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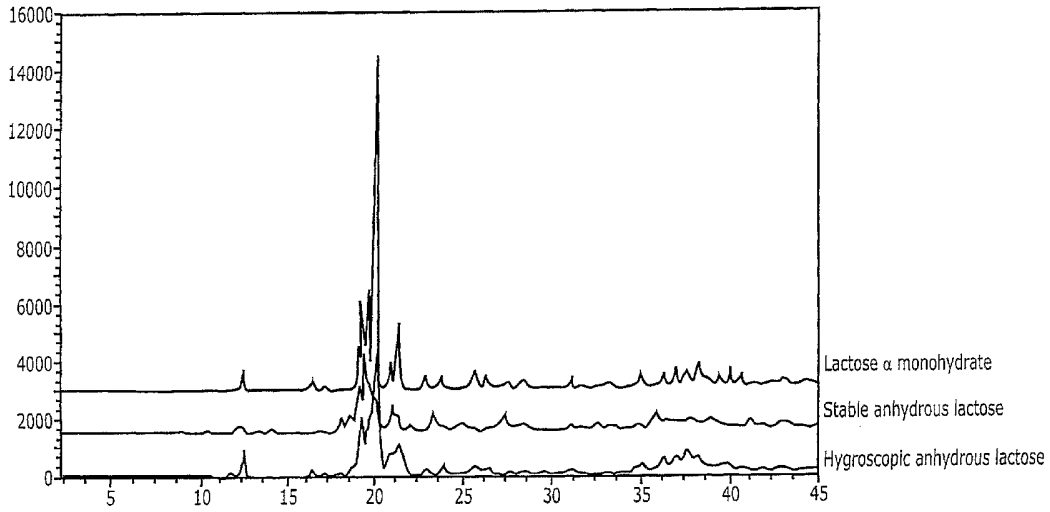
(54) **Title:** INHALABLE PHARMACEUTICAL FORMULATIONS EMPLOYING LACTOSE ANHYDRATE AND METHODS OF ADMINISTERING THE SAME



(57) **Abstract:** Pharmaceutical formulations suitable for inhalation comprise at least one pharmaceutically active medicament and lactose anhydrate.

WO 2006/124556 A2

INHALABLE PHARMACEUTICAL FORMULATIONS EMPLOYING LACTOSE ANHYDRATE AND METHODS OF ADMINISTERING THE SAME

Field of the Invention

The invention generally relates to pharmaceutical formulations suitable for inhalation which employ lactose and methods of administering the same.

Background of the Invention

Inhalers are well known devices for administering medicinal products to the respiratory tract. They are commonly used for local relief of respiratory diseases, but the pulmonary route also provides a conduit for the potential systemic delivery of a variety of medicinal products such as analgesics and hormones.

The two main types of inhalers are the pressurized metered dose inhaler (MDI) and the dry powder inhaler (DPI). The MDI uses a volatile propellant to produce an aerosol cloud containing the active ingredient for inhalation. DPIs deliver the active ingredient in the form of dry powder particles to the respiratory tract. To facilitate targeting to the lung, the active ingredient used within an inhaler is typically less than 5μm, and consequently inherently cohesive. Dispersion upon aerosolisation is achieved by a combination of the inhaler dispersion mechanics and the formulation.

Dry powder formulations for inhalation commonly comprise at least one micronised active substance and a biologically inert carrier. The latter is used in dry powders for inhalation as a diluent, to facilitate manufacture, and as an aerosolisation aid. It typically comprises defined proportions of finely divided and coarser particles to optimise and control the manufacture of the drug product and delivery of the active ingredient to the lung. The carrier may include any acceptable pharmacologically inert material or combination of materials. The most commonly used excipient in DPIs is α-lactose monohydrate.

Lactose can exist as either the alpha or beta form of the crystal. Beta lactose is an anhydrate and is non-hygroscopic below 97% relative humidity (RH). Above 97%RH, it absorbs moisture and mutarotates to form the alpha-monohydrate. Alpha monohydrate is non hygroscopic. Angberg *et al*, Int. J. Pharm. **73**, 209-220 (1991) disclose employing microcalorimetry at 25°C to investigate the incorporation of hydrate water in roller-dried anhydrous lactose that consisted of 31% alpha- and 69% beta-lactose. Differential scanning calorimetry and water vapor uptake measurements were also performed. Additionally, Angberg *et al.* disclose that the anhydrous alpha-lactose can accommodate a water molecule to become alpha-lactose monohydrate. Beta-lactose can only exist as the anhydrous form, but it can mutarotate to alpha-lactose and subsequently incorporate water.

The performance of dry powder inhalers is typically affected by the environmental conditions in which they are stored and used, unless the formulation is protected in some way from the environment. In particular, high relative humidity of the ambient air is believed to adversely affect the physical stability and the in vitro performance of the powder. For example, Jashnani *et al* (Int. J. Pharm. 113, 123-130. 1995) disclose a decrease in fine particle dose or fine particle percent for both albuterol and albuterol sulfate with increasing relative humidity at any given temperature with differences being more marked at higher temperatures. Ganderton and Kassem (Advances in Pharm Sci. **6** 165-191, 1992) disclose that high relative humidity results in an increase in adhesive forces between drug and carrier due to capillary action. Hickey et al (Pharm. Tech. 58-82, 1994) disclose that interparticle cohesion usually increases as the relative humidity of the air increases. At humidities greater than 65% fluid condenses in the space between particles that are close together. This can lead to liquid bridges between neighboring particles, and the effect of surface tension gives rise to attractive forces. Additionally, Jashnani *et al* (Int. J. Pharm, 130, 13-24, 1996) disclose a comparison of aerosols formed by three salts and the free base of albuterol following their formation from similarly micronized crystalline powders held in a model dry powder inhaler under varying environmental conditions. Overall, Jashnani *et al* disclose that albuterol stearate, the most hydrophobic salt, emptied and

aerosolized best from the inhaler and showed least sensitivity to temperature and humidity.

Various methodologies have been employed in an attempt to assess and prevent the drop in physical performance induced by adverse environmental storage. Maggi *et al* (Int. J. Pharm. 177, 1, 83-91, 1999)) disclose employment of an accelerated stability test on two prototypes of a new dry powder inhaler to verify the influence of moisture uptake on the performance of the device. The reservoir based multi dose dry powder inhalers (e.g., Turbuhaler® made commercially available by Astra Zeneca of Wilmington, Delaware (see e.g., Wetterlim (Pharm. Res 5, 506-508, 1988)) contain a desiccant store in such inhalers. Williams *et al* (STP Pharma Sci 19(3) 243-250, 2000) have demonstrated that the inclusion of moisture scavengers within MDI systems helped minimize the undesired consequences caused by moisture ingress into the MDI canisters.

The use of a desiccant integral to the device has also been shown to enhance chemical stability of inhaled products. For example, Wu *et al* (WO 2000/078286) disclose a medicinal aerosol steroid solution formulation product with enhanced chemical stability. The steroid is a 20-ketosteroid having an OH group at the C-17 or C-21 position and the aerosol container has a non-metal interior surface which has been found to reduce chemical degradation of such steroids.

Alternatively the susceptibility of physical performance dry powder formulations to environmental humidity may be potentially reduced by increasing the moisture resistance of the dry powder formulation to the environment. Keller and Mueller-Waltz (WO 2000/028979) disclose the use of magnesium stearate for improving the resistance to moisture, i.e., for lowering the sensitivity of powder mixtures to moisture. Such a concept has also been disclosed for formulations containing formoterol fumarate, salbutamol sulphate and salbutamol base by Mueller-Waltz et al (Drug Delivery to the Lungs XI, The Aerosol Society, London, 2000, 26-29).

The use of dehydrated lactose forms have been disclosed. More specifically, Figura and Epple, *Journal of Thermal Analysis*, **44**, (1995) 45-53 disclose an investigation of dehydrated lactose forms α_H and α_S by time- and

temperature-resolved X-ray powder diffraction and differential scanning calorimetry.

For all of the above disclosures to be used in practice, the desiccant or ternary agent should be either non-inhaled, or safety data generated to demonstrate the clinical acceptability of any additional inhaled excipients within the formulation. As such, there exists a desire for excipients for use within inhalation formulations to manifest physical and chemical stability enhancing contributions to the formulation. There is also a need in the art to address potential problems associated with stability problems and a decrease in fine particle mass as a function of storage length, i.e., the time commencing with the point at which the formulation is placed within the inhalation device. As known in the art, "fine particle fraction" or "FP fraction" refers to the percentage of particles within a given dose of aerosolized medicament that is of "respirable" size, as compared to the total emitted dose. It is highly desirable to provide a pharmaceutical formulation which produces a consistent FP fraction throughout the life of the product, as well as potentially provide chemical stability benefits.

Summary of the Invention

In one aspect, the invention provides a pharmaceutical formulation suitable for inhalation comprising at least one pharmaceutically active medicament and lactose anhydrate.

In another aspect, the invention provides a method for treating a respiratory disorder in a mammal. The method comprising administrating a therapeutically effective amount of the pharmaceutical formulation to the mammal.

In another aspect, the invention provides an inhalation device employing a pharmaceutical formulation.

The present invention offers a number of surprising advantages and benefits. For example, the present invention is highly advantageous in that it provides inhalable pharmaceutical formulations which are capable of displaying improved desiccating ability, particularly at lower relative humidity conditions. Moreover, the inhalable pharmaceutical formulations are capable

of exhibiting improved FP fraction stability relative to conventional inhalable formulations. Moreover, it is believed that the chemical degradation of the active material can be mediated by the presence of moisture in such formulations. The inhalable pharmaceutical formulations are thus capable of increased chemical stability of the active material relative to conventional formulations. Surprisingly, the pharmaceutical formulations of the invention are capable of exhibiting little, if any, aggregation upon storage, notwithstanding the moisture absorption capabilities of the formulations.

Brief Description of the Drawings

Figure 1 is a chart illustrating the X-Ray diffraction patterns for anhydrous lactose in comparison with alpha lactose monohydrate.

Figure 2 is a graph illustrating GVS moisture uptake for various types of lactose.

Figure 3 is a graph illustrating the weight change of various types of anhydrous lactose upon extended storage at 25°C/75%RH.

Figure 4 is a graph illustrating FP fraction values for various formulation blends containing different levels of various types of anhydrous and monohydrate lactose.

Figure 5 is a graph illustrating expected vs. observed moisture absorption at various temperature and relative humidity conditions for salmeterol xinafoate/fluticasone propionate containing formulations.

Figure 6 is a graph illustrating the moisture uptake of anhydrous lactose (coarse and fines) and monohydrate lactose.

Figure 7 is a graph illustrating the moisture uptake of various formulation blends containing different levels of anhydrous (fine and coarse) and monohydrate lactose upon exposure to 25°C/40%RH.

Figure 8 is a graph illustrating the calculated percent rehydration for various formulation blends containing different levels of anhydrous (fine and coarse) and monohydrate lactose upon storage at 25°C/40%RH.

Figure 9 is a graph illustrating the equilibrium relative humidity of various formulation blends containing different levels of anhydrous (fine and coarse) and monohydrate lactose.

Figure 10 is a graph illustrating the desiccant capacity of various formulation blends containing different levels of anhydrous (fine and coarse) and monohydrate lactose.

Figure 11 is a graph illustrating expected vs. observed moisture absorption for various salmeterol xinafoate/fluticasone propionate formulations at a number of temperature and humidity conditions.

Figure 12 is a graph illustrating FP fraction values for various formulation blends containing different levels of anhydrous (fine and coarse) and monohydrate lactose with storage at 25°C/75%RH.

Figure 13 is a graph illustrating FP fraction values for various formulation blends containing different levels of anhydrous (fine and coarse) and monohydrate lactose with storage at 40°C/75%RH.

Figure 14 is a graph illustrating the desiccant capacity of various formulation blends containing different levels of anhydrous (fine and coarse) and monohydrate lactose.

Figure 15 is a graph illustrating FP fraction values for various formulation blends containing different levels of anhydrous (fine and coarse) and monohydrate lactose with storage at 25°C/75%RH.

Figure 16 is a graph illustrating FP fraction values for various formulation blends containing different levels of anhydrous (fine and coarse) and monohydrate lactose with storage at 40°C/75%RH.

Figure 17 illustrates the percentage weight loss for runs carried out at 30 mBar at various temperatures during the drying of lactose in an agitated vacuum pan dryer oven.

Figure 18 illustrates moisture content vs. drying time in the dehydration of lactose at the Krauss Maffei drying trials.

Figure 19 is a graph illustrating the FP fractions of formulations containing lactose monohydrate and dehydrated lactose at various temperature and humidity conditions.

Figure 20 is a graph illustrating total impurities for formulations containing lactose monohydrate and dehydrated lactose at various temperature and humidity conditions.

Figure 21 is a graph illustrating the equilibrium relative humidity of formulations containing lactose monohydrate and dehydrated lactose.

Figure 22 is a graph illustrating the desiccant capacity of various formulations containing dehydrated lactose after blending and filling in dry powder strips.

Figure 23 is a graph illustrating the desiccant capacity of various formulations containing dehydrated lactose after filling in dry powder strips.

Figure 24 is a graph illustrating the desiccant capacity for formulations determined at various temperature and humidity conditions.

Figure 25 is a graph illustrating the FP fraction of formulations at various temperature and humidity conditions.

Figure 26 is a graph illustrating total emitted dose of formulations at various temperature and humidity conditions.

Figure 27 is a graph illustrating the FP fraction of formulations including cellobiose octaacetate and dehydrated lactose.

Figure 28 is a graph illustrating total emitted dose of formulations at 30°C/65%RH.

Figure 29 is a graph illustrating total impurities as a function of time for dehydrated lactose.

Figure 30 is a graph illustrating the equilibrium relative humidity maintained by using various levels of partially dehydrated lactose.

Figure 31 is a graph illustrating the rehydration of various levels of partially dehydrated lactose.

Figure 32 is a graph illustrating the equilibrium relative humidity of various formulations containing partially dehydrated lactose.

Figure 33 is a graph illustrating the moisture absorption for formulations containing dehydrated lactose at various temperature and humidity conditions.

Figure 34 is a graph illustrating the FP fraction performance for various formulations containing partially dehydrated lactose.

Figure 35 is a graph illustrating the FP fraction performance for various formulations containing partially dehydrated lactose after storage for six weeks at 40°C/75%RH.

Figure 36 is a graph illustrating the FP fraction performance for a formulation containing dehydrated lactose compared to a formulation containing lactose monohydrate.

Figure 37 is a graph illustrating drug impurities formation for a formulation containing dehydrated lactose compared to a formulation containing lactose monohydrate.

Figure 38 is a graph illustrating the FP fraction for formulations with and without dehydrated lactose at various temperature and humidity conditions.

Figure 39 is a graph illustrating moisture absorption for formulations containing dehydrated lactose, dehydrated lactose + α-D-cellobiose octaacetate and dehydrated lactose + magnesium stearate.

Figure 40 is a graph illustrating FP fraction changes for a formulation employing lactose monohydrate and formulations employing dehydrated lactose.

Figure 41 is a graph illustrating impurities formation in a formulation containing lactose monohydrate at various temperature and humidity conditions.

Figure 42 is a graph illustrating the FP fraction for a formulation containing lactose monohydrate at various temperature and humidity conditions.

Figure 43 is a graph illustrating impurities formation in a formulation containing lactose monohydrate at various temperature and humidity conditions.

Figure 44 is a graph illustrating the FP fraction for a formulation containing lactose monohydrate at various temperature and humidity conditions.

Detailed Description of the Invention

The invention will now be described with respect to the embodiments set forth herein. It should be appreciated that these embodiments are set forth to illustrate the invention, and that the invention is not limited to these embodiments.

All publications, patents, and patent applications cited herein, whether *supra* or *infra*, are hereby incorporated herein by reference in their entirety to the same extent as if each individual publication, patent, or patent application was specifically and individually indicated to be incorporated by reference.

It must be noted that, as used in the specification and appended claims, the singular forms "a", "an" and "the" include plural referents unless the content clearly dictates otherwise.

In one aspect, the invention provides a pharmaceutical formulation suitable for inhalation. The pharmaceutical formulation comprises at least one pharmaceutically active medicament and lactose anhydrate. In one embodiment, the pharmaceutical formulation consists essentially of at least one pharmaceutically active medicament and lactose anhydrate. In one embodiment, the pharmaceutical formulation consists of at least one pharmaceutically active medicament and lactose anhydrate.

Advantageously, the pharmaceutical formulation exhibits a weight gain of at least 0.3 percent when equilibrated at 25°C and 40 percent relative humidity. More preferably, the formulation exhibits a weight gain of at least 0.2 percent when equilibrated 25°C and 30 percent relative humidity. Most preferably, the formulation exhibits a weight gain of at least 0.1 percent when equilibrated at 25°C and 20 percent relative humidity. For the purposes of the invention, the term "equilibrated" is defined as a weight change of less than 0.1% w/w following storage for 4 hours.

For the purposes of the invention, the term "lactose" as used herein is to be broadly construed. As an example, lactose is intended to encompass crystalline, amorphous, isomeric and polymorphic forms of lactose, including, but not limited to, lactose monohydrate, the stereoisomers α-lactose monohydrate and β-anhydrous lactose, as well as alpha-anhydrous lactose. Lactose (i.e., milk sugar) is preferably obtained from cheese whey, which can be manufactured in different forms depending on the process employed. As used herein, the term "particle" is to be broadly interpreted to encompass those of various shapes, sizes, and/or textures which can include those that may have varying degrees of irregularities, disuniformities, etc. or which may possess regular and/or uniform properties.

The term "lactose anhydrate" is defined to encompass lactose having various levels of water content. For example, in one embodiment, the lactose anhydrate includes less than 1 mole of water (e.g., including, without limitation, water) per mole of lactose. In an embodiment, lactose anhydrate may encompass anhydrous lactose. By virtue of employment of the lactose, the pharmaceutical formulation contains varying levels of water. For example in one embodiment, the pharmaceutical formulation is free of water. In another embodiment, the pharmaceutical formulation is substantially free of water. In another embodiment, the pharmaceutical formulation contains less than or equal to about 1, 2, 3, 4, or 5 %w/w of water.

In accordance with the invention, the amount of lactose employed in the formulation is believed to assist in achieving the benefits described herein. For example, in one embodiment, the lactose includes at least 1, 3, or 5 %w/w lactose anhydrate, more preferably at least 10 %w/w lactose anhydrate. In other embodiments, the lactose includes from, at a lower end 1, 2, 3, 5, 10, 20, 30, or 40 %w/w to, at a higher end, 5, 10, 20, 30, 40, 50, 60, 70, 80, 90, or 100 %w/w lactose anhydrate. In the above embodiments, the balance of the lactose present is monohydrate lactose.

The lactose anhydrate is preferably present as hygroscopic alpha anhydrous lactose or α_H anhydrous lactose. For the purposes of the invention "hygroscopic alpha anhydrous lactose" is characterized by having a crystallographic structure, and anomeric ratio consistent with that of the predominantly alpha form of lactose whilst being essentially anhydrous in nature (represented by the lack of water of crystallization). The alpha-anhydrous form is also hygroscopic in nature as demonstrated by the propensity of the material to sorb water (at least 1% w/w) under low environmental relative humidity conditions (20%RH) at 25°C. The above properties apply to fully dehydrated lactose. Nonetheless, it should be understood that other hygroscopic properties may be displayed by partially dehydrated forms of lactose encompassed by the invention.

The lactose anhydrate may possess various physical properties. As an example, in one embodiment, the lactose anhydrate has a surface area ranging from, at a lower end, about 0.1, 1, 2, 3, or 4 m^2/g to, at a higher end,

about 6, 7, 8, 9, or 10 m^2/g. In one embodiment, the lactose anhydrate has a porosity ranging from, at a lower end, about 0.0001, 0.005, or 0.001 ml/g to, at a higher end, about 0.05 or 0.01 ml/g, measured using BET N_2 adsorption. In one embodiment, the lactose anhydrate has a beta content ranging from, at a lower end, about 0, 5, 10, 15, 20, or 25 %w/w to, at a higher end, about 20, 25, 30, 35, or 40 %w/w measured using gas chromatography. In one embodiment, the lactose anhydrate possesses a water content ranging from about 0.001 to about 5 percent measured using thermo-gravimetric analysis. In one embodiment, the lactose anhydrate has a dispersive surface energy ($\gamma^D s$) ranging from about 30 to about 60 mJm^{-2} measured using inverse gas chromatography.

In one embodiment, the lactose anhydrate may encompass both coarse and fine fractions. The relative amounts of coarse and fines employed may be varied in accordance with the present invention. In various embodiments, the coarse and fine fractions have preferred size profiles. For example, when employed in a dry powder device (e.g., Diskus®), the coarse fraction preferably has a volume median diameter (D_{50}) ranging from about 60 to about 90 µm, and a volume of sub-14.2 µm particles ranging from about 0 to about 10%v/v. The fine fraction preferably has a volume median diameter (D_{50}) particle size ranging from about 1 to about 30 µm and a volume of sub 14.2 µm particles ranging from about 30 to about 100 %v/v, measured using laser diffraction. In general, in one embodiment, the pharmaceutical formulation of the invention, and in particular the lactose employed, is free or substantially free of particle size change as a result of water uptake when exposed a variety of humidity conditions including, without limitation, those set forth herein.

In addition to the above, the lactose anhydrate employed in accordance with the invention may optionally further be present, to a certain level, in amorphous form. In one embodiment, the lactose anhydrate includes at least 1 %w/w of amorphous lactose. In one embodiment, the lactose anhydrate includes at least 10 %w/w of amorphous lactose. In other embodiments, the anhydrous lactose includes from, at a lower end 0, 1, 5, 10, 20, 30, or 40 %w/w to, at a higher end, 5, 10, 20, 30, 40, 50, 60, 70, 80, 90 or

100 %w/w amorphous lactose, based on the lactose weight. The balance in the above embodiments is crystalline lactose anhydrate. The above weight percentages are based on the weight of the lactose.

In general, lactose may be formed by various processes known in the art. One example is set forth in Figura, L.O. and Epple M., *J, Thermal Anal.*, (1995) **44** 44-53. In one embodiment, for example, hygroscopic anhydrous lactose (i.e., α_H anhydrous lactose) may be manufactured by a rapid thermal dehydration by heating at 120°C under 20 mbar pressure for 3 hours. Other processes may also be employed.

Medicaments, for the purposes of the invention, include a variety of pharmaceutically active ingredients, such as, for example, those which are useful in inhalation therapy. In general, the term "medicament" is to be broadly construed and include, without limitation, actives, drugs and bioactive agents, as well as biopharmaceuticals. In various embodiments, medicament may be present in micronized form. Appropriate medicaments may thus be selected from, for example, analgesics, (e.g., codeine, dihydromorphine, ergotamine, fentanyl or morphine); anginal preparations, (e.g., diltiazem; antiallergics, e.g., cromoglicate, ketotifen or nedocromil); antiinfectives (e.g., cephalosporins, penicillins, streptomycin, sulphonamides, tetracyclines and pentamidine); antihistamines, (e.g., methapyrilene); anti-inflammatories, (e.g., beclometasone dipropionate, fluticasone propionate, flunisolide, budesonide, rofleponide, mometasone furoate, ciclesonide, triamcinolone acetonide, 6α, 9α-difluoro-11β-hydroxy-16α-methyl-3-oxo-17α-propionyloxy-androsta-1,4-diene-17β-carbothioic acid S-(2-oxo-tetrahydro-furan-3-yl) ester)), (6α,11β,16α,17α)-6,9-difluoro-17-{[(fluoromethyl)thio]carbonyl}-11-hydroxy-16-methyl-3-oxoandrosta-1,4-dien-17-yl 2-furoate, or (6α,11β,16α,17α)-6,9-difluoro-17-{[(fluoromethyl)thio]carbonyl}-11-hydroxy-16-methyl-3-oxoandrosta-1,4-dien-17-yl 4-methyl-1,3-thiazole-5-carboxylate; antitussives, (e.g., noscapine; bronchodilators, e.g., albuterol (e.g. as sulphate), salmeterol (e.g. as xinafoate), ephedrine, adrenaline, fenoterol (e.g as hydrobromide), formoterol (e.g., as fumarate), isoprenaline, metaproterenol, phenylephrine, phenylpropanolamine, pirbuterol (e.g., as acetate), reproterol (e.g., as hydrochloride), rimiterol, terbutaline (e.g., as sulphate), isoetharine,

tulobuterol,4-hydroxy-7-[2-[[2-[[3-(2-(henylethoxy)propyl]sulfonyl]ethyl]-amino]ethyl-2(3H)-benzothiazolone), 3-(4-{[6-({(2*R*)-2-hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl}amino)hexyl]oxy}butyl) benzenesulfonamide, 3-(3-{[7-({(2*R*)-2-hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl}amino)heptyl]oxy}propyl)benzenesulfonamide, 4-{(1*R*)-2-[(6-{2-[(2,6-dichlorobenzyl)oxy] ethoxy}hexyl)amino]-1-hydroxyethyl}-2-(hydroxymethyl)phenol, 2-hydroxy-5-((1*R*)-1-hydroxy-2-{[2-(4-{[(2*R*)-2-hydroxy-2- phenylethyl]amino}phenyl)ethyl]amino}ethyl)phenylformamide, or 8-hydroxy-5-{(1*R*)-1-hydroxy-2-[(2-{4-[(6-methoxy-1,1'-biphenyl-3-yl)amino] phenyl} ethyl)amino]ethyl}quinolin-2(1*H*)-one; diuretics, (e.g., amiloride; anticholinergics, e.g., ipratropium (e.g., as bromide), tiotropium, atropine or oxitropium); hormones, (e.g., cortisone, hydrocortisone or prednisolone); xanthines, (e.g., aminophylline, choline theophyllinate, lysine theophyllinate or theophylline); therapeutic proteins and peptides, (e.g., insulin). It will be clear to a person skilled in the art that, where appropriate, the medicaments may be used in the form of salts, (e.g., as alkali metal or amine salts or as acid addition salts) or as esters (e.g., lower alkyl esters) or as solvates (e.g., hydrates) to optimise the activity and/or stability of the medicament. Combinations of any of the above medicaments may also be used. It will be further clear to a person skilled in the art that where appropriate, the medicaments may be used in the form of a pure isomer, for example, R-salbutamol or RR-formoterol.

Particular medicaments for administration using pharmaceutical formulations in accordance with the invention include anti-allergics, bronchodilators, beta agonists (e.g., long-acting beta agonists), and anti-inflammatory steroids of use in the treatment of respiratory conditions as defined herein by inhalation therapy, for example cromoglicate (e.g. as the sodium salt), salbutamol (e.g. as the free base or the sulphate salt), salmeterol (e.g. as the xinafoate salt), bitolterol, formoterol (e.g. as the fumarate salt), terbutaline (e.g. as the sulphate salt), reproterol (e.g. as the hydrochloride salt), a beclometasone ester (e.g. the dipropionate), a fluticasone ester (e.g. the propionate), a mometasone ester (e.g., the furoate), budesonide, dexamethasone, flunisolide, triamcinolone, tripredane, (22R)-6α,

9α-difluoro-11β,21-dihydroxy-16α,17α -propylmethylenedioxy-4-pregnen-3,20-dione. Medicaments useful in erectile dysfunction treatment (e.g., PDE-V inhibitors such as vardenafil hydrochloride, along with alprostadil and sildenafil citrate) may also be employed. It should be understood that the medicaments that may be used in conjunction with the inhaler are not limited to those described herein.

Salmeterol, especially salmeterol xinafoate, salbutamol, fluticasone propionate, beclomethasone dipropionate and physiologically acceptable salts and solvates thereof are especially preferred.

It will be appreciated by those skilled in the art that the formulations according to the invention may, if desired, contain a combination of two or more medicaments. Formulations containing two active ingredients are known for the treatment of respiratory disorders such as asthma, for example, formoterol (e.g. as the fumarate) and budesonide, salmeterol (e.g. as the xinafoate salt) and fluticasone (e.g. as the propionate ester), salbutamol (e.g. as free base or sulphate salt) and beclometasone (as the dipropionate ester) are preferred.

In one embodiment, a particular combination that may be employed is a combination of a beta agonist (e.g., a long-acting beta agonist) and an anti-inflammatory steroid, and particularly at least one beta agonist and at least one anti inflammatory steroid. One embodiment encompasses a combination of fluticasone propionate and salmeterol, or a salt thereof (particularly the xinafoate salt). The ratio of salmeterol to fluticasone propionate in the formulations according to the present invention is preferably within the range 4:1 to 1:20. The two drugs may be administered in various manners, simultaneously, sequentially, or separately, in the same or different ratios. In various embodiments, each metered dose or actuation of the inhaler will typically contain from 25 µg to 100 µg of salmeterol and from 25 µg to 500 µg of fluticasone propionate. The pharmaceutical formulation may be administered as a formulation according to various occurrences per day. In one embodiment, the pharmaceutical formulation is administered twice daily.

The pharmaceutical formulation may include various amounts of the one or more excipient and lactose anhydrate. As an example, in various embodiments, the formulation may include, at a lower end, from 0.05, 0.1, 1, 2 3, 5, 10, 15, 20, 25 or 30 to, at a higher end 5, 6, 7, 8, 9, 10, 15, 20, 25, 30, 35, 40, 45 or 50 % w/w of the at least one pharmaceutically active medicament. The remaining portion of the formulation includes lactose anhydrate, as well as optionally other pharmaceutically inert ingredients.

The pharmaceutical formulations may be present in the form of various inhalable formulations. In one embodiment, the pharmaceutical formulation is present in the form of a dry powder formulation, the formulation of such may be carried out according to known techniques. Dry powder formulations for topical delivery to the lung by inhalation may, for example, be presented in capsules and cartridges of for example gelatine, or blisters of for example laminated aluminium foil, for use in an inhaler or insufflator. Powder blend formulations generally contain a powder mix for inhalation of the compound of the invention and a suitable powder base which includes lactose and, optionally, at least one additional excipient (e.g., carrier, diluent, etc.). In various embodiments, each capsule or cartridge may generally contain between 20 µg and 10 mg of the at least one medicament. In one embodiment, the formulation may be formed into particles comprising at least one medicament, and excipient material(s), such as by co-precipitation or coating. When employed as a dry powder, packaging of the formulation may be suitable for unit dose or multi-dose delivery. In the case of multi-dose delivery, the formulation can be pre-metered (e.g., as in Diskus®, see GB 2242134/ U.S. Patent Nos. 6,032,666, 5,860,419, 5,873,360, 5,590,645, 6,378,519 and 6,536,427 or Diskhaler, see GB 2178965, 2129691 and 2169265, US Pat. Nos. 4,778,054, 4,811,731, 5,035,237) or metered in use (e.g. as in Turbuhaler, see EP 69715, or in the devices described in U.S. Patent No 6,321,747). An example of a unit-dose device is Rotahaler (see GB 2064336). In one embodiment, the Diskus® inhalation device comprises an elongate strip formed from a base sheet having a plurality of recesses spaced along its length and a lid sheet hermetically but peelably sealed thereto to define a plurality of containers, each container having therein an

inhalable formulation containing the at least one medicament, the lactose, optionally with other excipients. Preferably, the strip is sufficiently flexible to be wound into a roll. The lid sheet and base sheet will preferably have leading end portions which are not sealed to one another and at least one of the leading end portions is constructed to be attached to a winding means. Also, preferably the hermetic seal between the base and lid sheets extends over their whole width. The lid sheet may preferably be peeled from the base sheet in a longitudinal direction from a first end of the base sheet.

In one embodiment, the formulations may be employed in or as suspensions or as aerosols delivered from pressurised packs, with the use of a suitable propellant, e.g. dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, 1,1,1,2,3,3,3-heptafluoropropane, 1,1,1,2-tetrafluoroethane, carbon dioxide or other suitable gas. Such formulations may be delivered via a pressurized inhaler, e.g., a Metered Dose Inhaler (MDI). Exemplary MDIs typically include canisters suitable for delivering the pharmaceutical formulations. Canisters generally comprise a container capable of withstanding the vapour pressure of the propellant used such as a plastic or plastic-coated glass bottle or preferably a metal can, for example an aluminum can which may optionally be anodised, lacquer-coated and/or plastic-coated, which container is closed with a metering valve. Aluminum cans which have their inner surfaces coated with a fluorocarbon polymer are particularly preferred. Such polymers can be made of multiples of the following monomeric units: tetrafluoroethylene (PTFE), fluorinated ethylene propylene (FEP), perfluoroalkoxyalkane (PFA), ethylene tetrafluoroethylene (EFTE), vinyldienefluoride (PVDF), and chlorinated ethylene tetrafluoroethylene. Embodiments of coatings used on all or part of the internal surfaces of an MDI are set forth in U.S. Patent Nos. 6,143,277; 6,511,653; 6,253,762; 6,532,955; and 6,546,928.

MDIs may also include metering valves are designed to deliver a metered amount of the formulation per actuation and incorporate a gasket to prevent leakage of propellant through the valve. The gasket may comprise any suitable elastomeric material such as for example low density polyethylene, chlorobutyl, black and white butadiene-acrylonitrile rubbers,

butyl rubber and neoprene. Suitable valves are commercially available from manufacturers well known in the aerosol industry, for example, from Valois, France (e.g. DF10, DF30, DF60), Bespak plc, UK (e.g. BK300, BK356) and 3M-Neotechnic Ltd, UK (e.g. Spraymiser™). Embodiments of metering valves are set forth in U.S. Patent Nos. 6,170,717; 6,315,173; and 6,318,603.

In various embodiments, the MDIs may also be used in conjunction with other structures such as, without limitation, overwrap packages for storing and containing the MDIs, including those described in U.S. Patent No. 6,390,291, as well as dose counter units such as, but not limited to, those described in U.S. Patent Nos. 6,360,739 and 6,431,168.

In another aspect, the invention relates to a container suitable for use in conjunction with a pharmaceutical formulation. The container comprises at least one pharmaceutically active medicament and lactose anhydrate. The container is structured such that the formulation possesses moisture sorption properties as described herein. The container may be employed in conjunction with the various inhalation devices described, e.g., dry powder inhalers and metered dose inhalers. If used in a dry powder inhaler, the container may be present in various forms such as, without limitation, those described hereinabove such as a capsule, cartridge, reservoir, as well as a container formed from a base sheet and a lid sheet. If used in a metered dose inhaler, the container may be present as described herein, e.g., as a canister.

The pharmaceutical formulation of the invention may be used to treat a number of respiratory conditions. Such respiratory conditions include, without limitation, diseases and disorders associated with reversible airways obstruction such as asthma, chronic obstructive pulmonary diseases (COPD) (e.g. chronic and wheezy bronchitis, emphysema), respiratory tract infection and upper respiratory tract disease (e.g. rhinitis, such as allergic and seasonal rhinitis). Accordingly, and in view of the above, in another aspect, the invention provides a method for treating a respiratory disorder in a mammal such as a human. The method comprises administrating a pharmaceutically effective amount of a pharmaceutical formulation as defined

herein. For the purposes of the invention, the term "pharmaceutically effective amount" is to be broadly interpreted and encompass the prophylaxis and/or treatment of the disorder.

In another aspect, the invention provides a method of treating a respiratory condition. The method comprises administering to a patient by oral or nasal inhalation a pharmaceutically effective amount of a pharmaceutical formulation by using a device as defined herein.

Advantageously, and in accordance with the present invention, the medicament(s) present in the pharmaceutical formulation is believed to exhibit a more stable FP fraction relative to medicaments present in conventional inhalable formulations. As an example, in one embodiment, the medicament(s) may experience a decrease in FP fraction of not greater than 10% from initial following 2.5 months storage at 40°C/75%RH, and/or a drop of no more than 15% from initial following 3 months storage at 25°C/75%RH.

Additionally, the pharmaceutical formulation may exhibit increased chemical stability relative to a similar formulation employing lactose monohydrate. As an example, in one embodiment, the medicament(s) experiences at least 25 percent less degradation as measured by impurity content.

The invention will now be described with respect to the following examples. It should be appreciated that the examples are set forth for illustrative purposes only, and do not limit the scope of the invention as defined by the claims. In the examples, "AF" refers to anhydrous fines and "AC" refers to "anhydrous coarse" as defined above herein. All entries contained various percentages of lactose monohydrate to produce matched concentrations of coarse and fine lactose across the formulations. The FP fraction described within the following examples is defined as the amount of active ingredient as a proportion of the total emitted dose, depositing in Stage 2 of a Twin Impinger or Stages 1 to 5 of an Andersen Cascade Impactor, both impactors operating at a vacuum flow rate of 60 $lmin^{-1}$.

Additionally, the following compounds are assigned these designations:

Compound	Designation
3-(4-{[6-({(2*R*)-2-hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl}amino)hexyl] oxy}butyl)benzenesulfonamide	"A"
(6α,11β,16α,17α)-6,9-difluoro-17-{[(fluoromethyl) thio]carbonyl}-11-hydroxy-16-methyl-3-oxoandrosta - 1,4-dien-17-yl 2-furoate	"B"
2-hydroxy-5-((1*R*)-1-hydroxy-2-{[2-(4-{[(2*R*)-2-hydroxy-2-phenylethyl] amino}phenyl)ethyl]amino}ethyl)phenylformamide	"C"
N-(3,5-dichloro-4-pyridinyl)-2-{1-[(4-fluorophenyl) methyl]-5-hydroxyindol-3-yl}-2-oxoacetamide	"D"

Where referred to hereinbelow, these abbreviations have the following definitions:

"LMH" refers to lactose monohydrate

"ERH" refers to equilibrium relative humidity

"DHL" refers to dehydrate lactose

"PDHL" refers to partially dehydrated lactose

"RH" refers to relative humidity

"DC" refers to desiccant capacity testing

Example 1

Use of anhydrous lactose within dry powder formulations

The effect of various types of anhydrous lactose on FP Fraction stability of dry powder inhalers is illustrated herein.

Two batches of anhydrous lactose were manufactured by thermally dehydrating a coarse classification of lactose monohydrate (MPS 92μm) under vacuum. This method of dehydration was carried out according to the teachings of Figura, L.O. and Epple M., *J, Thermal Anal.*, **44** (1995) 44-53 purported to produce a stable and a hygroscopic form of anhydrous lactose

(as defined by the authors). For the purposes of this example, the manufacturing conditions of the stable and hygroscopic anhydrous lactose are defined as follows:

Stable: 120°C, 985mbar, 5.5hr

Hygroscopic 120°C, 20mbar, 3.5hr

A third batch of anhydrous lactose was sourced commercially (Anhydrous Lactose NF DT; Quest International, Illinois, US).

Example 2

Physical properties of anhydrous lactose

The physical properties of the three anhydrous lactose batches are detailed in Table 1. Included are physical properties of the monohydrate batch used as the input material to produce the two dehydrated lactose batches. Figure 1 provides a chart illustrating the X-Ray diffraction patterns for the anhydrous lactose in comparison with the lactose monohydrate. The anhydrous nature of the dehydrated forms of lactose is exemplified by the low water contents, whilst the predominance of alpha lactose within the material is demonstrated by the anomeric purity i.e. low beta lactose content. In contrast, whilst the commercial lactose is anhydrous in nature, it contains a high level of beta lactose.

Table 1: Physical properties of anhydrous lactose

	SSA (m^2/g)[a]	H_2O content (%)[b]	β content (%)[c]	Particle size[d]	
				D_{50} (μm)	%<14.2μm
Monohydrate	0.35	4.85	2.2	72.0	5.7
Commercial	0.51	0.59	75.8	59.1	14.6
Hygroscopic	1.5	2.03*	7.5	72.5	5.3
Stable	0.53	N/d	17.6	71.9	4.5

[a] measured using BET N_2 absorption

[b] measured using thermo-gravimetric analysis

[c] measured using gas chromatography

[d] measured using laser diffraction

n/d not determined

* This value is unduly high and is believed to be due to moisture uptake prior to analysis as it is not consistent with further moisture uptake data detailed in Figures 2 and 3

Example 3

Moisture uptake of anhydrous lactose batches

The moisture uptake of the lactose batches was measured. Figure 2 shows the moisture uptake of the two manufactured anhydrous lactose batches, in comparison with the monohydrate control, measured using gravimetric vapor sorption (GVS), and demonstrates different degrees of hygroscopicity between the material. The hygroscopic anhydrous lactose manifests a weight change at significantly lower relative humidity (RH) than the stable anhydrous lactose, although both materials undergo a weight change of approximately 5% w/w, consistent with rehydration.

Figure 3 illustrates the weight change of the three batches of anhydrous lactose over several days storage at 25°C/75%RH, and demonstrates the differences in hygroscopicity of the materials. This was measured by storing samples of each material at this condition and measuring the weight change from initial at regular timepoints. The hygroscopic alpha anhydrous lactose increases in weight by about 5% within 24 hours, whilst the stable alpha anhydrous lactose achieved this weight gain after nine days. However, the commercial anhydrous lactose only underwent a weight change of less than 1% after nine days storage.

This illustrates the differences in hygroscopicity between the different batches of anhydrous lactose in terms of rate of moisture uptake and critical RH for moisture uptake.

Example 4

FP fraction of pharmaceutical formulations

Dry powder blends containing 0.58% w/w salmeterol xinafoate and 0.8%w/w fluticasone propionate were manufactured using a combination of anhydrous lactose and lactose monohydrate with the anhydrous lactose component present in the concentrations described in Table 2.

Table 2: Lactose components used to investigate the effect of anhydrous lactose on physical stability of blends

Lactose	% Anhydrous lactose	% Monohydrate lactose	
		Coarse[a]	Fine[b]
Monohydrate control 1	0	75	25
Commercial	1	76.5	22.5
	10	70	20
	60	36.5	3.5
Stable	1	76	23
	10	67	23
	60	17	23
Hygroscopic	1	75	24
	10	67	23
Monohydrate control 2	0	75	25

[a] Coarse classification of lactose (MPS 92µm)

[b] Fine classification of lactose (MPS 23µm)

The particle size distributions of the blends were matched using lactose monohydrate. Control batches were manufactured using lactose monohydrate. The lactose blends were manufactured in situ using a high shear blender, and sufficient lactose blend removed to enable addition of the active ingredients in order to achieve to desired drug concentrations. The formulation was manufactured according to methodology described in EP416951 and filled into MDPI foil strips (see e.g., U.S. Patent No. 5,860,419) using perforated bed filling methodology.

The change in FP fraction of the dry powder formulations following storage at elevated temperature and humidity are shown in Figure 4 and Table 3. These data illustrate the smaller drop in FP fraction of both salmeterol and fluticasone propionate of the dry powder formulation containing stable and hygroscopic alpha anhydrous lactose, in comparison with the dry powder formulation containing lactose monohydrate. Dry powder formulations containing hygroscopic alpha anhydrous lactose performed better on stability than those containing stable alpha-anhydrous lactose, demonstrated by the lower drop in FP fraction from initial.

Table 3: Drop in FP Fraction from initial of anhydrous lactose based dry powder formulations following 3 months storage at 25°C/75%RH

Anhydrous %w/w	Salmeterol	Fluticasone Propionate
1% Stable	29.7	23.0
10% Stable	21.3	17.3
60% Stable	24.2	12.7
1% Commercial	21.4	19.0
10% Commercial	32.7	28.7
60% Commercial	24.2	12.2
1% Hygroscopic	28.5	25.1
10% Hygroscopic	12.7	9.5
Monohydrate 1	36.3	31.7
Monohydrate 2	36.7	34.0

The FP fraction of the 10% hygroscopic batch was measured after 12 months storage at 25°C/60%RH and 25°C/75%RH and showed a comparable decrease with that of the monohydrate control. To determine whether the anhydrous lactose had rehydrated, the blisters were emptied and the contents weighed before and after storage at 60% humidity for a day. The results are presented in Figure 5 and show less than 0.1% weight gain occurred compared to the 0.5% weight gain that is believed to be expected if no rehydration had occurred.

Example 5

Use of hygroscopic anhydrous lactose within dry powder formulations

Fine and coarse classifications of lactose monohydrate (MPS 23µm and 92µm respectively) were thermally dehydrated under vacuum (120°C, 20mbar) until they had achieved a weight loss of 5%w/w. This dehydration method is purported to produce a hygroscopic form of anhydrous lactose (Figura, L.O. and Epple M., *J, Thermal Anal.*, **44** (1995) 44-53)

Physical properties of dehydrated lactose

Effect of dehydration on physical properties

The physical properties of the following types of lactose are determined and compared as set forth in Table 4.

Table 4: Physical properties of dehydrated lactose and monohydrate

Lactose type	β content [a] (%)	SSA [b] (m^2/g)	Porosity [c] (ml/g)	H_2O content [d] (%)	DSE [e] mJm^{-2}	Particle size[f]	
						%<14.2μm	D50 (μm)
Monohydrate coarse	2.05	0.22	0.0006	5.16	33.31	5.9	71.1
Anhydrous coarse	7.25	1.53	0.0041	0.58	42.66	5.8	71.6
Monohydrate Fines	2.35	0.69	0.0014	5.27	n/p	33.6	21.8
Anhydrous fines	8.75	1.88	0.0061	0.28	45.4	33.2	22.1

[a] measured using gas chromatography
[b,c] measured using BET N_2 sorption
[d] measured using thermo-gravimetric analysis
[e] measured using inverse gas chromatography
[f] measured using laser diffraction
n/p not performed

As seen, there appear to be little if any significant differences in physical properties with variations in particle size. Dehydration does not appear to affect the particle size of either size classification of lactose. The material is shown to be anhydrous by its low water content.

Moisture uptake of dehydrated lactose

The results are set forth in Figure 6. As shown, anhydrous lactose is capable of being significantly more hygroscopic than the monohydrate taking up of greater than 5 %w/w water at an RH of up to approximately 90 percent. As shown from Figure 5, the rate and magnitude of water uptake appear to be not significantly dependent on particle size.

Example 6

Effect of storage on physical properties of dehydrated lactose

Samples of the two dehydrated lactose batches were stored at 33 and 58% RH, for about 5 days, until they had undergone a weight increase of 5%, consistent with rehydration. The physical properties of the samples (Table 5) show no change in particle size, beta content or surface area upon rehydration, demonstrated to have occurred as a result of increase in water content. In particular, gross weight change measurements tend to show that dehydrated lactose is capable of taking up approximately 5 percent moisture following 5 days storage at both 33 percent RH and 58 percent RH, with little if any effect on particle size.

Table 5: Physical properties of dehydrated lactose on storage

Lactose type		β content [a] (%)	SSA [b] (m2/g)	Porosity [c] (ml/g)	H_2O content [d] (%)	DSE [e] mJm^{-2}	Particle size [f]	
							%<14.2μm	D50 (μm)
Coarse	Initial	7.25	1.53	0.0041	0.58	42.66	5.8	71.6
	58%	6.35	1.50	0.0073	4.86	46.03	6.0	72.7
	33%	7.2	Not performed					
Fines	Initial	8.75	1.88	0.0061	0.29	33.2	33.2	22.1
	58%	7.8	1.73	0.0090	4.77	48.5	33.4	22.2
	33%	8.7	Not performed					

[a] measured using gas chromatography
[b,c] measured using BET N2 sorption
[d] measured using thermo-gravimetric analysis
[e] measured using inverse gas chromatography
[f] measured using laser diffraction

Example 7

Use of dehydrated lactose in dry powder formulations

Manufacture of dry powder formulations

The dehydrated coarse and fine lactose batches were used to make dry powder blends containing 0.58% w/w salmeterol xinafoate and 0.8% fluticasone propionate according to an experimental design devised to investigate the effect of anhydrous lactose concentration and particle size on FP fraction stability. The particle size distributions of the blends were

matched using lactose monohydrate (Table 6). The lactose blends were manufactured *in situ* using a high shear blender, and sufficient lactose blend removed to enable addition of the active ingredients in order to achieve to desired drug concentrations. The formulation was manufactured according to methodology described in EP416951 and filled into MDPI foil strips (see e.g., U.S. Patent No. 5,860,419) using perforated bed filling methodology (PCT/EP00/04499).

Table 6: Lactose components used for dry powder formulations

Batch	Target %/% AF/AC*	Anhydrous fines %w/w	Monohydrate fines %w/w	Anhydrous coarse %w/w	Monohydrate coarse %w/w
0AF/0AC	0/0	0	22		78
0AF/30AC	0/30	0	22	30	48
0AF/60AC	0/60	0	22	60	18
11AF/0AC	11/0	11	11	0	78
11AF/30AC	11/30	11	11	30	48
11AF/60AC	11/60	11	11	60	18
22AF/0AC	22/0	22	0	0	78
22AF/30AC	22/30	22	0	30	48
22AF/60AC	22/60	22	0	60	18
22AF/78AC	22/78	22	0	78	0

* AF/AC Anhydrous fines/anhydrous coarse

Water uptake of dry powder formulations

The weight change of the powder formulations was measured under storage at 25°C/40%RH using gravimetric vapor sorption. Figure 7 shows that the weight change upon storage increases with the concentration of anhydrous lactose within the formulation. When the weight change is translated into the degree of rehydration of the anhydrous lactose component within each formulation (Figure 8), the rate and degree of rehydration of each formulation is similar, regardless of anhydrous lactose content or particle size.

Particle size of pharmaceutical formulations following storage

Samples of the formulations described in Table 6 containing 0.58% salmeterol xinafoate and 0.8% w/w fluticasone propionate were stored at

ambient temperature/58%RH for 7 days. The particle size of the formulations, defined here as the volume percentage of particles less the 14.2µm measured using laser diffraction, are shown in Table 7. The formulations using anhydrous lactose undergo a similar small reduction in fines following storage following storage at 58%RH, to a control lactose monohydrate formulation.

Table 7: Particle size of dry powder formulations following storage

Lactose AF/AC %	% less than 14.2µm	
	Initial	Post-storage
0/0	16.6 (0.27)	14.4 (0.46)
0/30	17.0 (0.46)	13.7 (0.07)
0/60	13.7 (0.09)	11.1 (0.14)
11/0	17.2 (0.41)	15.1 (0.67)
11/30	14.6 (0.10)	11.2 (0.08)
11/60	16.8 (0.33)	13.9 (0.16)
22/0	17.2 (0.20)	13.8 (0.16)
22/30	17.0 (0.33)	14.4 (0.46)
22/60	16.2 (0.18)	14.5 (0.12)
22/78	16.6 (0.43)	14.8 (0.40)

Data presented as mean (SD), n=3

ERH of pharmaceutical formulations

The ERH was measured during the manufacuring process in order to determine the relative humidity within the powder. This parameter represents the relative humidity within the interparticulate void spaces and as such, gives an indication of the ability of the powder to absorb moisture from the immediate storage environment to the extent that it reduces the relative humidity of the bulk powder.

The ERH data or the pharmaceutical formulations described in Table 6 were determined as a function of the filling process. The formulations each contain 0.58% salmeterol xinafoate and 0.8% fluticasone propionate. The ERH was measured by inserting an RH probe into the powder blend on the filling apparatus. This was performed at the start of the filling process, after the manufacture of a sub-batch of MDPI strips (batch 1). Each blend was then left on the filling apparatus for approximately one hour before the

manufacture of a second sub-batch of MDPI strips (batch 2). The ERH of the blend was measured at the start and end of the manufacture of this batch.

The blends containing various levels of fine and coarse material have a lower ERH relative to blends not containing fine and coarse alpha anhydrous lactose, which is advantageous (Figure 9). This demonstrates that the dry powder formulations have reduced the water content within the powder bulk, in comparison with the monohydrate control, the ERH of which tracks the relative humidity of the room.

Desiccant capacity of pharmaceutical formulations

Desiccant capacities of pharmaceutical formulations (0.8% fluticasone propionate and 0.58% salmeterol xinafoate) are determined for various levels of fine and coarse alpha anhydrous lactose, as well as for those employing conventional lactose, i.e., 0/0 AF/AC percent. Desiccant capacity was assessed as the propensity of samples of each formulation to undergo a further water induced weight change upon storage at 58%RH, and is used as an indication of the ability of a formulation to retain a degree of dehydration during a manufacturing process. Naked blends and those blends present in blister strips are evaluated. Samples of blend were taken at the start of the filling process and having been exposed to the environment on the filling apparatus for approximately one hour (labeled 1 and 2 respectively). Blend was tested from two batches of MDPI strip – one manufactured upon immediate exposure of blend, and one after the blend had been exposed to the environment for approximately one hour. The strips were tested approximately 4 weeks after filling, having been stored under ambient environment conditions. Figure 10 illustrates the results. The text represents the expected percentage weight change, had no rehydration occurred during the filling process. These data suggest that the dry powder formulations containing anhydrous lactose appear to not significantly rehydrate during the manufacturing process, such that they retained their desiccant capacity within the MDPI strip up to four weeks post filling.

As shown, the blends and strips having the anhydrous fine and coarse fractions generally demonstrate greater desiccating ability relative to those utilizing conventional monohydrate lactose.

To assess the desiccant capacity of the filled strips samples of selected batches were taken after storage for 6.5 -8 months at 25/60, 25/75 and 40/75. The data are presented in Figure 11 and show that the moisture absorption of all batches is significantly less than expected due to moisture ingress through the foil laminate on storage. As expected, storage at 40/75 causes the greatest reduction in moisture sorption capacity and that formulation containing a greater proportion of anhydrous lactose show a lesser decrease on storage.

FP fraction of pharmaceutical formulations

The FP Fraction for salmeterol and fluticasone propionate of formulations following storage at 25°C/75%RH and 40°C/75%RH are determined for dry powder formulations containing various levels of fine and coarse alpha anhydrous lactose, as well as for those employing conventional lactose, i.e., 0/0 AF/AC percent. The formulations are employed in strips for use in a dry powder Diskus® inhaler. Figures 12 and 13 illustrate the results.

The drop in FP fraction from initial following storage at 25°C/75%RH and 40°C/75%RH are tabulated in Tables 8 and 9. The dry powder formulations containing hygroscopic anhydrous lactose generally exhibit a lower drop in FP fraction of both salmeterol and fluticasone on storage in comparison with the lactose monohydrate formulation.

Table 8: Drop in FP fraction of dry powder formulations containing anhydrous lactose following 3 months storage at 25°C/75%RH

Lactose type (AF/AC%)	Drop in FP fraction from Initial (%)	
	Salmeterol	Fluticasone propionate
0AF/0AC	10.8	9.4
0AF/30AC	-1.6	2.3
0AF/60AC	-4.9	-2.2
11AF/0AC	-1.2	-3.7
11AF/30AC	-8.0	-2.4
11AF/60AC	-8.8	-2.6
22AF/0AC	1.5	7.7
22AF/30AC	-11.1	-6.0
22AF/60AC	6.2	2.8
22AF/78AC	2.3	3.8

Table 9: Drop in FP fraction of dry powder formulations containing anhydrous lactose following 2.5 months storage at 40°C/75%RH

Lactose type (AF/AC%)	Drop in FP fraction from Initial (%)	
	Salmeterol	Fluticasone propionate
0AF/0AC	18.8	17.4
0AF/30AC	-0.7	5.3
0AF/60AC	-2.4	5.2
11AF/0AC	0.6	-1.2
11AF/30AC	2.0	4.3
11AF/60AC	3.5	10.8
22AF/0AC	7.0	10.8
22AF/30AC	4.3	7.7
22AF/60AC	7.4	14.1
22AF/78AC	9.7	10.9

Chemical Stability of dry powder formulations

The chemical stability of formulations following storage at 40°C/75%RH is determined for dry powder formulations containing various levels of fine and coarse alpha anhydrous lactose, as well as for those employing conventional lactose, i.e., 0/0 AF/AC percent. This was assessed by performing a drug related impurity analysis on dry powder blend emptied from MDPI strips that had been on stability for 2.5 months. The resultant chromatograms of the assay were compared and the level of 1-Hydroxy-4-(2-hydroxy-5-{1-hydroxy-2-[6-(4-phenyl-butoxy)-hexylamino]-ethyl}-benzyl)-naphthalene-2-carboxylic acid, the principal degradation product within each formulation, quantified. Results are detailed in Table 10.

Table 10: 1-Hydroxy-4-(2-hydroxy-5-{1-hydroxy-2-[6-(4-phenyl-butoxy)-hexylamino]-ethyl}-benzyl)-naphthalene-2-carboxylic acid content of dry powder formulations containing anhydrous lactose following 2.5 months storage at 40°C/75%RH

Anhydrous lactose (%/% AF/AC)	1-Hydroxy-4-(2-hydroxy-5-{1-hydroxy-2-[6-(4-phenyl-butoxy)-hexylamino]-ethyl}-benzyl)-naphthalene-2-carboxylic acid (%w/w)
0/0	1.65
22/0	0.85
11/30	0.41
0/60	0.39
22/60	0.52

The concentration of 1-hydroxy-4-(2-hydroxy-5-{1-hydroxy-2-[6-(4-phenyl-butoxy)-hexylamino]-ethyl}-benzyl)-naphthalene-2-carboxylic acid is highest in the dry powder formulation containing conventional lactose monohydrate i.e. 0/0 AF/AC percent. The chromatographic data show that the dry powder formulations employing anhydrous lactose contain lower levels of drug related impurities, particularly 1-hydroxy-4-(2-hydroxy-5-{1-hydroxy-2-

[6-(4-phenyl-butoxy)-hexylamino]-ethyl}-benzyl)-naphthalene-2-carboxylic acid, than the monohydrate based dry powder formulation.

Example 8

Use of hygroscopic anhydrous lactose within dry powder formulations

The dehydrated coarse and fine lactose batches described in Example 5 were used to make dry powder blends containing 0.58% w/w salmeterol xinafoate and 0.4% fluticasone propionate with varying concentration of anhydrous fine and coarse lactose, as described in Table 11. The particle size distributions of the blends were matched using lactose monohydrate. The lactose blends were manufactured in situ using a high shear blender, and sufficient lactose blend removed to enable addition of the active ingredients in order to achieve to desired drug concentrations. The formulation was manufactured according to methodology described in EP416951 and filled into MDPI foil strips (see e.g., U.S. Patent No. 5,860,419) using perforated bed filling methodology (PCT/EP00/04499).

Table 11: Lactose components used to make dry powder formulations

Lactose AF/AC %	Anhydrous fines %	Monohydrate fines %	Anhydrous coarse %	Monohydrate coarse %
0AF/0AC	0	22	0	78
22AF/60AC	22	0	60	18
22AF/78AC	22	0	78	0

Example 9

Desiccant Capacity of Pharmaceutical Formulations

Desiccant capacities of pharmaceutical formulations (0.4% w/w fluticasone propionate and 0.58% w/w salmeterol xinafoate) are determined for various levels of fine and coarse alpha anhydrous lactose, as well as for those employing conventional lactose, i.e., 0/0 AF/AC percent. Desiccant capacity was assessed as the propensity of samples of each formulation to undergo a further water induced weight change upon storage at 58%RH, and is used as an indication of the ability of a formulation to retain a degree of

dehydration during a manufacturing process. Naked blends and those blends present in blister strips are evaluated. The strips were tested approximately 4 weeks after filling, having been stored under ambient environment conditions. Figure 14 illustrates the results. The text represents the expected percentage weight change, had no rehydration occurred during the filling process. These data illustrate that the dry powder formulations containing anhydrous lactose are not believed to significantly rehydrate during the manufacturing process, such that they retained their desiccant capacity within the MDPI strip up to four weeks post filling.

As shown, the blends and strips having the fine and coarse fractions demonstrate greater desiccating ability relative to those utilizing conventional monohydrate lactose.

FP fraction of Pharmaceutical Formulations

The FP Fraction for salmeterol and fluticasone propionate following storage at 25°C/75%RH and 40°C/75%RH are determined for dry powder formulations, as well as for those employing conventional lactose, i.e., 0/0 AF/AC percent. The formulations are employed in strips for use in a dry powder Diskus® inhaler. Figures 15 and 16 illustrate the results. The drop in FP fraction from initial following storage at 25°C/75%RH and 40°C/75%RH are tabulated in Tables 12 and 13. The dry powder formulations containing hygroscopic anhydrous lactose exhibit a lower drop in FP fraction of both salmeterol and fluticasone on storage in comparison with the lactose monohydrate formulation.

Table 12: Drop in FP fraction of dry powder formulations following 3 months storage at 25°C/75%RH.

Lactose % AF/AC	Drop in FP fraction from Initial (%)	
	Salmeterol	Fluticasone propionate
0AF/0AC	19.1	12.2
22AF/60AC	-1.7	2.0
22AF/78AC	-17.5	-8.2

Table 13: Drop in FP fraction of dry powder formulations following 3 months storage at 40°C/75%RH.

Lactose % AF/AC	Drop in FP fraction from Initial (%)	
	Salmeterol	Fluticasone propionate
0AF/0AC	33.9	31.4
22AF/60AC	-2.8	1.4
22AF/78AC	-12.4	4.6

Examples 10 –13

Formation of Anhydrous Lactose by Drying

Examples 11–14 illustrate the making of anhydrous lactose employing various drying conditions.

Example 10

Formation of Anhydrous Lactose Using Contact Drying

Example 11 explores the effects of employing contact drying in forming anhydrous lactose and more specifically α_H anhydrous lactose.

A conventional laboratory oven (Heraeus Vacutherm, Type VT 6060M, DIN 12880/1, maximum temperature 200°C made commercially available by Kendro Laboratory Products of Charlotte, North Carolina) was used to investigate drying conditions which would give hygroscopic anhydrous α_H lactose. Experiments were performed at 100g scale of α-lactose monohydrate until a 5% weight loss was observed. When the oven temperature was set at temperatures between 90°C and 120°C, α_H was formed. If the drying was performed at 140°C a 5% weight loss was observed after only 1 hour but on analysis by XRPD the sample found to be the stable (non-hygroscopic) form of anhydrous lactose (α_S).

The following observations were made as a result of this study:

- When no nitrogen bleed is used, a weight loss of only 3.5%w/w was observed over 6 days, at 50mmbar, with sample discoloration. The preferred weight loss is 5%w/w.
- Using a nitrogen bleed at 90°C resulted in 5.2% weight loss in 24h, at 500mbar. Anhydrous α_H lactose by GVS and XRPD.
- At 140°C, a 5.32% weight loss is observed in less than 1 hour and dehydrated α_S lactose is formed.
- Both forms of anhydrous lactose (i.e., α_H and α_S) can be re-hydrated to α-lactose monohydrate but re-hydration occurs at different relative humidity.
- Anhydrous α_H lactose can be formed by drying at 90 -110°C using an air or nitrogen bleed (latter preferred) at 500mbar. Under these drying conditions a total impurities content of up to 1% may result.

Example 11

Formation of Anhydrous Lactose Using an Agitated Vacuum Pan Dryer

Using agitated vacuum pan dryer, contact drying was investigated at different temperatures and pressures. The agitated vacuum pan dryer had the following operating parameters with tolerances in brackets:

Operating pressure	10 - 200 mbara (+/- 1 mbara) 200 mbara (+/- 5 mbara)
Operating temperature	ambient to 100°C (+/- 1°C) 100°C - 150°C (not determined but believed to be better than +/- 2°C)
Agitator speed	1 – 60 rpm (+/- 10%)
Weight loss	+/- 0.02g

Heating occurred via a jacket with fluid present therein.

This equipment is mounted on a weigh cell and its contents were agitated. Temperature, pressure and weight are logged continuously through out the duration of the experiment.

A nitrogen bleed of 10litres/hour was used at all times. All experiments were carried out on a 40g scale at an agitation of 10rpm. Drying experiments were carried out at different pressures at 30 and 500mbar. At 500mbar drying was incomplete at 100°C. Drying was found to be incomplete at temperatures using less than 90°C at 30mbar pressure. Results from various runs carried out at 30mBar are set forth in Table 14.

The impurity profiles of samples dried at 90, 95 and 100°C were very similar to each other. Various experiments were carried out and drying was stopped after 18 and 12h respectively based on previous data. The XRPD's of all these batches are believed to be consistent with α_H lactose.

Figure 17 illustrates the percentage weight loss of water against time for various temperatures at 30 mbar of pressure. As shown, drying increases as a function of temperature for these runs.

Table 14: Purity of lactose from drying experiments carried at 30mbar

"A" 80°C/30mbar	"B" 90°C/30mbar	"C" 95°C/30mbar	"D" 100°C/30mbar	"E" 90°C/30mbar	"F" 95°C/30mbar
99.60 Incompletely dry	**99.25** Preferred conditions (Dried for 24h)	**99.22**	**99.20**	**99.50** "B" conditions repeated (Dried for 18h)	**99.42** "C" conditions repeated (Dried for 12h)

Note: the runs set forth in Table 14 were carried out at 10rpm, 90°C/30mbar, and nitrogen bleed -10litres/h, for 12h.

Purity is defined as 100 minus the impurity content.

Example 12

Formation of Anhydrous Lactose Using a Charles Thompson Filter Dryer

Anhydrous lactose was formed by employing a Charles Thompson Filter Dryer (Model No. TNFD 0301) made commercially available by Charles Thompson Limited of Mexborough, United Kingdom. Table 15 illustrates the conditions under which such drying took place and the results.

Table 15: Lactose drying in the Charles Thompson filter dryer

Batch	Drying conditions		Analytical		Comment
	Temp °C	Pressure Mbar	Water	Purity	
1	Required 90°C. Batch temp 105°C	50	0.26	98.88	Sampled every 2h for 24h. presence of άH noted by XRPD, 9.5%w/w β-anomer, good flow properties. Pale brown.
Best conditions identified as drying set point 90°C (batch temp of 105°C), full vacuum (as low as possible ie.50mbar) and nitrogen through the headspace. Two further batches carried out to 'validate' drying conditions.					
2	Set temp 90°C. Batch temp 105°C	50	0.18	99.00	Sampled after 22h.Essentially dry at this stage. presence of άH noted by XRPD, 7.5%w/w β-anomer, good flow properties. Pale brown.
3	Batch 2 conditions, repeated for batch 3		0.13	99.02	Sampled after 22h.Essentially dry at this stage. presence of άH noted by XRPD, 8.5%w/w β-anomer, good flow properties. Pale brown.

Example 13

Formation of Anhydrous Lactose Using a Bolz Dryer

Anhydrous lactose was formed using a Bolz dryer (Manufacturing No. M-2911, Date of manufacture 1993, Capacity 149 Litres, Material Hastelloy-C) made commercially available by Bolz-Summix, A Division of MPE Group, Inc. of Pennsauken, New Jersey. A diagram of the dryer can be found at the website: http://www.kmpt.net/dryers-page/plate-dryers.htm. The drying was carried out on an 18kg (ca.36litres) scale. A nitrogen bleed (8-10litres/min) was introduced into the drying chamber via a nitrogen sparge ring housed near the base of the vessel. In a drying trial with the jacket temperature set 110°C the temperature differential between the jacket and the batch was found to be ca.20 - 25°C. Using a given vacuum (ca.90mbar) the batch was incompletely dry after 24h. With an increase in the jacket temperature, an improvement in the vacuum and better agitation in batch 2 the target KF

(<0.5) was achieved within 12h. Batch 3 was repeated under batch 2 conditions. The drying conditions and comments are set forth in Table 16.

Table 16: Lactose drying in the Bolz Dryer

Batch	Drying conditions		Analytical		Comment
	Temp °C	Pressure Mbar	Water	Purity (a/a)	
1	Jacket - 110°C Batch - 86 – 88°C	85 -95	1.72	99.2	Agitator at 5rpm. Sample every 2h for 24h. >20°C temp difference between jacket and batch temp. Slow drying.
2	Jacket - 120°C Batch - 98 – 100°C	30 – 45	0.14	98.4	Jacket at maximum (120°C) set point for the equipment. Agitator at 10rpm. Sampled after every 2h. The batch was essentially dry after 10 - 12h
3	Jacket - 120°C Batch - 98 – 100°C	ca.50	0.29	98.93	Sample taken after 8 and 10h. Drying discontinued after 12h.

Tabulated below is the analytical data for the trial runs conducted at K-M test facility in Munich, Germany using a single plate simulator:

Table 17: Krauss Maffei drying trials

DryingTrial	Operating Pressure	Temp. C		Nitrogen Temp C	Water (% w/w)	Purity
		Product	Plate			
1	Atmospheric	101	103	103	0.83	99.40
2	50 mbar	111	113	30	0.09	98.86
3	Atmospheric	110	111	106	3.09	99.78
4	50 mbar	80	81	ambient	Incomplete drying	
5	50 mbar	90	91	ambient	"	
6	50 mbar	100	101	ambient	"	

Moisture content vs. drying time for the Krauss Maffei trials are illustrated in Figure 18.

The particle size analysis of the materials prepared in the Charles Thompson and in the Bolz show that little or no crystal attrition takes place during the drying process as evidenced by Malvern sizing in Table 18.

Table 18: Particle size data for batches of dehydrated lactose

	Particle size (liquid dispersion)				
	x10	x50	x90	XRPD	GVS
Batch "A" (mono-hydrate)	44	89	154	Mono hydrate	
Charles Thompson Batch 1	43	94	180	α_H	α_H
Batch 2	45	96	163	α_H	α_H
Batch 3	43	91	154	α_H	α_H
Bolz Batch 1	44	92	157	Mono + α_H	Mono + α_H
Batch 2	42	89	155	α_H	α_H

Example 14

Formulations of Compound "A" with fully dehydrated lactose

The following three formulations containing 0.1%w/w of the maleate salt of compound "A" (compound "A1") were evaluated for drug-related impurities and FP fraction on storage :

1. **100% LMH:** 0.1%w/w micronised compound "A1" Lactose monohydrate (LMH) (8% fines)
2. **10% DHL:** 0.1%w/w micronised compound "A1" +10%w/w dehydrated lactose (DHL, previously referred to as α_H) (8% fines) + 90% LMH (8% fines)
3. **100% DHL:** 0.1%w/w micronised compound "A1" + 100%w/w DHL (8% fines)

The fines content of all formulations was designed to be equivalent at 8%. Dehydrated lactose (DHL) used in formulations 2 and 3, was prepared from lactose monohydrate (8% fines) in a contact oven set to an oven temperature of 120°C, with a vacuum pressure of 20mbars. For the purposes of these experiments, the dehydration process was deemed completed when a 5% weight reduction had been achieved. All three blends were

manufactured with a high shear blender and were filled into MDPI foil strips via a process similar to that set forth in PCT International Patent Application No. PCT/EP2003/012159 to achieve a fill weight of 12.5mg per blister. Testing was performed using the Andersen Cascade Impactor with a flow rate of 60L/Min for 3 seconds, compound "A1" was quantified by HPLC. In this example, the FP fraction is the total deposition on stages 1-5 divided by the emitted dose.

The total amount of drug-related impurities was assessed by HPLC.

Data in Figure 19 shows inclusion of 10 and 100% DHL stabilises the FP fraction over 3 months compared to the 100% LMH formulation.

Figure 20 shows inclusion of DHL in the formulation does not reduce or suppress the rise in total impurities over 3 months storage at 40/75 but does show reduced impurity formation with 30/65 storage.

The ERH was measured by inserting an RH probe into the blend post filling and taking the reading after an equilibration time 10 – 15minutes. This gave an indication of the expected RH of the blend within the blister pack. Figure 21 showed the inclusion of 10 & 100% DHL in 12.5µg compound "A1" lowers the RH of the blends compared to the control (LMH) which had an RH of 40.9%, similar to the lab RH.

Example 15

Formulation of Compound "B" with Fully Dehydrated Lactose

The following six formulations containing 0.8%w/w micronised compound "B" were filled into foil laminate blister strip, using equipment as described in U.S. Patent No. 5,187,921 (Table 19). The foil laminates used in this study had different polymers in the base foil which were in contact with the blend; 30µm PVC 100µm PVC and 40µm HDPE.

1. **1 Control batch:** 0.8%w/w micronised compound "B" + Lactose monohydrate (10% fines) + 20% coarse lactose (3% fines).
2. **5 Batches of 20% DHL:** 0.8%w/w micronised compound "B" + 90% Lactose monohydrate (10% fines) + 20%w/w dehydrated lactose (3% fines).

Table 19: Compound "B" Blends and strip batches numbers

Blend Description	Base foil polymer in contact with blend
0.8%w/w compound "B" + 80% LMH (10% fines Lactose) +20% LMH (3% fines) (machine setting).	100µm PVC
0.8%w/w mic compound "B" + 80% LMH (10% fines Lactose) +20% DHL Lactose (3% fines).	100µm PVC
0.8%w/w mic compound "B" + 80% LMH (10% fines Lactose) +20% DHL Lactose (3% fines) (machine setting).	30µm PVC
0.8%w/w mic compound "B" + 80% LMH (10% fines Lactose) +20% DHL Lactose (3% fines).	30µm PVC
0.8%w/w mic compound "B" + 80% LMH (10% fines Lactose) +20% DHL Lactose (3% fines) (machine setting).	40µm HDPE
0.8%w/w mic compound "B" + 80% LMH (10% fines Lactose) +20% DHL Lactose (3% fines).	40µm HDPE

DHL was prepared from lactose monohydrate (3% fines) in a contact oven (Charles Thompson) set to an oven temperature of 120°C, with a vacuum pressure of 20mbars to give a total water loss 5%. All six blends were manufactured with a high shear blender and were filled into MDPI foil strips, using equipment as described in U.S. Patent No. 5,187,921 to achieve a fill weight of 13mg per blister. The ability of blister contents to absorb moisture was measured by DC which measured the wt gain of blend samples stored at 20/60 for a day. The DC of blends after manufacture and after filling was performed (see Figure 22).

Strips from the end of the spool were be used for stability as end strips had the highest desiccant capacity (see Figure 23).

Figure 24 show the desiccant capacity of strips stored at 30/65 and 40/75 over 3 months. The values in the boxes indicate the percentage change in DC from initial value. Overall the graph indicates that the 40µm HDPE foil

showed less change in DC over 3 months compared to 100µm and 30µm PVC foil.

Figure 25 shows the FP fraction of compound "B" over 3 months, the initial %FP fraction of the control batch (100µmPVC) is much higher than the 100µm PVC DHL, 30µm PVC DHL and 40µm HDPE DHL. Overall the %FP fraction of the control shows a possible decrease in %FP fraction over 3 months whilst the DHL formulations show an upward trend in FP fraction.

Figure 26 shows the total ex-device drug content measured by cascade impaction (CI).

Example 16

Compound "B" Formulations including Fully Dehydrated Lactose with α, D – Cellobiose Octaacetate (COA)

The following four formulations were evaluated for fine particle mass stability.

1. **50µg** Micronised Compound "B" + 1% micronised cellobiose octaacetate (COA) + LMH (10% fines) + 20% LMH (3% fines)
2. **50µg** Micronised Compound "B" + 20%w/w DHL (3% fines) +1% micronised COA + LMH (10% fines)
3. **400µg** Micronised Compound "B" + 1% micronised COA + LMH (10% fines) + 20%LMH (3% fines)
4. **400µg** Micronised Compound "B" + 20%w/w DHL (3% fines) +1% micronised COA + LMH (10% fines)

Fully dehydrated lactose (DHL) was used in formulations 2 and 4, DHL was prepared from lactose monohydrate (3% fines) in a contact oven set to an oven temperature of 120°C, with a vacuum pressure of 20mbars. All four blends were manufactured with a high shear blender and were filled into foil laminate blister strip using equipment as described in PCT Application No. PCT/GB03/01447 to achieve a fill weight of 13mg.

The FP fraction data are presented in Figure 27 and suggests that the incorporation of dehydrated lactose is capable of reducing the FP fraction and that the FP fraction can increase on storage. Figure 28 suggests the reasonable consistency of the total emitted dose measured by cascade impaction.

Table 20: Initial particle size of 50 and 400µg Compound "B", 1% COA & with and without 20%w/w DHL by Sympatec Laser Diffraction

Batch	X50µm (%RSD)	X90µm (%RSD)	X10µm (%RSD)	%<4.5µm (%RSD)	%<15µm (%RSD)
1 50ug COA	64.75 (0.42)	136.9 (0.31)	5.80 (0.46)	8.73 (0.23)	17.03 (0.22)
2 50ug COA/DHL	65.54 (0.50)	143.47 (0.20)	6.33 (1.42)	8.32 (0.78)	16.59 (0.75)
3 400ug COA	57.02 (0.35)	132.36 (0.33)	2.74 (1.26)	13.92 (1.10)	23.45 (0.93)
4 400ug COA/DHL	59.30 (1.33)	136.23 (1.79)	3.11 (1.34)	12.82 (1.26)	22.29 (2.84)

Example 17

Use of PDHL with Compound "A1"

PDHL with differing levels of dehydration was made by heating 320g of lactose monohydrate (6%w/w < 15µm) at 120°C under vacuum (20 mbar). The level of dehydration was measured by the weight loss.

Samples were analysed by HPLC to determine the total amount of thermal degradation products that formed as a result of the dehydration process. The data are set forth in Figure 29 and show that the total amount of thermal degradation impurities increases after removal of 2% water.

The PDHLs were evaluated in terms of the ERH that they were capable of maintaining. This was conducted by immersion of an RH probe into the PDHL for a period of 10 minutes. The measurements were conducted at an ambient environment of 17°C/45%RH and compared to a Control (6% fines lactose monohydrate) (Figure 30). All PDHLs show a lower ERH reading than the input lactose monohydrate.

Differences were observed in the rate of moisture absorption for the different PDHLs at a 30%RH storage condition (Figure 31).

The PDHLs were then blended with compound "A1" to produce a range of blends, all containing 12.5µg compound "A" base/12.5mg (Table 21). The control formulation is the one shown to contain 0% DHL and 100% lactose monohydrate. The formulations were produced using a high shear blender. The first stage involved blending a respiratory grade of lactose monohydrate with the required amount of PDHL. The next stage involved incorporation of compound "A1" into the formulation by an additional blending cycle.

Table 21: Blends produced with compound "A1" (10µg/12.5mg); relative proportions of the partially dehydrated lactoses added and the expected moisture absorption of the blends.

Weight loss of lactose during dehydration (%w/w)	Proportion of dehydrated lactose mixed with lactose monohydrate (%)	Expected moisture absorption as blend rehydrates (%w/w)
1	50	0.5
2	25	0.5
3	10	0.3
3	17	0.7
4	12.5	0.5
5	10	0.5
0	100	0

The equilibrium RH of the blends in Table 21 was measured and the data are set forth in Figure 32. The data suggest that for blends with the same expected moisture sorption (i.e. 0.5%) the ERH is lowest for blends with the least dehydration. The data also suggest that as the proportion of the PDHL is increased the %ERH is lowered.

The blends were then filled into pre-formed foil laminated blister strips using a manually operated version of the process described in PCT Application No. PCT/GB03/01447 to achieve a mean blister fill weight of

approximately 12.5mg. The multiple unit dose strips were then stored at 30°C/60%RH or 40°C/75%RH. The strips were then loaded into a Diskus® inhaler.

The moisture absorption capacity of the contents of the blister strips from a selection of batches was determined after approximately 2.5 months storage at either 30°C/60%RH or 40°C/75%RH and compared against a theoretical (expected) moisture absorption capacity. This was done by emptying the contents of several blisters into an aluminum weighing boat, then leaving the boat at approximately 60%RH for a period of 24 hours. The weight difference was then determined as a % weight change. This process is conducted on a composite sample of 14 blisters. The data are presented in Figure 33.

The aerosolisation performance of some of the blends listed in Table 21 was determined at Initial and stability timepoints using a Twin Impinger apparatus at 60L/min. The data that were obtained are presented in Figure 34 (Initial timepoint) and Figure 35 (6 week 40°/75%RH).

The FP fraction and drug-related impurities data that were obtained for the compound "A1"-DHL blend relative to the control over a 3MN period are shown in Figures 36 and 37.

The impurities data in Figure 37 suggest that the inclusion of DHL with compound "A1" results in the formation of a lower level of degradation impurities relative to the lactose monohydrate control.

Example 18

Use of Fully Dehydrated Lactose with Compound "C1"

A number of blends have also been produced with another respiratory drug substance designated compound "C1" (10µg compound "C" base/12.5mg). The input DHL that was used in this campaign was produced by using both coarse lactose monohydrate (3% fines) and lactose monohydrate (10% fines) by dehydration at 120°C and 20mbar. The blends manufactured contained 0.08% w/w micronised Compound "C1" (as hydrochloride) in the excipient mixtures shown below:

Batch details
80 % lactose monohydrate (10% fines), 20% dehydrated lactose (10% fines)
90% lactose monohydrate (3.% fines), 10% cellobiose octaacetate:
70% lactose monohydrate (3.% fines): 20% dehydrated lactose, (3% fines) 10% cellobiose octaacetate
98% lactose monohydrate (10% fines), 2% Magnesium Stearate
78% lactose monohydrate (10% fines), 20% dehydrated lactose (10% fines), 2% Magnesium Stearate

The DHL blends were produced on a commercial high shear blender. All the blends produced were seen to have acceptable blend uniformities (%RSD <5% for 10 samples of weight 19-31mg), however one blend showed a higher value of approximately 7%. This was deemed suitable for experimental investigations. The blends were filled according to the teachings of PCT/GB03/01447 to achieve 13mg per blister.

The FP fraction at initial and at various stability timepoints was determined and the data presented in Figure 38. In two of the tested sample lots, the blister pack has been pierced through the lidding foil and the samples stored for 1 week at 30°C/65%RH in an effort to accelerate changes in the formulation. The data suggest that the inclusion of DHL results in a lower FP fraction than the respective control formulations.

The moisture absorbing potential of two of the compound "C1"-dehydrated lactose (20%w/w) in conventional lactose monohydrate (10µg compound "C" base/12.5mg) blends was determined immediately prior to blend uniformity analysis. The expected moisture absorbing potential in these blends was calculated to be 1%w/w whilst the observed moisture absorbing potential for the two blends tested was seen to be 0.94 and 1.01%. The change in the measured RH of dehydrated lactose blends throughout the manufacturing process has been studied for a series of compound "C1" based formulations (Table 22).

Table 22: The change in ERH of a compound "C1" (10µg base/12.5mg) - dehydrated lactose (20%w/w)-lactose monohydrate formulation through the manufacturing process.

Manufacturing Stage	Measured Temperature & RH
DHL post-dehydration stage	21.6°C/3.2%RH
DHL pre-blending stage	22.2°C/3.8%RH
DHL blend post-blending stage	22.2°C/7.1%RH
DHL blends pre-filling stage	18.8°C/7.2%RH
DHL blends post-filling stage	18.6°C/20.9%RH

The moisture absorbing capacity of the compound "C1" (10µg base/12.5mg blend)-dehydrated lactose (20%w/w)-lactose monohydrate 80% formulations produced in this campaign have been determined and the data presented in Figure 39. These formulations contain either no additional excipient, or α-D-cellobiose octaacetate or magnesium stearate. The data show the moisture absorbing capacity of the blends pre- and post filling, and also determine the moisture absorbing capacity for the blends after filling into Diskus® strip.

Some compound "C1" formulations (10µg/12.5mg blend) containing 20% fully dehydrated lactose were evaluated in terms of their flow properties. The data that have been obtained are presented in Table 23. The blends were filled using an automated filling process described in PCT Application No. PCT/GB03/01447 and had Carr's Index values (%) of between 26-28%.

Table 23: Density and Carr's Index data for compound "C1" (10µg/12.5mg blend) dehydrated lactose blends.

Batch composition	Initial Bulk Density (g/cm^3)	Tapped Bulk Density (g/cm^3)	Carr's Index (%)
DHL	0.73	0.98	26
DHL	0.71	0.99	28
DHL and COA	0.71	0.97	27
DHL and MgSt	0.80	1.08	26

DHL = fully dehydrated lactose, COA= α-D-cellobiose octaacetate; MgSt = Magnesium Stearate.

Example 19

Use of Dehydrated Lactose with Compound "D"

The FP fraction stability benefits of DHL have been assessed in combination with another respiratory molecule designated compound "D". The DHL has been prepared as described previously using lactose monohydrate (6% fines).

The following blends were manufactured using 8%w/w of micronised compound "D" and the following excipients:

100% LMH (6% fines)

80% LMH (6% fines), 20% DHL (6% fines)

100% DHL (6% fines)

The blends were filled into pre-formed Diskus® blister strips using a manually operated version of the process described in PCT Application No. PCT/GB03/01447. Mean blister fill weights of approximately 12.5-13mg were achieved. The FP fraction data are presented in Figure 40. The control formulation shows increases in the FP fraction in excess of 100% of initial after 1 month storage at 40°C/75%RH.

Examples 20-21

Studies Performed Using Lactose Monohydrate Formulations at Low Relative Humidity

Example 20

Compound "A1"

Compound "A1" (12.5µg/12.5mg blister, micronised, as maleate salt) was formulated in lactose monohydrate (6% <15µm) using a high shear blending process. The blend was then filled into preformed Diskus blister strip using the process described in PCT Application No. PCT/GB03/01447. The strips were pierced through the lidding foil to enable the entry of moisture. The strips were then immediately placed onto stability at 20, 30 and 40°C at 0, 10 and 20%RH. The strips were stored at these conditions for 1 month before being assessed for their FP fraction and drug-related impurities content. The

twin impinger was used to assess the FP fraction. The drug-related impurity content was determined by HPLC. The data that were obtained are presented in Figures 41 and 42.

Example 22

Compound "C1"

A similar study to that performed in the previous section has also been conducted with compound "C1". A formulation of compound "C1" (10µg/12.5mg) in lactose monohydrate was formulated on a high shear blender, then filled into Diskus® blister strips as described previously. The strips were pierced through the lidding foil to enable the rapid entry of moisture. The strips were then immediately placed onto stability at 20, 30 and 40°C at 0, 10 and 20%RH. The strips were stored at these conditions for 2 months before being assessed for their FP fraction and chemical stability performance. The approach used to determine the FP fraction of inhalational blends has been described previously. The chemical impurities were determined by dissolving a suitable amount of the blend in a solvent and running an appropriate HPLC impurities method. The data that were obtained are presented in Figures 43 and 44.

The invention has been described in reference to the embodiments set forth above. It should be appreciated that such embodiments are for illustrative purposes only, and do not limit the scope of the invention as defined by the claims.

THAT WHICH IS CLAIMED:

1. A pharmaceutical formulation suitable for inhalation, said formulation comprising:

a beta agonist selected from the group consisting of 3-(4-{[6-({(2*R*)-2-hydroxy-2-[4-hydroxy-3-(hydroxymethyl) phenyl]ethyl}amino) hexyl]oxy}butyl) benzenesulfonamide, 3-(3-{[7-({(2*R*)-2-hydroxy- 2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl}amino)heptyl]oxy}propyl) benzenesulfonamide, 4-{(1*R*)-2-[(6-{2-[(2,6-dichlorobenzyl)oxy] ethoxy}hexyl)amino]-1-hydroxyethyl}-2-(hydroxymethyl)phenol, 2-hydroxy-5-((1*R*)-1-hydroxy-2-{[2-(4-{[(2*R*)-2-hydroxy-2- phenylethyl]amino} phenyl)ethyl]amino}ethyl)phenylformamide, 8-hydroxy-5-{(1*R*)-1-hydroxy-2-[(2-{4-[(6-methoxy-1,1'-biphenyl-3-yl)amino] phenyl} ethyl)amino]ethyl}quinolin-2(1*H*)-one, and combinations thereof;

an anti-inflammatory selected from the group consisting of (6α,11β,16α,17α)-6,9-difluoro-17-{[(fluoromethyl)thio]carbonyl}-11-hydroxy-16-methyl-3-oxoandrosta-1,4-dien-17-yl 2-furoate, (6α,11β,16α,17α)-6,9-difluoro-17-{[(fluoromethyl)thio]carbonyl}-11-hydroxy-16-methyl-3-oxoandrosta-1,4-dien-17-yl 4-methyl-1,3-thiazole-5-carboxylate, and combinations thereof; and

lactose anhydrate.

2 The pharmaceutical formulation according to Claim 1, wherein said formulation exhibits a weight gain of at least 0.3 percent equilibrated 25°C and 40 percent RH.

3. The pharmaceutical formulation according to Claim 1, wherein said formulation comprises at least about 1% w/w of said lactose anhydrate.

4. The pharmaceutical formulation according to Claim 1, wherein said formulation is a dry powder formulation.

5. The pharmaceutical formulation according to Claim 1, wherein said formulation is an aerosol formulation.

6. The pharmaceutical formulation according to Claim 1, further comprising at least one additional excipient.

7. The pharmaceutical formulation according to Claim 1, wherein the anti-inflammatory steroid is (6α,11β,16α,17α)-6,9-difluoro-17-{[(fluoromethyl)thio] carbonyl}-11-hydroxy-16-methyl-3-oxoandrosta-1,4-dien-17-yl 2-furoate.

8. The pharmaceutical formulation according to Claim 7, wherein the beta agonist is 3-(4-{[6-({(2*R*)-2-hydroxy-2-[4-hydroxy-3-(hydroxymethyl) phenyl]ethyl}amino) hexyl]oxy}butyl) benzenesulfonamide

9. The pharmaceutical formulation according to Claim 7, wherein the beta agonist is 3-(3-{[7-({(2*R*)-2-hydroxy- 2-[4-hydroxy-3-(hydroxymethyl)phenyl] ethyl}amino)heptyl] oxy}propyl) benzenesulfonamide.

10. The pharmaceutical formulation according to Claim 7, wherein the beta agonist is 4-{(1*R*)-2-[(6-{2-[(2,6-dichlorobenzyl)oxy] ethoxy}hexyl)amino]-1-hydroxyethyl}-2-(hydroxymethyl)phenol.

11. The pharmaceutical formulation according to Claim 7, wherein the beta agonist is 2-hydroxy-5-((1*R*)-1-hydroxy-2-{[2-(4-{[(2*R*)-2-hydroxy-2-phenylethyl]amino}phenyl)ethyl]amino} ethyl)phenylformamide.

12. The pharmaceutical formulation according to Claim 7, wherein the beta agonist is 8-hydroxy-5-{(1*R*)-1-hydroxy-2-[(2-{4-[(6-methoxy-1,1'-biphenyl-3-yl)amino] phenyl} ethyl)amino]ethyl}quinolin-2(1*H*)-one.

13. A pharmaceutical formulation according to Claim 1 consisting essentially of said beta agonist, said anti-inflammatory, and said lactose anhydrate.

14. An inhalation device comprising a container, wherein the container comprises the pharmaceutical formulation suitable for inhalation according to Claim 1.

15. A method for treating a respiratory disorder in a mammal comprising administrating a pharmaceutically effective amount of a pharmaceutical formulation according to Claim 1.

16. The method according to Claim 15, wherein the respiratory disorder is asthma.

17. The method according to Claim 15, wherein the respiratory disorder is chronic obstructive pulmonary disease (COPD).

18. A pharmaceutical formulation suitable for inhalation, said formulation comprising:

a beta agonist selected from the group consisting of 3-(4-{[6-({(2*R*)-2-hydroxy-2-[4-hydroxy-3-(hydroxymethyl) phenyl]ethyl}amino) hexyl]oxy}butyl) benzenesulfonamide, 3-(3-{[7-({(2*R*)-2-hydroxy- 2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl}amino)heptyl]oxy}propyl) benzenesulfonamide, 4-{(1*R*)-2-[(6-{2-[(2,6-dichlorobenzyl)oxy] ethoxy}hexyl)amino]-1-hydroxyethyl}-2-(hydroxymethyl)phenol, 2-hydroxy-5-((1*R*)-1-hydroxy-2-{[2-(4-{[(2*R*)-2-hydroxy-2- phenylethyl]amino} phenyl)ethyl]amino}ethyl)phenylformamide, 8-hydroxy-5-{(1*R*)-1-hydroxy-2-[(2-{4-[(6-methoxy-1,1'-biphenyl-3-yl)amino] phenyl} ethyl)amino]ethyl}quinolin-2(1*H*)-one, and combinations thereof;

an anti-inflammatory steroid selected from the group consisting of (6α,11β,16α,17α)-6,9-difluoro-17-{[(fluoromethyl)thio]carbonyl}-11-hydroxy-16-methyl-3-oxoandrosta-1,4-dien-17-yl 2-furoate, (6α,11β,16α,17α)-6,9-difluoro-17-{[(fluoromethyl)thio]carbonyl}-11-hydroxy-16-methyl-3-oxoandrosta-1,4-dien-17-yl 4-methyl-1,3-thiazole-5-carboxylate, and combinations thereof; and

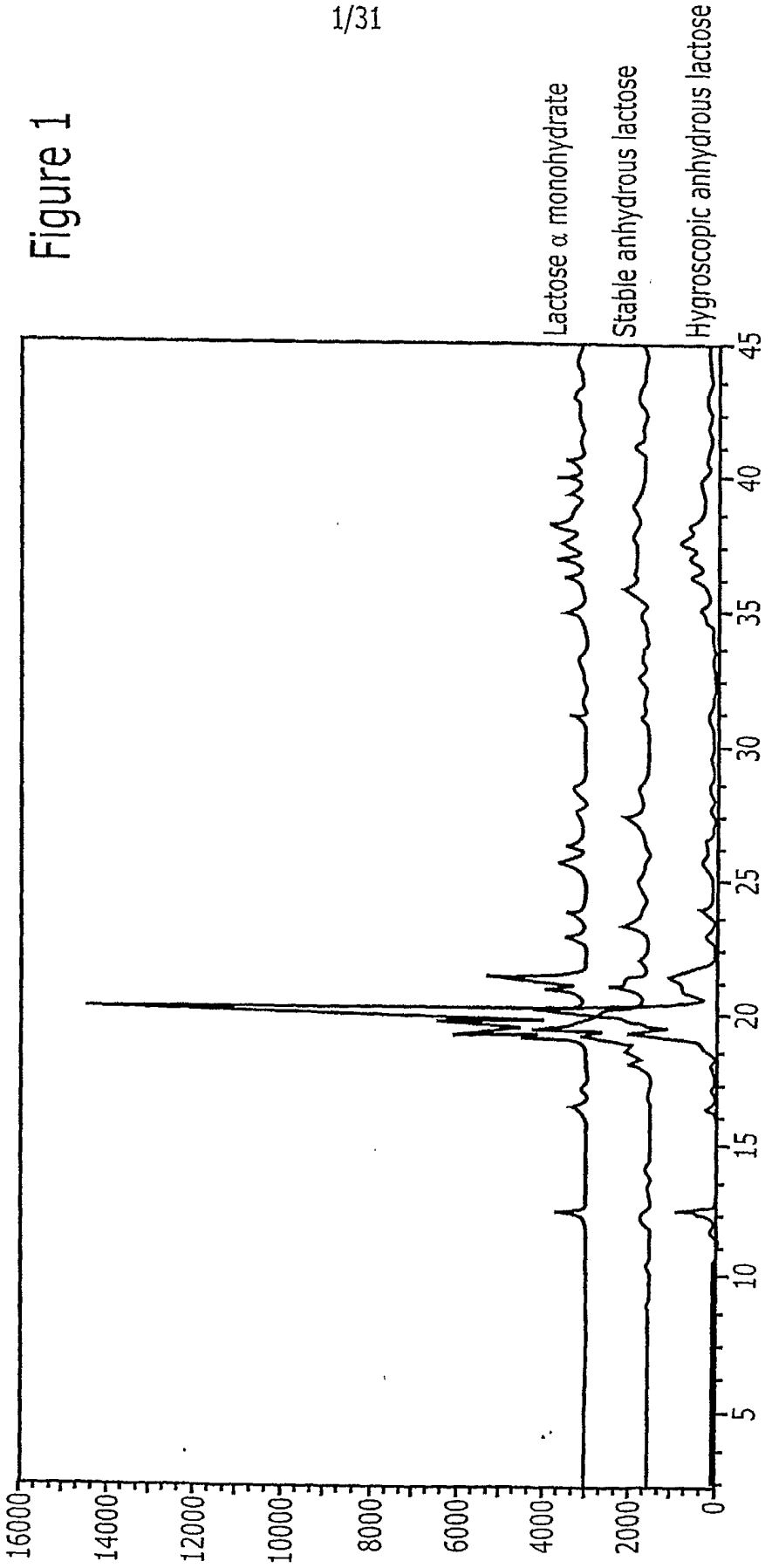
α_H anhydrous lactose.

19. A pharmaceutical formulation suitable for inhalation, said formulation comprising:

a beta agonist selected from the group consisting of 3-(4-{[6-({(2*R*)-2-hydroxy-2-[4-hydroxy-3-(hydroxymethyl) phenyl]ethyl}amino) hexyl]oxy}butyl) benzenesulfonamide, 3-(3-{[7-({(2*R*)-2-hydroxy- 2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl}amino)heptyl]oxy}propyl) benzenesulfonamide, 4-{(1*R*)-2-[(6-{2-[(2,6-dichlorobenzyl)oxy] ethoxy}hexyl)amino]-1-hydroxyethyl}-2-(hydroxymethyl)phenol, 2-hydroxy-5-((1*R*)-1-hydroxy-2-{[2-(4-{[(2*R*)-2-hydroxy-2- phenylethyl]amino} phenyl)ethyl]amino}ethyl)phenylformamide, 8-hydroxy-5-{(1*R*)-1-hydroxy-2-[(2-{4-[(6-methoxy-1,1'-biphenyl-3-yl)amino] phenyl} ethyl)amino]ethyl}quinolin-2(1*H*)-one, and combinations thereof; and

lactose anhydrate.

Figure 1


Lactose α monohydrate
Stable anhydrous lactose
Hygroscopic anhydrous lactose
16000
14000
12000
10000
8000
6000
4000
2000
0
5
10
15
20
25
30
35
40
45

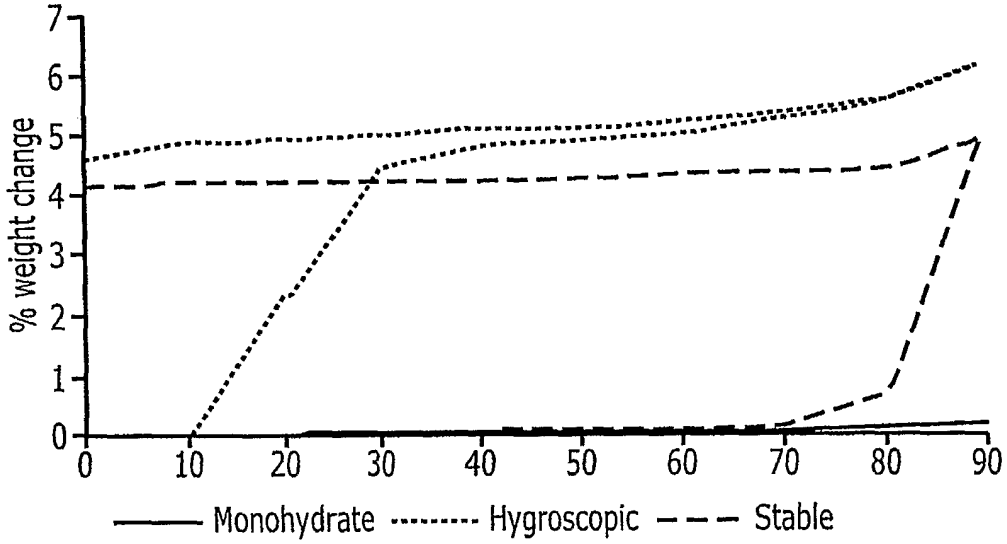


Figure 2

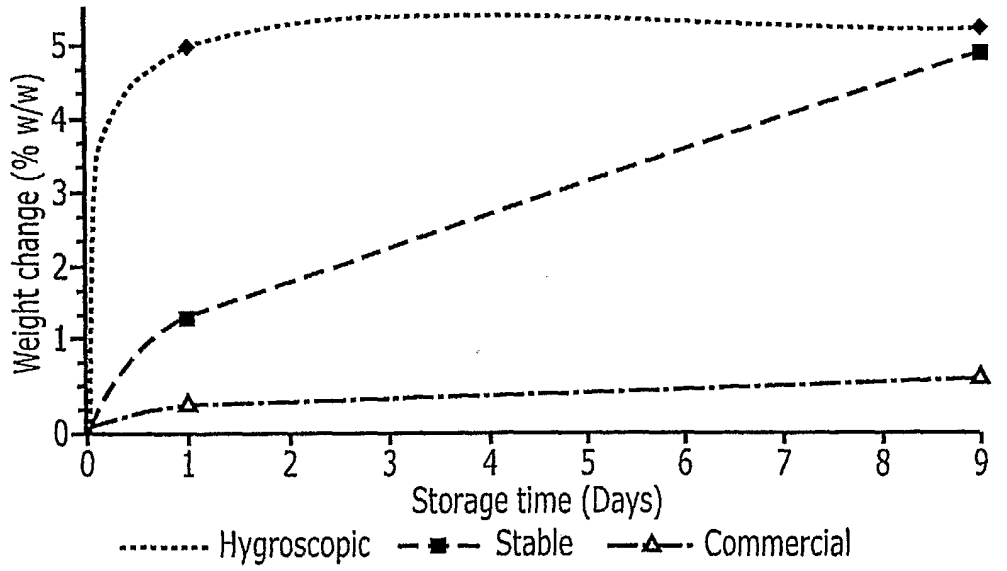


Figure 3

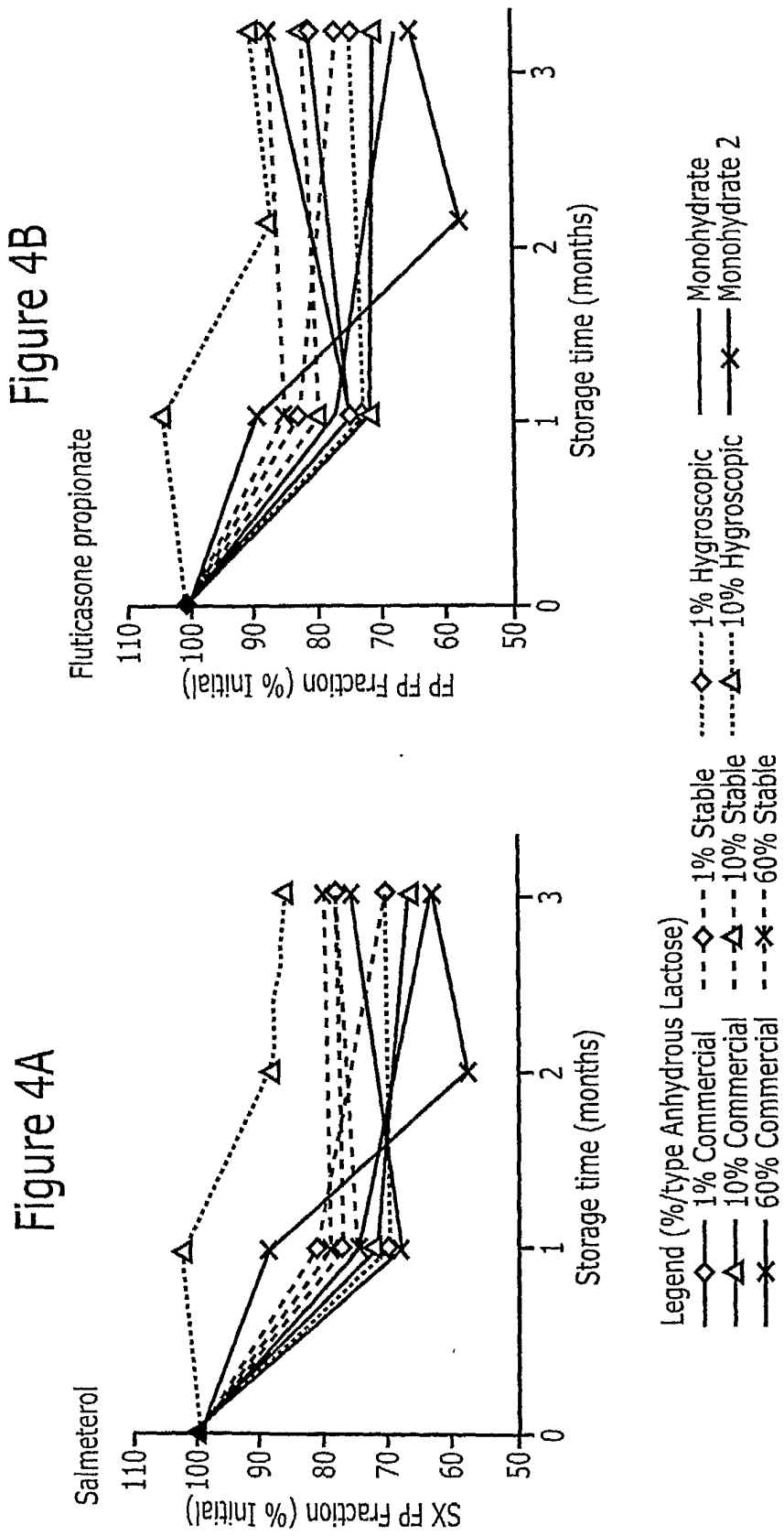


Figure 4A
Salmeterol
SX FP Fraction (% Initial)
110
100
90
80
70
60
50
0
1
2
3
Storage time (months)
Figure 4B
Fluticasone propionate
FP FP Fraction (% Initial)
Storage time (months)
Legend (%/type Anhydrous Lactose)
1% Commercial
10% Commercial
60% Commercial
1% Stable
10% Stable
60% Stable
1% Hygroscopic
10% Hygroscopic
Monohydrate
Monohydrate 2

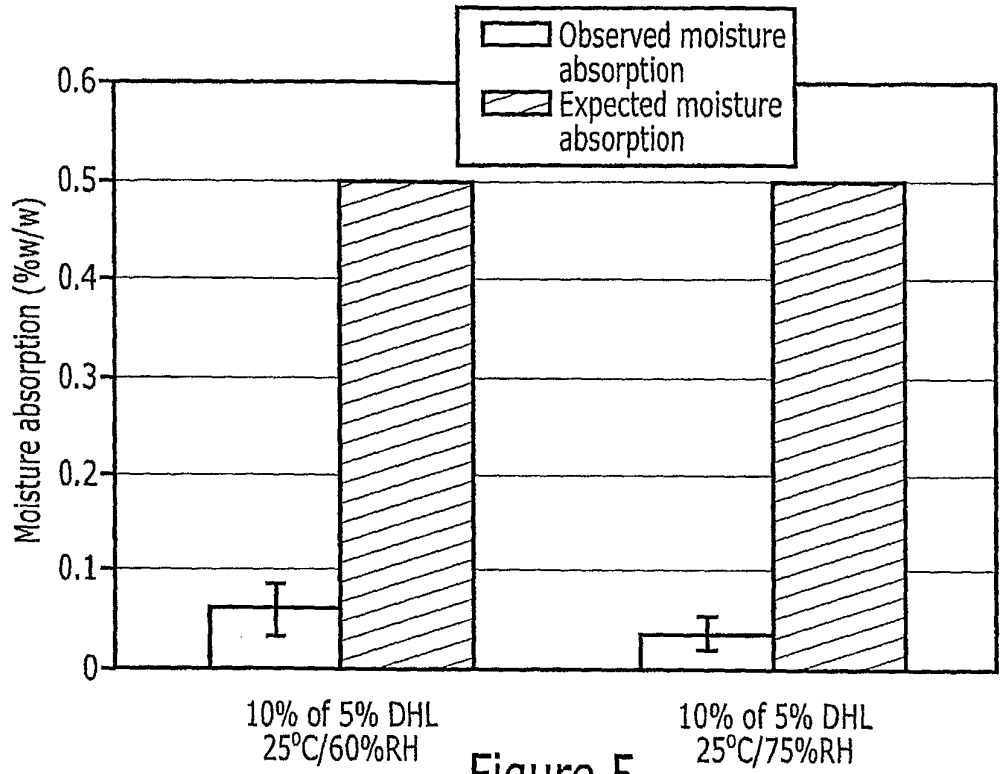


Figure 5

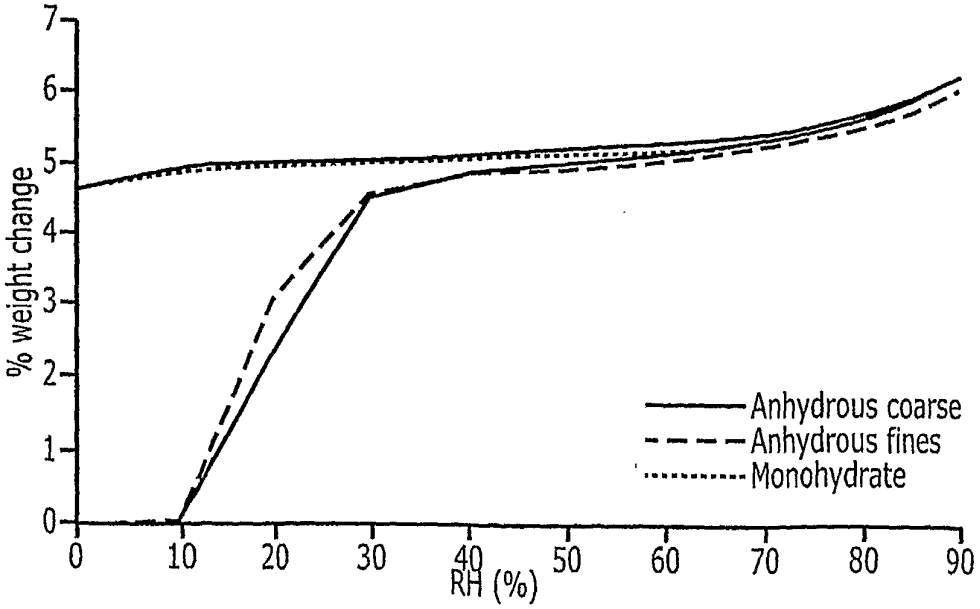


Figure 6

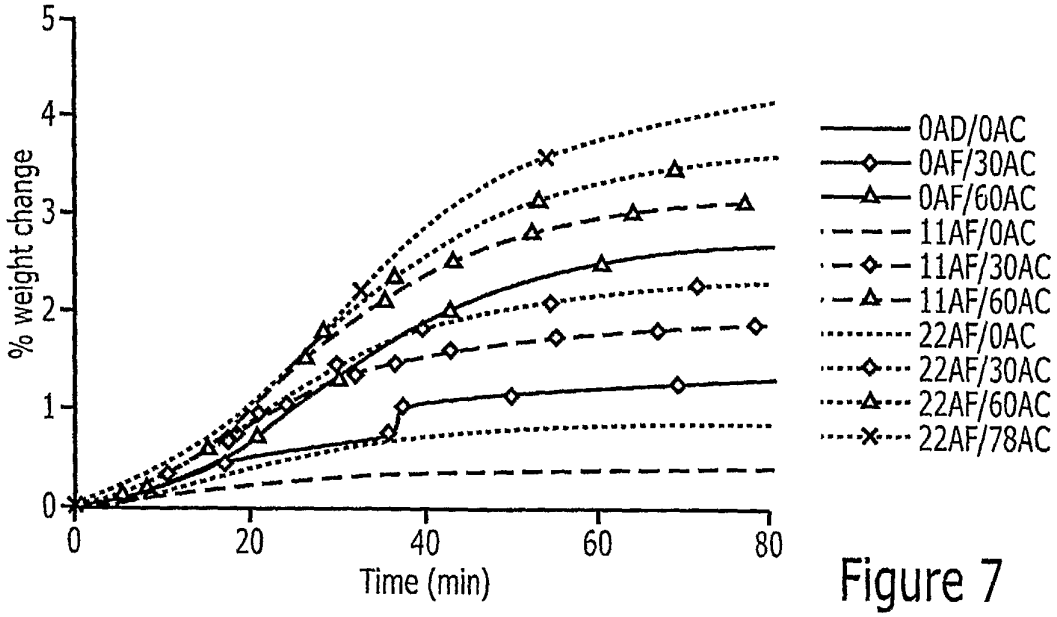


Figure 7

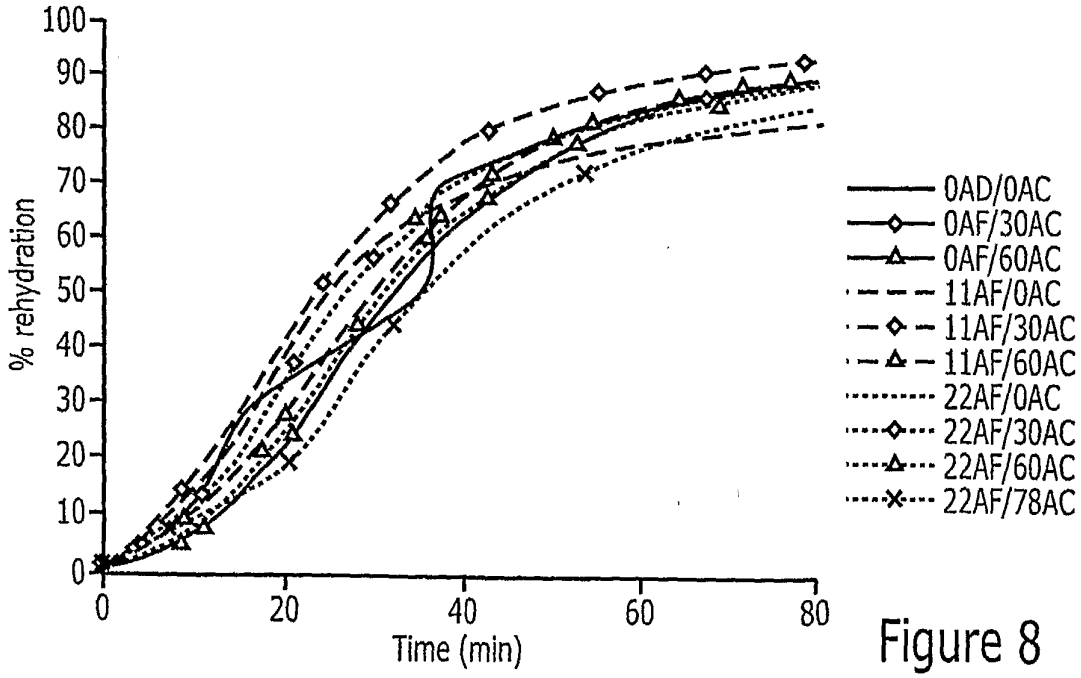
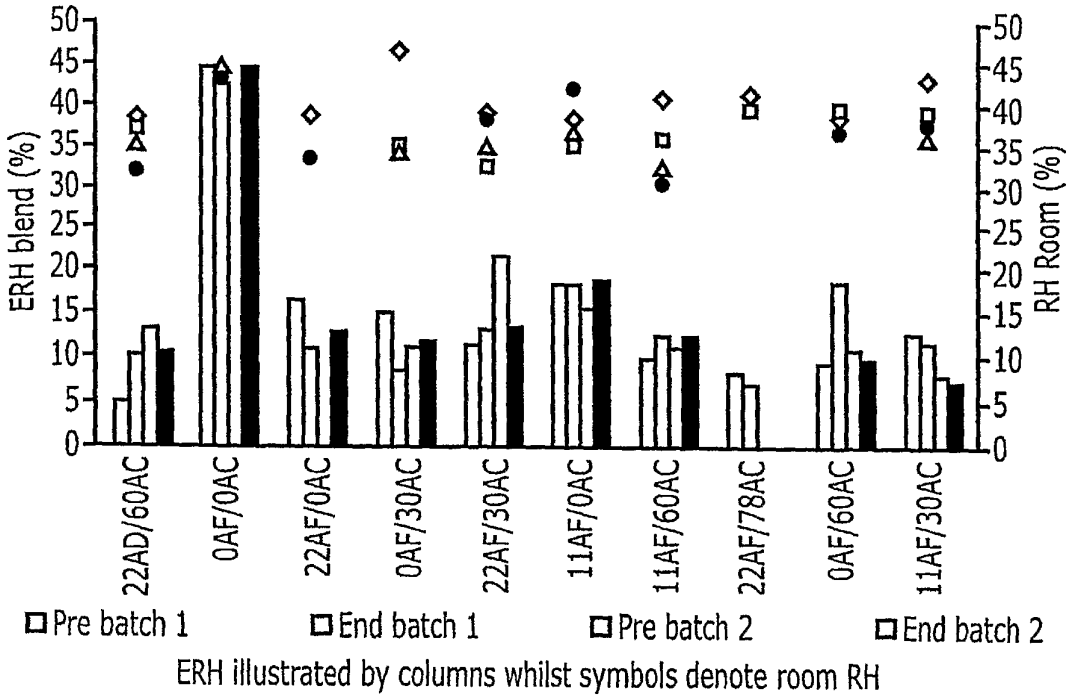


Figure 8



ERH illustrated by columns whilst symbols denote room RH

Figure 9

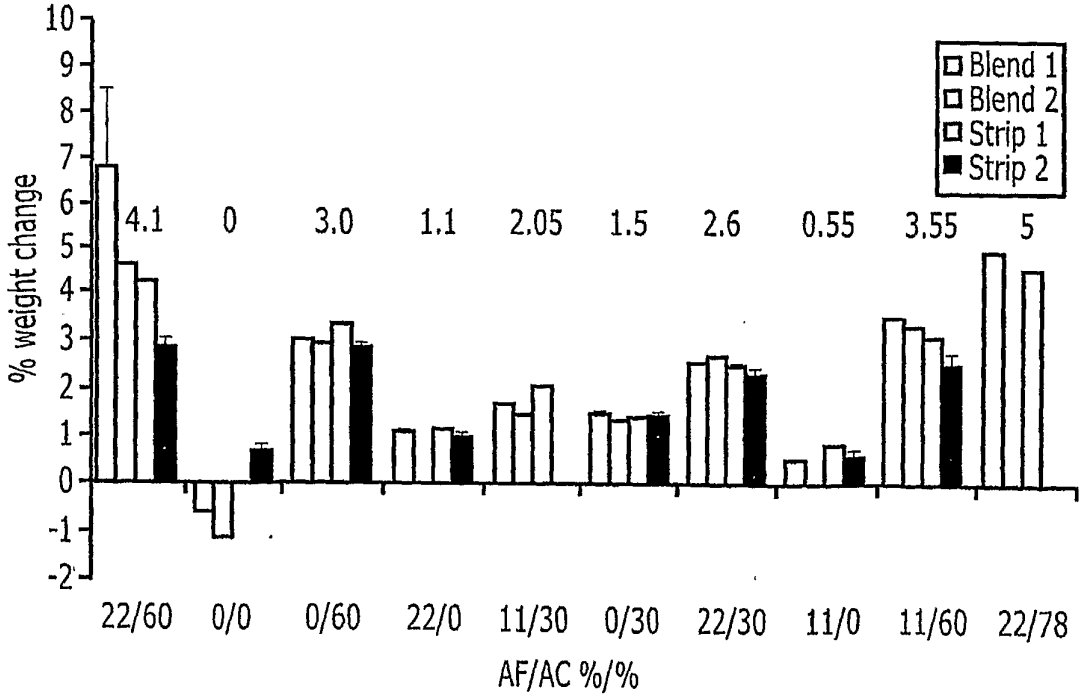


Figure 10

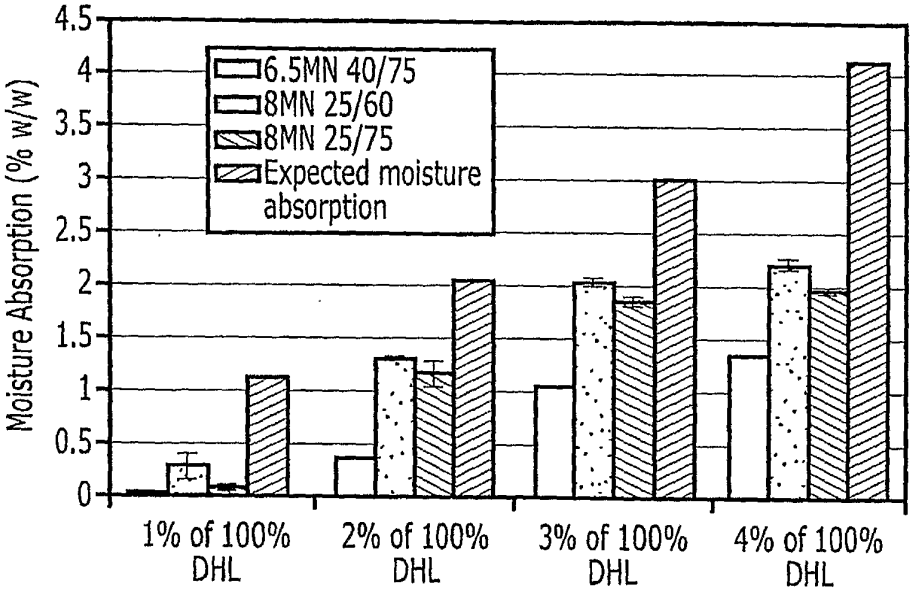

4.5
4
3.5
3
2.5
2
1.5
1
0.5
0
Moisture Absorption (% w/w)
6.5MN 40/75
8MN 25/60
8MN 25/75
Expected moisture absorption
1% of 100% DHL
2% of 100% DHL
3% of 100% DHL
4% of 100% DHL

Figure 11

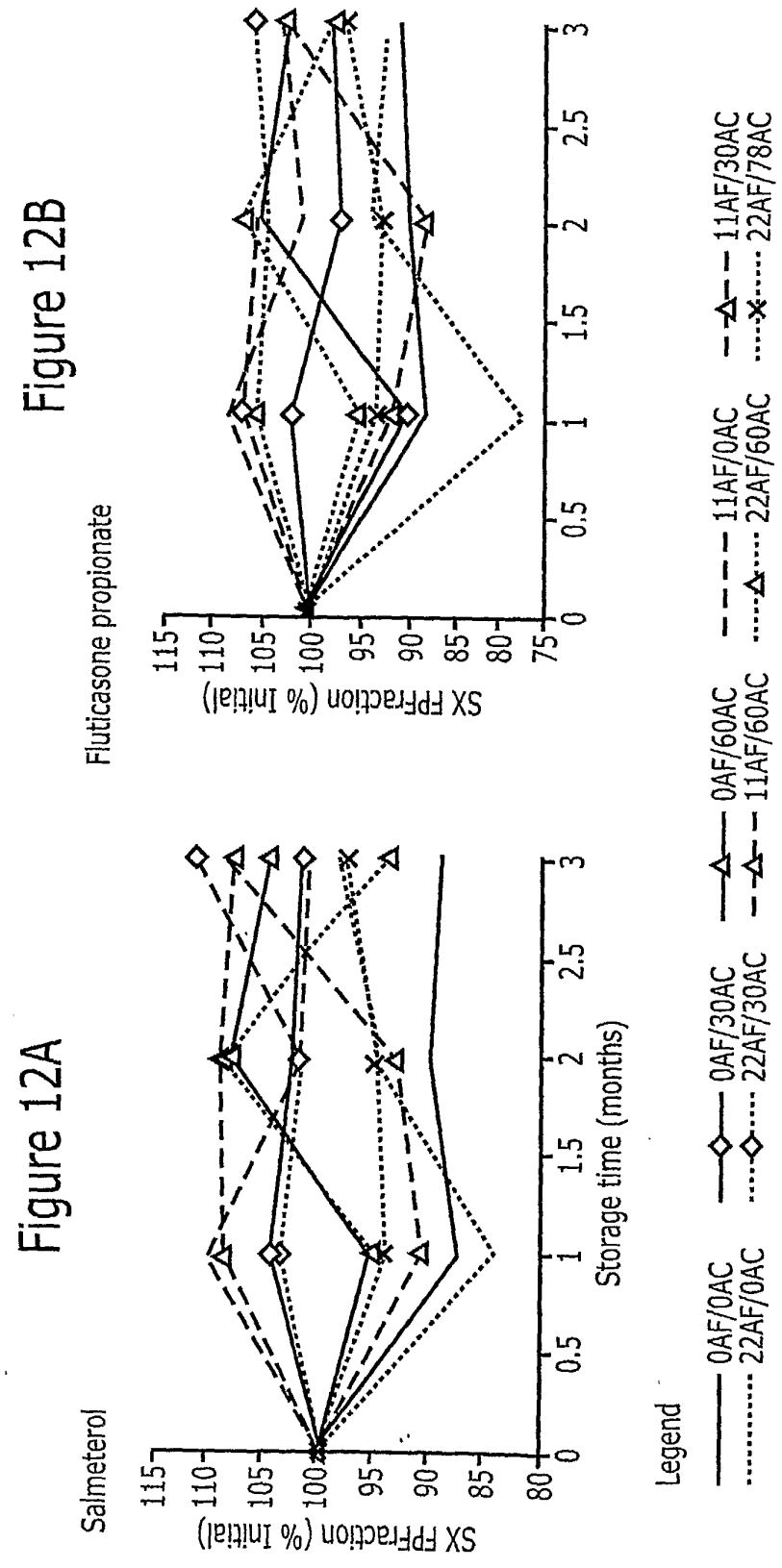


Figure 12A
Salmeterol
SX FPFraction (% Initial)
115
110
105
100
95
90
85
80
0
0.5
1
1.5
2
2.5
3
Storage time (months)
Figure 12B
Fluticasone propionate
SX FPFraction (% Initial)
115
110
105
100
95
90
85
80
75
0
0.5
1
1.5
2
2.5
3
Legend
0AF/0AC
22AF/0AC
0AF/30AC
22AF/30AC
0AF/60AC
11AF/60AC
11AF/0AC
22AF/60AC
11AF/30AC
22AF/78AC

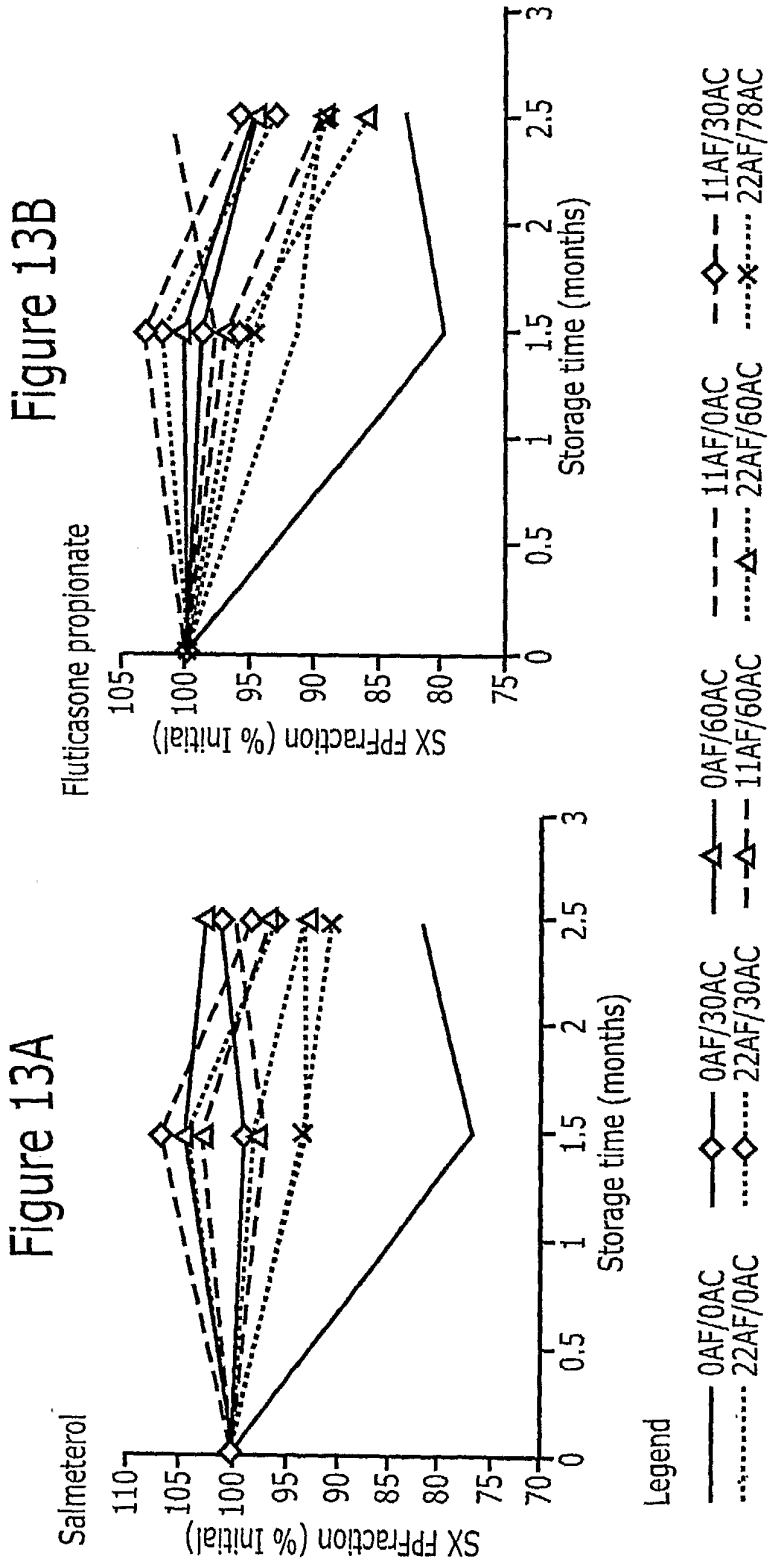


Figure 13A
Salmeterol
SX FPFraction (% Initial)
110
105
100
95
90
85
80
75
70
0
0.5
1
1.5
2
2.5
3
Storage time (months)
Figure 13B
Fluticasone propionate
SX FPFraction (% Initial)
105
100
95
90
85
80
75
0
0.5
1
1.5
2
2.5
3
Storage time (months)
Legend
0AF/0AC
22AF/0AC
0AF/30AC
22AF/30AC
0AF/60AC
11AF/60AC
11AF/0AC
22AF/60AC
11AF/30AC
22AF/78AC

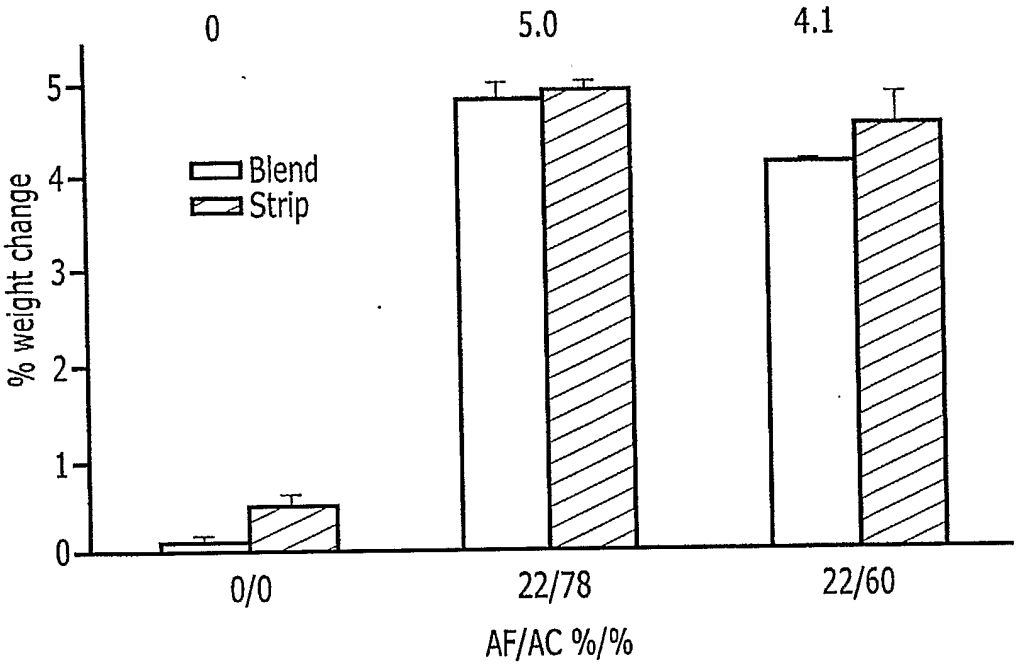


Figure 14

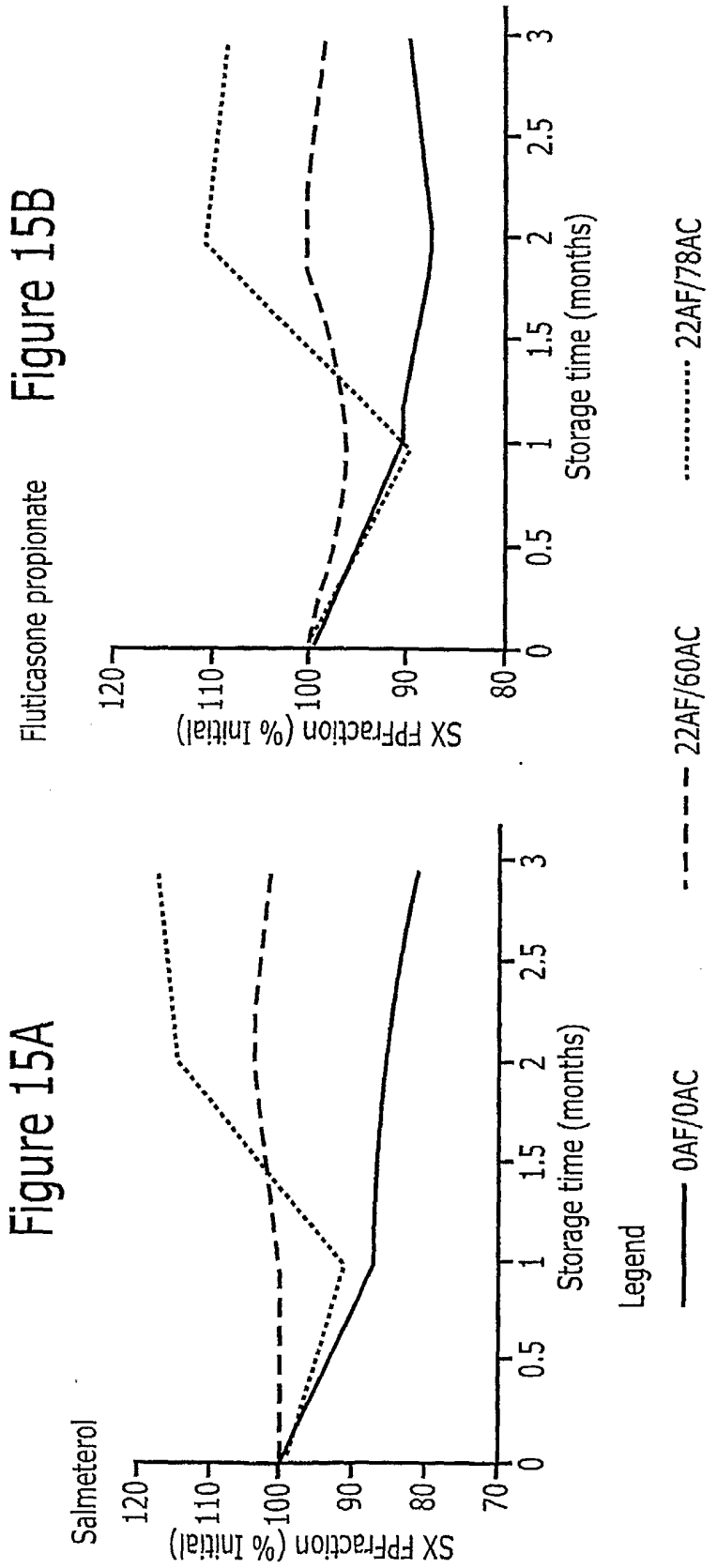


Figure 15A
Salmeterol
SX FPFraction (% Initial)
120
110
100
90
80
70
0
0.5
1
1.5
2
2.5
3
Storage time (months)
Figure 15B
Fluticasone propionate
SX FPFraction (% Initial)
120
110
100
90
80
0
0.5
1
1.5
2
2.5
3
Storage time (months)
Legend
0AF/0AC
22AF/60AC
22AF/78AC

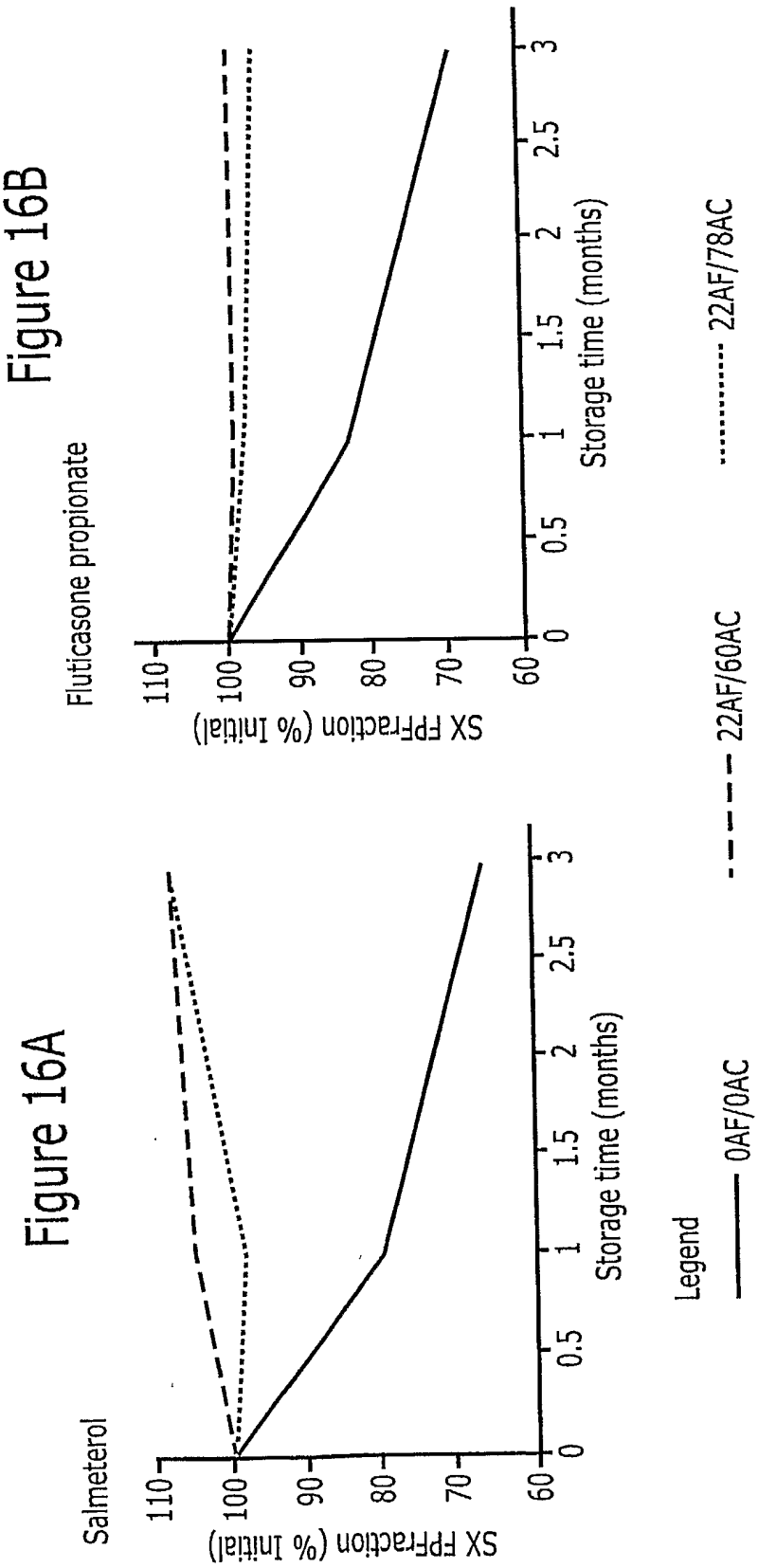


Figure 16B
Fluticasone propionate
SX FPFraction (% Initial)
110
100
90
80
70
60
0
0.5
1
1.5
2
2.5
3
Storage time (months)
Figure 16A
Salmeterol
SX FPFraction (% Initial)
Storage time (months)
Legend
0AF/0AC
22AF/60AC
22AF/78AC

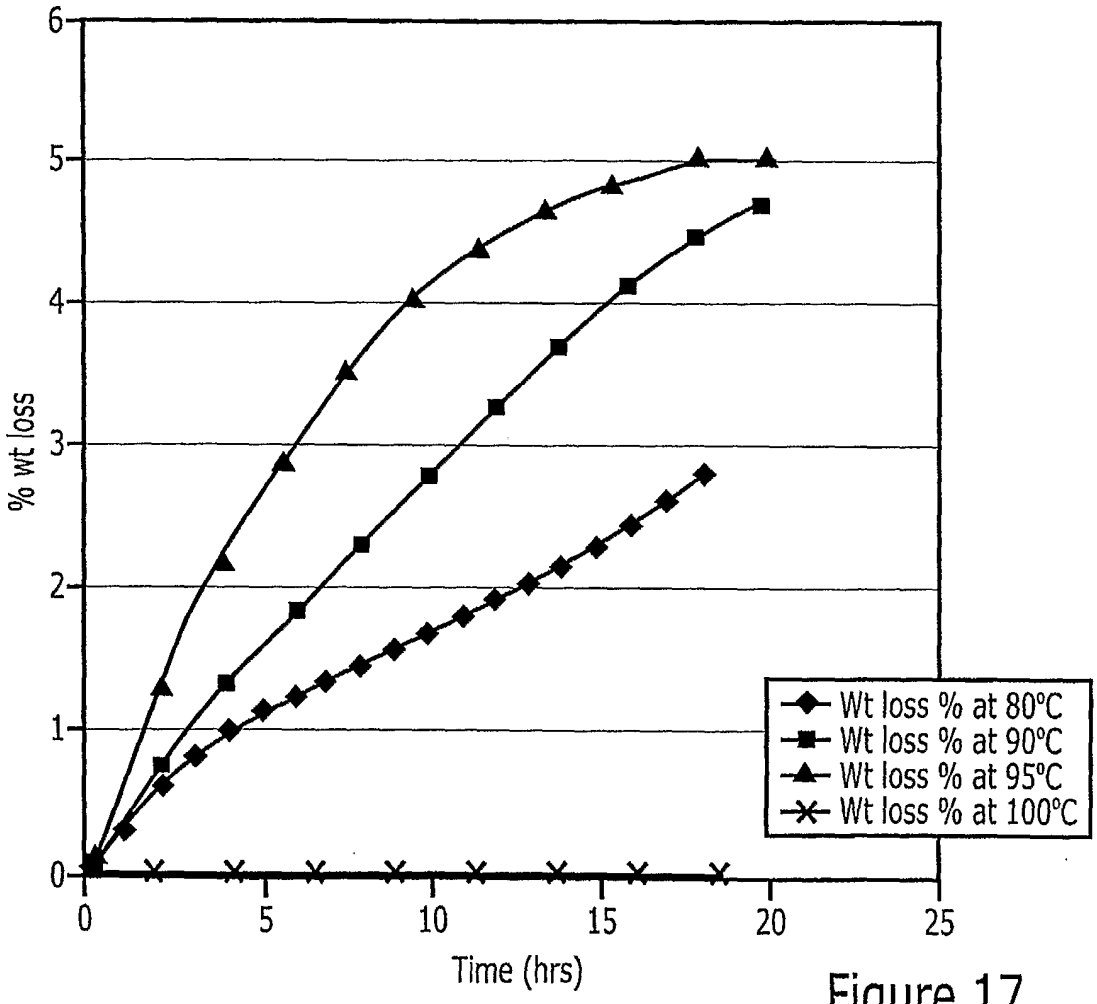

6
5
4
3
2
1
0
% wt loss
0
5
10
15
20
25
Time (hrs)
Wt loss % at 80°C
Wt loss % at 90°C
Wt loss % at 95°C
Wt loss % at 100°C

Figure 17

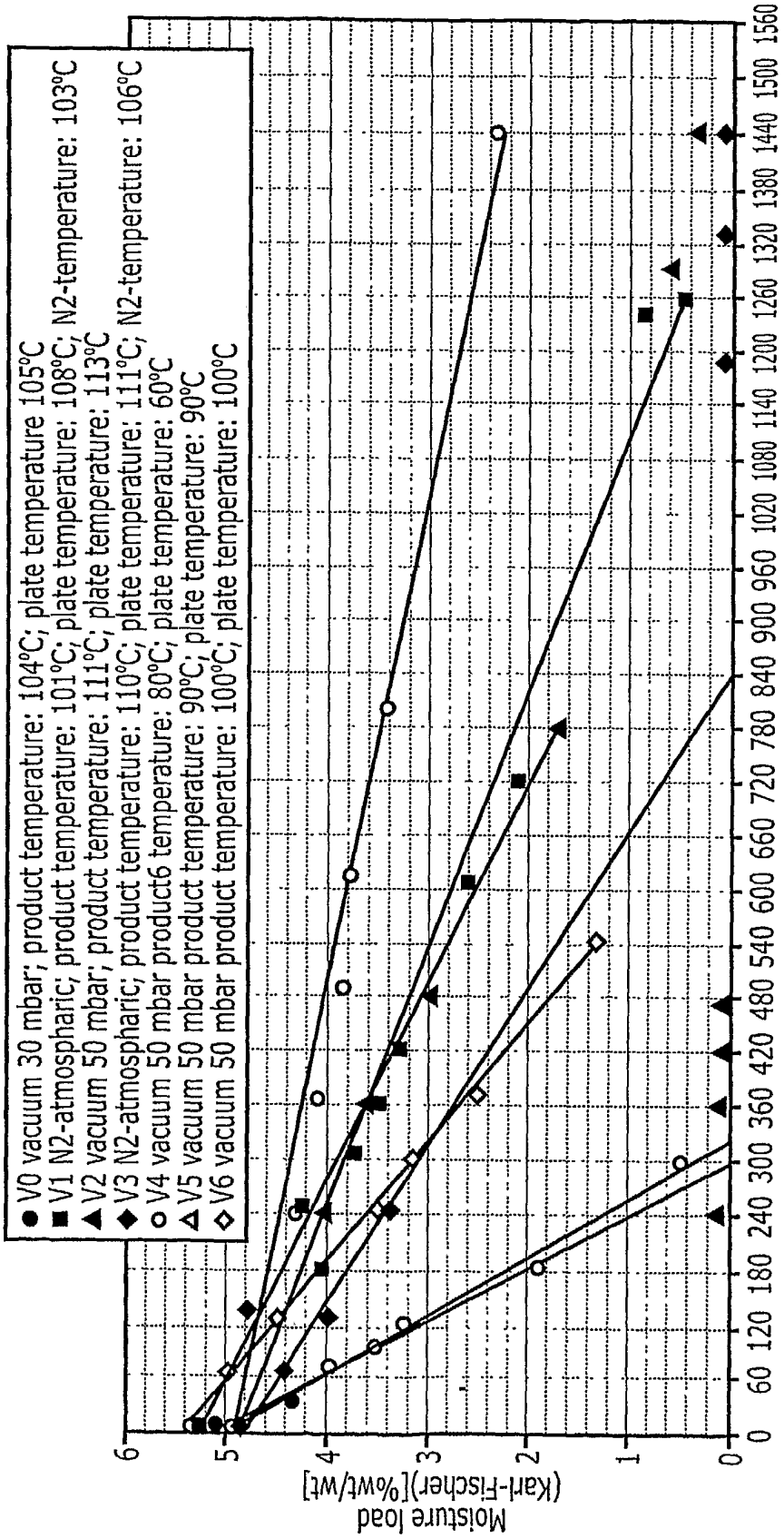

● V0 vacuum 30 mbar; product temperature: 104°C; plate temperature 105°C
■ V1 N2-atmospharic; product temperature: 101°C; plate temperature: 108°C; N2-temperature: 103°C
▲ V2 vacuum 50 mbar; product temperature: 111°C; plate temperature: 113°C
◆ V3 N2-atmospharic; product temperature: 110°C; plate temperature: 111°C; N2-temperature: 106°C
○ V4 vacuum 50 mbar product6 temperature: 80°C; plate temperature: 60°C
△ V5 vacuum 50 mbar product temperature: 90°C; plate temperature: 90°C
◇ V6 vacuum 50 mbar product temperature: 100°C; plate temperature: 100°C
Moisture load (Karl-Fischer)[%wt/wt]
0
1
2
3
4
5
6
0 60 120 180 240 300 360 420 480 540 600 660 720 780 840 900 960 1020 1080 1140 1200 1260 1320 1380 1440 1500 1560
Drying Time [min]

Figure 18

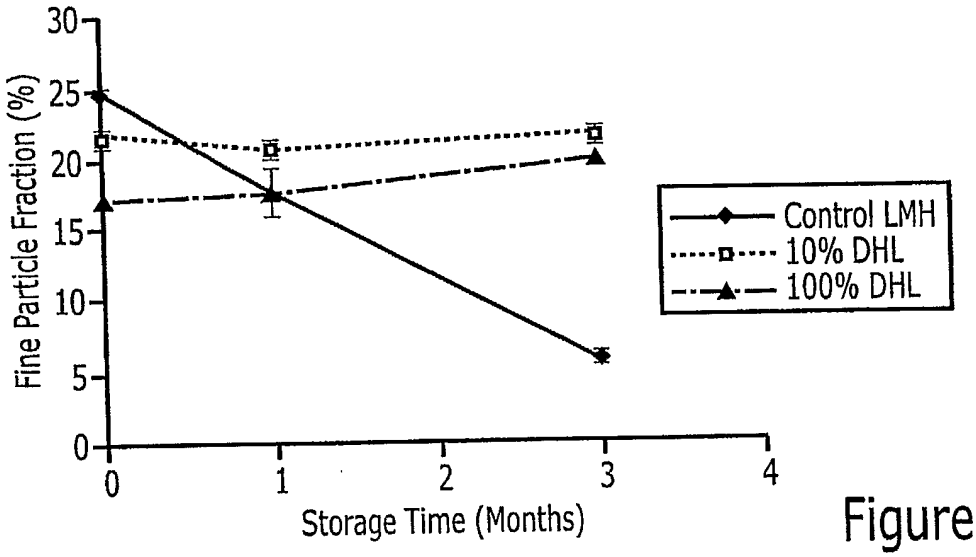


Figure 19

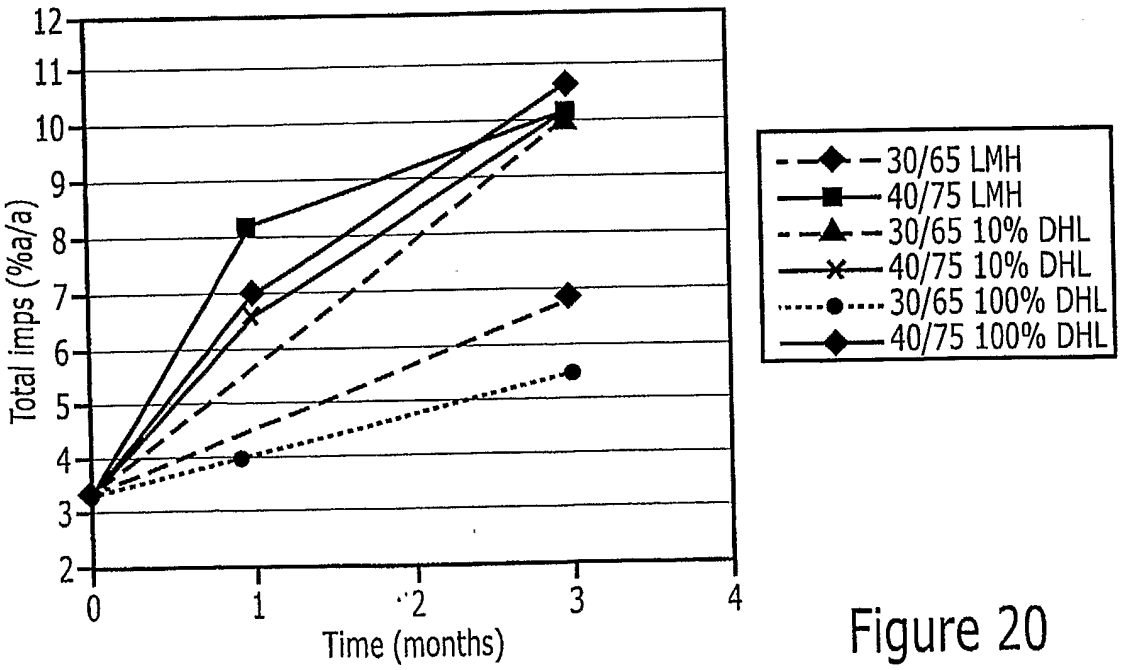


Figure 20

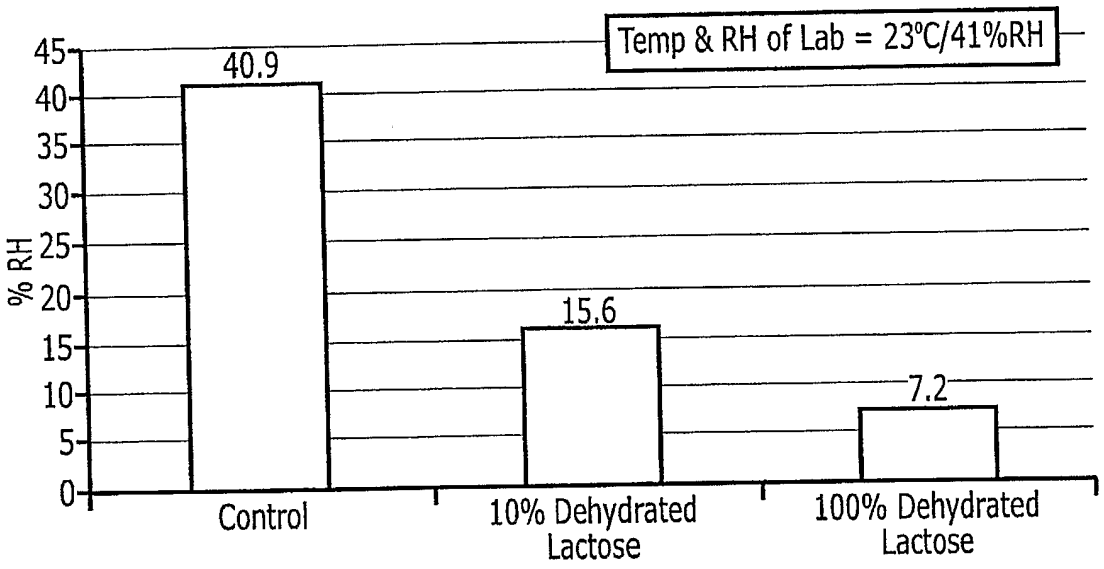

Temp & RH of Lab = 23°C/41%RH
% RH
45
40
35
30
25
20
15
10
5
0
40.9
15.6
7.2
Control
10% Dehydrated Lactose
100% Dehydrated Lactose

Figure 21

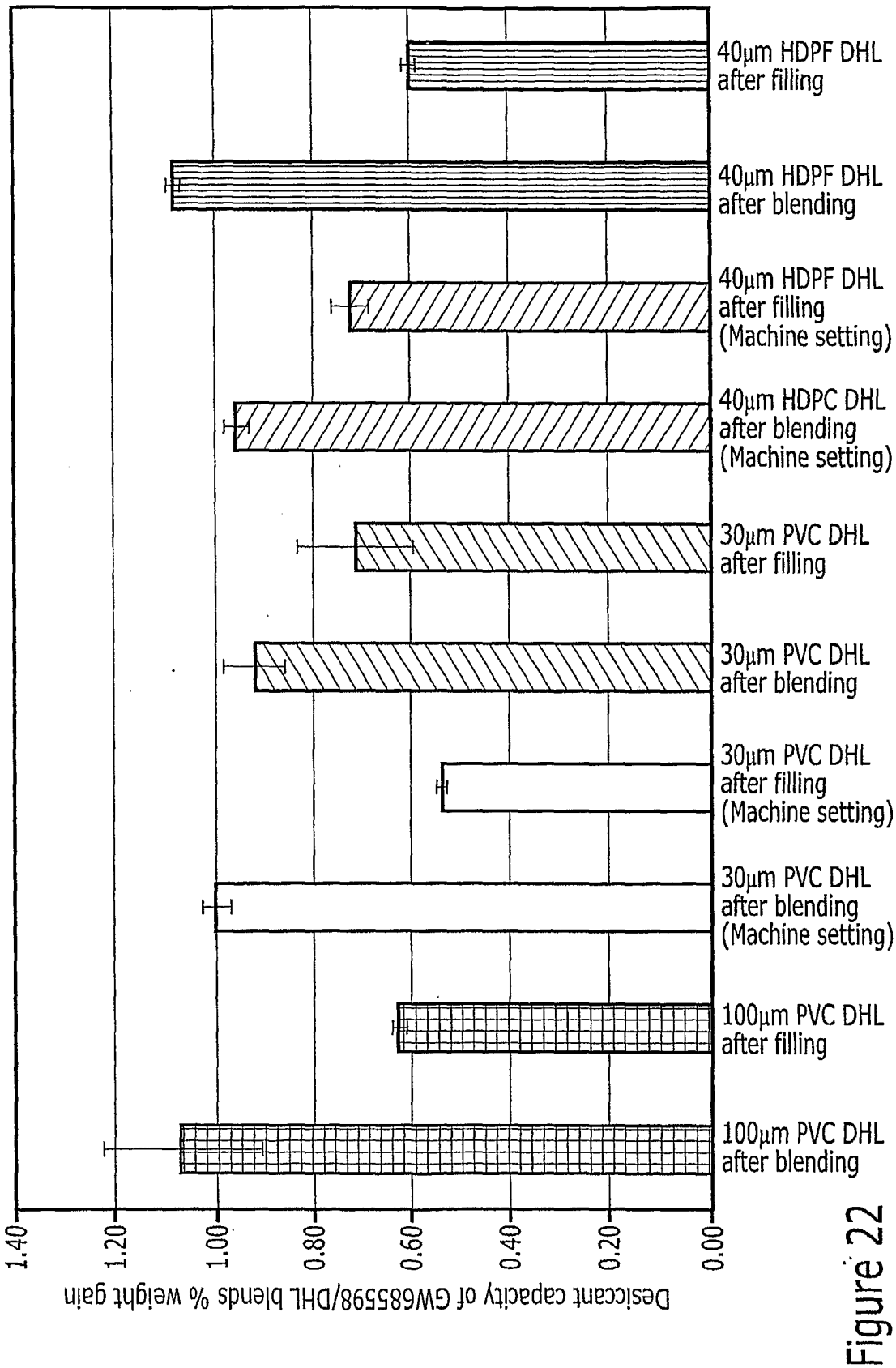

40µm HDPF DHL after filling
40µm HDPF DHL after blending
40µm HDPF DHL after filling (Machine setting)
40µm HDPC DHL after blending (Machine setting)
30µm PVC DHL after filling
30µm PVC DHL after blending
30µm PVC DHL after filling (Machine setting)
30µm PVC DHL after blending (Machine setting)
100µm PVC DHL after filling
100µm PVC DHL after blending
1.40
1.20
1.00
0.80
0.60
0.40
0.20
0.00
Desiccant capacity of GW68559B/DHL blends % weight gain

Figure 22

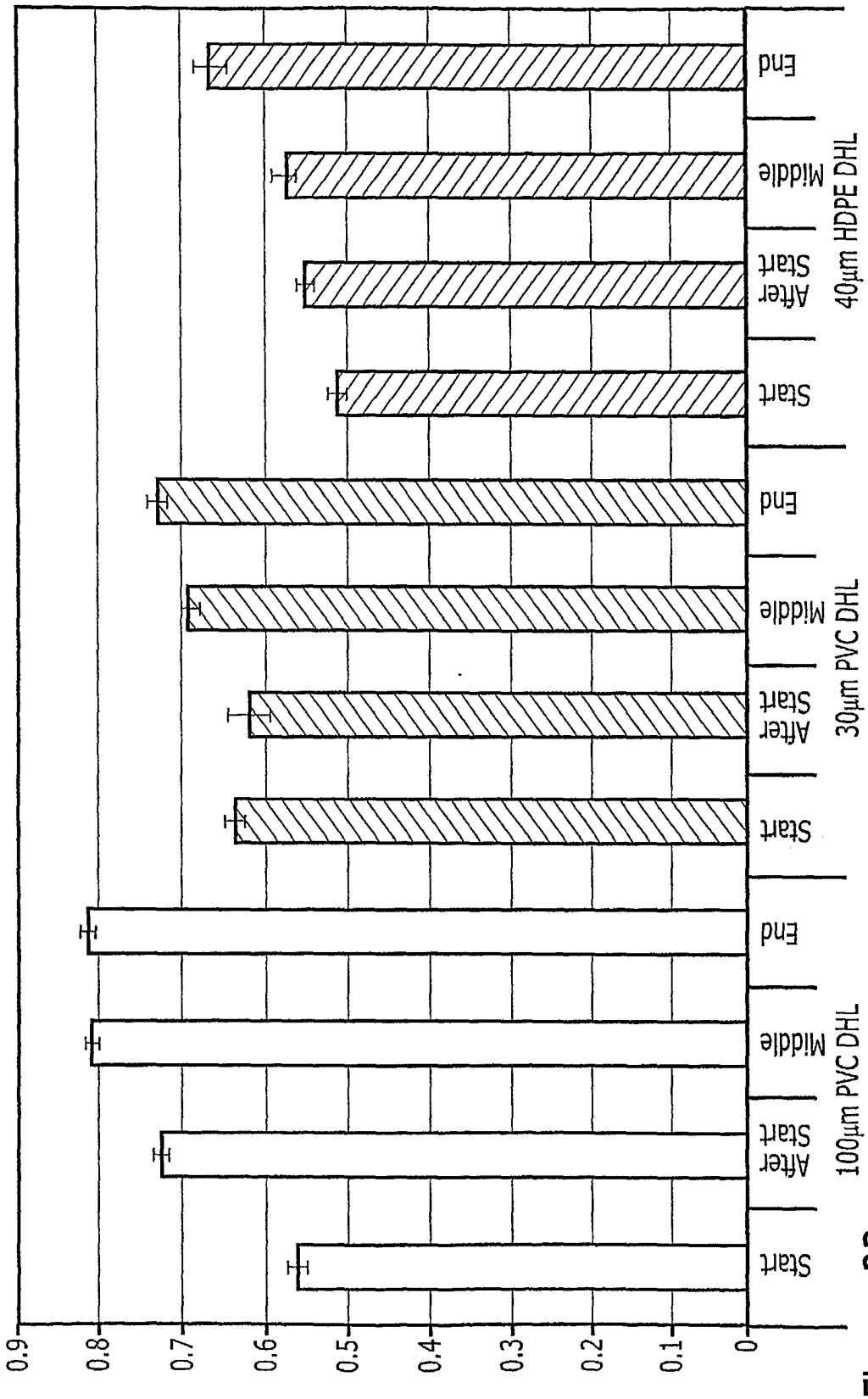

0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
Start
After Start
Middle
End
100µm PVC DHL
Start
After Start
Middle
End
30µm PVC DHL
Start
After Start
Middle
End
40µm HDPE DHL

Figure 23

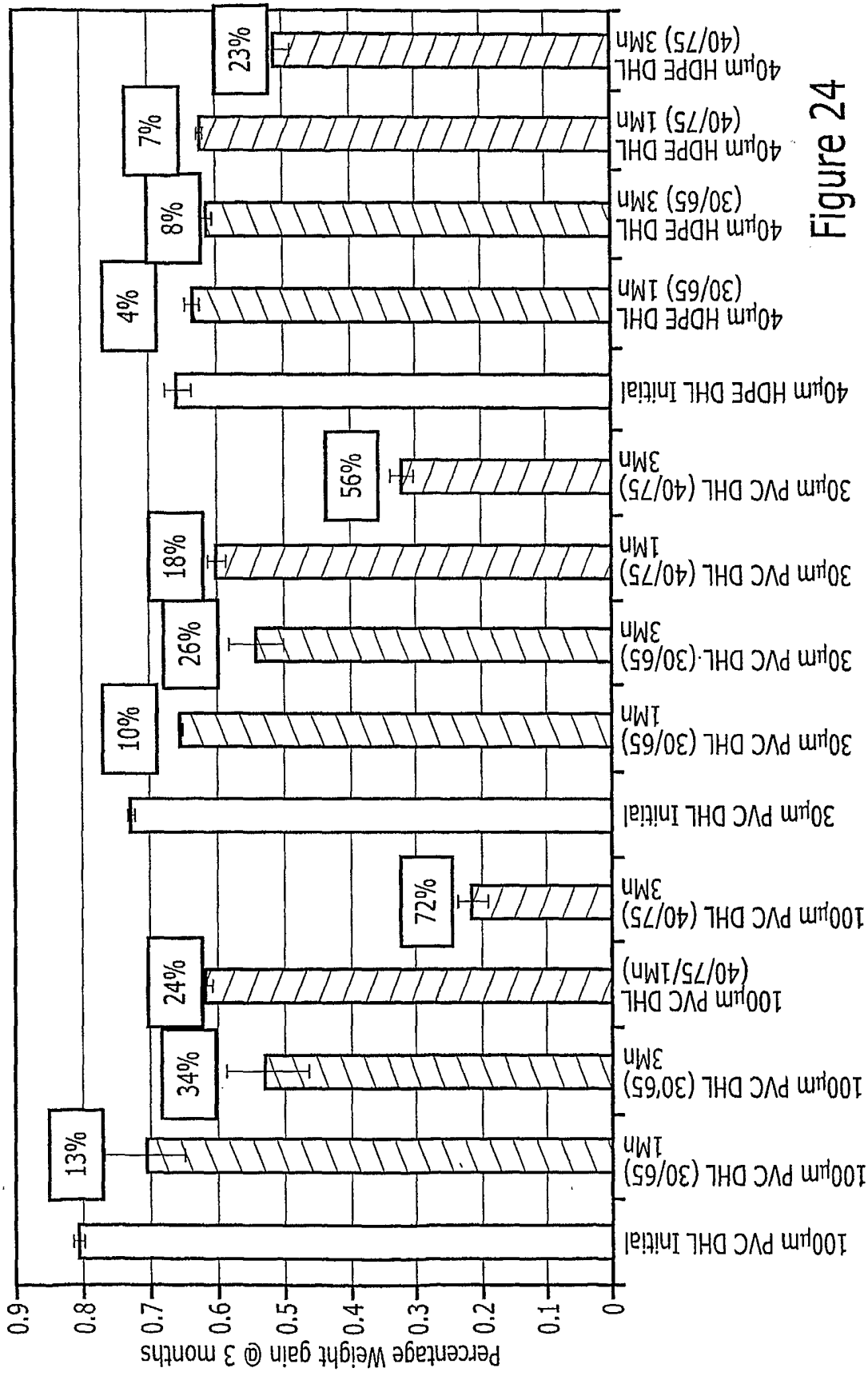

Percentage Weight gain @ 3 months
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
100µm PVC DHL Initial
100µm PVC DHL (30/65) 1Mn
100µm PVC DHL (30/65) 3Mn
100µm PVC DHL (40/75/1Mn)
100µm PVC DHL (40/75) 3Mn
30µm PVC DHL Initial
30µm PVC DHL (30/65) 1Mn
30µm PVC DHL (30/65) 3Mn
30µm PVC DHL (40/75) 1Mn
30µm PVC DHL (40/75) 3Mn
40µm HDPE DHL Initial
40µm HDPE DHL (30/65) 1Mn
40µm HDPE DHL (30/65) 3Mn
40µm HDPE DHL (40/75) 1Mn
40µm HDPE DHL (40/75) 3Mn
13%
34%
24%
72%
10%
26%
18%
56%
4%
8%
7%
23%

Figure 24

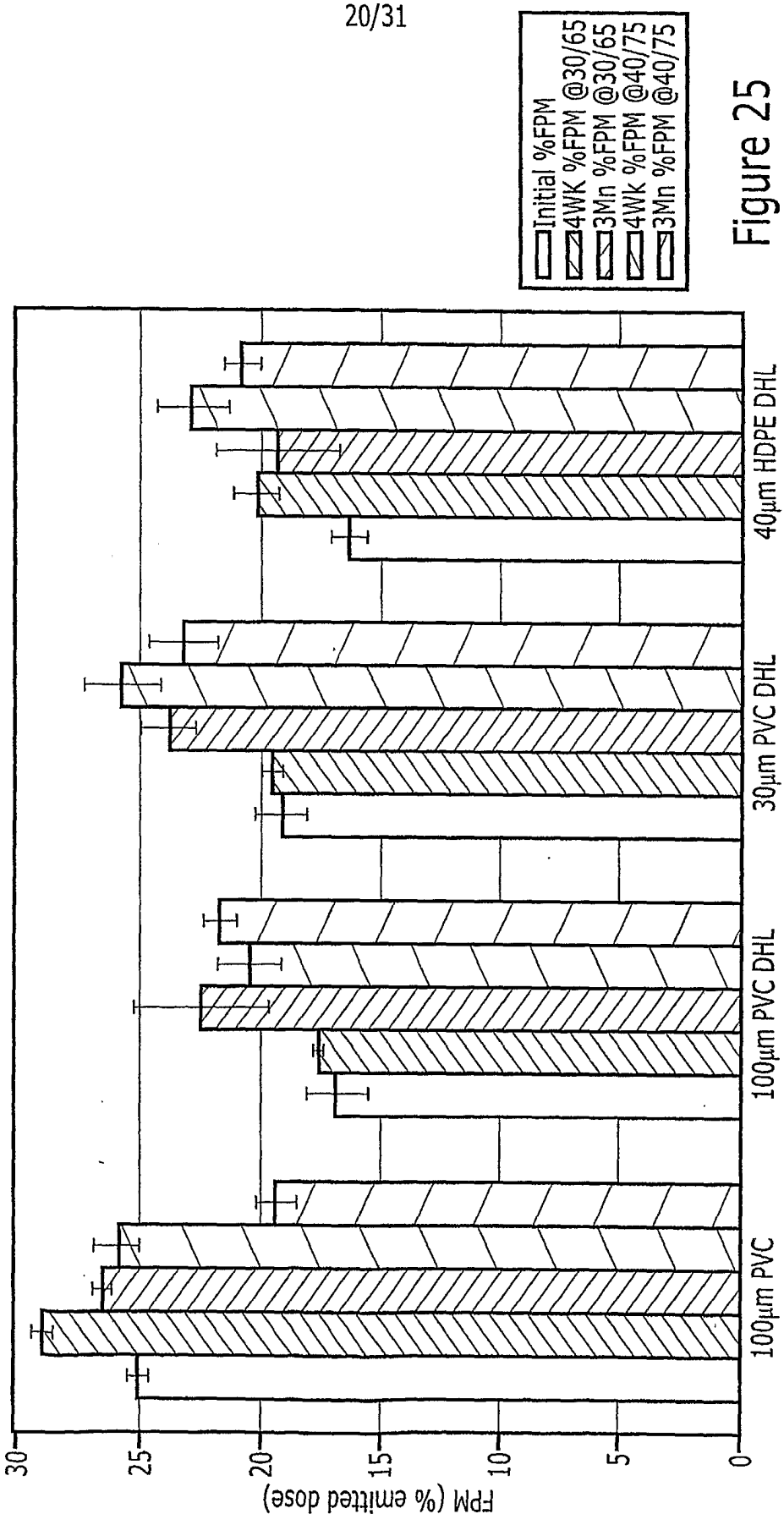

Initial %FPM
4WK %FPM @30/65
3Mn %FPM @30/65
4Wk %FPM @40/75
3Mn %FPM @40/75
FPM (% emitted dose)
0
5
10
15
20
25
30
100µm PVC
100µm PVC DHL
30µm PVC DHL
40µm HDPE DHL

Figure 25

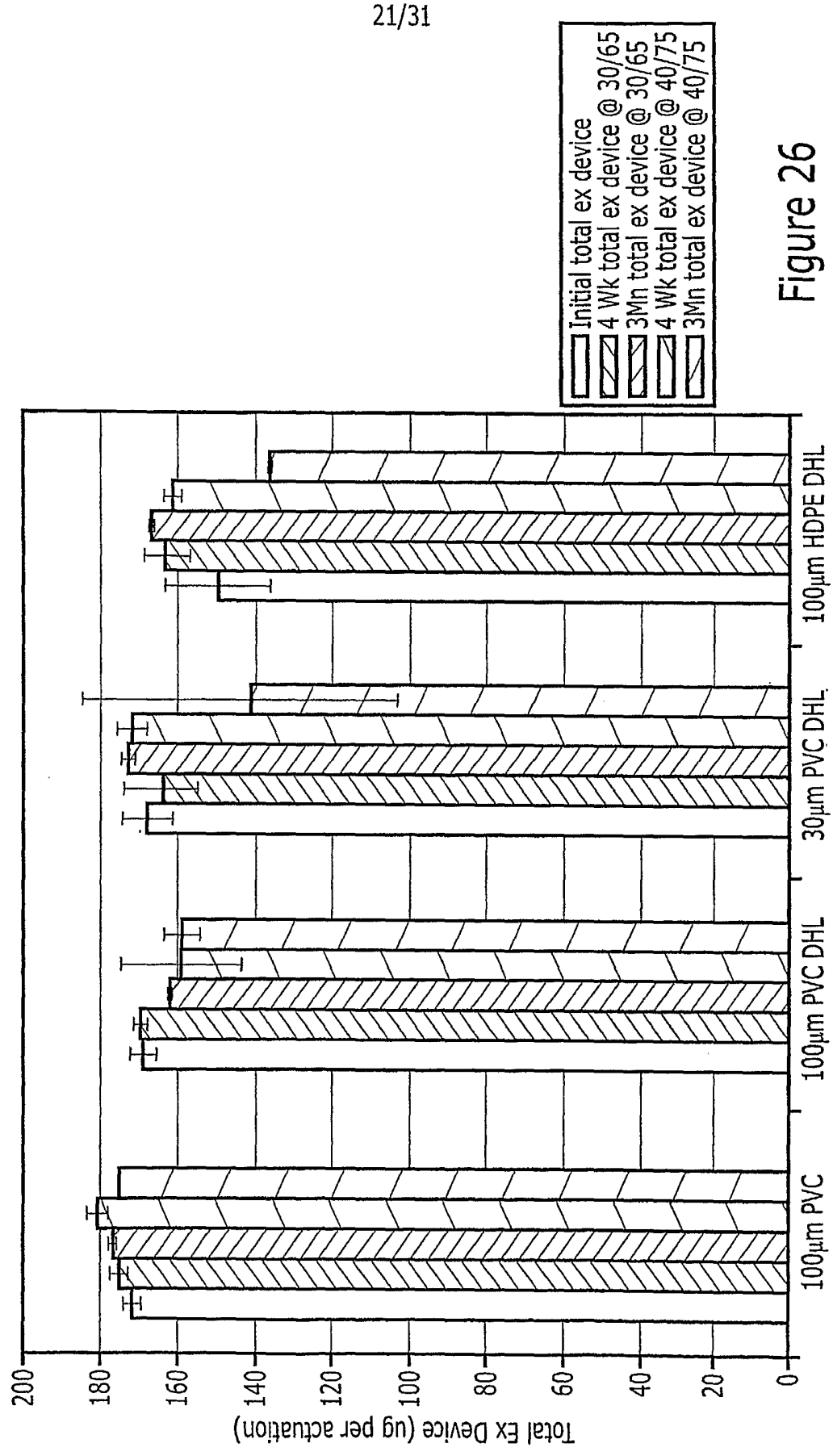

Initial total ex device
4 Wk total ex device @ 30/65
3Mn total ex device @ 30/65
4 Wk total ex device @ 40/75
3Mn total ex device @ 40/75
Total Ex Device (ug per actuation)
0
20
40
60
80
100
120
140
160
180
200
100µm PVC
100µm PVC DHL
30µm PVC DHL
100µm HDPE DHL

Figure 26

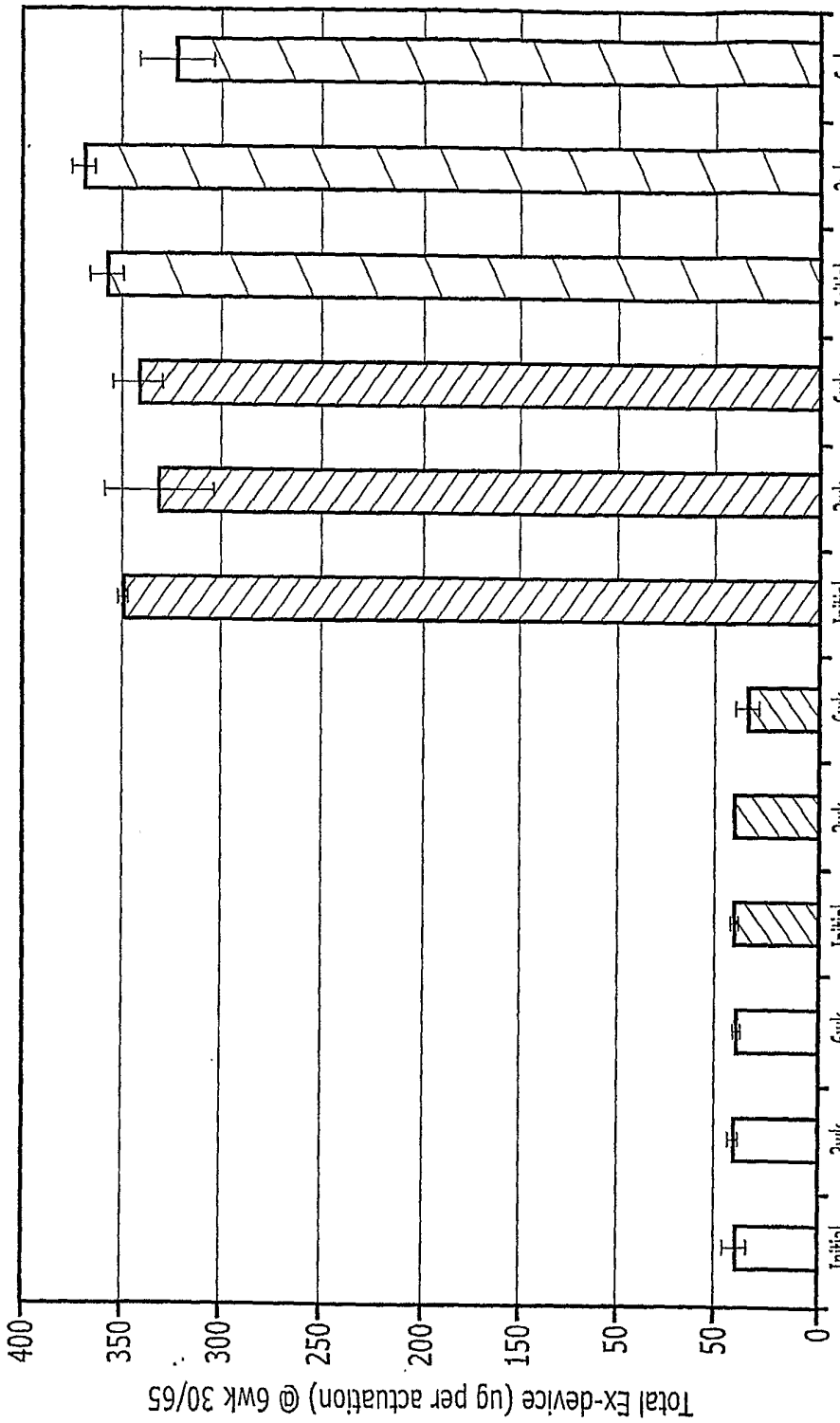

Total Ex-device (ug per actuation) @ 6wk 30/65
400
350
300
250
200
150
50
50
0
Initial R11615/4A 50ug COA
3wk R11615/4A 50ug COA
6wk R11615/4A 50ug COA
Initial R11615/5A 50ug COA/DHL
3wk R11615/5A 50ug COA/DHL
6wk R11615/5A 50ug COA/DHL
Initial R11615/6A 400ug COA
3wk R11615/6A 400ug COA
6wk R11615/6A 400ug COA
Initial R11615/7A 400ug COA/DHL
3wk R11615/7A 400ug COA/DHL
6wk R11615/7A 400ug COA/DHL

Figure 27

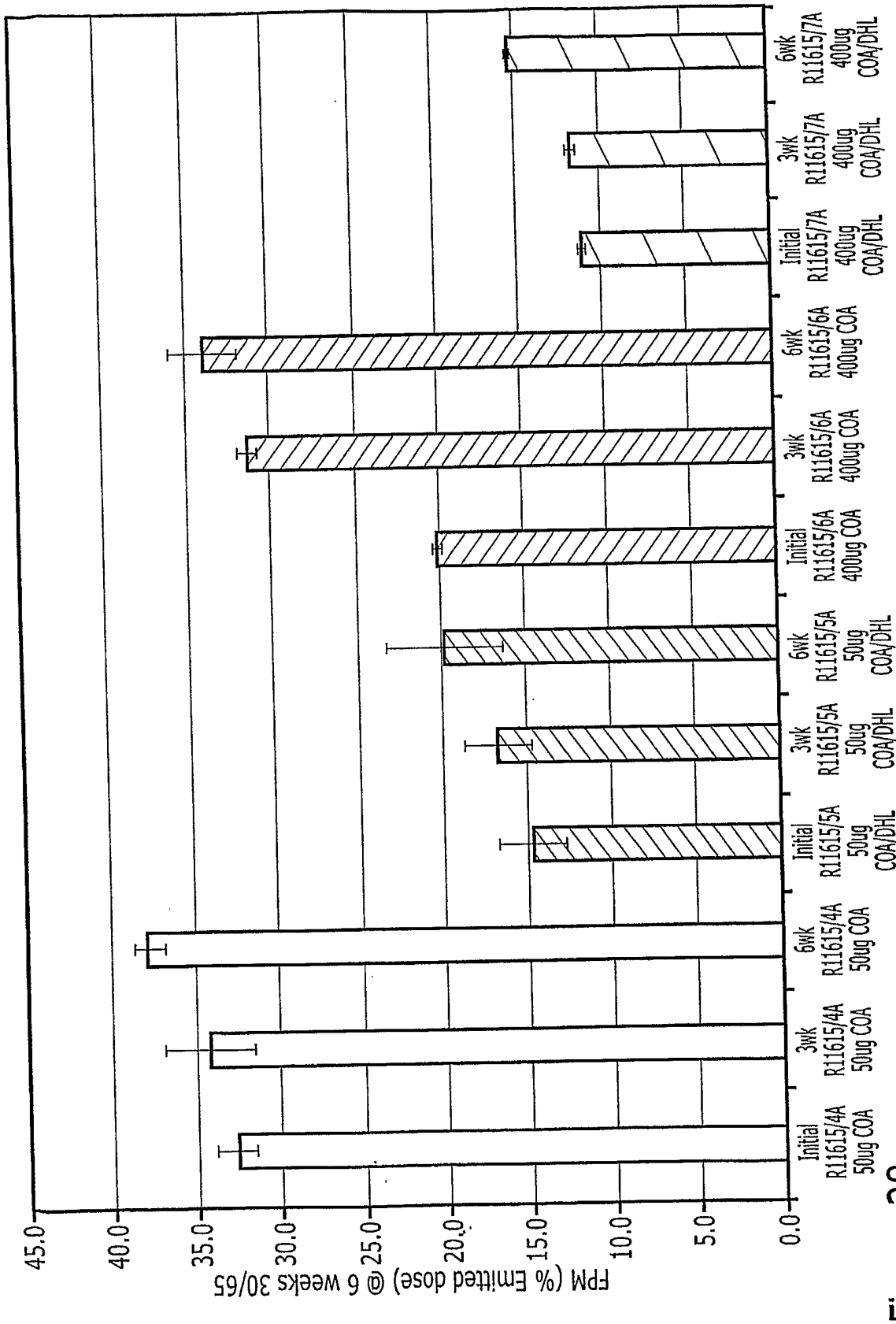

FPM (% Emitted dose) @ 6 weeks 30/65
45.0
40.0
35.0
30.0
25.0
20.0
15.0
10.0
5.0
0.0
Initial R11615/4A 50ug COA
3wk R11615/4A 50ug COA
6wk R11615/4A 50ug COA
Initial R11615/5A 50ug COA/DHL
3wk R11615/5A 50ug COA/DHL
6wk R11615/5A 50ug COA/DHL
Initial R11615/6A 400ug COA
3wk R11615/6A 400ug COA
6wk R11615/6A 400ug COA
Initial R11615/7A 400ug COA/DHL
3wk R11615/7A 400ug COA/DHL
6wk R11615/7A 400ug COA/DHL

Figure 28

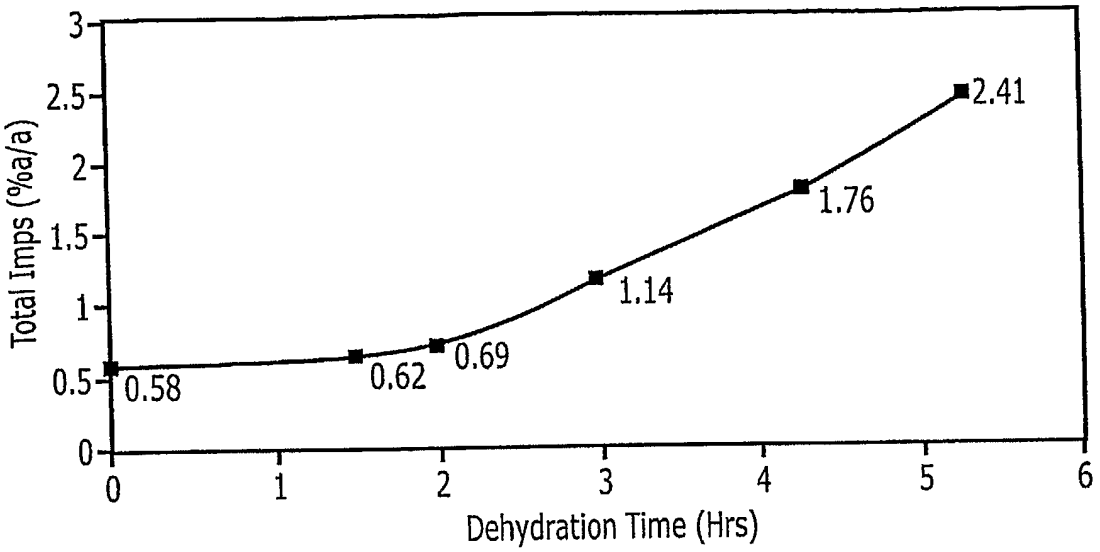


Figure 29

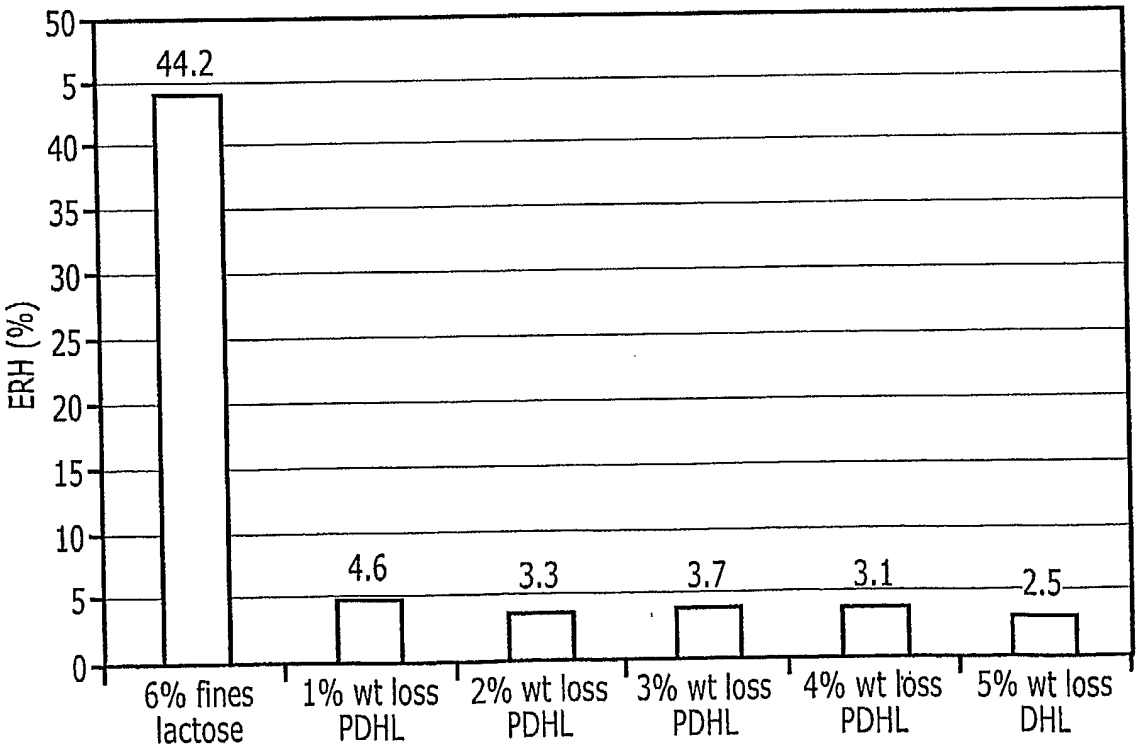


Figure 30

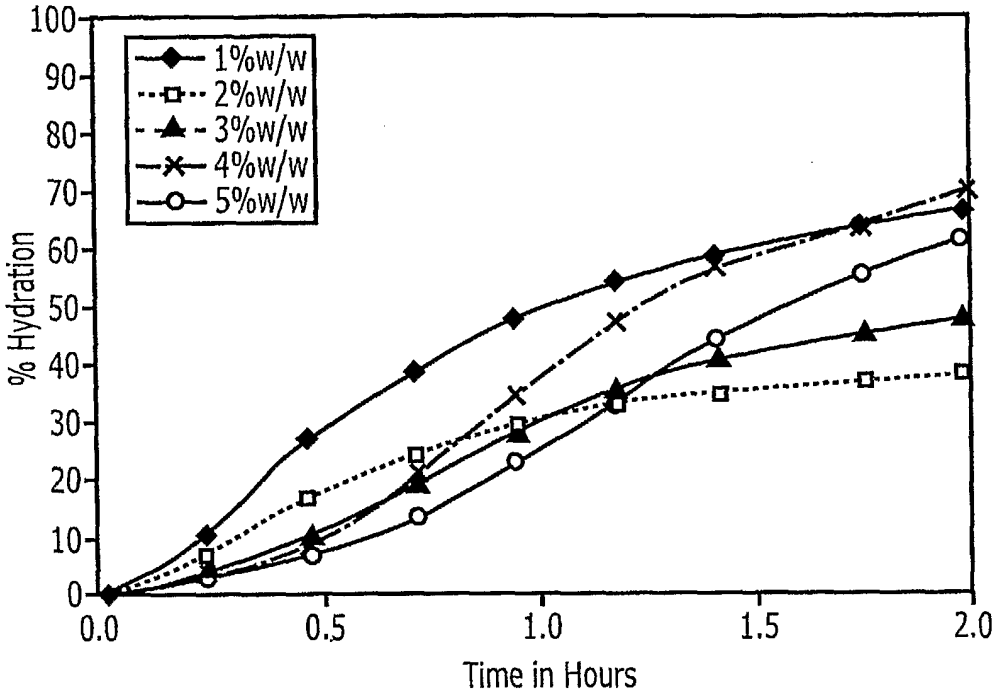


Figure 31

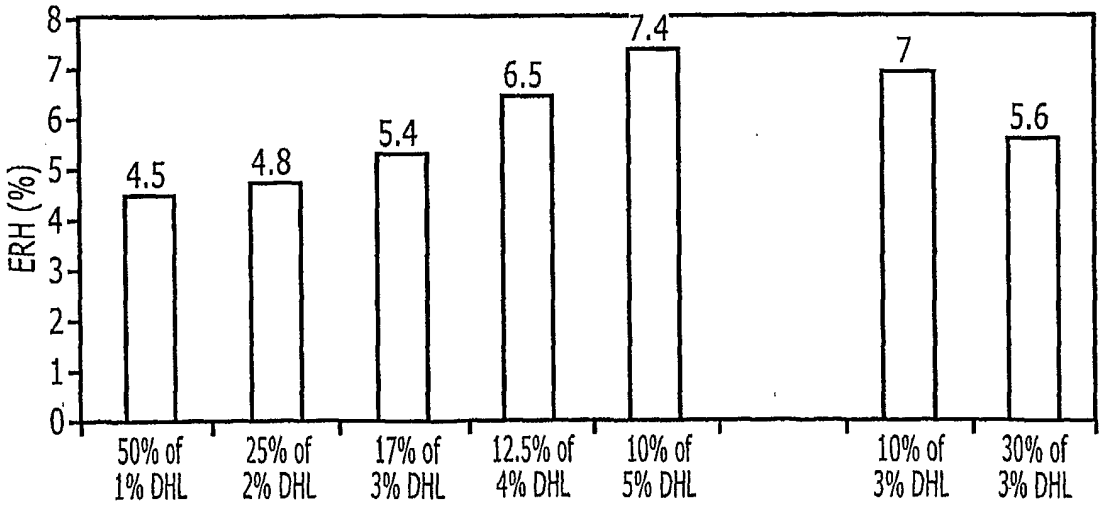


Figure 32

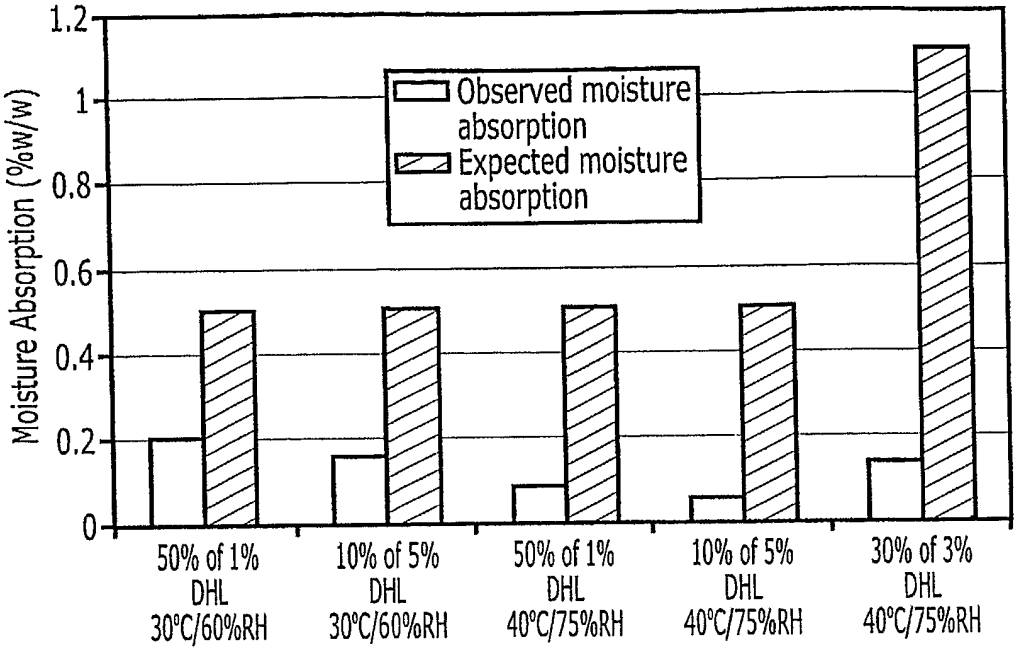


Figure 33

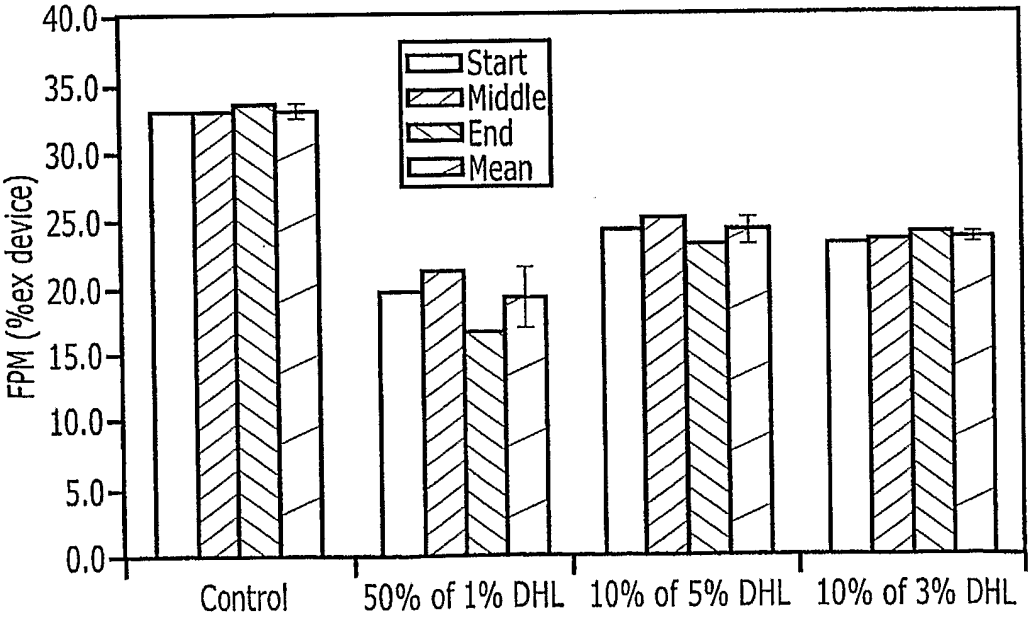


Figure 34

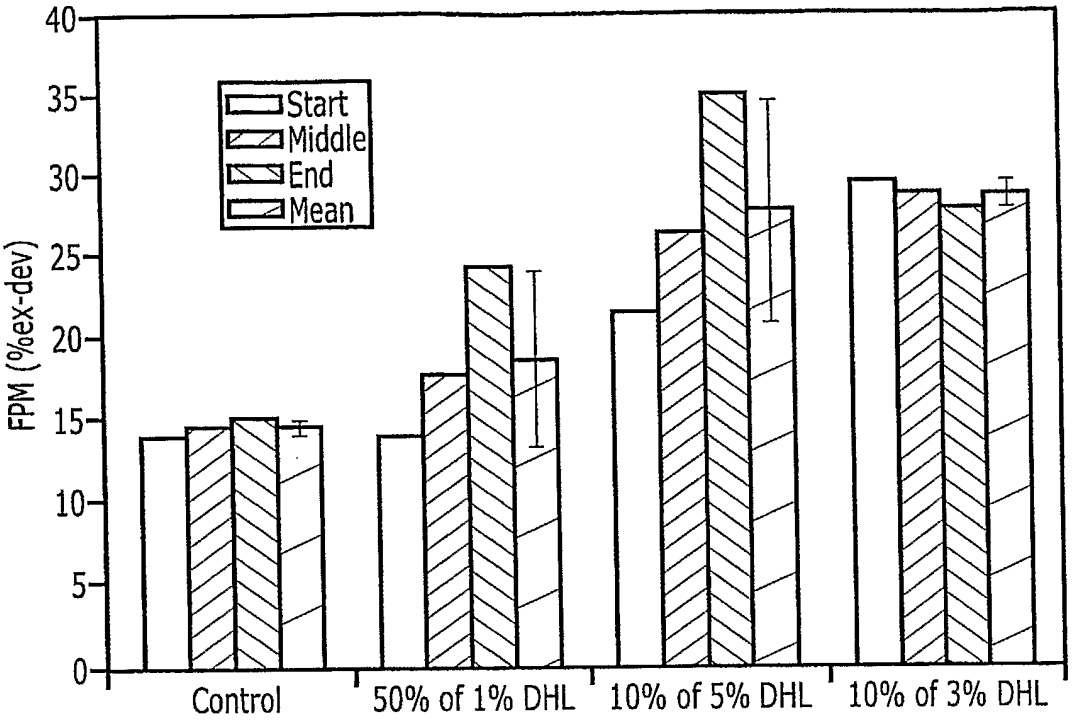


Figure 35

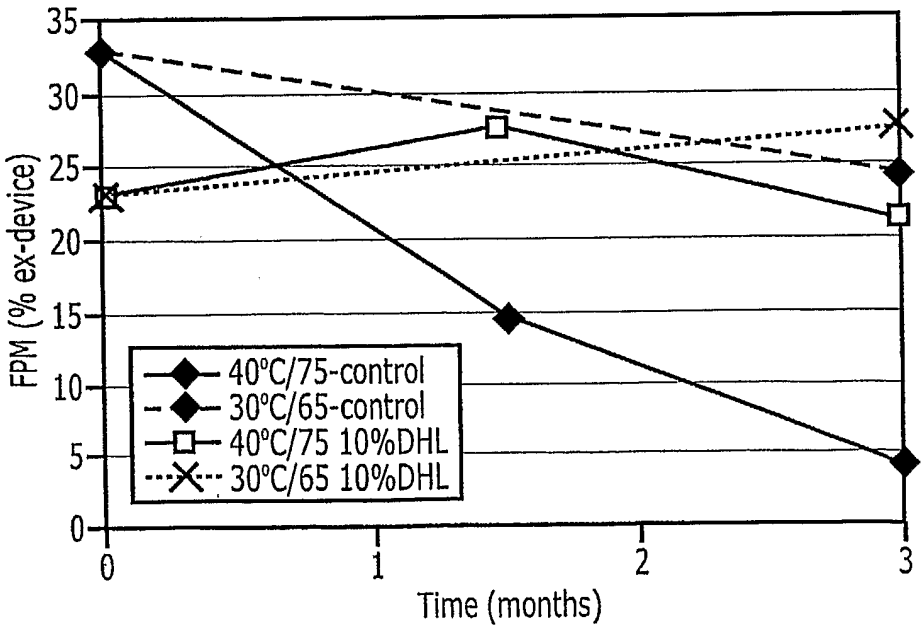


Figure 36

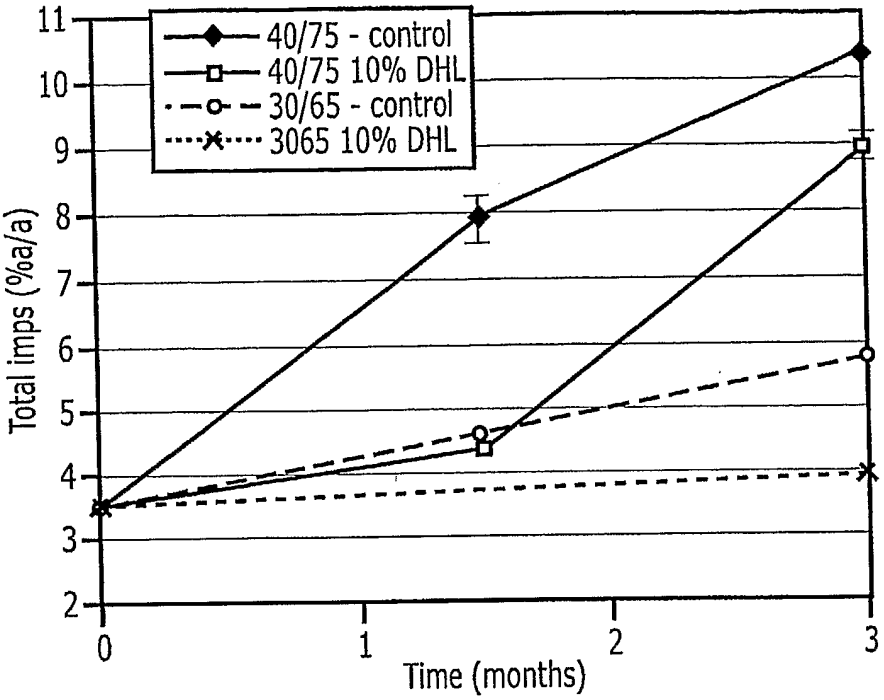


Figure 37

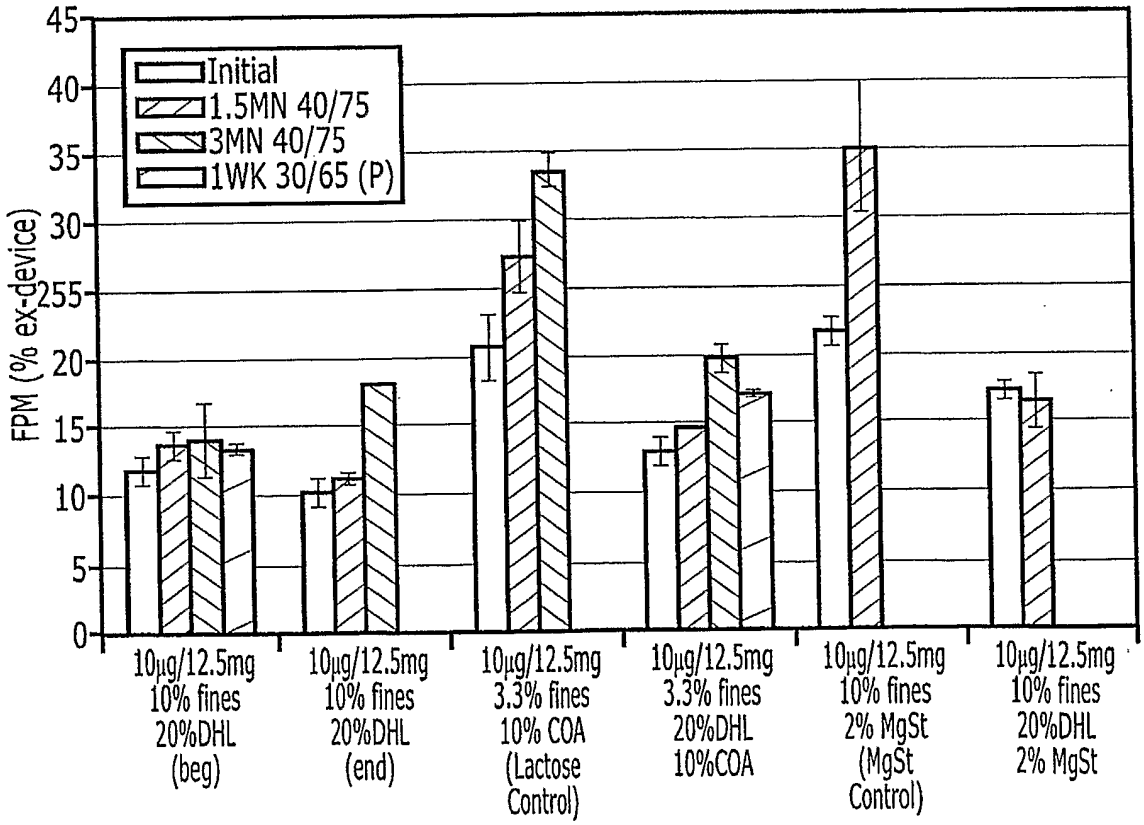


Figure 38

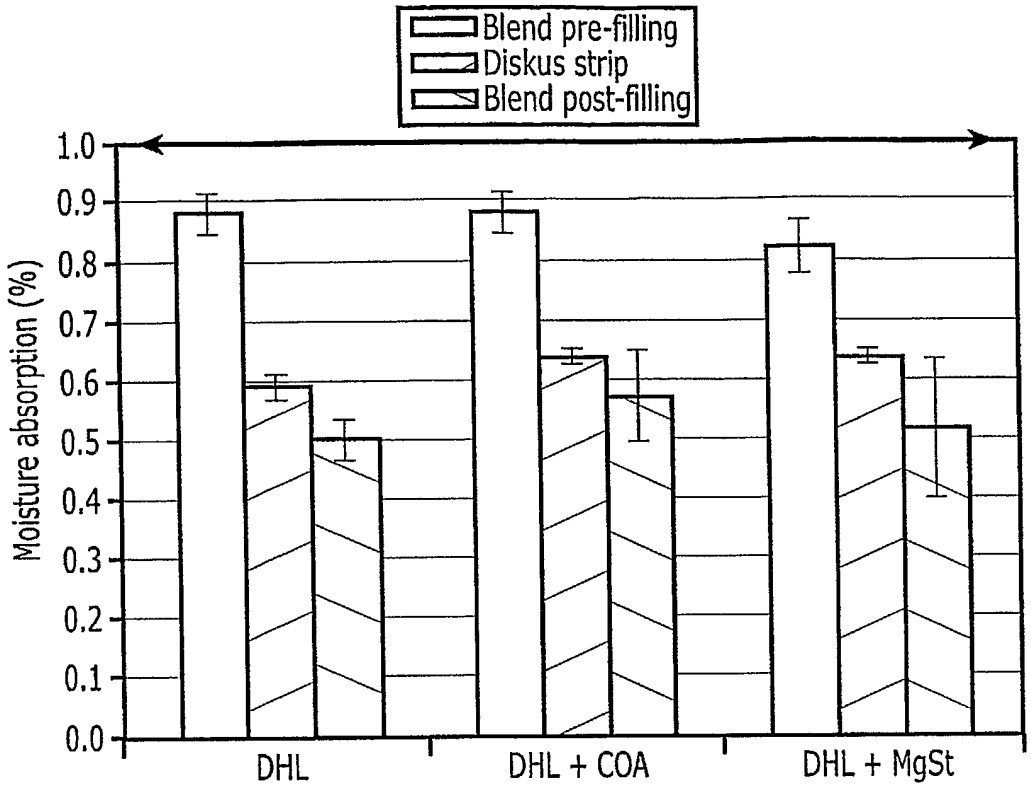


Figure 39

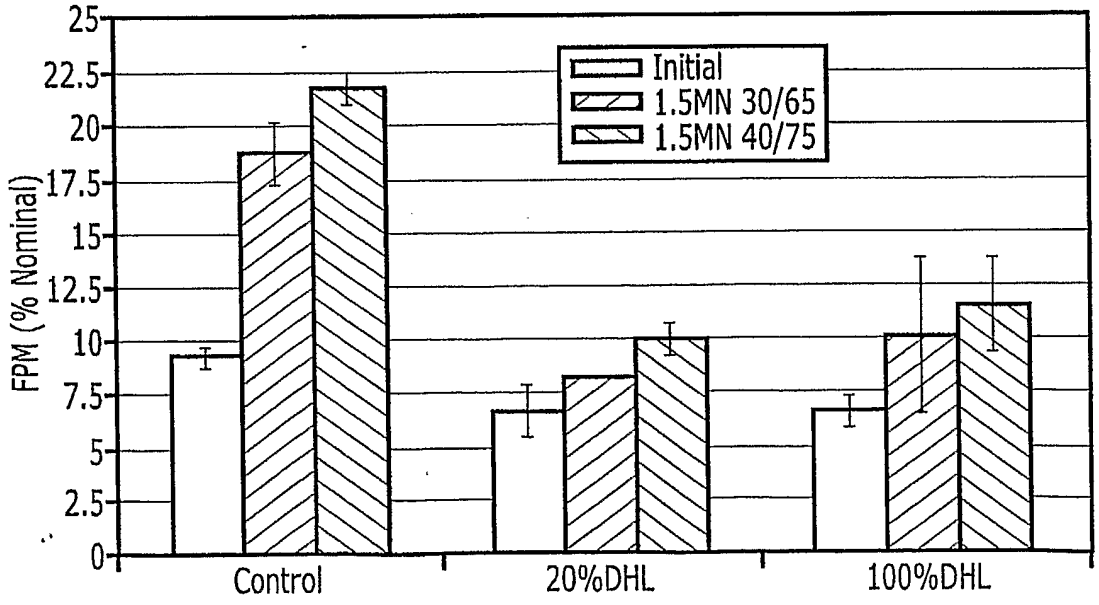


Figure 40

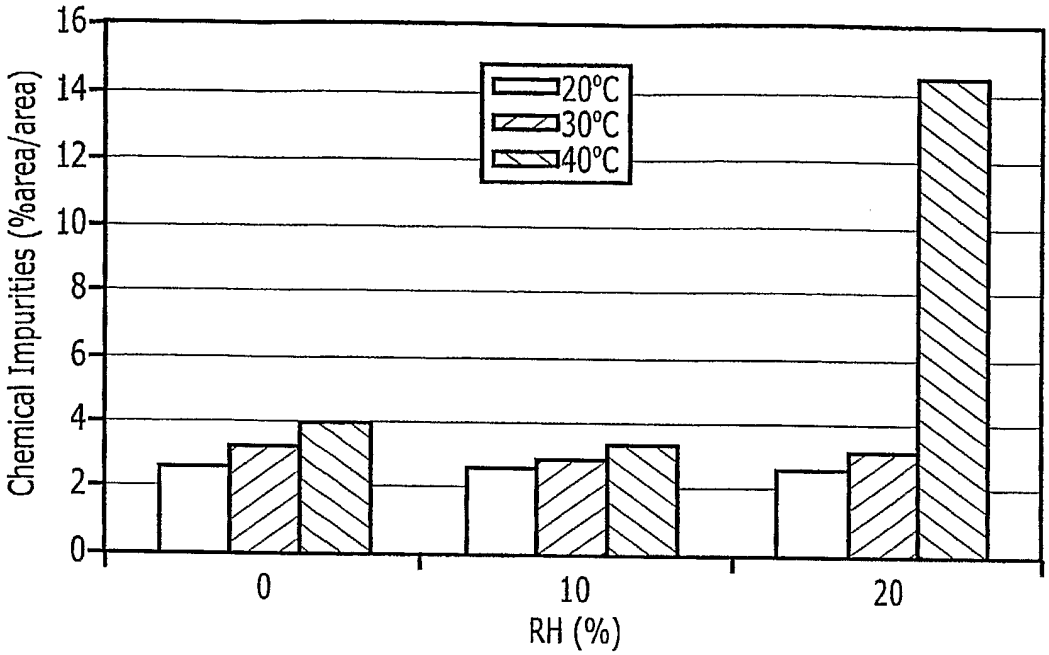


Figure 41

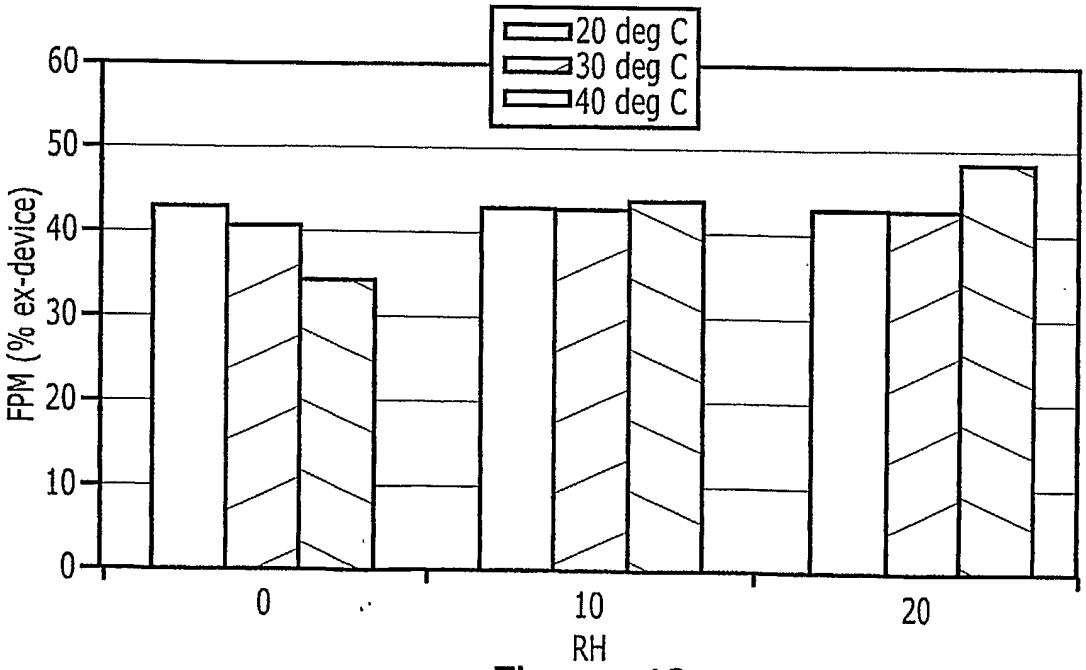


Figure 42

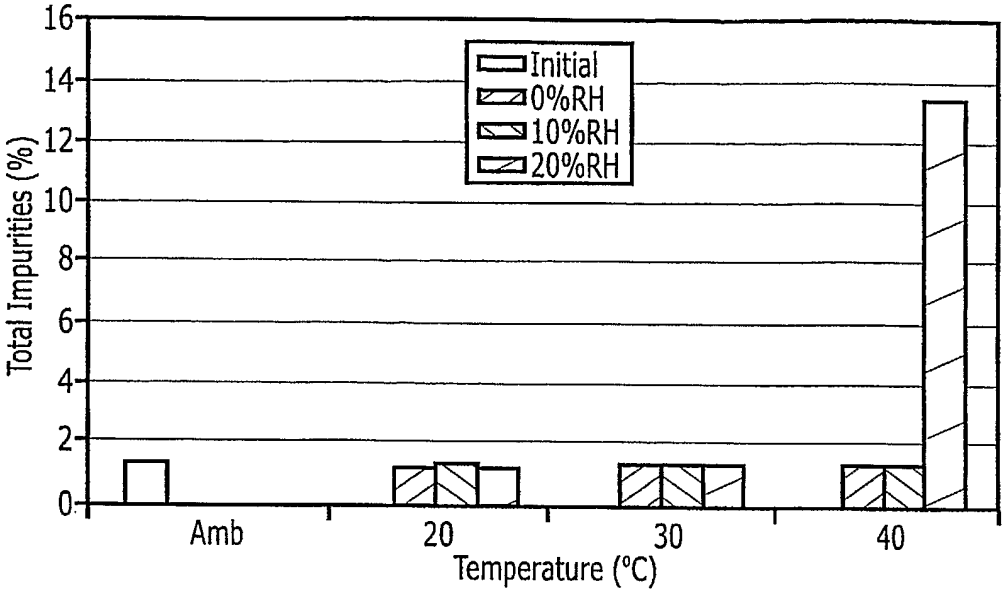


Figure 43

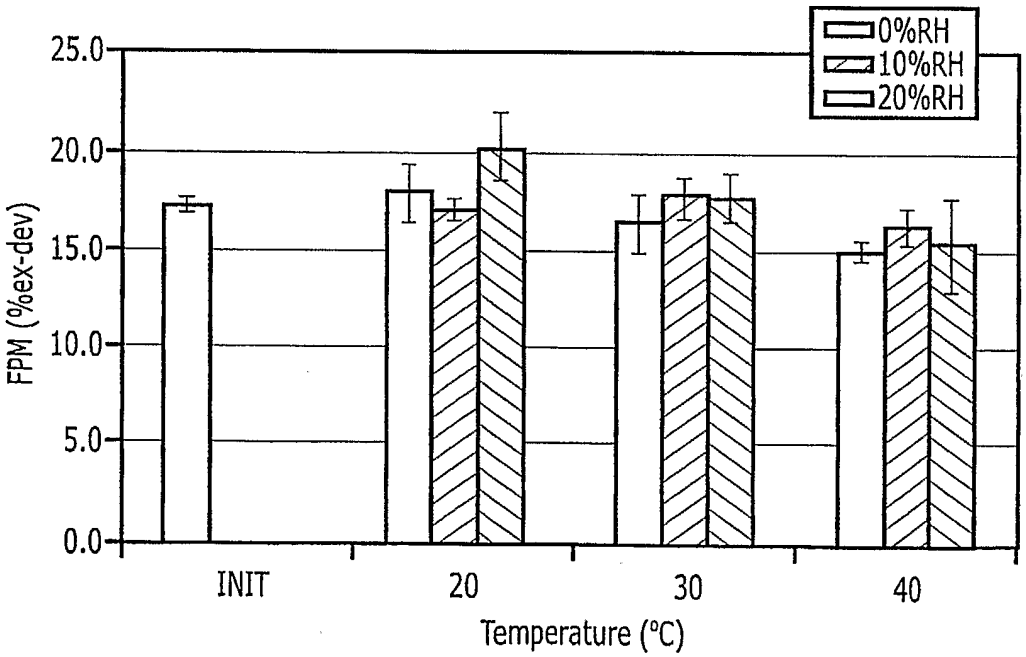


Figure 44