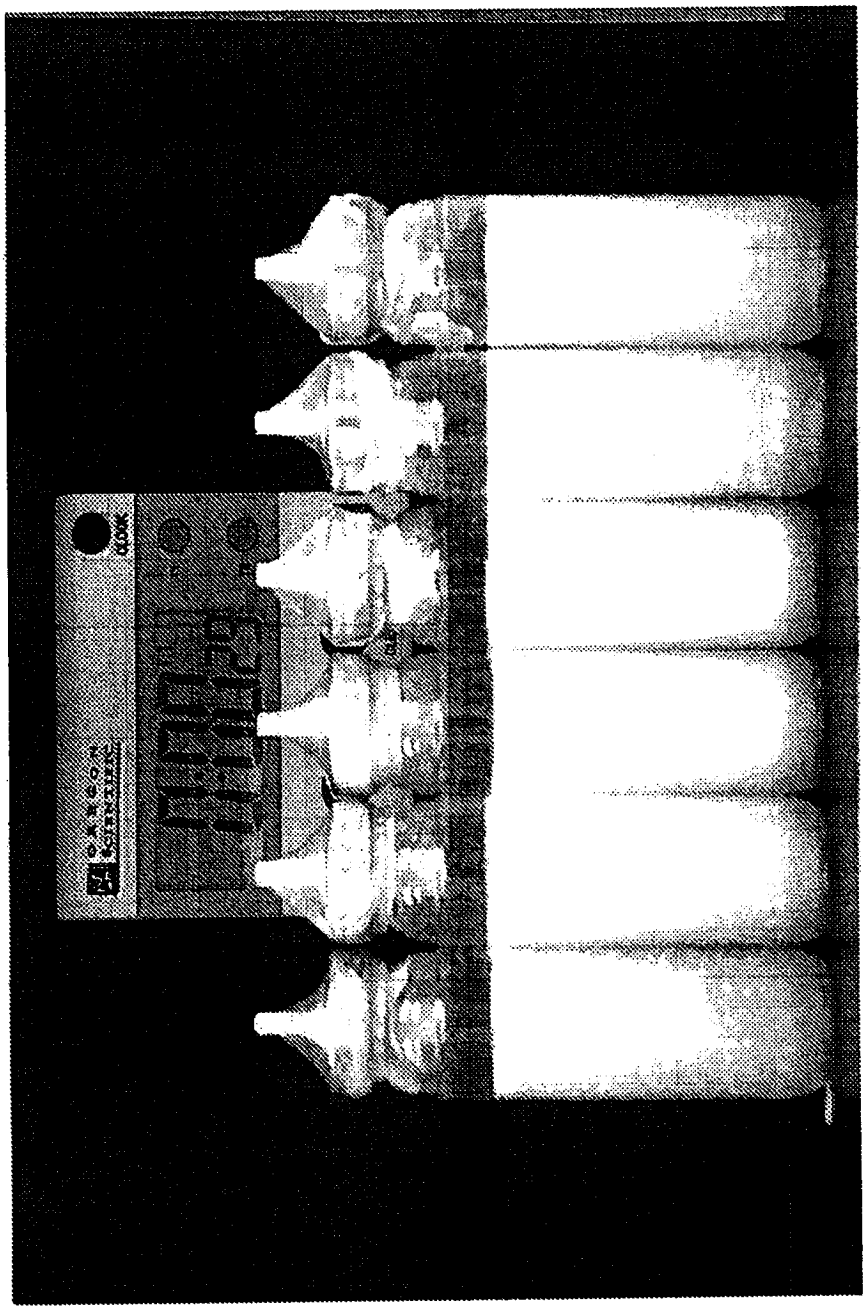


FIG.13

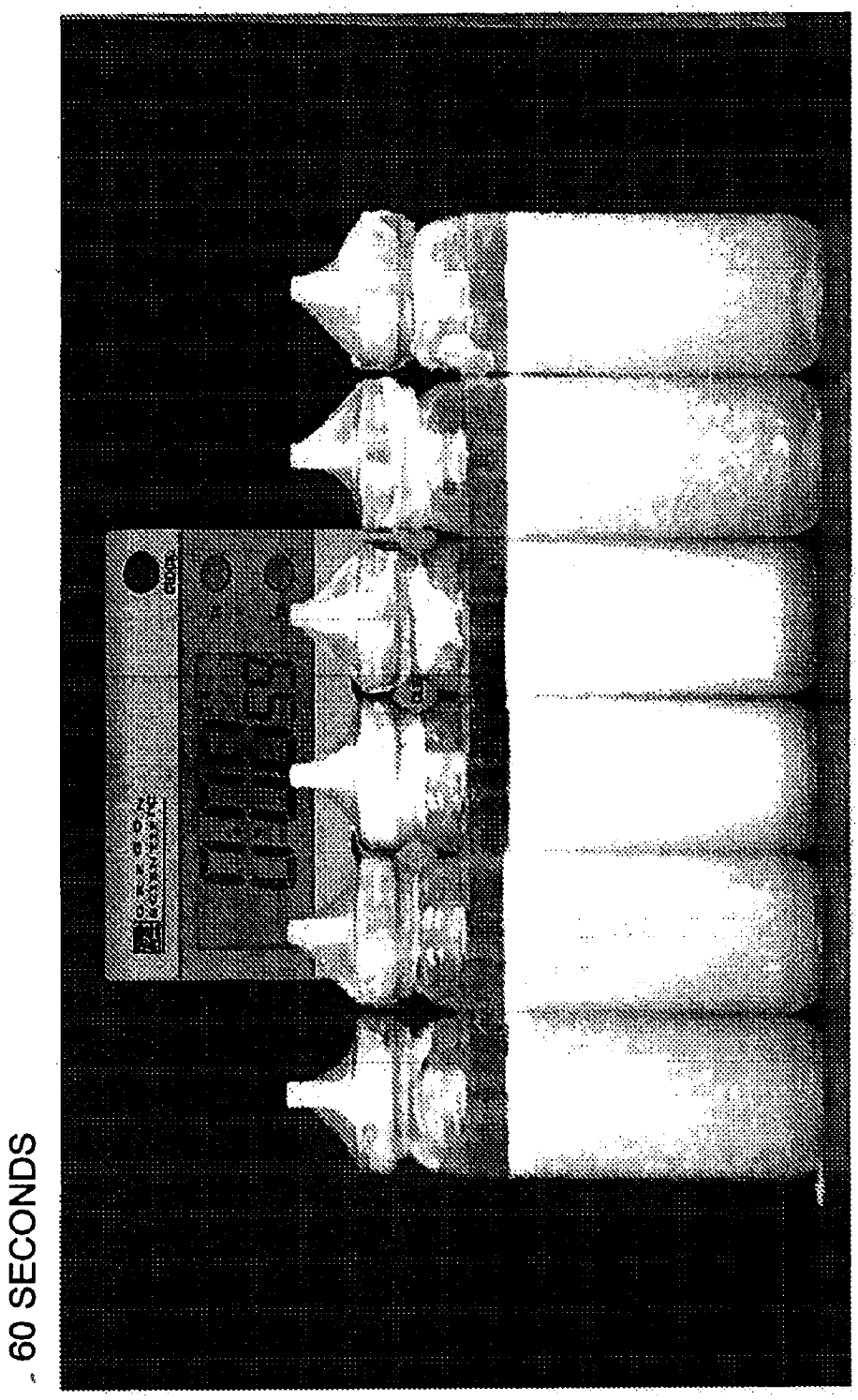


FIG. 14

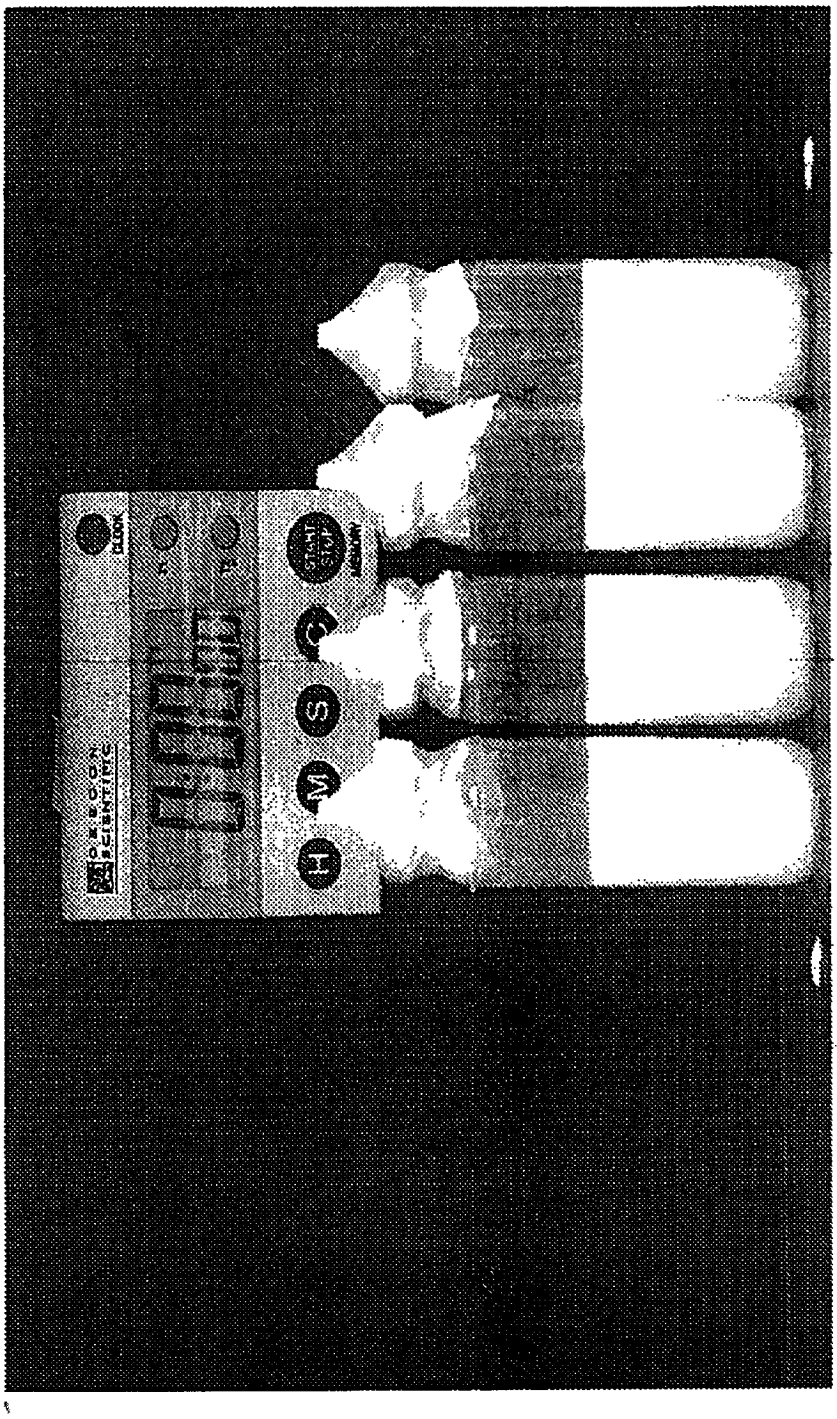


FIG. 15

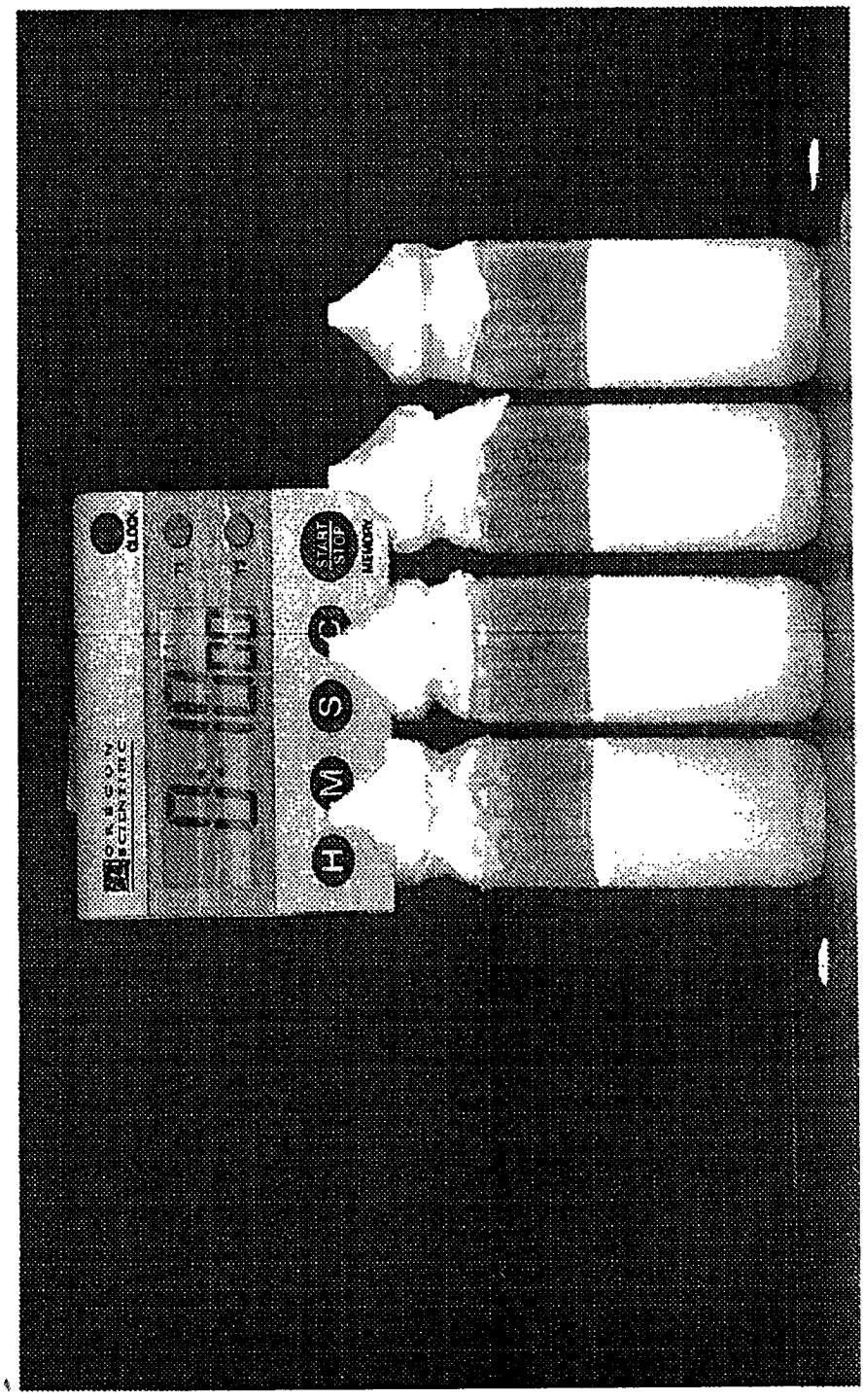


FIG. 16

COMPOSITION FOR INHALATION

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 Jan. 29, 2003, which claims priority to Swedish Application Serial No. 0200312-7, filed Feb. 1, 2002.

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 (1,1,1,2,3,3,3-heptafluoropropane), PVP and PEG characterized 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 (PVP having a nominal K-value of 25).

Preferably the PEG is present in an amount of 0.3% w/w. Preferably the PEG is PEG 1000 (PEG having an average molecular weight of 1000 Daltons).

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 4.5/320 mcg 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.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. **1** is a schematic drawing of an Optical Suspension Characterisation (OSCAR) setup.

FIGS. **2-3** are graphs showing the averages of OSCAR data (lower sensor) for formulations in HFA 227 containing 4.5 μg formoterol; 0.3% w/w PEG 1000; 0.0001%-0.05% w/w PVP K25; and 160 μg budesonide (FIG. **2**) or 80 μg budesonide (FIG. **3**).

FIGS. **4-6** are graphs showing the averages of Turbiscan data for formulations in HFA 227 containing 4.5 μg formoterol; 0.3% w/w PEG 1000; 0.0001%-0.05% w/w PVP K25; and 160 μg budesonide (FIG. **4**), 80 μg budesonide (FIG. **5**), or 40 μg budesonide (FIG. **6**).

FIG. **7** is a graph showing the effect of PEG 1000 concentration on stem return force for formulations containing 4.5 μg formoterol; 160 μg budesonide; and 0.1%, 0.3%, or 0.5% w/w PEG 1000.

FIG. **8** is a graph showing the averages of Turbiscan data for formulations in HFA 227 containing 80 μg budesonide; 4.5 μg formoterol; 0.0001% PVP K25; and 0.005%-0.5% w/w PEG 1000.

FIGS. **9-11** are a series of digital photographs, taken after standing times of 0 seconds (FIG. **9**), 30 seconds (FIG. **10**), and 60 seconds (FIG. **11**), of suspensions in HFA 227 containing budesonide (160 μg/actuation); formoterol (4.5 μg/actuation); 0.3% PEG 1000; and PVP K25 at 0.0001%, 0.0005%, 0.001%, 0.01%, 0.03%, and 0.05% w/w.

FIGS. **12-14** are a series of digital photographs, taken after standing times of 0 seconds (FIG. **12**), 30 seconds (FIG. **13**), and 60 seconds (FIG. **14**), of suspensions in HFA 227 containing budesonide (80 μg/actuation); formoterol (4.5 μg/actuation); 0.3% PEG 1000; and PVP K25 at 0.0001%, 0.0005%, 0.001%, 0.01%, 0.03%, and 0.05% w/w.

FIGS. **15-16** are digital photographs, taken after standing times of 0 minutes (FIG. **15**) and 10 minutes (FIG. **16**), of suspensions in HFA 227 containing budesonide (80 μg/actuation); formoterol (4.5 μg/actuation); 0.001% PVP K25; and PEG 1000 at 0.005, 0.05, 0.35, and 0.5% w/w.

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 FIG. 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, 5 ml cylindrical glass cell, which takes readings of transmitted and backscattered light every 40 μm on a maximum sample height of 80 mm. 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 homogeneity, 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 0.09 mg/ml (equivalent to 4.5 mcg formoterol fumurate dihydrate per actuation) and the budesonide concentration varied between approximately 1 mg/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.

FUTHER 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 tech-

niques 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

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

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

Table of Degree of Dispersion of Suspensions Over Time: (All Samples)

Photographs were taken of all doses (320 μg/4.5 μg to 40 μg/4.5 μg) 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 4.5 μg/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 Degree of Dispersion of Suspensions Over Time: All Samples

Dose μg/shot	Time	PVP concentration (% w/w)					
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

-continued

Dose μg/shot	Time	PVP concentration (% w/w)					
Budesonide	Sec/mins	0.0001	0.0005	0.001	0.01	0.03	0.05
	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)

FIG. **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 FIG. **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 FIG. **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

FIGS. **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.

Methodology—Force to Fire (Return Force at 0.5 mm 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 proto-

col. 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 0.5 mm 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

FIG. 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 (FIG. **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).

FIGS. **15** and **16** show Budesonide 80 μg/shot, Formoterol 4.5 μg/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)	Drug	Fine particle fraction (% cumulative undersize for 4.7 μm cut-off) 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 IHFA-227

Product strength (μg) (FFD/budesonide)	Drug	Fine particle fraction (% cumulative undersize for 4.7 μm cut-off) 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

The invention claimed is:

1. A pharmaceutical composition comprising formoterol fumarate dihydrate, budesonide, 1,1,1,2,3,3,3-heptafluoropropane (HFA227), PVP K25 (polyvinyl pyrrolidone with a nominal K-value of 25), and PEG-1000 (polyethylene glycol with an average molecular weight of 1,000), wherein the formoterol fumarate dihydrate is present at a concentration of 0.09 mg/ml, the budesonide is present at a concentration in the range of 1 mg/ml to 8 mg/ml, the PVP K25 is present at a concentration of 0.001% w/w, and the PEG-1000 is present at a concentration of 0.3% w/w.

2. A pharmaceutical composition according to claim **1**, in which the formoterol fumarate dihydrate is the R, R-enantiomer.

3. A pharmaceutical composition according to claim **1**, in which the budesonide is the 22R-epimer.

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

5. The method of claim **4**, wherein the respiratory disorder is asthma.

6. The method of claim **4**, wherein the respiratory disorder is rhinitis.

7. The method of claim **4**, wherein the respiratory disorder is COPD.

8. The method of claim **4**, wherein the concentration of budesonide is 1 mg/ml.

9. The method of claim **4**, wherein the concentration of budesonide is 2 mg/ml.

10. The method of claim **4**, wherein the concentration of budesonide is 4 mg/ml.

11. The method of claim **4**, wherein the concentration of budesonide is 8 mg/ml.

12. A pharmaceutical composition comprising formoterol fumarate dihydrate, budesonide, HFA227, PVP K25, and PEG-1000, wherein the formoterol fumarate dihydrate is present at a concentration of 0.09 mg/ml, the budesonide is present at a concentration of 1 mg/ml, the PVP K25 is present at a concentration of 0.001% w/w, and the PEG-1000 is present at a concentration of 0.3% w/w.

13. A pharmaceutical composition comprising formoterol fumarate dihydrate, budesonide, HFA227, PVP K25, and PEG-1000, wherein the formoterol fumarate dihydrate is present at a concentration of 0.09 mg/ml, the budesonide is present at a concentration of 2 mg/ml, the PVP K25 is present at a concentration of 0.001% w/w, and the PEG-1000 is present at a concentration of 0.3% w/w.

14. A pharmaceutical composition comprising formoterol fumarate dihydrate, budesonide, HFA227, PVP K25, and PEG-1000, wherein the formoterol fumarate dihydrate is

present at a concentration of 0.09 mg/ml, the budesonide is present at a concentration of 4 mg/ml, the PVP K25 is present at a concentration of 0.001% w/w, and the PEG-1000 is present at a concentration of 0.3% w/w.

15. A pharmaceutical composition comprising formoterol fumarate dihydrate, budesonide, HFA227, PVP K25, and PEG-1000, wherein the formoterol fumarate dihydrate is present at a concentration of 0.09 mg/ml, the budesonide is present at a concentration of 8 mg/ml, the PVP K25 is present at a concentration of 0.001% w/w, and the PEG-1000 is present at a concentration of 0.3% w/w.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 7,759,328 B2
APPLICATION NO. : 10/502685
DATED : July 20, 2010
INVENTOR(S) : Nayna Govind and Maria Marlow

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

On the Title Page Item (56) Line 14 – Delete "Pipkom" and insert -- Pipkorn -- therefor.

On the Title Page Item (56) Line 18 – Delete "Zettersträm" and insert -- Zetterström -- therefor.

Signed and Sealed this

Second Day of November, 2010

David J. Kappos

David J. Kappos
Director of the United States Patent and Trademark Office

US008143239B2

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

(10) **Patent No.: US 8,143,239 B2**
(45) **Date of Patent: *Mar. 27, 2012**

(54) **COMPOSITION FOR INHALATION**

(75) Inventors: **Nayna Govind**, Leicestershire (GB); **Maria Marlow**, Leicestershire (GB)

(73) Assignee: **AstraZeneca AB**, Södertälje (SE)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

This patent is subject to a terminal disclaimer.

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Related U.S. Application Data

(63) Continuation of application No. 10/502,685, filed as application No. PCT/SE03/00156 on Jan. 29, 2003, now Pat. No. 7,759,328.

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A61K 31/335 (2006.01)

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(58) **Field of Classification Search** ..... None
See application file for complete search history.

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(74) *Attorney, Agent, or Firm* — Fish & Richardson P.C.

(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.

31 Claims, 16 Drawing Sheets

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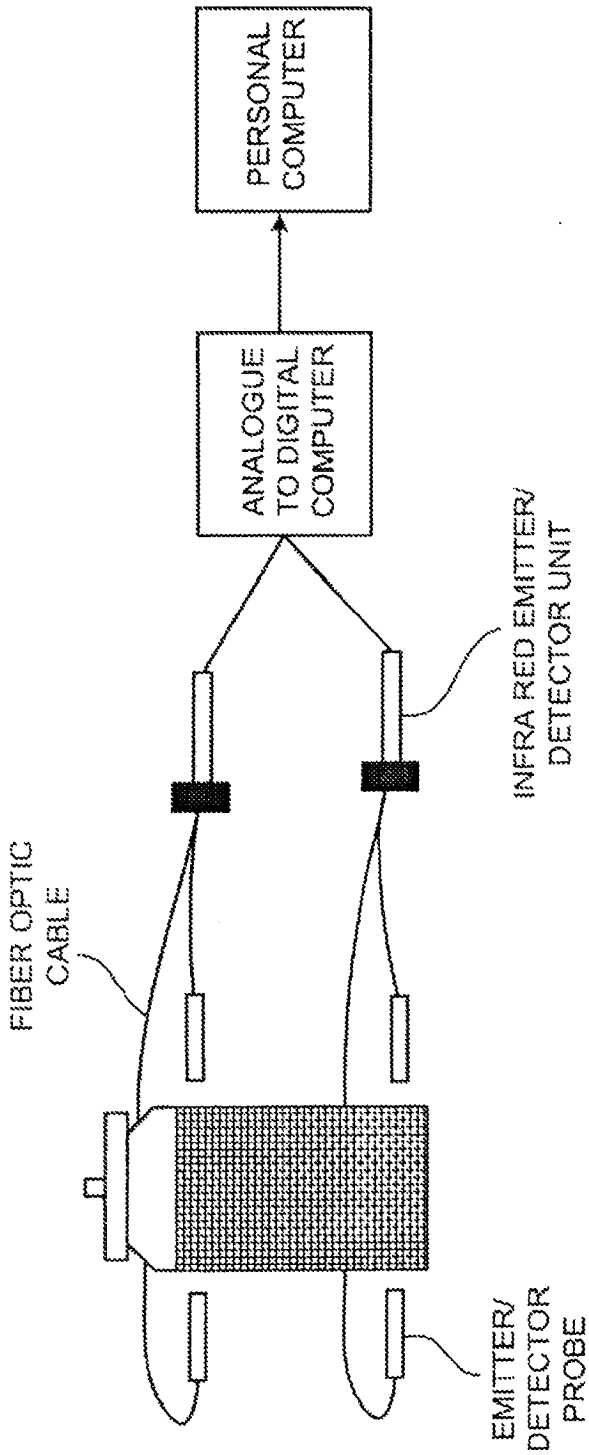


SCHEMATIC FOR OSCAR SET-UP

FIG. 1

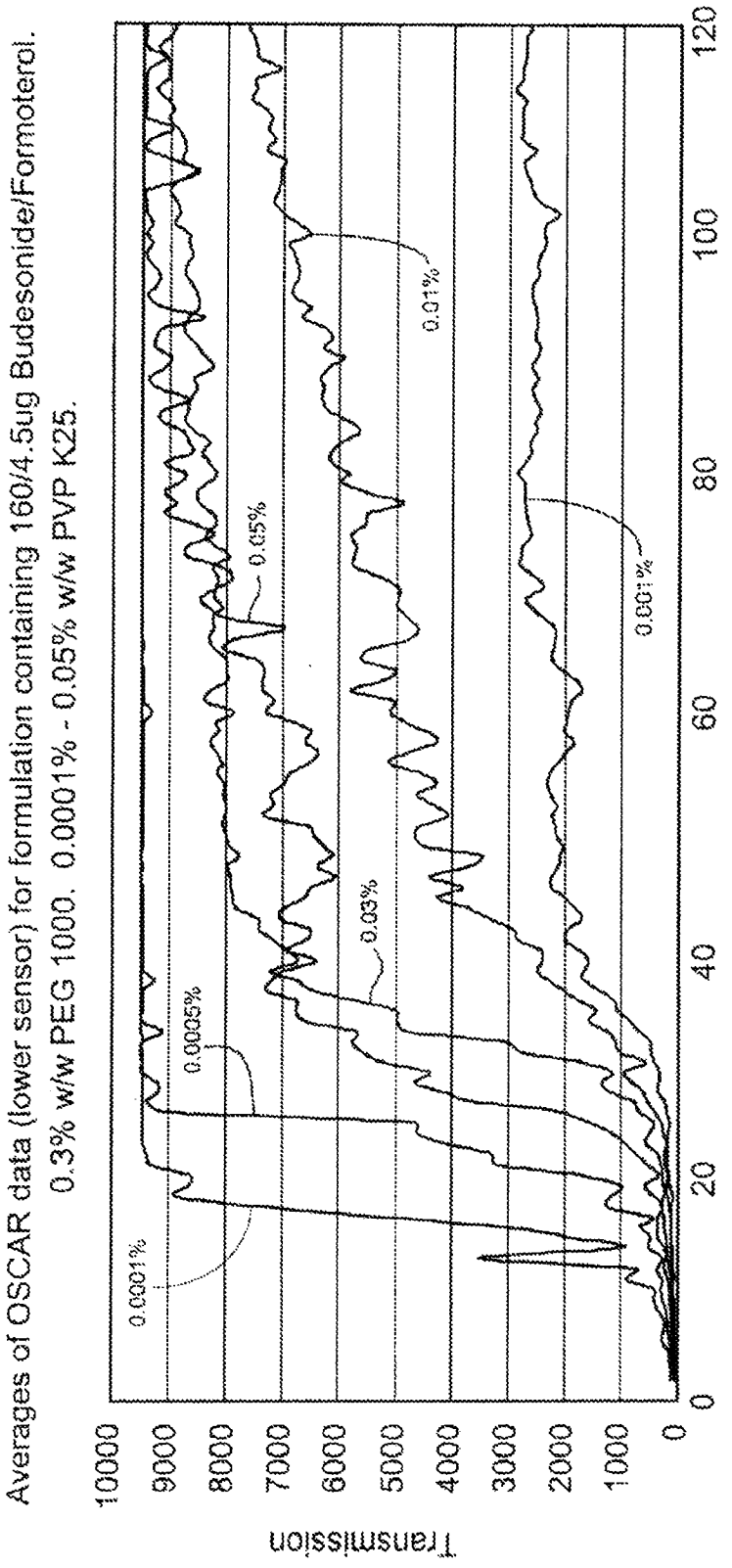


FIG. 2

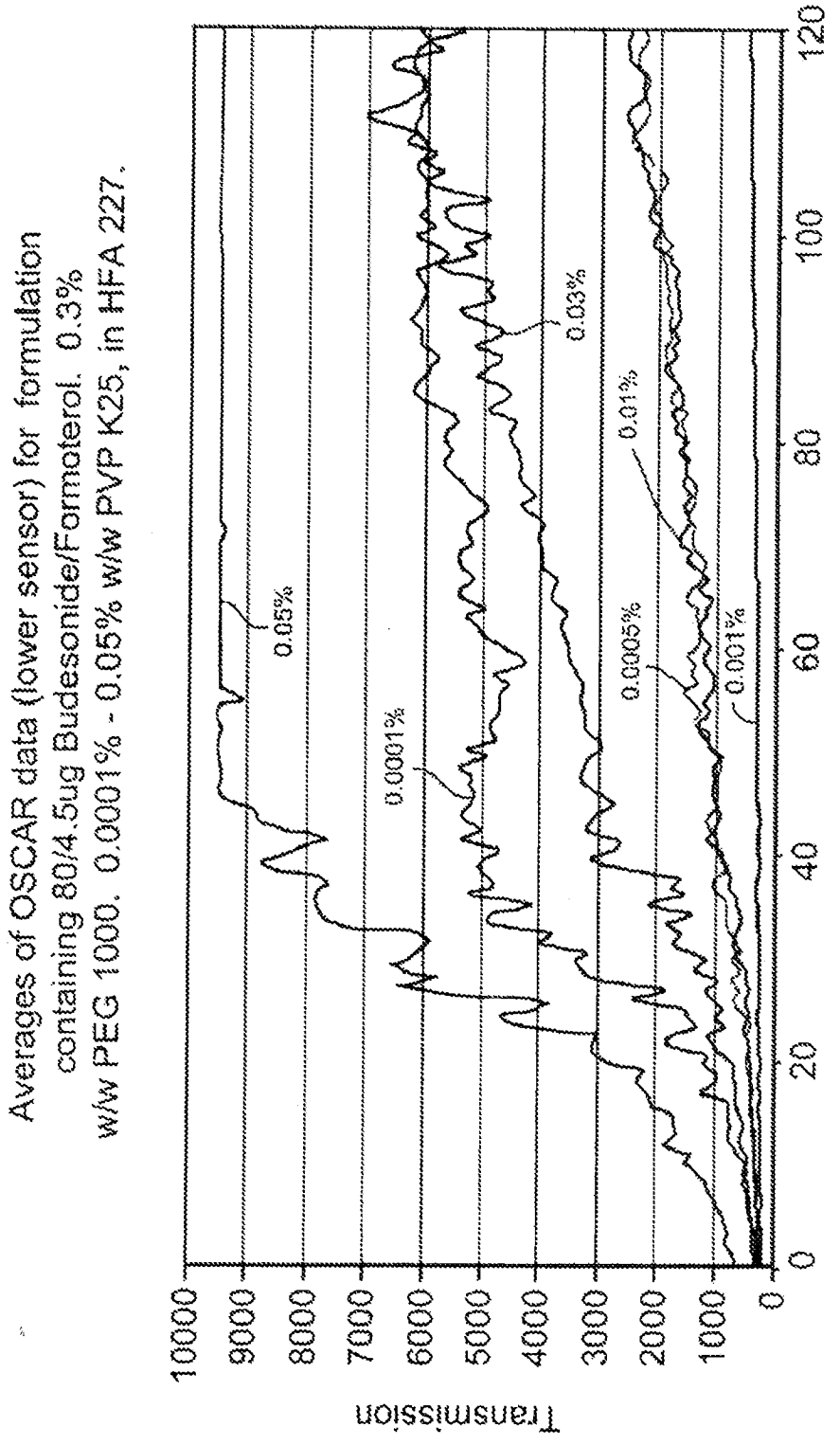


FIG. 3

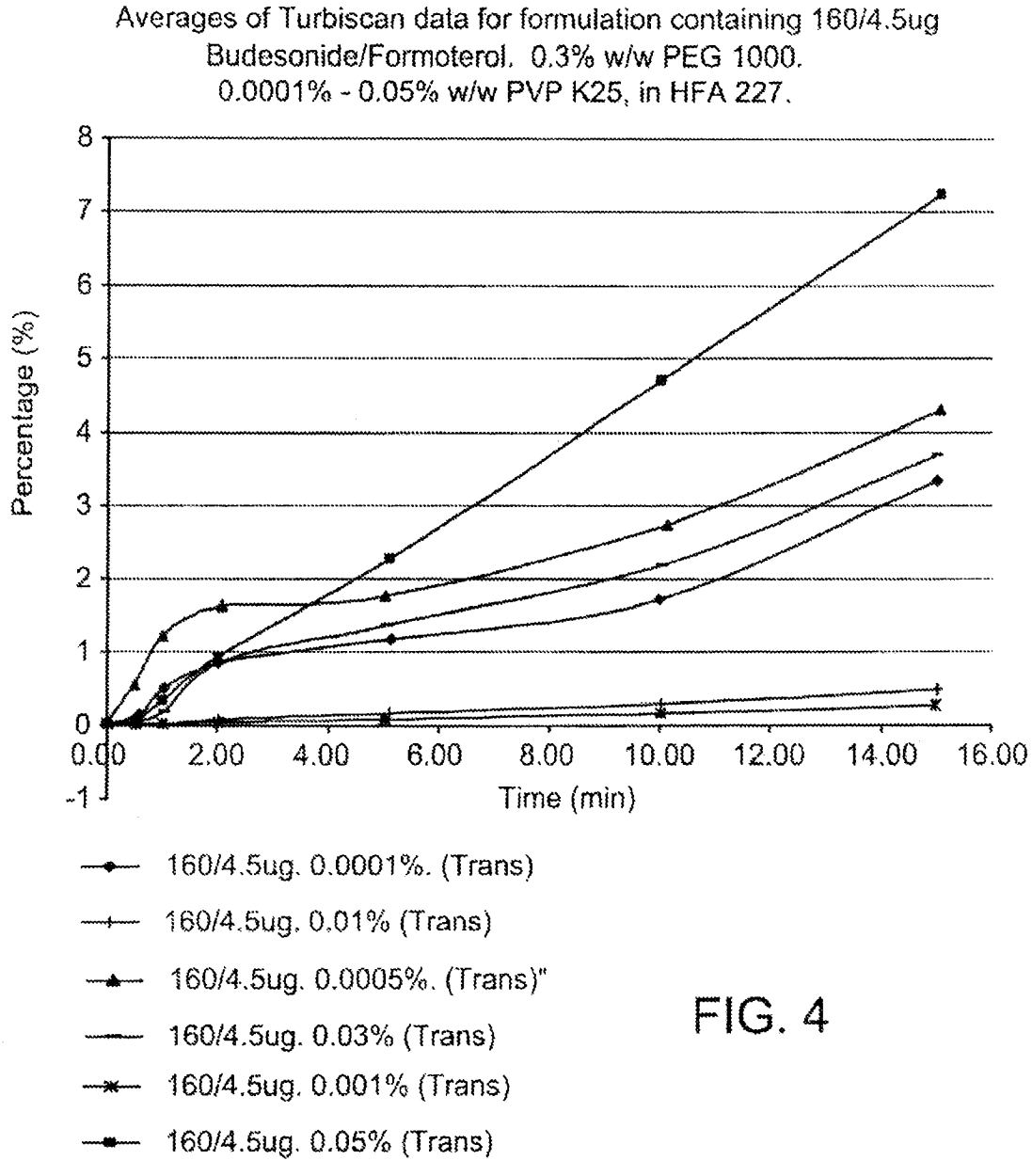


FIG. 4

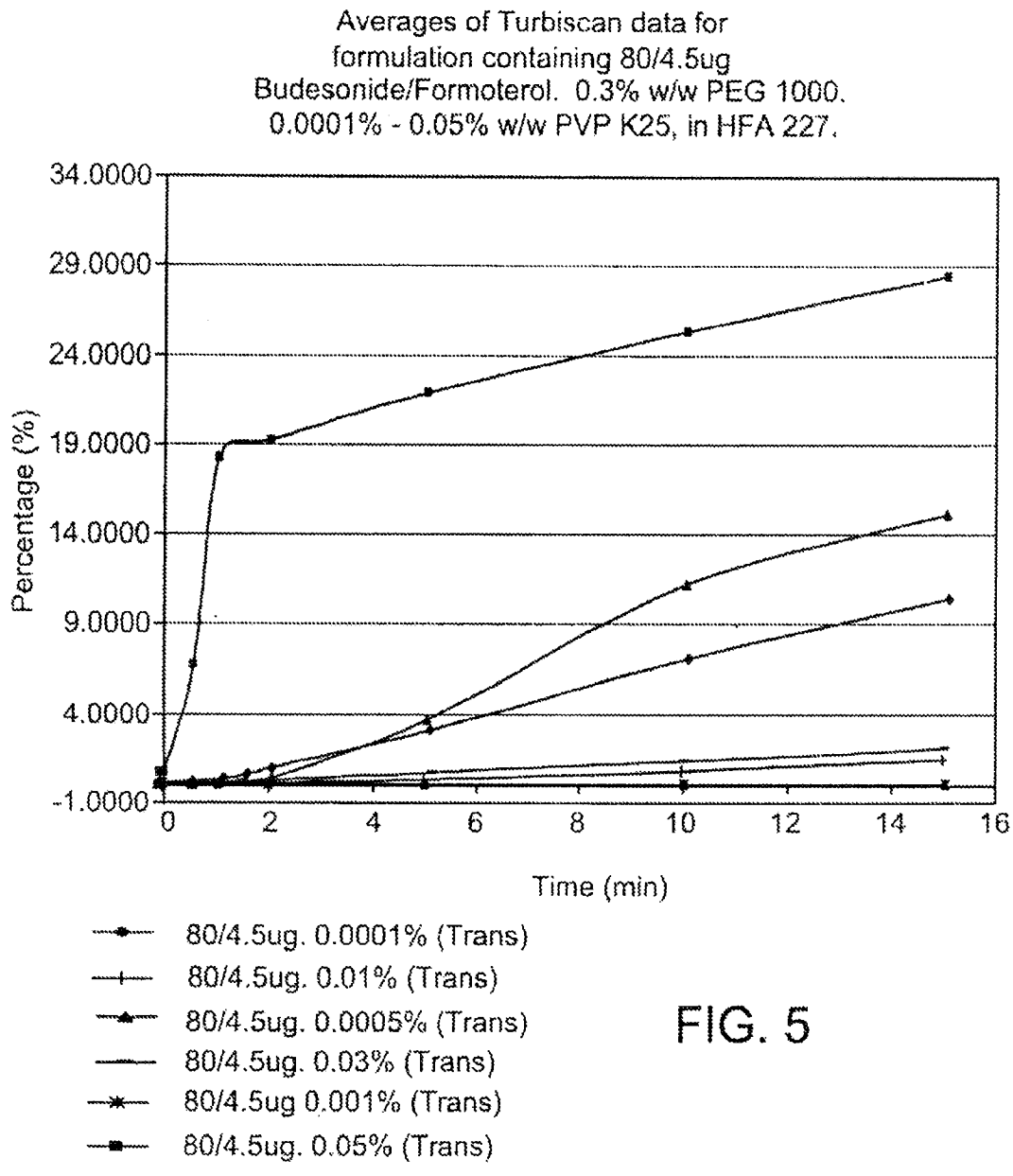


FIG. 5

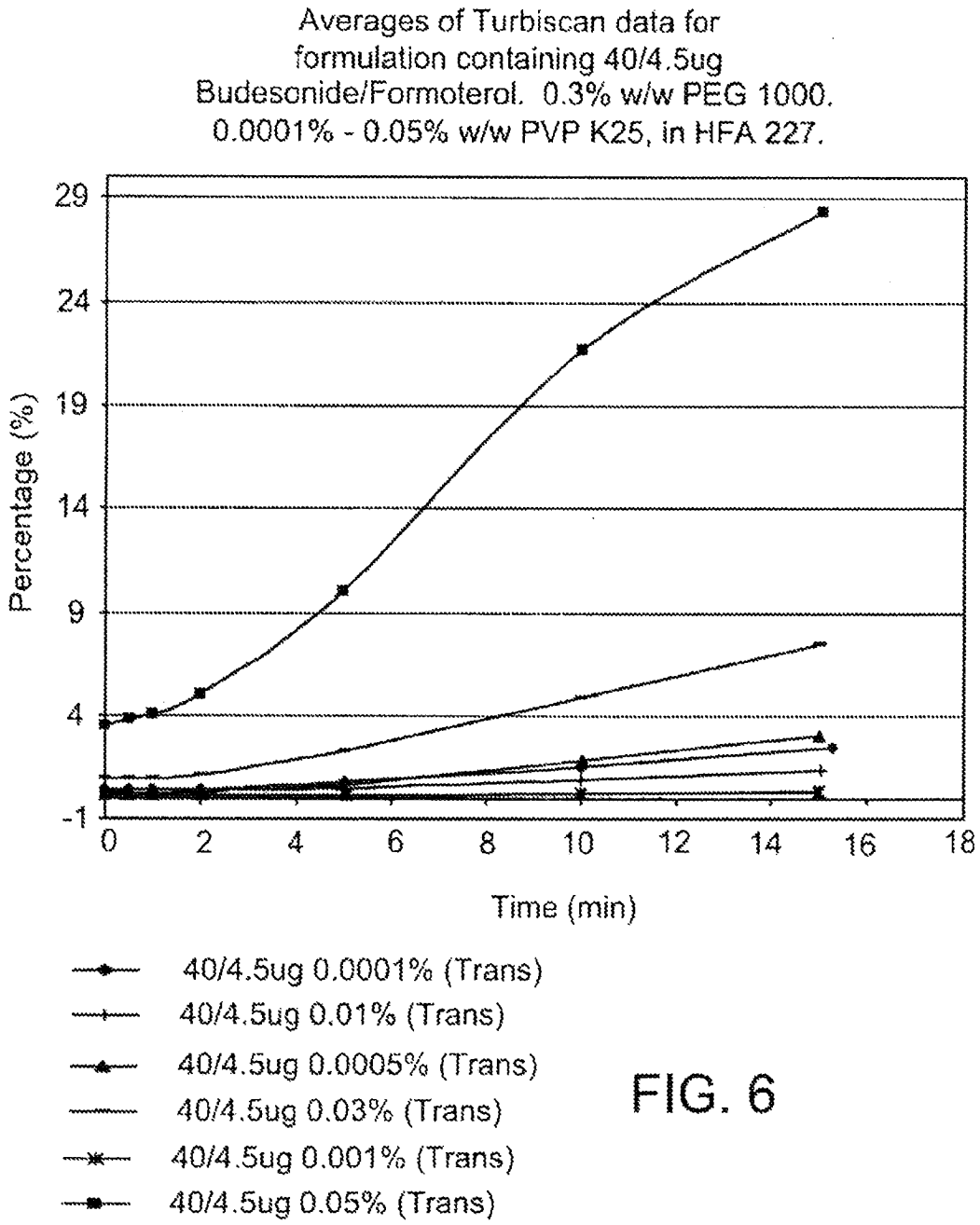


FIG. 6

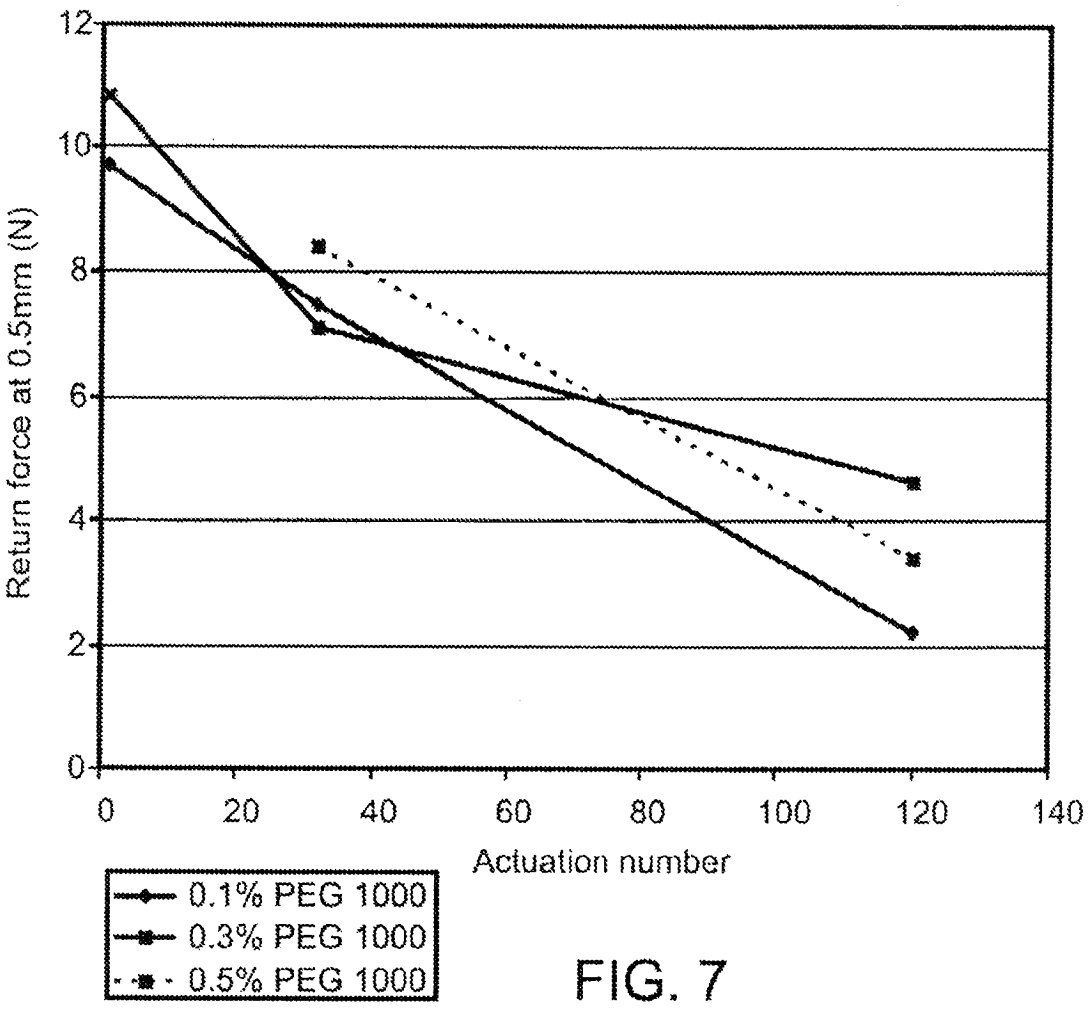


FIG. 7

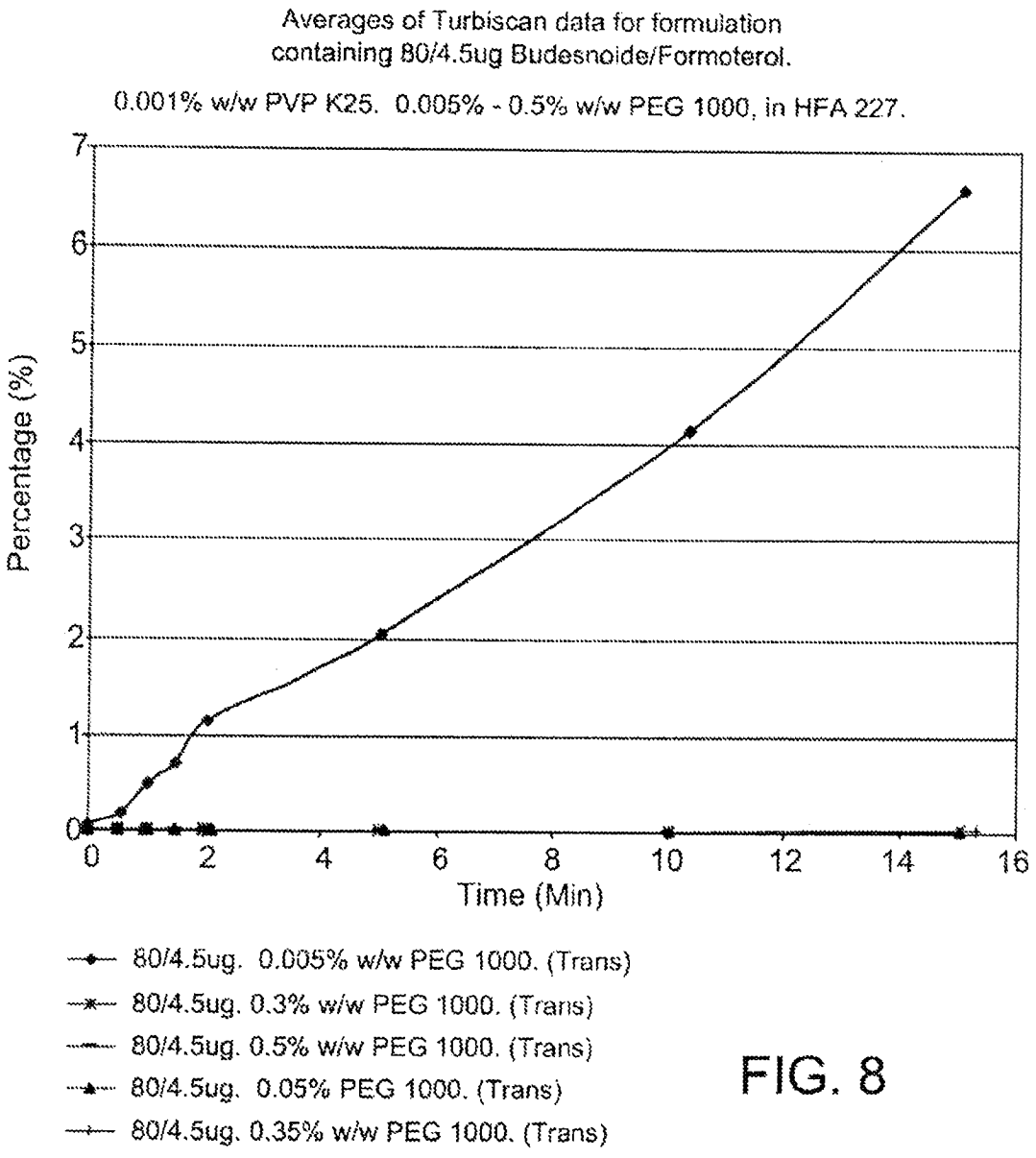


FIG. 8

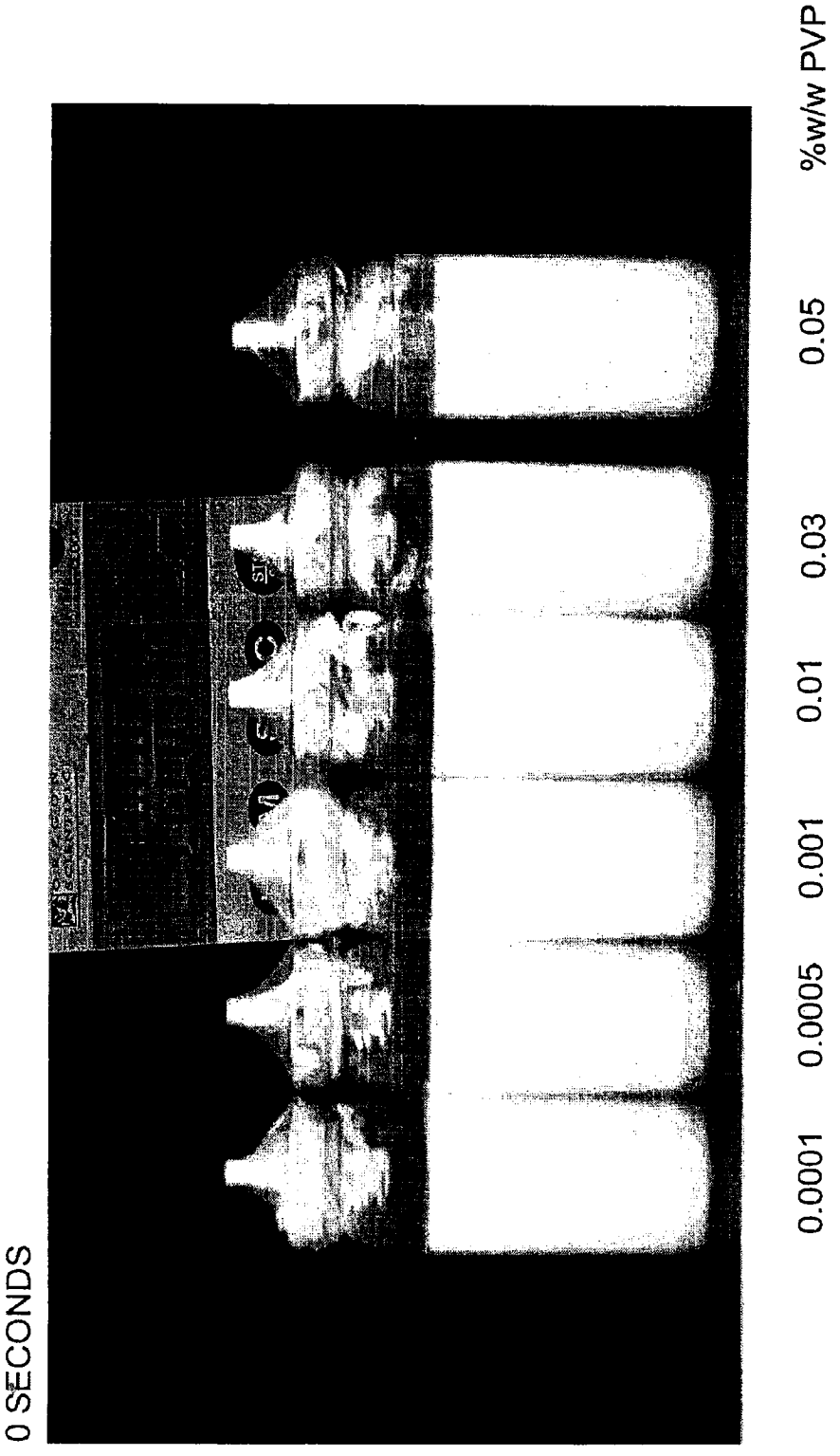


FIG. 9

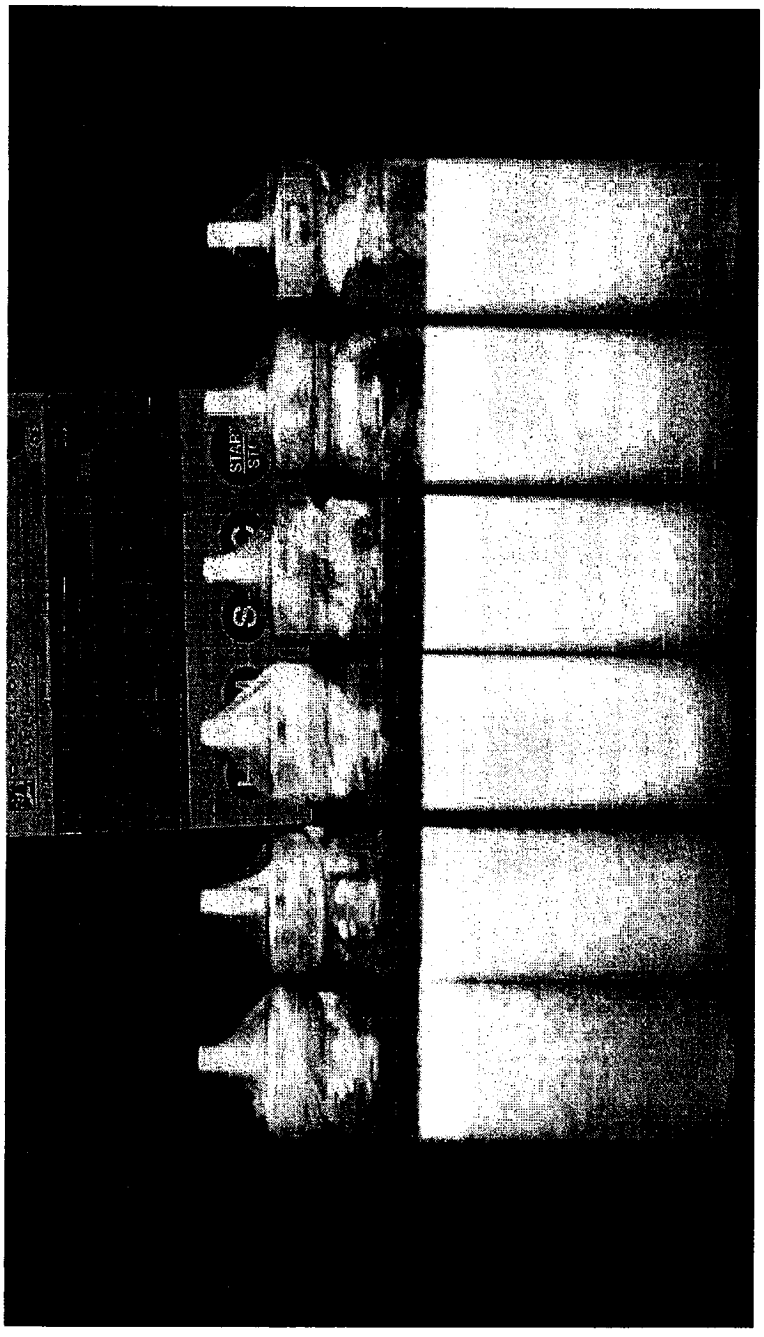


FIG. 10

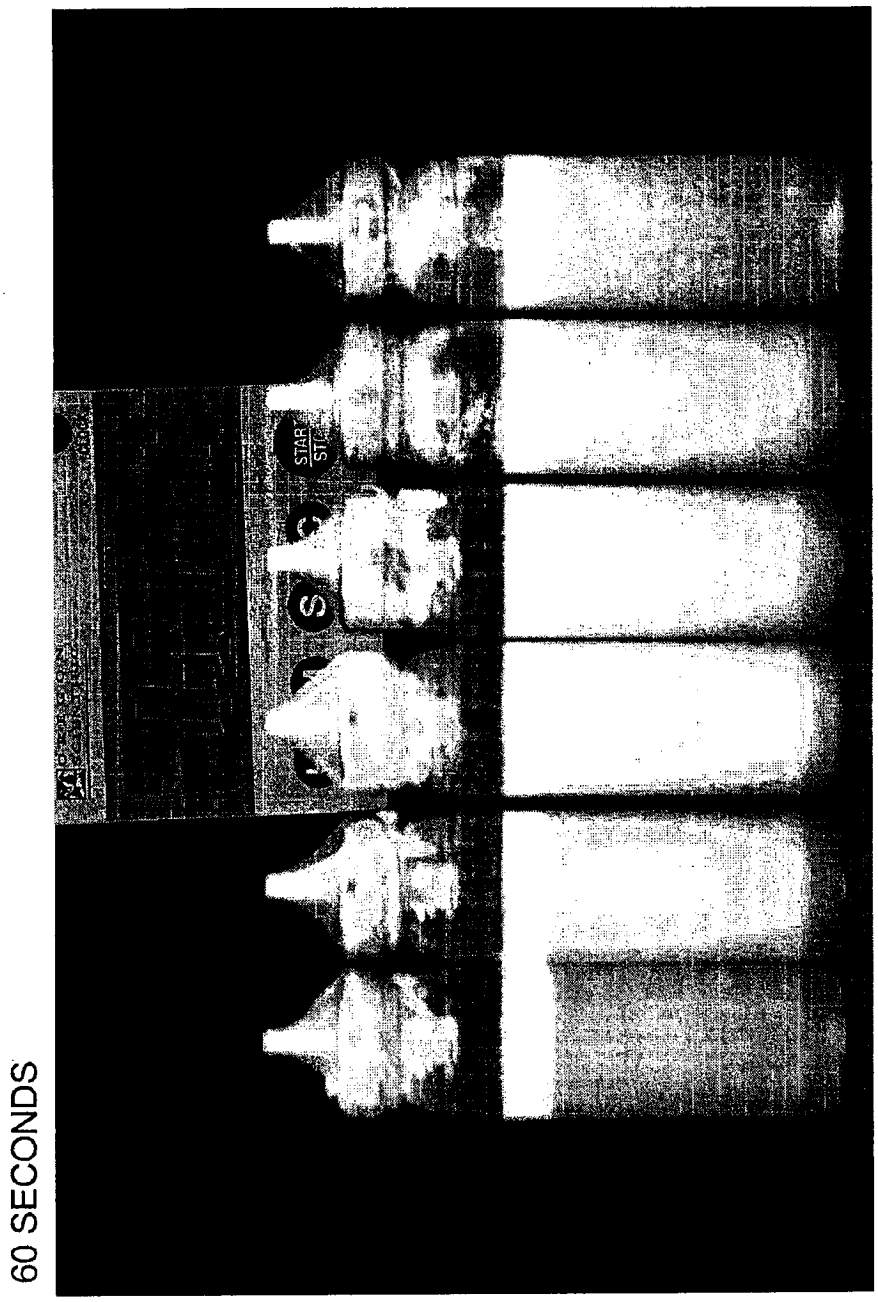


FIG. 11

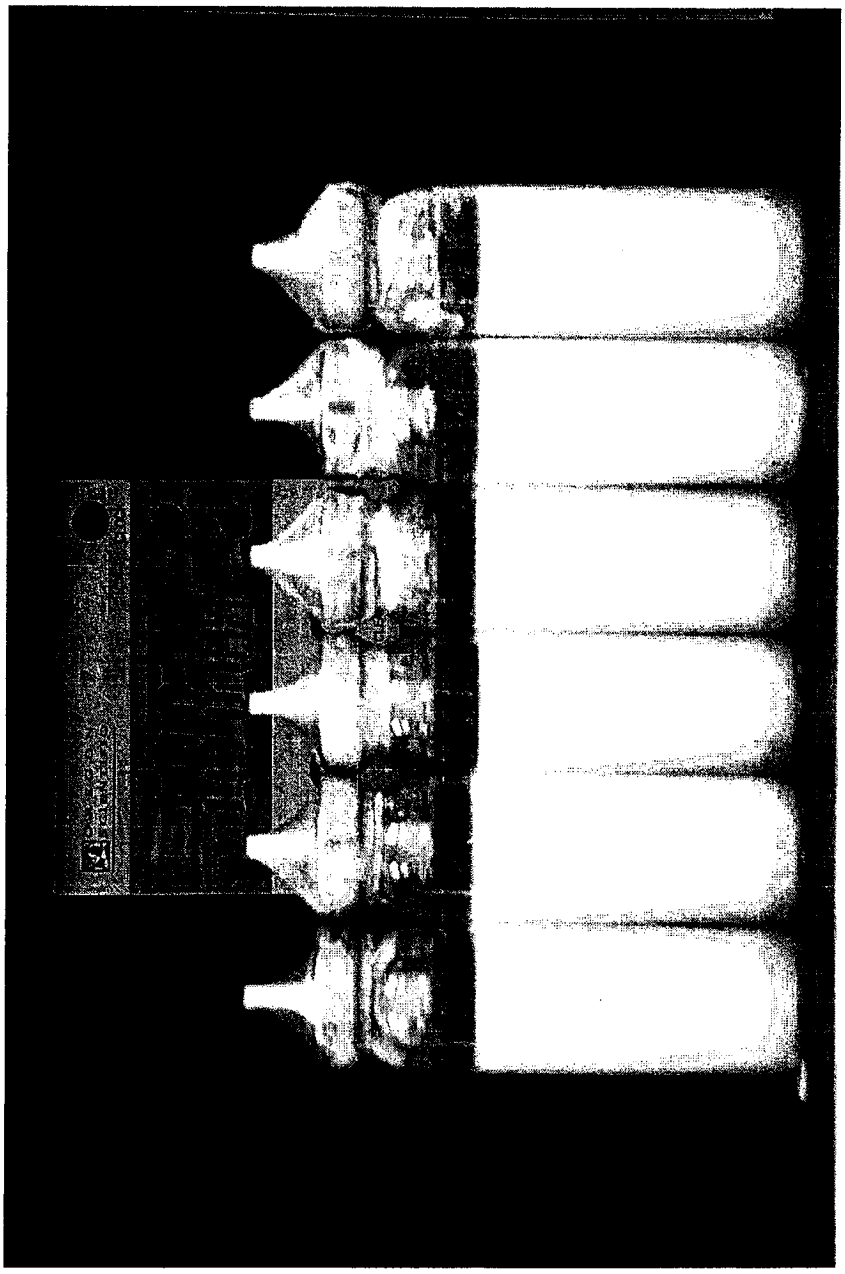


FIG. 12

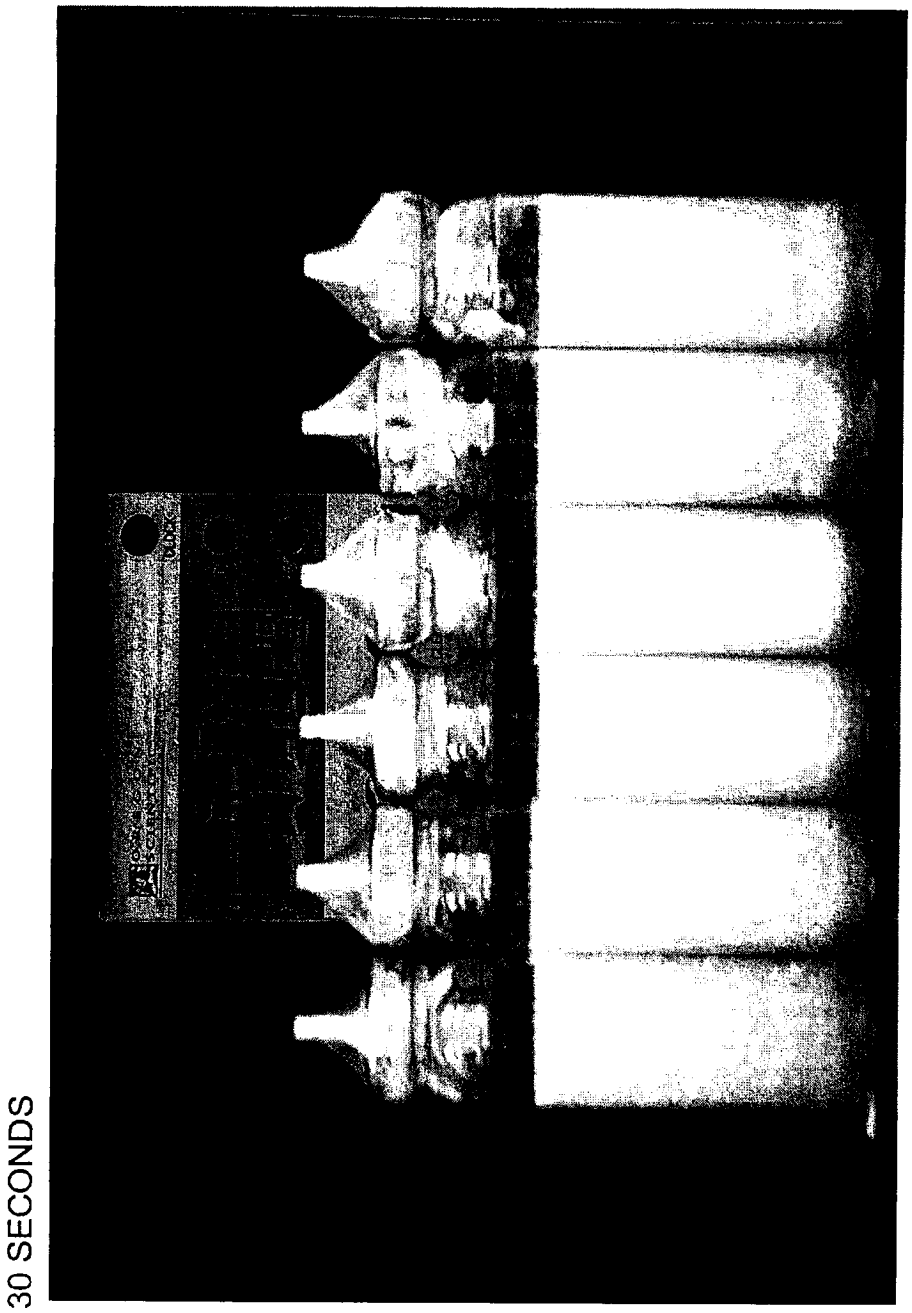


FIG.13

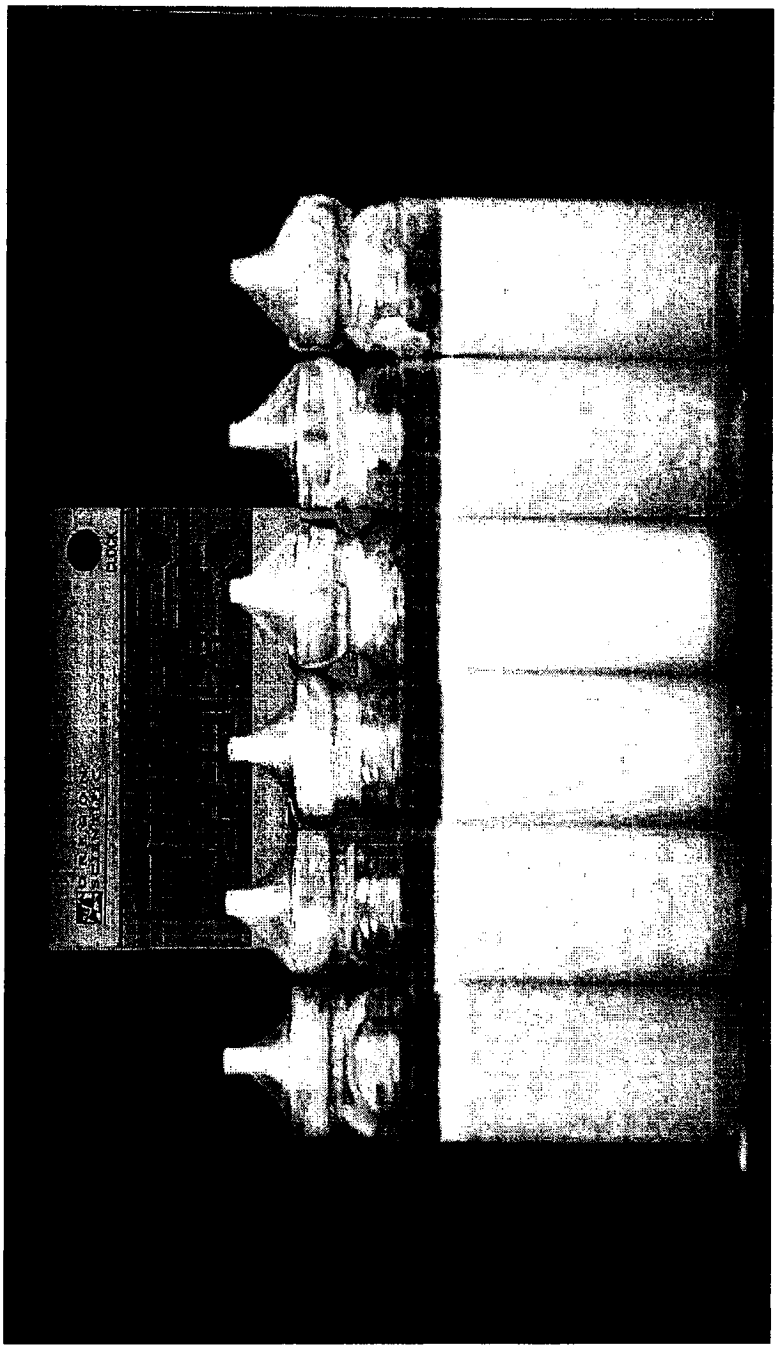
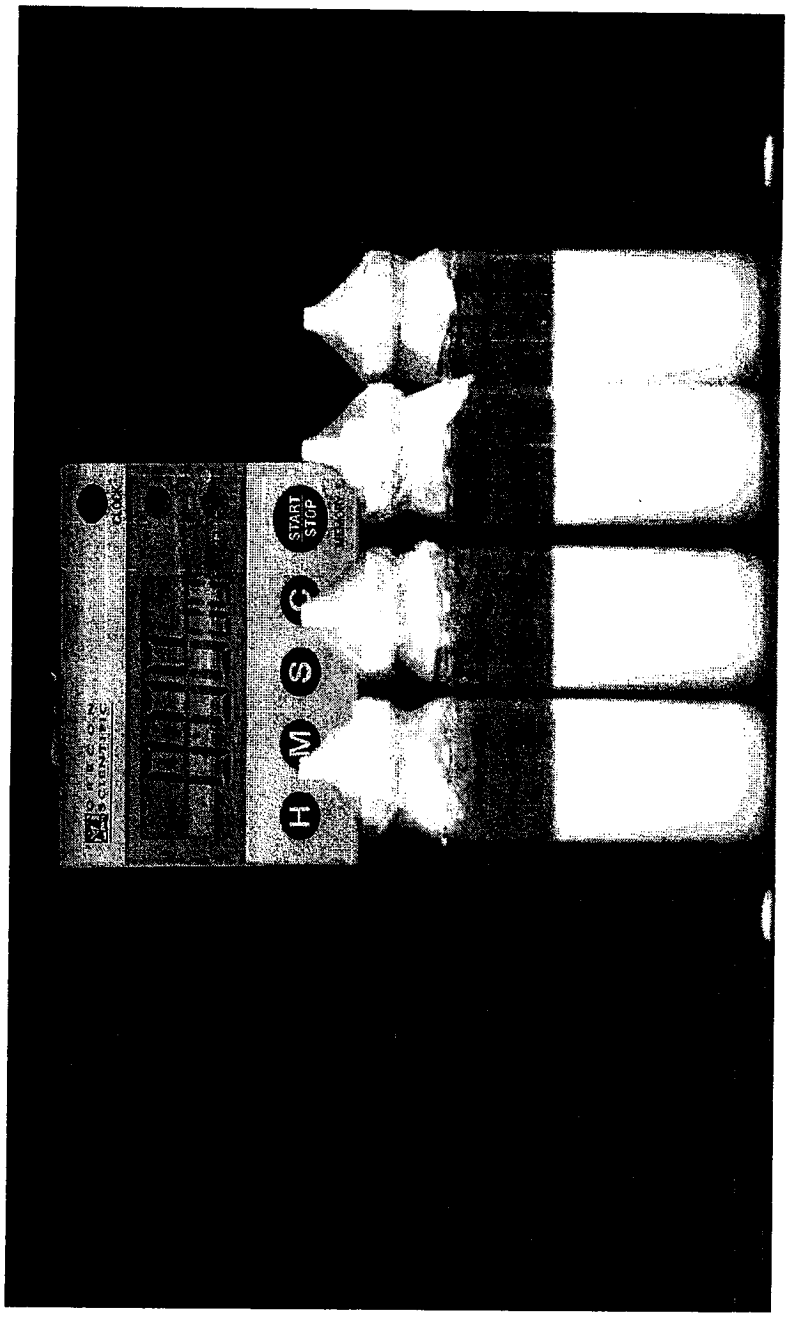


FIG. 14



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

FIG. 15

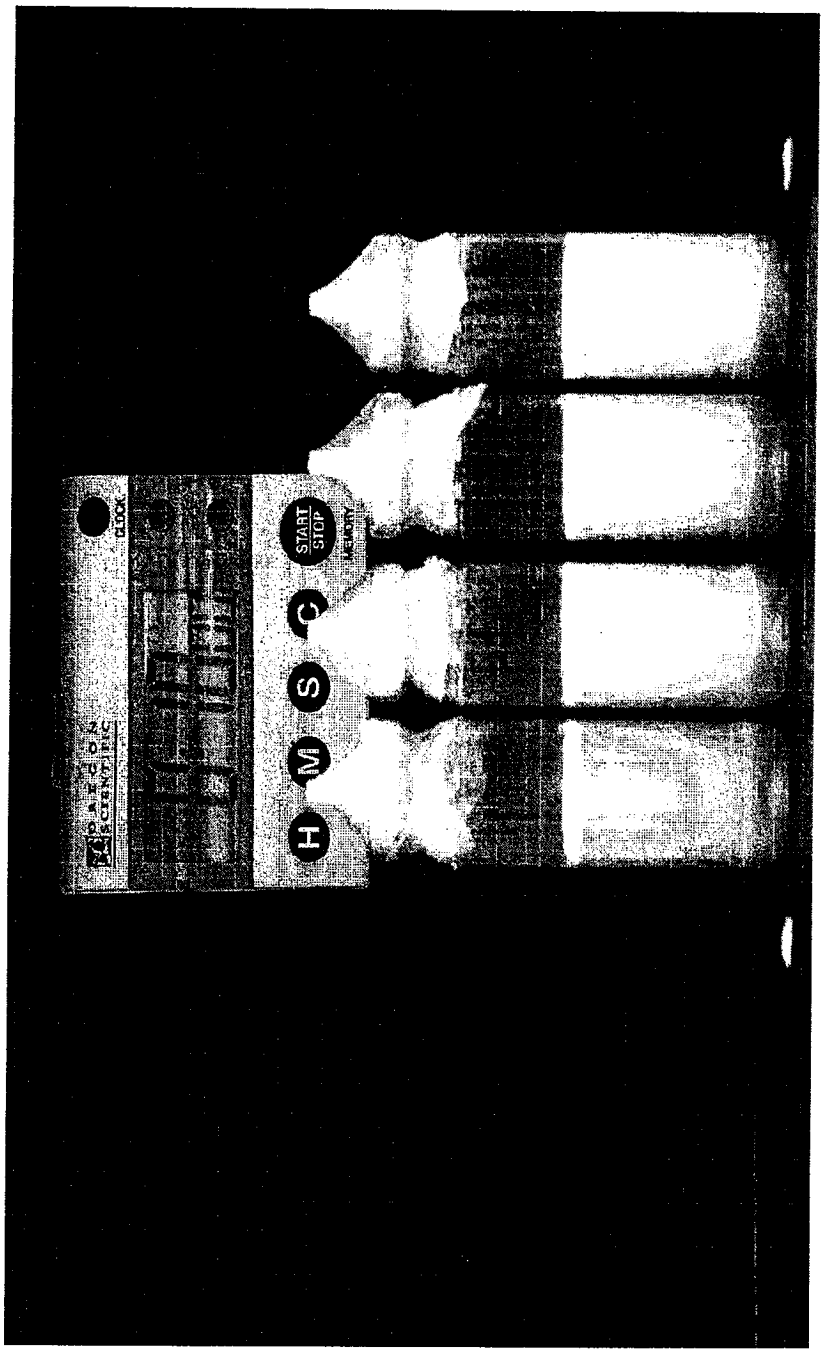


FIG. 16

COMPOSITION FOR INHALATION

CROSS-REFERENCE TO RELATED APPLICATIONS

This application is a continuation of U.S. application Ser. No. 10/502,685, filed on Jul. 27, 2004 and now issued as U.S. Pat. No. 7,759,328, which was a national phase application under 35 U.S.C. §371 of PCT International Application No. PCT/SE2003/000156, filed on Jan. 29, 2003, which claims priority to Swedish Application Serial No. 0200312-7, filed Feb. 1, 2002. The contents of these prior applications are incorporated herein by reference in their entirety.

TECHNICAL FIELD

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

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

In accordance with the present invention, there is provided a pharmaceutical composition comprising formoterol, budesonide, HFA 227 (1,1,1,2,3,3,3-heptafluoropropane), 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 (PVP having a nominal K-value of 25).

Preferably the PEG is present in an amount of 0.3% w/w. Preferably the PEG is PEG 1000 (PEG having an average molecular weight of 1000 Daltons).

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 4.5/320 mcg 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.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. **1** is a schematic drawing of an Optical Suspension Characterisation (OSCAR) set-up.

FIGS. **2-3** are graphs showing the averages of OSCAR data (lower sensor) for formulations in HFA 227 containing 4.5 μg formoterol; 0.3% w/w PEG 1000; 0.0001%-0.05% w/w PVP K25; and 160 μg budesonide (FIG. **2**) or 80 μg budesonide (FIG. **3**).

FIGS. **4-6** are graphs showing the averages of Turbiscan data for formulations in HFA 227 containing 4.5 μg formoterol; 0.3% w/w PEG 1000; 0.0001%-0.05% w/w PVP K25; and 160 μg budesonide (FIG. **4**), 80 μg budesonide (FIG. **5**), or 40 μg budesonide (FIG. **6**).

FIG. 7 is a graph showing the effect of PEG 1000 concentration on stem return force for formulations containing 4.5 μg formoterol; 160 μg budesonide; and 0.1%, 0.3%, or 0.5% w/w PEG 1000.

FIG. **8** is a graph showing the averages of Turbiscan data for formulations in HFA 227 containing 80 μg budesonide; 4.5 μg formoterol; 0.0001% PVP K25; and 0.005%-0.5% w/w PEG 1000.

FIGS. **9-11** are a series of digital photographs, taken after standing times of 0 seconds (FIG. **9**), 30 seconds (FIG. **10**), and 60 seconds (FIG. **11**), of suspensions in HFA 227 containing budesonide (160 μg/actuation); formoterol (4.5 μg/actuation); 0.3% PEG 1000; and PVP K25 at 0.0001%, 0.0005%, 0.001%, 0.01%, 0.03%, and 0.05% w/w.

FIGS. **12-14** are a series of digital photographs, taken after standing times of 0 seconds (FIG. **12**), 30 seconds (FIG. **13**), and 60 seconds (FIG. **14**), of suspensions in HFA 227 containing budesonide (80 μg/actuation); formoterol (4.5 μg/actuation); 0.3% PEG 1000; and PVP K25 at 0.0001%, 0.0005%, 0.001%, 0.01%, 0.03%, and 0.05% w/w.

FIGS. **15-16** are digital photographs, taken after standing times of 0 minutes (FIG. **15**) and 10 minutes (FIG. **16**), of suspensions in HFA 227 containing budesonide (80 μg/actua-

tion); formoterol (4.5 μg/actuation); 0.001% PVP K25; and PEG 1000 at 0.005, 0.05, 0.35, and 0.5% w/w.

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 FIG. 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, P A 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, 5 ml cylindrical glass cell, which takes readings of transmitted and backscattered tight every 40 μm on a maximum sample height of 80 mm. 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 homogeneity, 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 sedimentation rate of different suspensions.

Turbiscan may be used in several modes, e.g., transmitted or backscattering modes. Turbiscan has been used here in these examples to measure the transmitted light as a function 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; and b) particle migration resulting in creaming or sedimentation. When a product is stable (i.e., 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 terephthalate (PET) bottles crimped with a continuous valve. For all formulations, the formoterol fumarate dihydrate concentration remained constant at 0.09 mg/ml (equivalent to 4.5 mcg formoterol fumarate dihydrate per actuation) and the budesonide concentration varied between approximately 1 mg/ml to 8 mg/ml (equivalent to 40 mcg to 320 mcg per actuation).

Early OSCAR data for Symbicort pMDI formulations

Budesonide dose	Formoterol dose	PVP K25 concentration	Time	Transmittance (mV) Lower sensor PEG concn % w/w	
ex-actuator	ex-actuator	(% w/w)	seconds	0.1	0.3
40 μg	4.5 μg	0.001	30 seconds		257
			60 seconds		264

-continued

Early OSCAR data for Symbicort pMDI formulations

Budesonide dose	Formoterol dose	PVP K25 concentration	Time	Transmittance (mV) Lower sensor PEG concn % w/w	
ex-actuator	ex-actuator	(% w/w)	seconds	0.1	0.3
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

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

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

Table of Degree of Dispersion of Suspensions Over Time: (all Samples)

Photographs were taken of all doses (320 μg/4.5 μg to 40 μg/4.5 μg) 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 representation of the degree of dispersion over time.

If the sample was fully suspended, the sample was rated 0, i.e., 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 4.5 μg/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, i.e., less than 20% clear liquid present 1

More than 60% dispersed, i.e., less than 40% clear liquid present 2

Less than 40% dispersed, i.e., more than 60% clear liquid present 3

Less than 20% dispersed, i.e., more than 80% clear liquid present 4

Fully creamed 5

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

Dose μg/shot	Time	PVP concentration (% w/w)					
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

-continued

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

Dose µg/shot	Time	PVP concentration (% w/w)					
Budesonide	Sec/mins	0.0001	0.0005	0.001	0.01	0.03	0.05
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)

FIG. **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 FIG. **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 interpreted 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 FIG. **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

FIGS. **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.

Methodology-Force to Fire (Return Force at 0.5 mm 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 0.5 mm 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 vaporize. Force to fire testing was performed at preset actuations.

Data

Force to Fire Data

FIG. **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 (FIG. **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).

FIGS. **15** and **16** show Budesonide 80 µg/shot, Formoterol 4.5 µg/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 fumarate 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)	Drug	Fine particle fraction (% cumulative undersize for 4.7 µm cut-off) 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)	Drug	Fine particle fraction (% cumulative undersize for 4.7 µm cut-off) 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

The invention claimed is:

1. A pressurized metered dose inhaler containing a suspension composition comprising formoterol fumarate dihydrate in the form of particles; budesonide in the form of particles; 1,1,1,2,3,3,3-heptafluoropropane (HFA227); polyvinyl pyrrolidone (PVP); and polyethylene glycol (PEG), wherein the budesonide is present in the composition at a concentration in

the range of 1 mg/ml to 8 mg/ml, the PVP is present at a concentration in the range of 0.001% to 0.01% w/w, and the PEG is present at a concentration in the range of 0.05 to 0.5% w/w, and wherein an actuation of the inhaler delivers 4.5 μg formoterol fumarate dihydrate and 40 to 320 μg budesonide.

2. The inhaler of claim **1**, wherein the PEG is PEG 1000 (PEG with an average molecular weight of 1,000).

3. The inhaler of claim **1**, wherein the PVP is PVP K25 (PVP with a nominal K-value of 25).

4. The inhaler of claim **1**, wherein the PVP is present in the composition at a concentration of 0.001% w/w.

5. The inhaler of claim **4**, wherein the PVP is PVP K25.

6. The inhaler of claim **5**, wherein the PEG is PEG 1000.

7. The inhaler of claim **1**, wherein an actuation of the inhaler delivers 40 μg budesonide.

8. The inhaler of claim **1**, wherein an actuation of the inhaler delivers 80 μg budesonide.

9. The inhaler of claim **1**, wherein an actuation of the inhaler delivers 160 μg budesonide.

10. A pressurized metered dose inhaler containing a suspension composition comprising formoterol fumarate dihydrate in the form of particles; budesonide in the form of particles; 1,1,1,2,3,3,3-heptafluoropropane (HFA227); PVP K25 (polyvinyl pyrrolidone with a nominal K-value of 25); and PEG-1000 (polyethylene glycol with an average molecular weight of 1,000), wherein the budesonide is present at a concentration in the range of 1 mg/ml to 8 mg/ml; the PVP K25 is present at a concentration of 0.001% w/w; and the PEG-1000 is present at a concentration of 0.3% w/w, and wherein an actuation of the inhaler delivers 4.5 μg formoterol fumarate dihydrate and 40 to 320 μg budesonide.

11. The inhaler of claim **10**, wherein an actuation of the inhaler delivers 40 μg budesonide.

12. The inhaler of claim **10**, wherein an actuation of the inhaler delivers 80 μg budesonide.

13. The inhaler of claim **10**, wherein an actuation of the inhaler delivers 160 μg budesonide.

14. The inhaler of claim **10**, wherein the budesonide is in the form of its 22R-epimer.

15. The inhaler of claim **10**, wherein the formoterol fumarate dihydrate is in the form of its R,R enantiomer.

16. A method of administering an inhalable composition to a patient, the method comprising

providing a pressurized metered dose inhaler containing a suspension composition comprising formoterol fumarate dihydrate in the form of particles, budesonide in the form of particles, HFA227, PVP K25, and PEG-1000, wherein the budesonide is present at a concentration in the range of 1 mg/ml to 8 mg/ml; the PVP K25 is present at a concentration of 0.001% w/w; and the PEG-1000 is present at a concentration of 0.3% w/w, and wherein an actuation of the inhaler delivers 4.5 μg formoterol fumarate dihydrate and 40 to 320 μg budesonide; and

causing the patient to inhale the composition from the inhaler.

17. The method of claim **16**, wherein an actuation of the inhaler delivers 40 g budesonide.

18. The method of claim **16**, wherein an actuation of the inhaler delivers 80 μg budesonide.

19. The method of claim **16**, wherein an actuation of the inhaler delivers 160 μg budesonide.

20. The method of claim **16**, wherein the patient is suffering from asthma.

21. The method of claim **16**, wherein the patient is suffering from chronic obstructive pulmonary disease (COPD).

22. The method of claim **16**, wherein the budesonide is in the form of its 22R-epimer.

23. The method of claim **16**, wherein the formoterol fumarate dihydrate is in the form of its R,R enantiomer.

24. A method of administering an inhalable composition to a patient, the method comprising

providing a pressurized metered dose inhaler containing a suspension composition comprising formoterol fumarate dihydrate in the form of particles; budesonide in the form of particles; HFA227; PVP; and PEG, wherein the budesonide is present in the composition at a concentration in the range of 1 mg/ml to 8 mg/ml, the PVP is present at a concentration in the range of 0.001% to 0.01% w/w, and the PEG is present at a concentration in the range of 0.05 to 0.5% w/w, and wherein an actuation of the inhaler delivers 4.5 μg formoterol fumarate dihydrate and 40 to 320 g budesonide; and

causing the patient to inhale the composition from the inhaler.

25. The method of claim **24**, wherein an actuation of the inhaler delivers 40 μg budesonide.

26. The method of claim **24**, wherein an actuation of the inhaler delivers 80 μg budesonide.

27. The method of claim **24**, wherein an actuation of the inhaler delivers 160 μg budesonide.

28. The method of claim **24**, wherein the patient is suffering from asthma.

29. The method of claim **24**, wherein the patient is suffering from chronic obstructive pulmonary disease (COPD).

30. The method of claim **24**, wherein the budesonide is in the form of its 22R-epimer.

31. The method of claim **24**, wherein the formoterol fumarate dihydrate is in the form of its R,R enantiomer.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 8,143,239 B2
APPLICATION NO. : 12/790196
DATED : March 27, 2012
INVENTOR(S) : Nayna Govind et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Title page, column 2, lines 45-46:

The text "Final Office Action, in U.S. Appl. No. 10/502,685, mailed Jan. 29, 2007 (6 pages)" should be deleted and reinserted as a new entry beginning at first page, column 2, line 46

Claim 17, column 10, line 7:

Delete "40 g" and insert --40 µg-- therefor

Claim 24, column 10, line 32:

Delete "320 g" and insert --320 µg-- therefor

Signed and Sealed this
Tenth Day of July, 2012

David J. Kappos

David J. Kappos
Director of the United States Patent and Trademark Office

CERTIFICATE OF COMPLIANCE WITH TYPE-VOLUME LIMITATION

1. This brief complies with the type-volume limitation of Federal Circuit Rule 32(b)(1). The brief contains 13,847 words, excluding the portions exempted by Federal Rule of Appellate Procedure 32(f) and Federal Circuit Rule 32(b)(2).

2. This brief complies with the typeface requirements of Federal Rule of Appellate Procedure 32(a)(5) and the type style requirements of Federal Rule of Appellate Procedure 32(a)(6). The brief has been prepared in a proportionally spaced typeface using Microsoft® Word and 14-point Times New Roman type.

Dated: April 6, 2021 /s/Shannon M. Bloodworth
Shannon M. Bloodworth

CERTIFICATE OF CONFIDENTIAL MATERIAL

The foregoing document contains one unique word (including numbers) marked confidential. This number does not exceed the maximum of 15 words permitted by Fed. Cir. R. 25.1(d)(1)(A).

Dated: April 6, 2021 /s/Shannon M Bloodworth
Shannon M. Bloodworth

CERTIFICATE OF AUTHORITY

I certify that I have the authority of my co-counsel Shannon M. Bloodworth to file this document with her electronic signature.

I declare under penalty of perjury under the laws of the United States that the foregoing is true and correct.

Dated: April 6, 2021

/s/Andrew T. Dufresne
Andrew T. Dufresne