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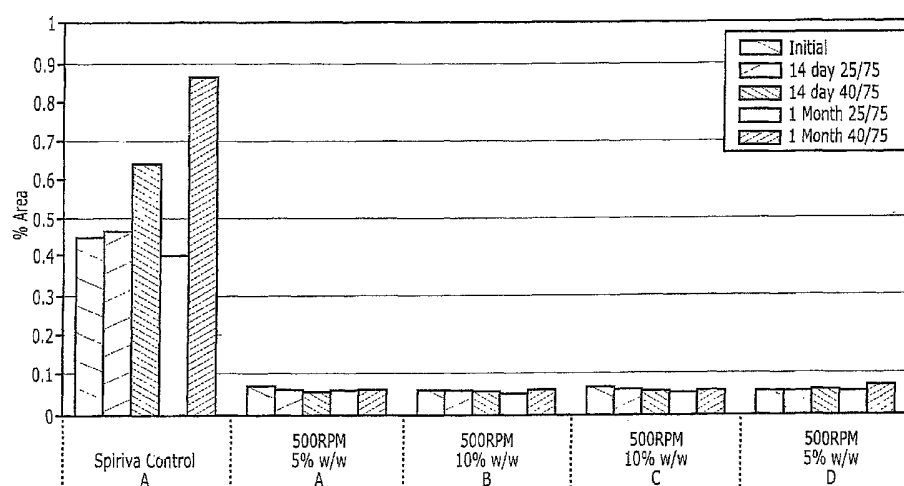
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(54) Title: PHARMACEUTICAL FORMULATIONS



(57) Abstract: The invention relates to an inhalable solid pharmaceutical formulation comprising (a) an anti-cholinergic agent, (b) a carrier and (c) a ternary agent that is a sugar ester, an inhaler comprising such a formulation, a method of reducing or inhibiting chemical interaction between an active ingredient substance and a carrier susceptible to chemical interaction, a method of reducing or inhibiting chemical degradation of an active ingredient substance in a formulation comprising a carrier and an active ingredient substance, a method for the treatment of a reversible airways obstruction by administering to a patient in need thereof the inhalable solid pharmaceutical formulation, and a method of preparing a solid pharmaceutical preparation comprising combining (a) an anti-cholinergic agent, (b) a carrier and (c) a ternary agent that is a sugar ester.

PHARMACEUTICAL FORMULATIONS

5 The present invention relates to solid pharmaceutical formulations which comprise an active ingredient drug substance, a carrier and ternary agent which is a sugar ester which inhibits or reduces chemical reaction or degradation of the active ingredient substance in the presence of the carrier. The invention also relates to the use of a sugar ester which inhibits or reduces chemical reaction or degradation of an active ingredient substance for
10 the stabilisation of an active ingredient drug substance in the presence of a carrier. The invention relates in particular to the use of cellobiose octaacetate to inhibit or reduce chemical reaction or degradation of an active ingredient substance and for the stabilisation of an active ingredient drug substance in the presence of a carrier.

15 An important requirement of pharmaceutical formulations is that they should be stable on storage in a range of different conditions. It is known that active ingredient substances can demonstrate instability to one or more of heat, light or moisture and various precautions must be taken in formulating and storing such substances to ensure that the pharmaceutical products remain in an acceptable condition for use over a reasonable
20 period of time, such that they have an adequate shelf-life. Instability of a drug substance may also arise from contact with one or more other components present in a formulation, for example a component present as an excipient.

It is usual practice in the pharmaceutical art to formulate active ingredient substance with
25 substances known as excipients which may be required as carriers, diluents, fillers, bulking agents, binders etc. Such excipients are often used to give bulk to a pharmaceutical formulation where the active ingredient substance is present in very small quantities. Such substances are generally chemically inert. Over prolonged storage times, or under conditions of extreme heat or humidity, and in the presence of other
30 materials, such inert substances can, however, undergo or participate in chemical degradation reactions.

Carrier substances that are commonly utilised in solid pharmaceutical formulations include reducing sugars, for example lactose, maltose and glucose. Lactose is particularly
35 commonly used. It is generally regarded as an inert excipient.

However, it has been observed that certain active ingredient substances may undergo a chemical reaction in the presence of lactose and other reducing sugars. For example, it was reported by Wirth *et al.* (*J. Pharm. Sci.*, 1998, **87**, 31-39) that fluoxetine hydrochloride (sold under the tradename Prozac®) undergoes degradation when present in solid tablets with a lactose excipient. The degradation was postulated to occur by formation of adducts via the Maillard reaction and a number of early Maillard reaction intermediates were identified. The authors conclude that drug substances which are secondary or primary amines undergo the Maillard reaction with lactose under pharmaceutically relevant conditions.

The present inventors have found that, under accelerated stability conditions, certain inhalable active ingredient substances also undergo degradation in the presence of lactose, possibly also via the Maillard reaction.

Some inhalable dry powder pharmaceuticals are sensitive to moisture, as reported, for example in WO 00/28979 (SkyePharma AG). The presence of moisture was found to interfere with the physical interaction between a carrier and a drug substance and thus with the effectiveness of drug delivery. Such interference with physical interactions between a carrier and a drug substance is distinct from chemical instability resulting from degradation.

WO00/28979 describes the use of magnesium stearate in dry powder formulations for inhalation to improve resistance to moisture and to reduce the effect of penetrating moisture on the fine particle fraction (FPF) of an inhaled formulation

WO 96/23485 (Coordinated Drug Development Ltd), WO01/78694 and WO01/78695 (Vectura Limited) each describe a powder for use in a dry powder inhaler including an active ingredient particles and carrier particles, wherein the carrier includes an additive which is able to promote release of the active particles from the carrier particles. Possible additive materials include amino acids, phospholipids, and surface active agents including *inter alia* sugar esters.

We have now surprisingly found that chemical interaction of active ingredient substance and carrier may be inhibited or reduced by the presence of a ternary agent which is a sugar ester as described below.

In a first aspect therefore the present invention provides the use of a ternary agent which is a sugar ester to inhibit or reduce chemical interaction between an active ingredient substance and a carrier in a solid pharmaceutical formulation, wherein the active
5 ingredient substance is susceptible to chemical interaction with the carrier.

The invention also provides the use of a ternary agent which is a sugar ester to inhibit or reduce chemical degradation of an active ingredient substance in a solid pharmaceutical formulation comprising the active ingredient substance and a carrier, wherein said active
10 ingredient substance is susceptible to chemical interaction with said carrier. The chemical stability of the active substance in the formulation during long term storage may thereby be improved.

In a second aspect the present invention provides a solid pharmaceutical formulation
15 comprising (a) an active ingredient substance susceptible to chemical interaction with a carrier, (b) a carrier and (c) a ternary agent that is a sugar ester.

In a third aspect the present invention provides a method of reducing or inhibiting chemical interaction between an active ingredient substance and a carrier susceptible to
20 chemical interaction, which comprises mixing with said active ingredient substance and said carrier a ternary agent that is a sugar ester. The invention also provides a method of inhibiting chemical degradation of an active ingredient substance in a formulation comprising a carrier and an active ingredient substance, which method comprises mixing with said active ingredient substance and said carrier a ternary agent that is a sugar ester.

25 An example of an ester of a sugar which may be employed in the present invention is cellobiose octaacetate.

Various amounts of the ester of a sugar may be employed in the pharmaceutical
30 formulation of the invention.

Pharmaceutical formulations that have been prepared according to the present invention have greater chemical stability than the corresponding formulations without said sugar ester.

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Figure 1 illustrates the hydrolysis impurity levels for various formulations of tiotropium bromide, lactose and cellobiose octaacetate as well as a control formulation.

Figure 2 illustrates the fine particle mass stability for various formulations of tiotropium bromide, lactose and cellobiose octaacetate.

5 **Figure 3** illustrates the emitted dose stability for various formulations of tiotropium bromide, lactose and cellobiose octaacetate.

Figure 4 illustrates the hydrolysis impurity levels for various formulations of tiotropium bromide, lactose and cellobiose octaacetate.

10 **Figure 5** illustrates the hydrolysis impurity levels for various formulations of tiotropium bromide and lactose.

Figure 6 illustrates the fine particle mass stability for various formulations of tiotropium bromide and lactose.

Figure 7 illustrates the fine particle fraction stability for various formulations of tiotropium bromide and lactose.

15 **Figure 8** illustrates the emitted dose stability for various formulations of tiotropium bromide and lactose.

Figure 9 illustrates the total ex-device for a formulation delivered from a Handihaler® device.

20 **Figure 10** illustrates the fine particle mass for a formulation of tiotropium bromide delivered from a Handihaler® device.

Figure 11 illustrates the fine particle fraction for formulations of tiotropium bromide delivered from Handihaler® and Diskus™ devices.

Figure 12 illustrates the normalized fine particle fraction for formulations of tiotropium bromide delivered from Handihaler® and Diskus™ devices.

25 **Figure 13** illustrates the fine particle mass stability for various blends of tiotropium bromide, cellobiose octaacetate, and lactose, as well as a control formulation.

Figure 14 illustrates the fine particle mass stability for various formulations of tiotropium bromide, cellobiose octaacetate, and lactose as well as a control formulation.

30 **Figure 15** illustrates the emitted dose for various formulations of tiotropium bromide, cellobiose octaacetate, and lactose as well as a control formulation.

Figure 16 illustrates the emitted dose for various formulations of tiotropium bromide, cellobiose octaacetate, and lactose as well as a control formulation.

Figure 17 illustrates the hydrolysis impurity levels for various formulations of tiotropium bromide, cellobiose octaacetate, and lactose as well as a control formulation.

35 **Figure 18** illustrates the hydrolysis impurity levels for various formulations of tiotropium bromide, cellobiose octaacetate, and lactose as well as a control formulation.

Figure 19 illustrates the hydrolysis impurity levels for various formulations of tiotropium bromide, cellobiose octaacetate, and lactose as well as a control formulation.

Figure 20 illustrates the hydrolysis impurity levels for various formulations of tiotropium bromide, cellobiose octaacetate, and lactose as well as a control formulation.

5 **Figure 21** illustrates a head-to-head comparison of the hydrolysis levels for a Spiriva® control formulation, a Spiriva® formulation used in conjunction with a Diskus™ device, and a Spiriva® formulation used in conjunction with a Diskus™ device employing a dessicant.

10 **Figure 22** illustrates the hydrolysis of tiotropium bromide as a function of H₂O at various times and temperatures.

In the context of the present invention the sugar ester may be referred to as a ternary
15 agent. 'Ternary agent' is used herein to mean a compound used in a formulation in addition to the active ingredient drug substance or substances (the 'primary' agent) and a bulk carrier material or materials (the 'secondary' agent). In some circumstances more than one ternary agent may be used. Optionally, further substances, possibly named 'quaternary agents', may also be present, for example as a lubricant. Any particular
20 ternary or quaternary agent may have more than one effect.

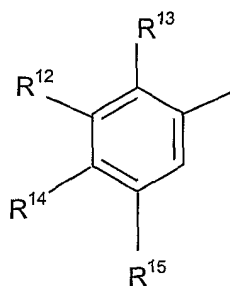
The invention finds particular application in formulations in which the carrier is a reducing sugar, for example lactose, maltose or glucose (for example monohydrate glucose or anhydrate glucose). In a preferred embodiment, the carrier is lactose. Alternative carriers
25 include maltodextrin.

The optimal amount of ternary agent present in a particular composition varies depending on the identity of the sugar ester ternary agent, the identity of the active ingredient drug substance present, the sizes of the particles and various other factors. In general, the
30 sugar ester is preferably present in an amount of from 0.1 to 20% w/w based on the total weight of the composition. More preferably the sugar ester is present in an amount of from 0.2 to 10% w/w based on the total weight of the composition. When cellobiose octaacetate is used as the ternary agent, it is preferably present in an amount of from 2 to 15% w/w, for example from 4 to 10% w/w. In another embodiment, for example, the
35 sugar ester may be present in an amount ranging from about 5 to 7 % w/w. In another embodiment, the sugar ester may be present in an amount of 6 % w/w.

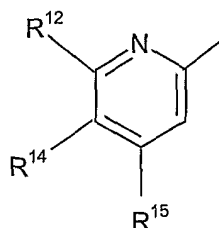
The active ingredient substance is typically present in an amount of from 0.01% to 50% w/w based on the total weight of the composition. Preferably, the active ingredient substance is present in an amount of from 0.02% to 10% w/w, more preferably in an amount of from 0.03 to 5%w/w, for example from 0.05% to 1% w/w, for example 0.1% w/w.

Preferably, the active ingredient drug substance is one which includes a primary or secondary amine group. Thus for example the drug substance may contain the group Ar-CH(OH)-CH₂-NH-R.

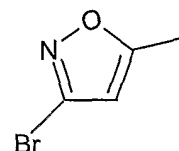
The group Ar may for example be selected from a group of formula (a) (b) (c) or (d):



(a)

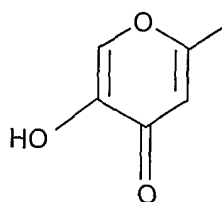


(b)



(c)

and



(d)

wherein R¹² represents hydrogen, halogen, -(CH₂)_qOR¹⁶, -NR¹⁶C(O)R¹⁷, -NR¹⁶SO₂R¹⁷, -SO₂NR¹⁶R¹⁷, -NR¹⁶R¹⁷, -OC(O)R¹⁸ or OC(O)NR¹⁶R¹⁷, and R¹³ represents hydrogen, halogen or C₁₋₄ alkyl;

or R¹² represents –NHR¹⁹ and R¹³ and –NHR¹⁹ together form a 5- or 6- membered heterocyclic ring;

R¹⁴ represents hydrogen, halogen, –OR¹⁶ or –NR¹⁶R¹⁷;

5

R¹⁵ represents hydrogen, halogen, haloC₁₋₄ alkyl, –OR¹⁶, –NR¹⁶R¹⁷, –OC(O)R¹⁸ or OC(O)NR¹⁶R¹⁷;

10 R¹⁶ and R¹⁷ each independently represents hydrogen or C₁₋₄ alkyl, or in the groups –NR¹⁶R¹⁷, –SO₂NR¹⁶R¹⁷ and –OC(O)NR¹⁶R¹⁷, R¹⁶ and R¹⁷ independently represent hydrogen or C₁₋₄ alkyl or together with the nitrogen atom to which they are attached form a 5-, 6- or 7- membered nitrogen-containing ring,

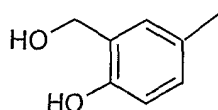
15 R¹⁸ represents an aryl (eg phenyl or naphthyl) group which may be unsubstituted or substituted by one or more substituents selected from halogen, C₁₋₄ alkyl, hydroxy, C₁₋₄ alkoxy or halo C₁₋₄ alkyl; and

q is zero or an integer from 1 to 4.

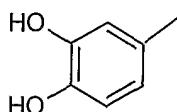
20 In a particular embodiment, the group Ar is as defined above except that R¹² is not hydrogen.

Within the definitions of (a) and (b) above, preferred groups may be selected from the following groups (i) to (xxi):

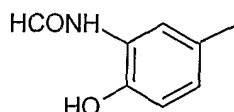
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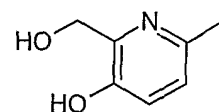
(i)



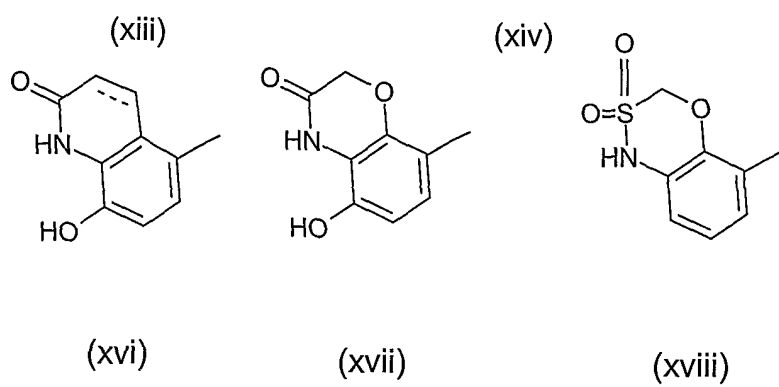
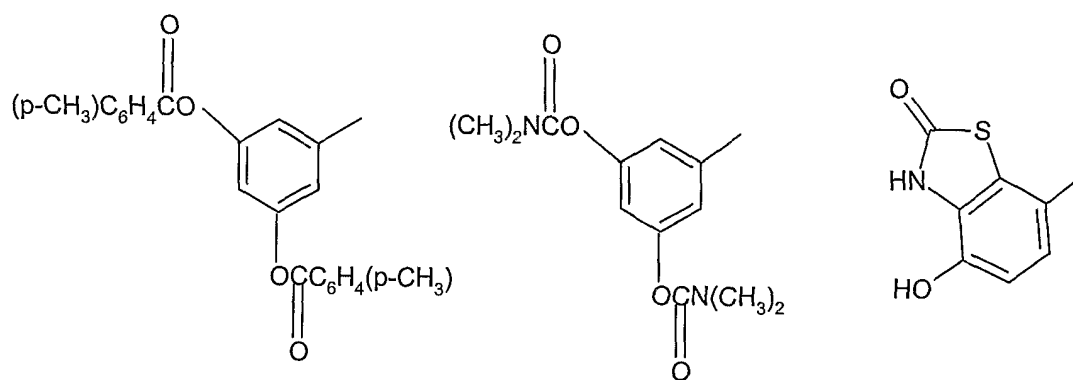
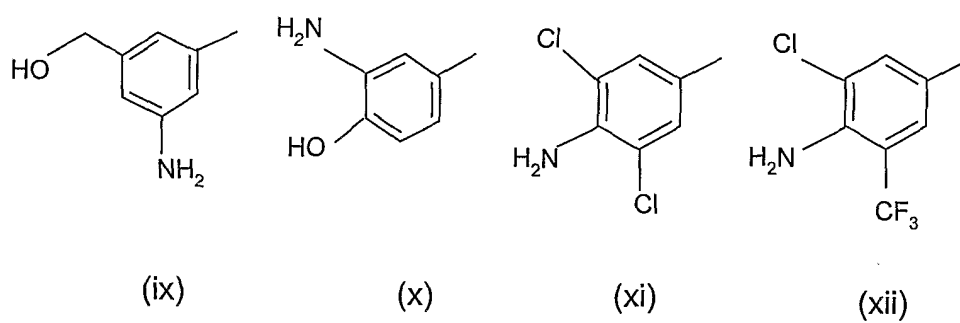
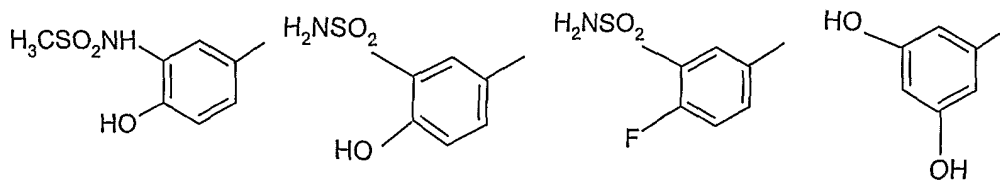
(ii)

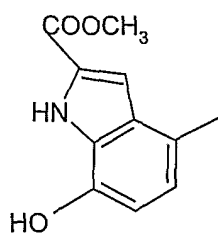


(iii)

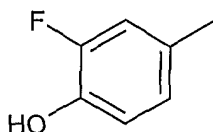


(iv)

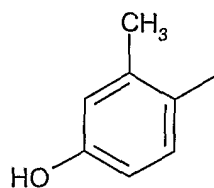




(xix)



(xx)



(xxi)

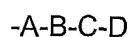
wherein the dotted line in (xvi) and (xix) denotes an optional double bond.

5 In a particular embodiment Ar represents a group (i) as defined above.

In another embodiment Ar represents a group (iii) as defined above.

The group R preferably represents a moiety of formula:

10



wherein

A may represent $(CH_2)_m$ wherein m is an integer from 1 to 10;

15 B may represent a heteroatom, e.g. oxygen, or a bond;

C may represent $(CH_2)_n$ wherein n is an integer from 1 to 10; and

D may represent an aryl group, e.g. an optionally substituted phenyl or pyridyl group.

20 Drug substances which may be formulated in accordance with the present invention include those described in International Patent Applications WO 02/066422, WO 02/070490, WO 02/076933, WO 03/024439, WO 03/072539, WO 03/091204, WO 04/016578, WO2004/022547, WO 2004/037807, WO 2004/037773, WO 2004/037768, WO 2004/039762, and WO 2004/039766.

25 Specific drug substances which may be formulated in accordance with the present invention include:

3-(4-[[6-({(2R)-2-hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl}amino)hexyl]oxy]butyl) benzenesulfonamide for example as its cinnamate salt;

3-(3-{{[7-{{(2R)-2-hydroxy-2-[4-hydroxy-3-hydroxymethyl]phenyl]ethyl}-amino}heptyl]oxy}propyl)benzenesulfonamide;

4-{{(1R)-2-[(6-{2-[(2,6-dichlorobenzyl)oxy]ethoxy}hexyl)amino]-1-hydroxyethyl}-2-(hydroxymethyl)phenol and

5 4-{{(1R)-2-[(6-{4-[3-(cyclopentylsulfonyl)phenyl]butoxy}hexyl)amino]-1-hydroxyethyl}-2-(hydroxymethyl)phenol

and salts, solvates and other physiologically functional derivatives thereof.

Other drug substances which may be formulated in accordance with the present invention include salmeterol, (R)-salmeterol, salbutamol, (R)-salbutamol, formoterol, (R,R)-

10 formoterol, fenoterol, etanterol, naminterol, clenbuterol, pirbuterol, flerobuterol, reproterol, bambuterol and terbutaline and salts, solvates and other physiologically functional derivatives thereof.

15 The active ingredient drug substance may be in the form of a free acid or base or may be present as a salt, a solvate, or other physiologically acceptable derivative. Salts and solvates which are suitable for use in medicine are those wherein the counterion or associated solvent is pharmaceutically acceptable.

20 Suitable salts for use in the invention include those formed with both organic and inorganic acids or bases. Pharmaceutically acceptable acid addition salts include those formed from hydrochloric, hydrobromic, sulphuric, citric, tartaric, phosphoric, lactic, pyruvic, acetic, trifluoroacetic, triphenylacetic, phenylacetic, substituted phenylacetic eg. methoxyphenylacetic, sulphamic, sulphanilic, succinic, oxalic, fumaric, maleic, malic, glutamic, aspartic, oxaloacetic, methanesulphonic, ethanesulphonic, arylsulphonic (for
25 example p-toluenesulphonic, benzenesulphonic, naphthalenesulphonic or naphthalenedisulphonic), salicylic, glutaric, gluconic, tricarballic, mandelic, cinnamic, substituted cinnamic (for example, methyl, methoxy, halo or phenyl substituted cinnamic, including 4-methyl and 4-methoxycinnamic acid and α -phenyl cinnamic acid (E or Z isomers or a mixture of the two)), ascorbic, oleic, naphthoic, hydroxynaphthoic (for
30 example 1- or 3-hydroxy-2-naphthoic), naphthaleneacrylic (for example naphthalene-2-acrylic), benzoic, 4-methoxybenzoic, 2- or 4-hydroxybenzoic, 4-chlorobenzoic, 4-phenylbenzoic, benzeneacrylic (for example 1,4-benzenediacrylic) and isethionic acids. Pharmaceutically acceptable base salts include ammonium salts, alkali metal salts such as those of sodium and potassium, alkaline earth metal salts such as those of calcium and
35 magnesium and salts with organic bases such as dicyclohexyl amine and N-methyl-D-glucamine.

A physiologically functional derivative of a drug substance may also be used in the invention. By the term "physiologically functional derivative" is meant a chemical derivative of a compound of having the same physiological function as the free compound, for example, by being convertible in the body thereto. According to the present invention, examples of physiologically functional derivatives include esters, for example compounds in which a hydroxyl group has been converted to a C₁₋₆alkyl, aryl, aryl C₁₋₆ alkyl, or amino acid ester.

The active ingredient drug substance is most preferably a selective long-acting β_2 -adrenoreceptor agonist. Such compounds have use in the prophylaxis and treatment of a variety of clinical conditions, including diseases 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, including seasonal and allergic rhinitis).

Other conditions which may be treated include premature labour, depression, congestive heart failure, skin diseases (e.g. inflammatory, allergic, psoriatic, and proliferative skin diseases), conditions where lowering peptic acidity is desirable (e.g. peptic and gastric ulceration) and muscle wasting disease.

Formulations to which the present invention may be applied include those suitable for oral, parenteral (including subcutaneous, intradermal, intramuscular, intravenous and intraarticular), inhalation (including fine particle dusts or mists which may be generated by means of various types of metered dose pressurised aerosols, nebulisers or insufflators), rectal and topical (including dermal, buccal, sublingual and intraocular) administration although the most suitable route may depend upon for example the condition and disorder of the recipient. The formulations may conveniently be presented in unit dosage form and may be prepared by any of the methods well known in the art of pharmacy. All methods include the step of bringing the active ingredient into association with the carrier and the ternary agent as well as any other accessory ingredients. In general the formulations are prepared by uniformly and intimately bringing into association the active ingredient, carrier, e.g. lactose, ternary agent and any other accessory ingredients, and then, if necessary, shaping the product into the desired formulation.

Formulations of the present invention suitable for oral administration may be presented as discrete units such as capsules, cachets or tablets each containing a predetermined amount of the active ingredient; as a powder or granules. The active ingredient drug substance may also be presented as a bolus, electuary or paste.

5

A tablet may be made by compression or moulding, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing in a suitable machine the active ingredient in a free-flowing form such as a powder or granules, optionally mixed with a binder, lubricant, inert diluent, lubricating, surface active or dispersing agent.

10 Moulded tablets may be made by moulding in a suitable machine a mixture of the powdered compound moistened with an inert liquid diluent. The tablets may optionally be coated or scored and may be formulated so as to provide slow or controlled release of the active ingredient therein.

15 Formulations for parenteral administration include sterile powders, granules and tablets intended for dissolution immediately prior to administration. The formulations may be presented in unit-dose or multi-dose containers, for example sealed ampoules and vials, and may be stored in a freeze-dried (lyophilised) condition requiring only the addition of the sterile liquid carrier, for example saline or water-for-injection, immediately prior to use.

20

Formulations for topical administration in the mouth, for example buccally or sublingually, include lozenges comprising the active ingredient in a flavoured basis such as sucrose and acacia or tragacanth, and pastilles comprising the active ingredient in a basis such as gelatin and glycerin or sucrose and acacia.

25

The invention finds particular application in dry powder compositions and in particular in dry powder compositions for topical delivery to the lung by inhalation.

Dry powder compositions 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. 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 (eg as in Diskus, see GB 2242134 or Diskhaler, see GB 2178965, 2129691 and 2169265) or metered in use (eg as in Turbuhaler, see EP 69715 or EP0237507). An example of a unit-dose device is Rotahaler (see GB 2064336). The Diskus inhalation device comprises an elongate strip formed from a base sheet having a

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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 an active compound. Preferably, the strip is sufficiently flexible to be wound into a roll.

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Medicaments for administration by inhalation desirably have a controlled particle size. The optimum particle size for inhalation into the bronchial system is usually 1-10 μ m, preferably 2-5 μ m (mass mean diameter, MMD). Particles having a size above 20 μ m are generally too large when inhaled to reach the small airways. To achieve these particle sizes the particles of the active ingredient substance as produced may be size reduced by conventional means eg by micronisation. The desired fraction may be separated out by air classification or sieving. Preferably, the particles will be crystalline. In general, the particle size of the carrier, for example lactose, will be much greater than the drug substance within the present invention. It may also be desirable for other agents other than the active drug substance to have a larger particle size than the active drug substance. When the carrier is lactose it will typically be present as milled lactose, for example with a mass mean diameter (MMD) of 60-90 μ m and with not more than 15% having a particle diameter of less than 15 μ m.

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The sugar ester will typically have a particle size in the range 1 to 50 μ m, and more particularly 1 - 20 μ m (mass mean diameter). The particle size of the sugar ester, e.g cellobiose octaacetate, for use in the preparation of compositions in accordance with this invention may be reduced by conventional methods to give particles with a mass mean diameter (MMD) in the range 1 to 10 μ m, for example 1 to 5 μ m. The sugar ester is typically micronised but may also be prepared using controlled precipitation, supercritical fluid methodology and spray drying techniques familiar to those skilled in the art.

Preferred unit dosage formulations are those containing an effective dose, as hereinbefore recited, or an appropriate fraction thereof, of the active ingredient.

30

It should be understood that in addition to the ingredients particularly mentioned above, the formulations of this invention may include other agents conventional in the art having regard to the type of formulation in question, for example those suitable for oral administration may include flavouring agents.

35

The compounds and pharmaceutical formulations according to the invention may be used in combination with or include one or more other therapeutic agents, for example a beta-agonist may be used in combination with one or more other therapeutic agents selected from anti-inflammatory agents (for example a corticosteroid, or an NSAID,) anticholinergic agents (particularly an M₁, M₂, M₁/M₂ or M₃ receptor antagonist), other β_2 -adrenoreceptor agonists, antiinfective agents (e.g. antibiotics, antivirals), or antihistamines. Moreover, in other embodiments, one or more of any of the therapeutic agents recited herein may be employed alone with carrier and ternary agent. In one embodiment, as an example, a formulation may comprise an anti-cholinergic agent, a carrier and a ternary agent, e.g., a sugar ester. In one embodiment, as an example, a formulation may consist essentially of an anti-cholinergic agent, a carrier and a ternary agent, e.g., a sugar ester. In one embodiment, as an example, a formulation may consist of an anti-cholinergic agent, a carrier and a ternary agent, e.g., a sugar ester.

Suitable corticosteroids include methyl prednisolone, prednisolone, dexamethasone, fluticasone propionate, 6 α ,9 α -difluoro-17 α -[(2-furanylcarbonyl)oxy]-11 β -hydroxy-16 α -methyl-3-oxo-androsta-1,4-diene-17 β -carbothioic acid S-fluoromethyl ester, 6 α ,9 α -difluoro-11 β -hydroxy-16 α -methyl-3-oxo-17 α -propionyloxy-androsta-1,4-diene-17 β -carbothioic acid S-(2-oxo-tetrahydro-furan-3S-yl) ester, beclomethasone esters (e.g. the 17-propionate ester or the 17,21-dipropionate ester), budesonide, flunisolide, mometasone esters (e.g. the furoate ester), triamcinolone acetonide, rofleponide, ciclesonide, butixocort propionate, RPR-106541, and ST-126.

Suitable NSAIDs include sodium cromoglycate, nedocromil sodium, phosphodiesterase (PDE) inhibitors (e.g. theophylline, PDE4 inhibitors or mixed PDE3/PDE4 inhibitors), leukotriene antagonists, inhibitors of leukotriene synthesis, iNOS inhibitors, tryptase and elastase inhibitors, beta-2 integrin antagonists and adenosine receptor agonists or antagonists (e.g. adenosine 2a agonists), cytokine antagonists (e.g. chemokine antagonists) or inhibitors of cytokine synthesis.

Suitable anticholinergic agents are those compounds that act as antagonists at the muscarinic receptor, in particular those compounds which are antagonists of the M₁ and M₂ receptors. Exemplary compounds include the alkaloids of the belladonna plants as illustrated by the likes of atropine, scopolamine, homatropine, hyoscyamine; these compounds are normally administered as a salt, being tertiary amines.

Preferred anticholinergics include ipratropium (e.g. as the bromide), sold under the name Atrovent, oxitropium (e.g. as the bromide) and tiotropium (e.g. as the bromide) (CAS-139404-48-1). One embodiment pertaining to tiotropium bromide that may be used
5 includes tiotropium bromide monohydrate (theoretical stoichiometric monohydrate 3.67% - actual drug substance by KF and TGS ~ 3.0%).

The drug substance may be prepared according to accepted techniques. As a n example, in one embodiment, the micronization of drug substance is performed with MC-1 at small
10 scale (particle sizes in range of 2.0 μm to 2.8 μm , water content (by TGA) decreases after micronization to 1.9% to 2.6%, XRD indicating that there is a slight change in lattice)

Suitable antihistamines (also referred to as H_1 -receptor antagonists) include any one or more of the numerous antagonists known which inhibit H_1 -receptors, and are safe for
15 human use. All are reversible, competitive inhibitors of the interaction of histamine with H_1 -receptors. Examples of preferred anti-histamines include methapyrilene and loratadine.

The invention further provides the use of an inhalable solid pharmaceutical formulation
20 according to the invention for the manufacture of a medicament for the treatment of diseases 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, including seasonal and allergic rhinitis). The invention also provides a method for treating
25 asthma, chronic obstructive pulmonary diseases (COPD), chronic or wheezy bronchitis, emphysema, respiratory tract infection upper respiratory tract, or rhinitis, including seasonal and allergic rhinitis comprising administering to a patient in need thereof an inhalable solid pharmaceutical formulation according to the invention.

30 In a further aspect, the invention provides a method of preparing a solid pharmaceutical preparation comprising combining in one or more steps: (a) an active ingredient substance susceptible to interaction with a carrier, (b) a carrier and (c) a sugar ester.

Examples 1-4Test compound

5 In the following examples, the drug compound, "Compound X" was the cinnamate salt of 3-(4-([6-((2R)-2-hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl}amino)hexyl]oxy)-butyl)benzene-sulfonamide. The synthesis of compound X is described in Examples 45 and 46 in WO 02/066422.

10 Method**Preparation of blends**

Lactose monohydrate was obtained from Borculo Domo Ingredients as BP/USNF form.

15 Before use, the Lactose Monohydrate was sieved through a coarse screen (mesh size 500 microns) to deaggregate the material. Compound X was micronised before use in an APTM microniser to give a MMD (mean mass diameter) of from 2 to 5 microns.

20 Cellobiose octaacetate was obtained from Ferro Pfanstiehl. It was used as supplied (Examples 1, 2, 3 and 4) or micronised (Examples 3 and 4).

25 The cellobiose octaacetate was combined with lactose monohydrate and blended using either a high shear mixer (a QMM, PMA or TRV series mixer) or a low shear tumbling blender (a Turbula mixer) to provide a cellobiose octaacetate /drug premix, hereinafter referred to as blend A.

30 Final blend B was obtained by first pre-mixing an appropriate quantity of blend A with compound X and then blending that blend A/compound X premix with further blend A in a weight ratio appropriate to provide blend B containing the cellobiose octaacetate in the required quantity, as indicated in Table 1 and Tables 2 and 3 below. The quantity of cellobiose octaacetate in Tables 2 and 3 is the amount by weight of cellobiose octaacetate present as a percentage of the total composition. The final concentration of compound X in the blends was 0.1% w/w calculated on the basis of the weight of free base drug present.

35

For use in example 2, the blended composition was transferred into blister strips of the type generally used for the supply of dry powder for inhalation and the blister strips were sealed in the customary fashion.

- 5 The quantity of the various materials used in the various blends are shown in Table 1:

Table 1:

Excipient	Mass of excipient	Mass of compound X	Mass of lactose
None	-	0.14g	99.86g
7% Cellobiose Octaacetate	7.00g	0.14g	92.86g
4% Cellobiose Octaacetate	4.00g	0.14g	95.86g
1% Cellobiose Octaacetate	1.00g	0.14g	96.86g

10 0.14g of compound X in the form of the cinnamate salt was used to provide 0.1g of compound X free base.

Blends for Examples 3 and 4 were prepared in a similar manner, using both micronised and unmicronised cellobiose octaacetate. The blends were prepared using the following target weights of the ingredients:

Cellobiose octaacetate: 200g

Compound X: 5.528g

Lactose: 3794.47g

For use in Example 3 the blended composition was transferred into blister strips of the type generally used for the supply of dry powder for inhalation and the blister strips were sealed in the customary fashion.

25 **Decomposition conditions**

The blends prepared as described above were subjected to accelerated decomposition conditions in a controlled atmosphere stability cabinet. In the tables below, the conditions to which the blends were subjected are given with reference to the temperature and the % relative humidity, for example 30/60 is 30°C and 60% relative humidity (RH). Samples were analysed for decomposition products after the time periods indicated in the tables.

Analysis of purity of blends after subjection to decomposition conditions

LC analysis was conducted on a Supelcosil ABZ+PLUS column (150 x 4.6mm ID), 3 micron, eluting with water containing 0.05% trifluoroacetic acid (solvent A) and acetonitrile containing 0.05% v/v trifluoroacetic acid (solvent B), using the following elution gradient:
5 time 0 = 90% solvent A, 10% solvent B; 40 mins = 10% solvent A, 90% solvent B; 41-45 mins 90% solvent A, 10% solvent B, . Flow rate was 1ml/min and the column temperature was 40°C. Detection was carried out by UV at 220nm with a HP1100 series detector model G1314A-VWD. The area under the LC trace curve for the total impurities was
10 compared with the total area under the curve, to give the %area/area figures given in Tables 2 and 3.

Results**Example 1: Comparison of compound X / lactose blends comprising 7% Cellobiose****5 Octaacetate with controls**

Table 2:

Blend Details	Timepoint	Condition °C/%RH	Total Impurities (% area/area)
Compound X with Lactose only	Week 2	30/60	5.0
		40/75	8.9
	MN6	30/60	12.7
		40/75	17.4
Compound X with Lactose and 7% Cellobiose Octaacetate	Week 2	30/60	4.1
		40/75	8.1
	MN6	30/60	9.1
		40/75	13.0

Example 2: Comparison of compound X / lactose blends comprising 1.0%, 4.0% and 7.0% Cellobiose Octaacetate filled into a Diskus™ strip with controls

5 Table 3:

Blend Details	Timepoint	Condition °C/%RH	Total Impurities (% area/area)
Compound X with Lactose only	Initial	Initial	3.7
	MN1	25/60	3.7
		30/60	4.3
		40/75	6.3
Compound X with 1.0% Cellobiose Octaacetate / Lactose	Initial	Initial	3.4
	MN1	25/60	3.7
		30/60	3.4
		40/75	4.7
Compound X with 4.0% Cellobiose Octaacetate / Lactose	Initial	Initial	3.4
	MN1	25/60	3.7
		30/60	3.3
		40/75	4.6
Compound X with 7.0% Cellobiose Octaacetate / Lactose	Initial	Initial	3.4
	MN1	25/60	3.3
		30/60	3.8
		40/75	4.6

Example 3

- 5 **Chemical Stability in Diskus™ Strip: Compound X in formulation with Micronised Cellobiose Octaacetate and lactose compared with Compound X in formulation with Non-Micronised Cellobiose Octaacetate and lactose**

Table 4

Blend Details	Time-point	Condition °C/%RH	Total Impurities (% area/area)
0.1% Compound X with 5% Unmicronised Cellobiose Octaacetate and 8.8% Lactose fines	Initial	Initial	4.5
	MN01	40°C/75%RH	4.4
	MN4.5	25°C/5%RH	3.6
		25°C/75%RH	4.0
		40°C/75%RH	9.4
	MN06	5°C/Amb RH	4.5
		25°C/75%RH	5.3
		40°C/75%RH	11.8
0.1% Compound X with 5% Micronised Cellobiose Octaacetate and 8.8% Lactose fines	Initial	Initial	3.9
	MN01	40°C/75%RH	4.2
	MN4.5	25°C/5%RH	4.1
		25°C/75%RH	4
		40°C/75%RH	7.1
	MN06	5°C/Amb RH	4
		25°C/75%RH	4.2
		40°C/75%RH	7.6

Example 4: Chemical Stability of Blend: Compound X in formulation with Micronised Cellobiose Octaacetate and lactose compared with Compound X in formulation with Non-Micronised Cellobiose Octaacetate and lactose

5 Table 5

Blend Details	Time-point	Condition °C/%RH	Total Impurities (% area/area)
0.1% Compound X with 5% Unmicronised Cellobiose Octaacetate and 8.8% Lactose fines	Initial	Initial	4.0
	MN01	40°C/75%RH	6.0
	MN02	5°C/ Amb RH	3.5
		40°C/75%RH	8.6
	MN03	40°C/75%RH	7.6
	MN06	40°C/75%RH	7.8
0.1% Compound X with 5% Micronised Cellobiose Octaacetate and 8.8% Lactose fines	Initial	Initial	4.1
	MN01	40°C/75%RH	5.1
	MN02	5°C/ Amb RH	3.3
		40°C/75%RH	6.3
	MN03	40°C/75%RH	5.2
	MN06	40°C/75%RH	5.5

Examples 5-28

10

For the purposes of Examples 5- 28, the following is applicable:

Lactose monohydrate used in the below examples was obtained from Borculo Domo Ingredients located in Zwolle, The Netherlands.

15

The term desiccant refers to a silica-based desiccating material present in the pouch of the overwrap of the device containing a formulation.

Compound "Y" is (6- α ,11- β ,16- α ,17- α)-S-(fluoromethyl) 6,9-difluoro-11-hydroxy-16-methyl-17-[[[4-methyl-5-thiazolyl]carbonyl]oxy]-3-oxo-androsta-1,4-diene-17-carbothioate

20

Grade 3 and Grade 5 lactose are defined in Table 6 as follows:

Table 6

<u>Grade</u>	<u>%w/w < 15 micron</u>	<u>Mean Particle Size (micron)</u>
3	8-12	65-85
5	4-8	70-90

- 5 Cellobiose Octaacetate ("COA") was obtained from Borregaard Synthesis located in Sarsborg, Norway

Formulations referred to in these examples were blended according to the following general procedure. A pre-blend of COA was obtained by blending these ingredients at
10 900rpm for 5 minutes. After blending, the blend was allowed to stand for three minutes and the above procedure was repeated twice. Approximately one-half of the blend was removed from the blender and drug and blend were "sandwiched" into a pre-blend. The sandwich was then hand mixed for two minutes and was thereafter added to the blender. The remaining pre-blend was then added to the mixer. The final blend was obtained by
15 mixing for five minutes, three times. The blender used was a Bohle BMG Blender made commercially available by L. B. Bohle Inc. of Bristol, Pennsylvania.

All Cascade Impaction and impurities data for formulations came from filled blister strips such as those exemplified in U.S. Patent No. 5,873,360, the disclosure of which is
20 incorporated herein by reference in its entirety. The control data came from Spiriva® capsules stored in foil pouches (the commercial pack was obtained from Boehringer Ingelheim of Ingelheim Germany minus the HandiHaler® devices).

With respect to the decomposition of the blends, filled Diskus™ strips in DISKUS™
25 devices according to U.S. Patent No. 5,873,360 were placed into stability chambers under the following conditions: 25°C/dessicate, 25°C/75%RH, 30°C/65%RH, and 40°C/75%RH.

The tiotropium bromide was obtained from Changzhou Upbiochemical Co. of Hangzhou, China.
30

The designations A and B refer to two different lot numbers of commercially-available Spiriva® product. The formulation used in Spiriva® A and Spiriva® B is estimated to be 22.5mcg Tiotropium Bromide salt (18mcg Tiotropium) in approx 6 mg inhalation grade lactose within a capsule.
35

Hydrolysis impurity levels were obtained by High Performance Liquid Chromatography having the following features as shown in Table 7:

Table 7

5

Column details	Phenomenex, Luna C18(2), PN OOF-4251-E0, 15 cm x 4.6 mm i.d. packed with 3.0 μ m packing, or validated equivalent
Column temperature	40C
Mobile phase A	0.05 % TFA in water
Mobile phase B	0.05 % TFA in acetonitrile
Flow rate	1.2 mL/min
Gradient profile	Time (mins) 0 14 14.1 19%A 90 0 90 90%B 10 100 10 10
Detector wavelength	238 nm
Injection volume	15 L + 60 L Water by injection program (Mix 3X in seat) See Figure 1
Typical Column Loading	1.3 g
Data collection time/reporting time	14 minutes
Run time	19 minutes
Autosampler wash solvent	diluent

Fine particle mass stability values were obtained by employing Anderson Cascade Impaction testing at 60L/min with High Performance Liquid Chromatography analysis of collected samples.

- 5 Emitted dose stability values were obtained by employing Anderson Cascade Impaction testing at 60L/min with High Performance Liquid Chromatography analysis of collected samples.

- 10 Fine particle fraction stability values were obtained by employing Anderson Cascade Impaction testing at 60L/min with High Performance Liquid Chromatography analysis of collected samples.

- 15 Details of the High Performance Liquid Chromatography used in Cascade Impaction Method (Emitted dose, fine particle mass, emitted dose, fine particle fraction) are shown in Table 8 as follows:

Table 8

Analytical Column	5 cm x 4.6 mm i.d. 3.5 m Zorbax Stable Bond SB-C18 or 5 cm x 4.6 mm i.d. 3.5 m Zorbax Exclipse XDB C18
Mobile Phase	Mobile phase A : 0.010M Sodium Dodecyl Sulfate containing 0.1% Glacial Acetic Acid:Methanol in the ratio 80:20 by volume Mobile phase B: Acetonitrile With a binary or quaternary pump use a 63:37 ratio of mobile phase A:B. Alternatively, manually mix the two components in the ratio 63:37 by volume
Flow Rate	2 mL per minute
Temperature	40C
UV detection wavelength	238 nm

Typical Column Loading	0.040 g
Typical Injection Volume	20L + 80L Water (use injector program and mix 3X) see Figure 2 Example Autosampler Program
Approximate Run Time	3 minutes
Autosampler wash solvent	Acetonitrile
1 This method generates narrow chromatographic peaks. Care should be taken to minimize extra column volume, and to adjust detector time constants and data processing acquisition rates appropriately.	

The hydrolysis of tiotropium bromide in H₂O was evaluated by High Performance Liquid Chromatography.

5

The term "micronized" is to be construed to mean the COA having a median volume diameter (D50) of about 2 microns or less. The term "unmicronized" refers to the COA having a D50 outside the range of the micronized sugar ester, e.g., a D50 of about 50 to 75 microns.

10

Example 5: Hydrolysis Impurity Levels of lactose/COA/tiotropium bromide formulations compared to Spiriva® Control

15

Formulations containing lactose, COA and tiotropium bromide were evaluated under various temperature and humidity conditions, namely 14 days/25°C/75% RH, 14 days/40°C/75% RH, 1 month/25°C/75 % RH and 1 month/40°C/75 % RH, and compared to Spiriva® control formulation A. The specific formulations employed in accordance with the invention are set forth as follows in Table 9.

Table 9

Formulations	%w/w tiotropium bromide	Blending Speed (RPM)	%w/w COA
A	0.3	500	5
B	0.1	500	10
C	0.3	500	10
D	0.1	500	5

As shown in Figure 1, the formulations of the invention exhibited improved stability relative to the Spiriva® control formulation.

Example 6: Fine Particle Mass Stability for lactose/COA/tiotropium bromide formulations compared to Spiriva® Control A

The fine particle mass stability was evaluated for the formulations described in Example 5 under the same temperature and humidity conditions and the results are set forth in Figure 2. The formulations were evaluated against an emitted dose target of 3 µg. As shown, Formulation B appears to exhibit the best stability.

Example 7: Emitted Dose Stability for lactose/COA/tiotropium bromide formulations compared to Spiriva® Control A

The emitted dose stability was evaluated for the formulations described in Example 6 under the same temperature and humidity conditions and the results are set forth in Figure 3. The formulations were evaluated against an emitted dose target of 10 µg. Formulation B appears to exhibit the best stability.

Example 8: Hydrolysis Impurity Levels of lactose/COA/tiotropium bromide formulations compared to Spiriva® Controls

Formulations described in Example 5 were evaluated under various temperature and humidity conditions, namely 14 days/40°C/75 % RH and 1 month/40°C/75 % RH, and compared to Spiriva® control formulations A and B. As shown in Figure 4, the formulations exhibited improved stability relative to the Spiriva® control formulations.

Example 9: Hydrolysis Impurity Levels of lactose/tiotropium bromide formulations compared to Spiriva® Control

Formulations containing lactose and tiotropium bromide were evaluated under various temperature and humidity conditions, namely 14 days/25°C/75 % RH, 14 days/40°C/75 % RH, 1 month/25°C/75 % RH and 1 month/40°C/75 % RH, and compared to Spiriva® control formulation A. The specific formulations employed in accordance with the invention are set forth as follows in Table 10. The formulations were evaluated using a Diskus™ device.

Table 10

Formulations	Lactose Grade	%w/w tiotropium bromide	Blending Speed (RPM)
E	5	0.1	300
F	3	0.3	300
G	3	0.3	840
H	3	0.1	840
I	5	0.3	840
J	5	0.3	300
K	5	0.1	840
L	3	0.1	300

As shown in Figure 5, the formulations of the invention exhibited improved stability relative to the Spiriva® control formulation.

Example 10: Fine Particle Mass Stability for lactose/tiotropium bromide formulations compared to Spiriva® Control A

The fine particle mass stability was evaluated for the formulations described in Example 9 under the same temperature and humidity conditions and the results are set forth in Figure 6.

Example 11: Fine Particle Fraction Stability for lactose/tiotropium bromide formulations compared to Spiriva® Control A

The fine particle fraction stability was evaluated for the formulations described in Example 9 under the same temperature and humidity conditions and the results are set forth in Figure 7.

5

Example 12: Emitted Dose Stability for lactose/tiotropium bromide formulations compared to Spiriva® Control A

The emitted dose stability was evaluated for the formulations described in Example 9 under the same temperature and humidity conditions and the results are set forth in Figure 8.

Example 13: Head to Head Comparison Study – Chemical Stability Data 14 Days

A head to head comparison of chemical stability was carried out between a formulation employed with a Spiriva® device and the Spiriva® formulation in a Diskus™ device. The testing was done at 25°C/60 % RH, 30°/65% RH and 40°C/75% RH. The time point for evaluating the stability was initially and at 14 days.

The results are set forth in Table 11. 14 day, 40°C, 75% Relative Humidity suggests a slight increase in the level of the hydrolysis peak.

Table 11

	Spiriva®		Diskus™	
Condition	Initial	14 day	Initial	14 day
25°C/60% RH	99.3	99.4	99.2	99.2
30°C/60% RH	99.3	99.3	99.2	99.4
40°C/75% RH	99.3	99.0	99.2	Not Avail

25

Example 14: Delivered Dose of Formulation Including Tiotropium Bromide from HandiHaler®

30

The total ex-device for a formulation of tiotropium bromide employed in a commercially-available Spiriva® device was evaluated for various temperature and humidity conditions,

namely 25°C/dessicant, 30°C/65% RH and 40°C/75% RH (N=3). The measurements were taken at various times delineated on the x-axis in Figure 9. The delivered dose target was 10 μ g.

5 **Example 15: Fine Particle Mass of Formulation Including Tiotropium Bromide Delivered from HandiHaler®**

The fine particle mass of a formulation of tiotropium bromide employed in a commercially-available Spiriva® device was evaluated for various temperature and humidity conditions,
10 namely 25°C/dessicant, 30°C/65% RH and 40°C/75% RH (N=3). The measurements were taken at various times delineated on the x-axis in Figure 10. The delivered dose target was 3 μ g. The volume throughput was 39 L/min and the test time was 3 s.

15 **Example 16: Fine Particle Fraction of Formulations Including Tiotropium Bromide Delivered from HandiHaler® and Diskus™**

The fine particle fraction of formulations of tiotropium bromide T and U were evaluated for various temperature and humidity conditions, namely 14 day/25°C/dessicant, 14
20 day/30°C/65% RH, 14 day/40°C/75% RH and 14 day/40°C/dessicant. Formulation T was a Spiriva formulation employed in conjunction with a Handihaler device (volume throughput 39L/min., test time 3s) and formulation U was a Spiriva formulation employed in conjunction with 14-pocket Diskus blister strips device (volume throughput 60L/min., test time 3s) stored in a non-overwrap configuration.

25

The results are set forth in Figure 11. As shown, the formulation employed in conjunction with the HandiHaler® device exhibits superior fine particle fraction values relative to the Diskus™ device.

30 **Example 17: Fine Particle Fraction of Formulations Including Tiotropium Bromide Delivered from HandiHaler® and Diskus™**

Normalized fine particle fraction values (N=3 ACIs) were obtained for the formulations described in Example 16. The results are set forth in Figure 12.

35

Example 18: Physical Property Measurements of Formulations Containing Tiotropium Bromide and Excipients

Various physical property measurements were determined for tiotropium bromide including COA or magnesium stearate. The results are set forth in Table 12.

Table 12

5

Excipient	Batch	PS @ 1 bar (micron)	GSD	PS @ 3 bar (micron)	GSD	SSA (m ² /g)
COA	Micronized E10366	1.76	1.75	1.59	1.70	6.3
Mg stearate	"AA" (tiotropium bromide)	6.2	3.19	4.19	3.32	~ 8
Mg stearate	"AA" (compound "Y")	6.15	2.50	4.55	2.65	7.72
Mg stearate	"BB" (compound "Y")	3.64	2.07	2.89	2.07	8.43

PS refers to the D50 particle size distribution.

GSD refers to the span or distribution of the particles defined by D84/D50.

SSA refers to specific surface area.

10 Formulation "AA" employs a vegetable magnesium stearate (LIGA MF-2-V).

Formulation "BB" employs a magnesium stearate (LIGA MF-3-V) similar to that used in formulation "AA" except that it possesses a higher surface area and a smaller average particle size.

15 **Example 19: Fine Particle Mass Stability Optimized Blends Using Tiotropium Bromide**

A number of formulations were evaluated for FPM stability. Formulations A', B', E', G', J', K', M', O', R' and S' were evaluated against a commercially-available Spiriva®
 20 formulation. The formulations were evaluated initially, 1 month/25°C/75% RH, 1 month/40°C/75% RH, 3 months/25°C/75% RH and 3 months/40°C/75% RH. Each one of formulations A', B', E', G', J', K', M', O', R' and S' contained 0.1%w/w tiotropium bromide.

Components and relative amounts present in the formulations are listed in Table 13.

Table 13

5

Formulation	Lactose	%COA
A'	Grade 3	6, micronized
B'	Grade 5	10, micronized
E'	Grade 5	2, unmicronized
G'	Grade 5	6, micronized
J'	Grade 3	6, unmicronized
K'	Grade 5	10, unmicronized
M'	Grade 3	6, unmicronized
O'	Grade 3	10, micronized
R'	Grade 5	2, micronized
S'	Grade 3	None

10 The results are set forth in Figure 13. Formulation G is desirable in that it exhibits the least amount of stability variation.

Example 20: Fine Particle Mass Stability Optimized Blends Using Tiotropium Bromide

15 A number of formulations were evaluated for FPM stability. Formulations C', D', F', H', I', L', N', P', Q' and T' were evaluated against a commercially-available Spiriva® formulation. The formulations were evaluated initially, 1 month/25°C/75% RH, 1 month/40°C/75% RH, 3 months/25°C/75% RH and 3 months/40°C/75% RH. Each one of formulations C', D', F', H', I', L', N', P', Q' and T' contained 0.2%w/w tiotropium bromide.

20

The results are set forth in Figure 14. The grades of lactose, % w/w of COA and the state of the COA (i.e., micronized or unmicronized) for each of these formulations are also set forth in Figure 14.

25 Components and relative amounts present in the formulations are listed in Table 14.

Table 14.

Formulation	Lactose	%COA
C'	Grade 5	10, unmicronized
D'	Grade 5	2, micronized
F'	Grade 3	2, micronized
H'	Grade 3	6, micronized
I'	Grade 5	6, unmicronized
L'	Grade 3	10, unmicronized
N'	Grade 3	2, unmicronized
P'	Grade 3	10, micronized
Q'	Grade 5	6, micronized
T'	Grade 5	None

5

Example 21: Emitted Dose for Optimized Blends Containing Tiotropium Bromide

The formulations described in Example 19 were evaluated for emitted dose against a commercially-available Spiriva® formulation. The results are set forth in Figure 15

10

Example 22: Emitted Dose for Optimized Blends Containing Tiotropium Bromide

The formulations described in Example 20 were evaluated for emitted dose against a commercially-available Spiriva® formulation. The results are set forth in Figure 16

15

Example 23: Hydrolysis Levels for Optimized Blends Containing Tiotropium Bromide

20

Hydrolysis impurity levels were evaluated for the formulations described in Example 19. In particular, the formulations were evaluated initially, 1 month/25°C/dessicant, 1 month/25°C/75% RH, 1 month/30°C/65% RH, 1 month/40°C/75% RH, 3 months/25°C/dessicant, 3 months/25°C/75% RH, 3 months/30°C/65% RH and 3 months/40°C/75% RH. The results are set forth in Figure 17 As shown, the formulations A', B', E', G', J', K', M', O', R' and S' display improved chemical stability relative to the control formulation.

25

Example 24: Hydrolysis Levels for Optimized Blends Containing Tiotropium Bromide

5 Hydrolysis impurity levels were evaluated for the formulations described in Example 20. In particular, the formulations were evaluated initially, 1 month/25°C/dessicant, 1 month/25°C/75% RH, 1 month/30°C/65% RH, 1 month/40°C/75% RH, 3 months/25°C/dessicant, 3 months/25°C/75% RH, 3 months/30°C/65% RH and 3 months/40°C/75% RH. The results are set forth in Figure 18. As shown, formulations C', D', F', H', I', L', N', P', Q' and
10 T' display improved chemical stability relative to the control formulation.

Example 25: Hydrolysis Impurity Levels for Optimized Blends containing Tiotropium Bromide

15 Hydrolysis impurity levels were evaluated for the formulations described in Example 23. The results are set forth in Figure 19 and are scaled differently in contrast to the results in Example 23. As shown, formulations A', B', E', G', J', K', M', O', R' and S' display improved chemical stability relative to the control formulation.

20

Example 26: Hydrolysis Impurity Levels for Optimized Blends containing Tiotropium Bromide

25 Hydrolysis impurity levels were evaluated for the formulations described in Example 24. The results are set forth in Figure 20. As shown, formulations C', D', F', H', I', L', N', P', Q' and T' display improved chemical stability relative to the control formulation.

Example 27: Head-to-Head Comparison – Spiriva® Blend in HandiHaler® vs. Spiriva® Blend in DISKUS™

A comparison of hydrolysis was made between a Spiriva® formulation contained in a HandiHaler device (control), a Spiriva® formulation contained in a Diskus™ device, and a
35 Spiriva® formulation contained in a Diskus™ device, protected with dessicant. The formulations were evaluated at various humidity and temperature conditions: initial, 14 day/25°C/dessicant, 14 day/30°C/65% RH, 14 day/40°C/75% RH, 1 month/25°C/dessicant, 1 month/30°C/65% RH, 1 month/40°C/75% RH, 3 month/25°C/dessicant, 3 month/30°C/65% RH, and 3 month/40°C/75% RH. The results are set forth in Figure 21.

As shown, the formulations in the Diskus™ device exhibit better chemical stability than the Spriva® control formulation.

Example 28: Hydrolysis of Tiotropium Bromide in H₂O

- 5 The hydrolysis of tiotropium bromide was evaluated in H₂O under different temperature and time conditions as set forth in Figure 22. As show, the level of hydrolysis increases as a function of temperature over time

CLAIMS

- 5 1. An inhalable solid pharmaceutical formulation comprising (a) an anti-cholinergic agent, (b) a carrier and (c) a ternary agent that is a sugar ester.
2. An inhalable solid pharmaceutical formulation as claimed in claim 1 wherein the sugar ester is cellobiose octaacetate.
- 10 3. An inhalable solid pharmaceutical formulation as claimed in claim 2 wherein the cellobiose octaacetate is micronized.
4. An inhalable solid pharmaceutical formulation as claimed in claim 1 wherein the carrier is lactose.
- 15 5. An inhalable solid pharmaceutical formulation as claimed in claim 1, wherein the anti-cholinergic agent is tiotropium bromide.
- 20 6. An inhalable solid pharmaceutical formulation as claimed in claim 1, wherein the formulation comprises from about 5 %w/w to about 7 %w/w of said ternary agent.
7. An inhalable solid pharmaceutical formulation comprising (a) tiotropium bromide, (b) lactose and (c) cellobiose octaacetate.
- 25 8. An inhaler comprising the inhalable solid pharmaceutical formulation as claimed in claim 1.
9. An inhaler as claimed in claim 8 wherein the sugar ester is cellobiose octaacetate.
- 30 10. An inhaler as claimed in claim 9 wherein the cellobiose octaacetate is micronized.
11. An inhaler as claimed in claim 8 wherein the carrier is lactose.
- 35 12. An inhaler as claimed in claim 8, wherein the anti-cholinergic agent is tiotropium bromide.

13. An inhaler as claimed in claim 8, wherein the formulation comprises from about 5 %w/w to about 7 %w/w of said ternary agent.

5 14. An inhaler wherein the formulation comprises (a) tiotropium bromide, (b) lactose and (c) cellobiose octaacetate.

15. A method of reducing or inhibiting chemical interaction between an active ingredient substance and a carrier susceptible to chemical interaction, which comprises mixing a
10 ternary agent which is a sugar ester with an anti-cholinergic agent and said carrier.

16. A method of reducing or inhibiting chemical degradation of an active ingredient substance in a formulation comprising a carrier and an active ingredient substance, which method comprises mixing a ternary agent which is a sugar ester with said active
15 ingredient substance which comprises an anti-cholinergic agent and said carrier.

17. A method for the treatment of a reversible airways obstruction, comprising administering to a patient in need thereof an inhalable solid pharmaceutical formulation comprising (a) an anti-cholinergic agent, (b) a carrier and (c) a ternary agent that is a
20 sugar ester.

18. A method according to claim 17, wherein the reversible airways obstruction is asthma.

19. A method according to claim 17, wherein the reversible airways obstruction is COPD.
25

20. A method of preparing a solid pharmaceutical preparation comprising combining (a) an anti-cholinergic agent, (b) a carrier and (c) a ternary agent that is a sugar ester.

TRANSLATION IN JP

INTERNATION SEARCH REPORT

国際調査報告

SUBSTITUTE SHEET (RULE 26)

差替え用紙（規則26）

SUBSTITUTE SHEET (RULE 26 ISA/JP)

差替え用紙（規則26 ISA/JP）

AMENDED SHEET (ARTICLE 19)

補正された用紙（条約第19条）

STATEMENT UNDER ARTICLE 19 (1)

条約第19条（1）に基づく説明書

RECTIFIED SHEET (RULE 91)

訂正された用紙（規則91）

RECTIFIED SHEET (RULE 91 ISA/JP)

訂正された用紙（規則91 ISA/JP）

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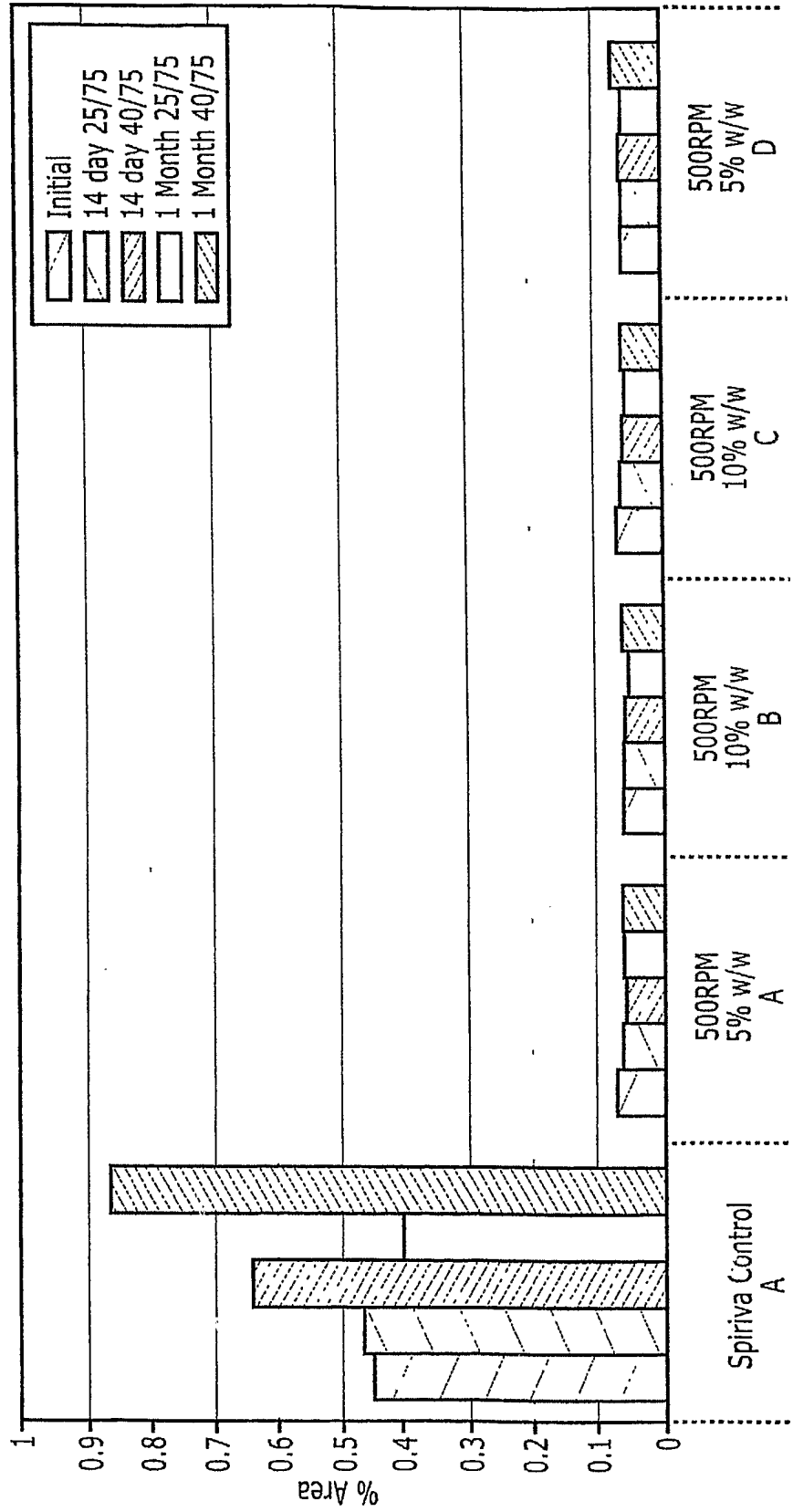


Figure 1

2/22

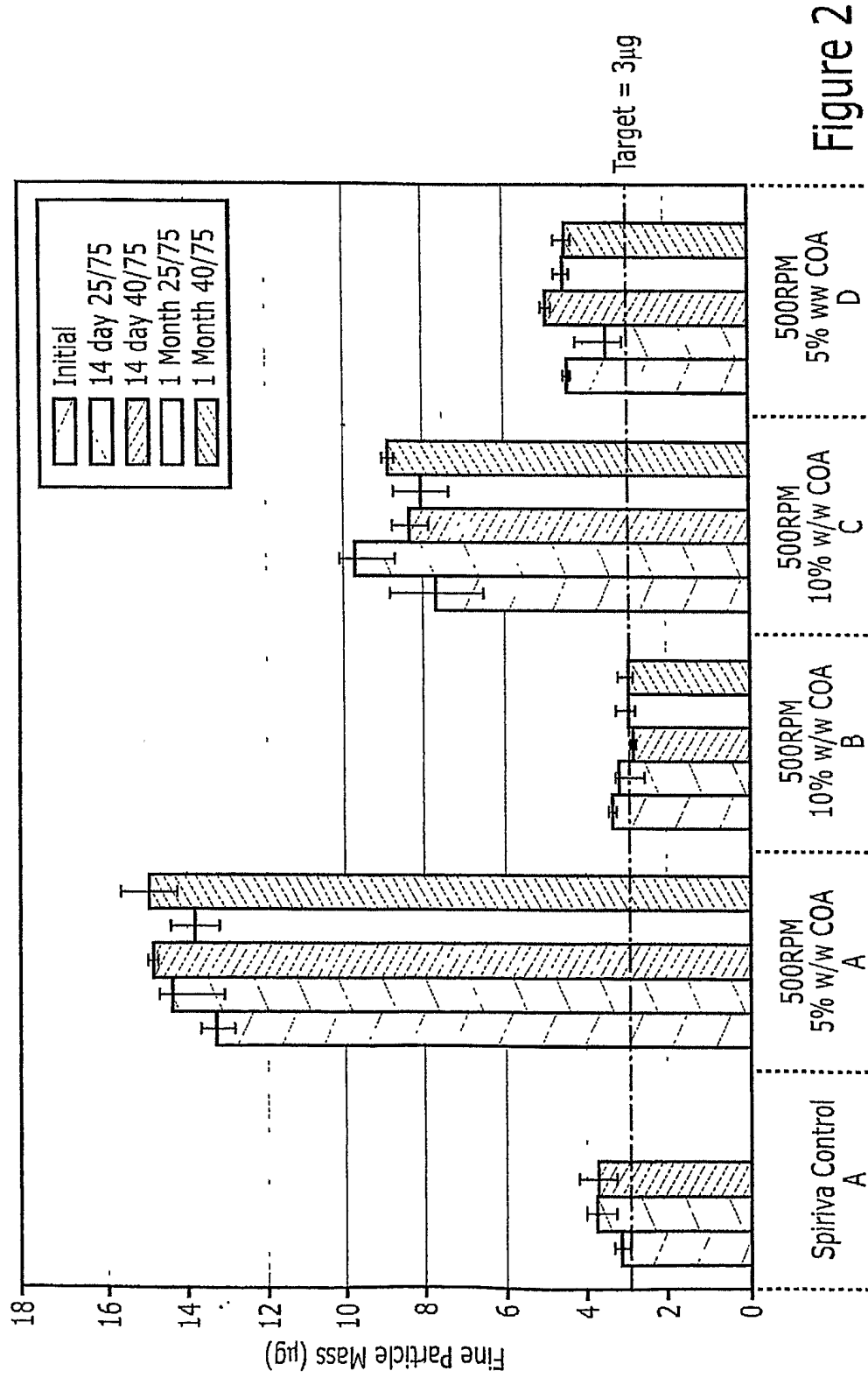


Figure 2

3/22

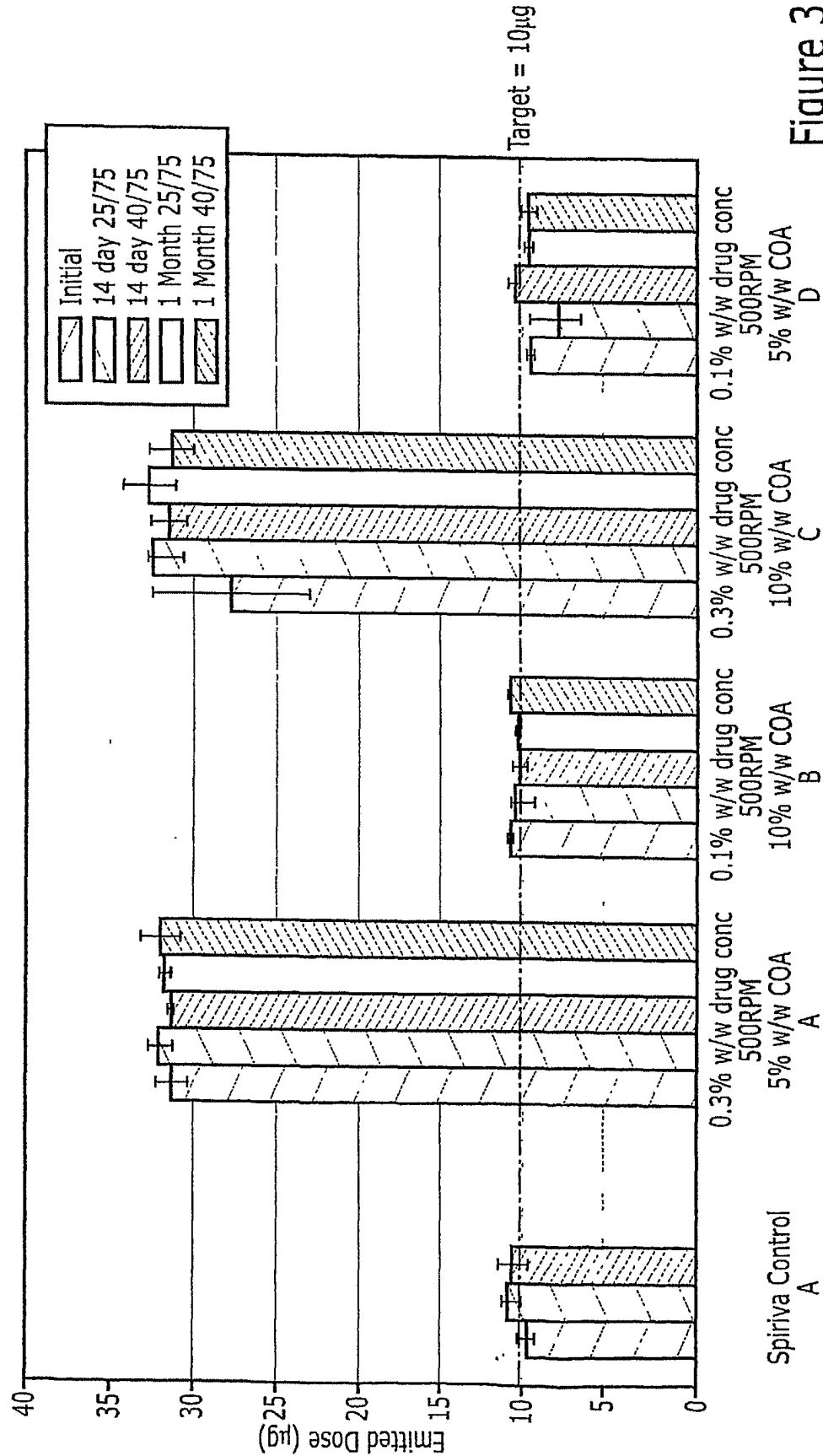


Figure 3

4/22

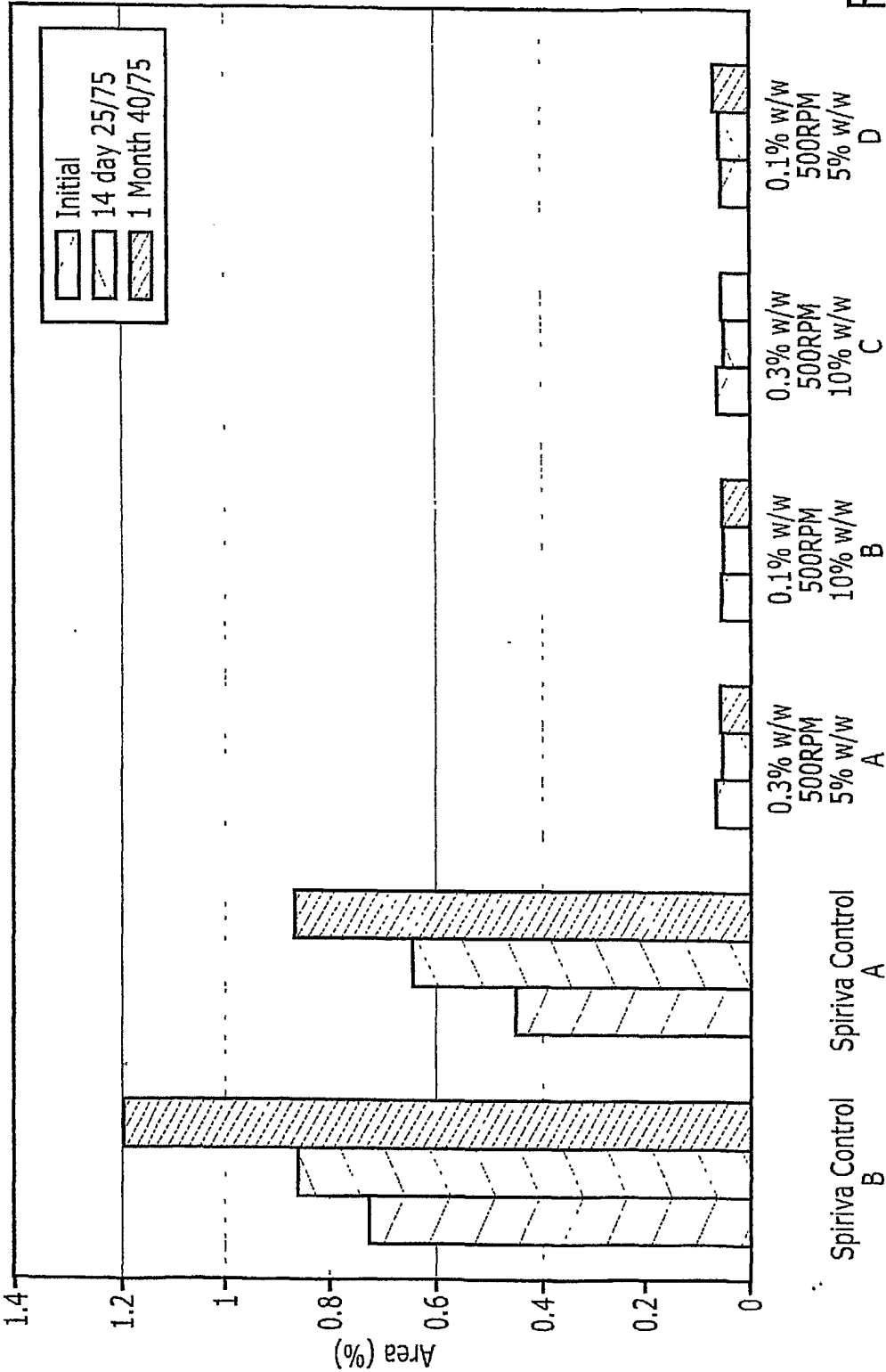


Figure 4

5/22

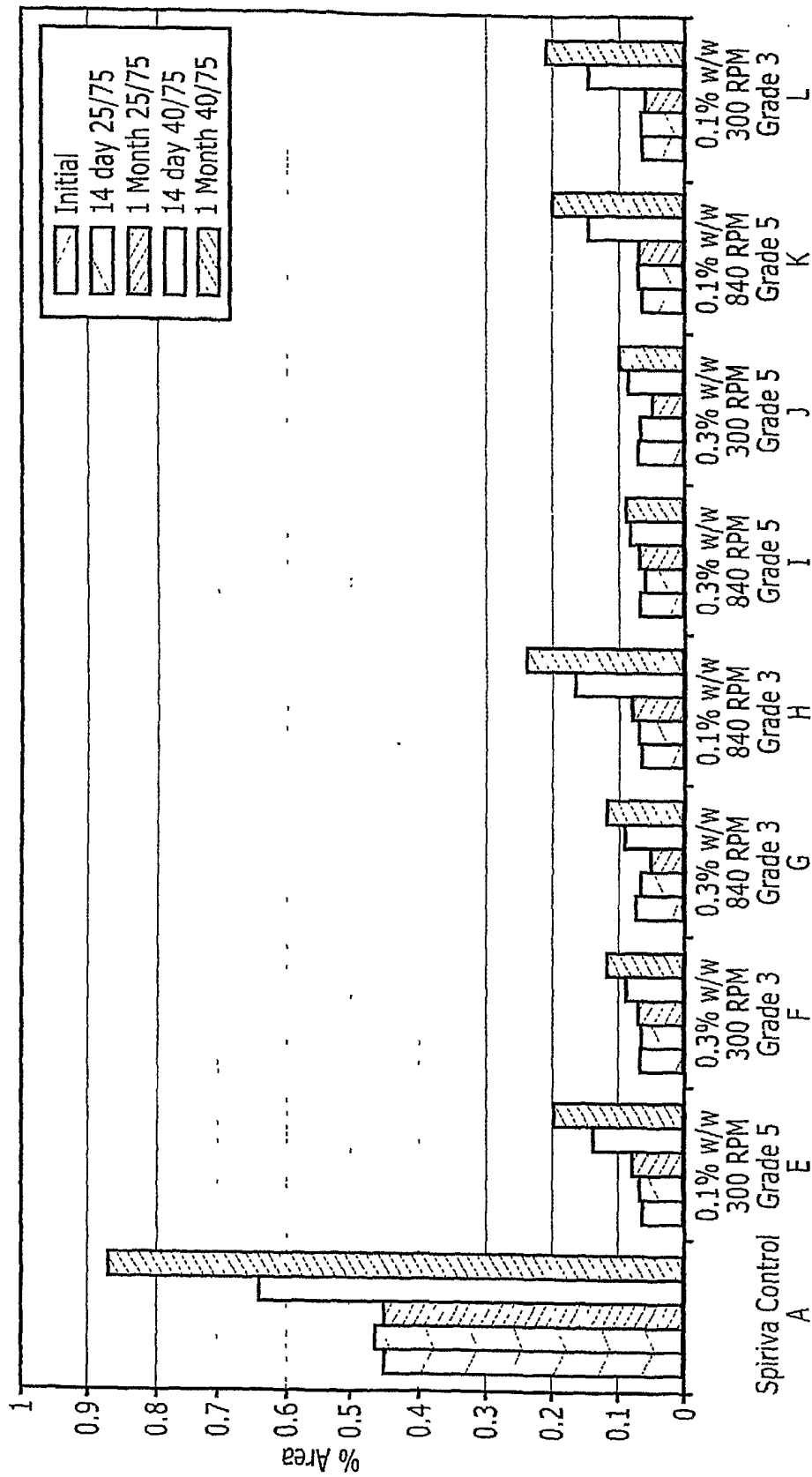
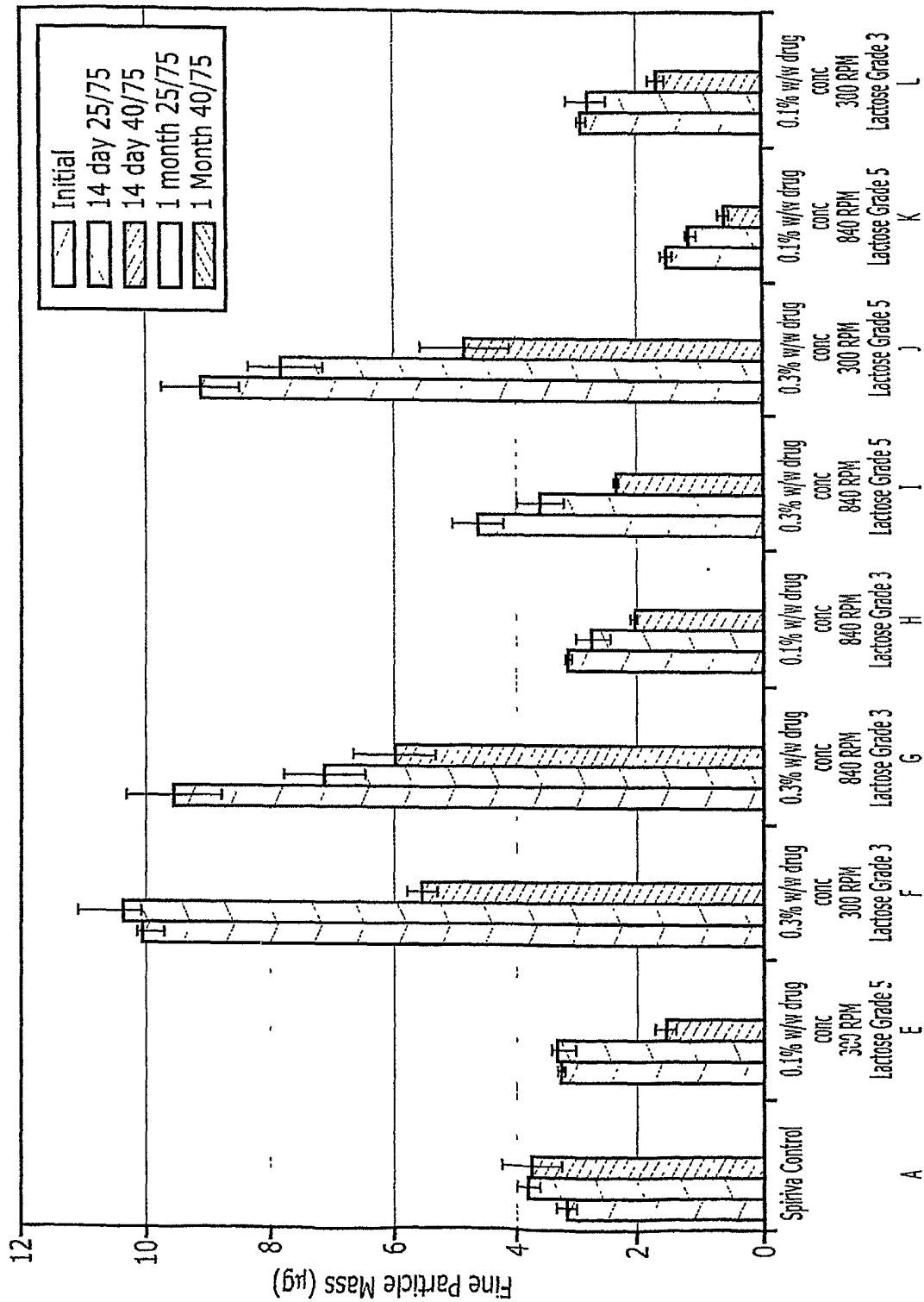


Figure 5

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Figure 6



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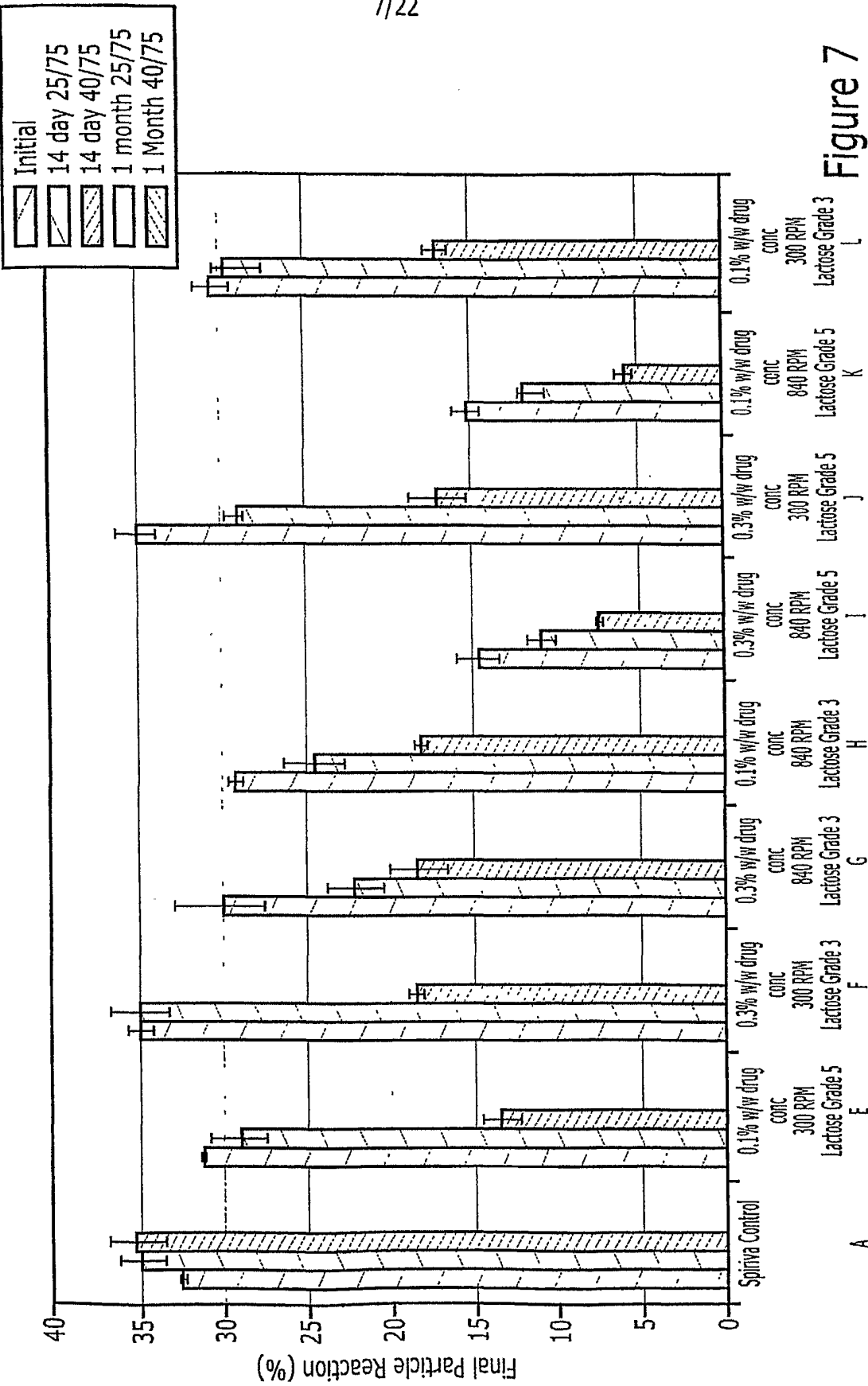


Figure 7

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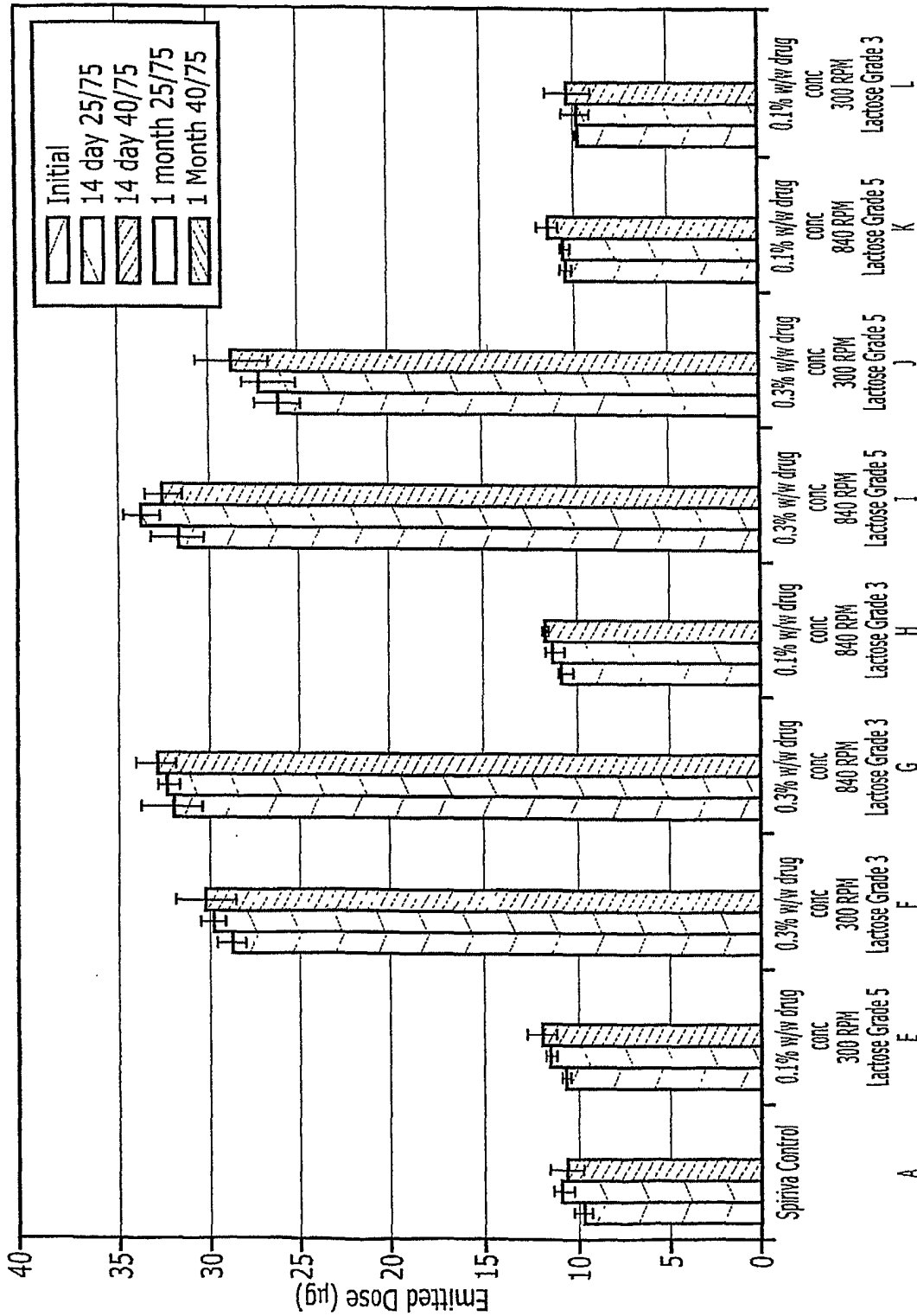


Figure 8

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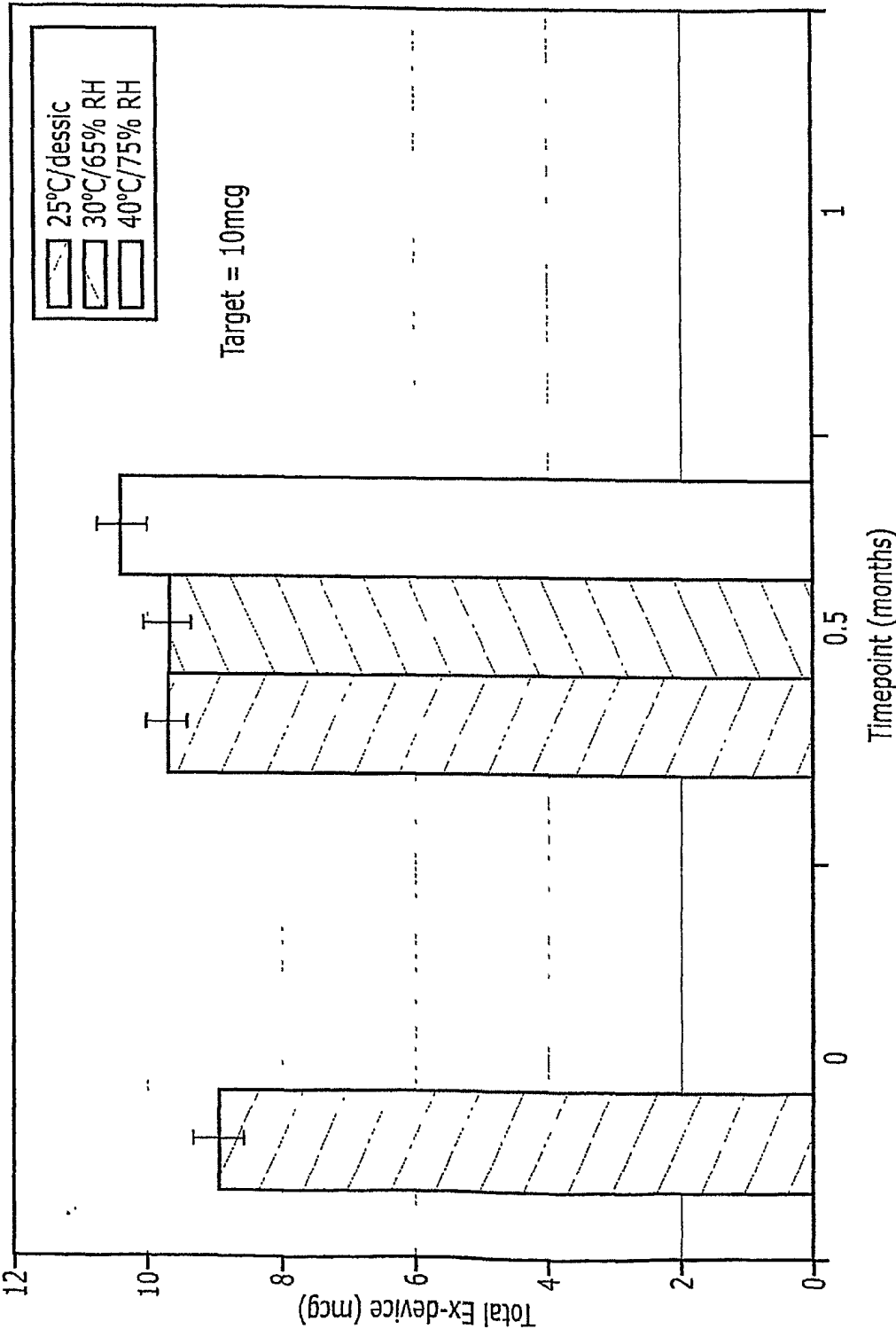


Figure 9

10/22

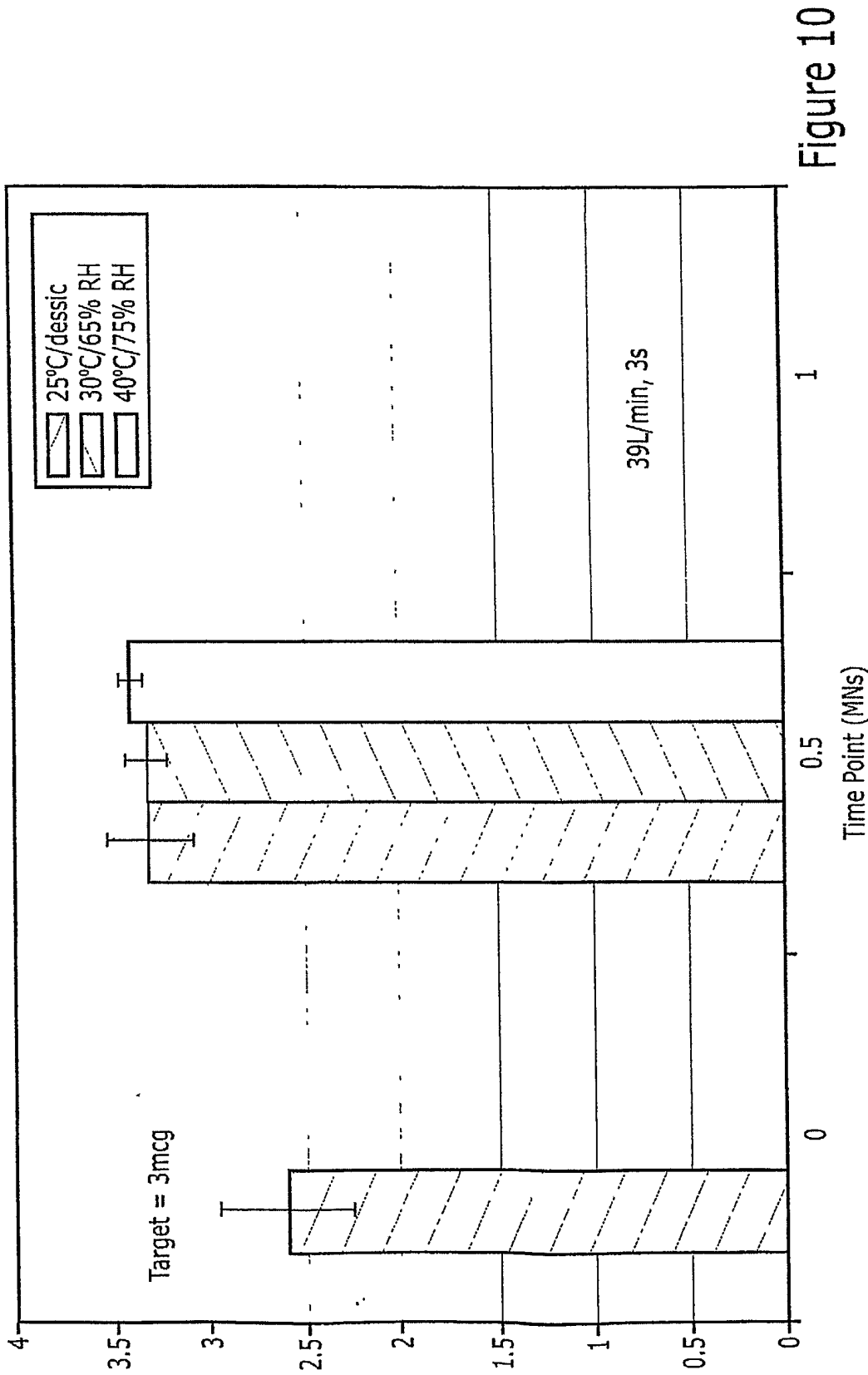


Figure 10

11/22

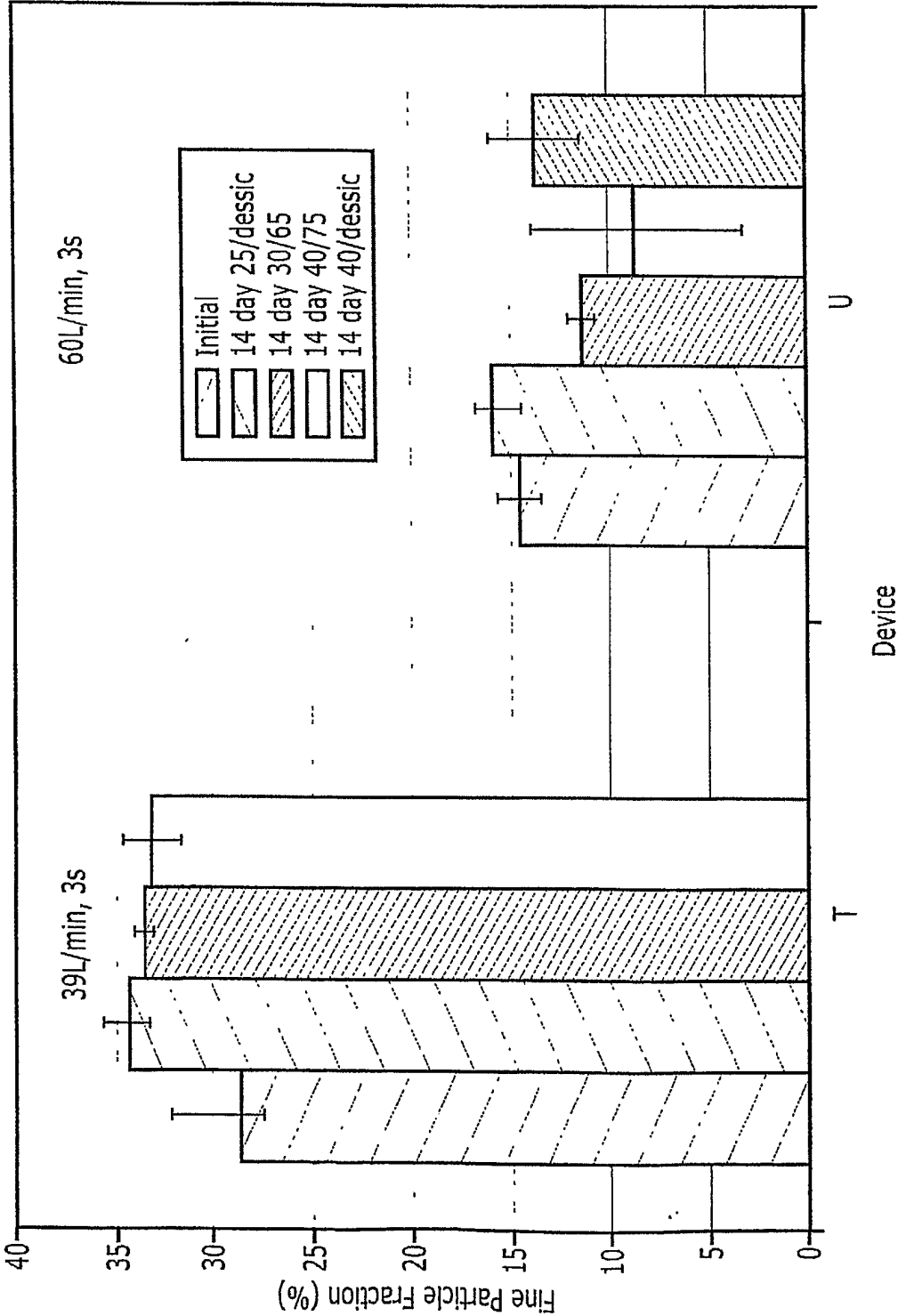


Figure 11

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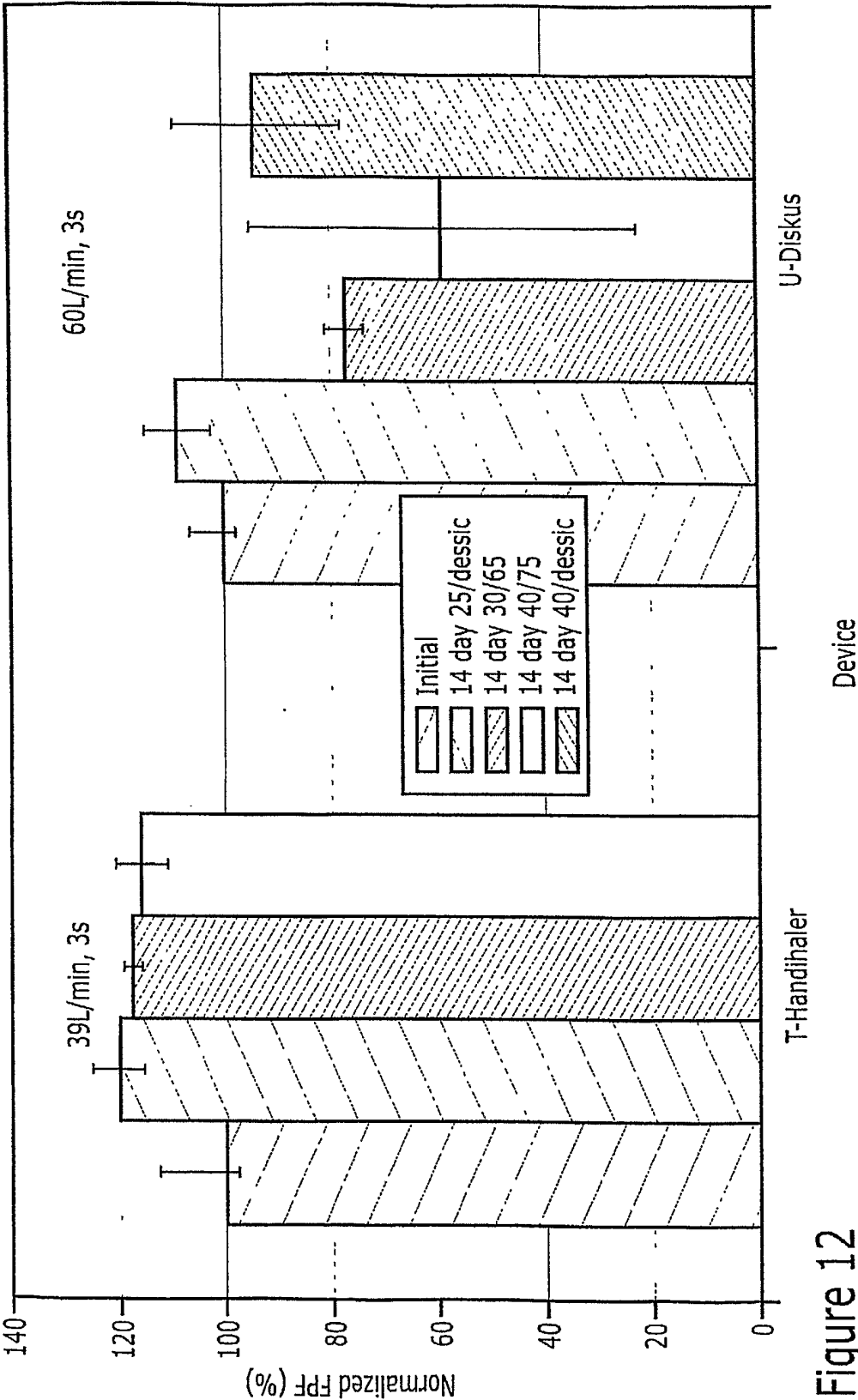


Figure 12

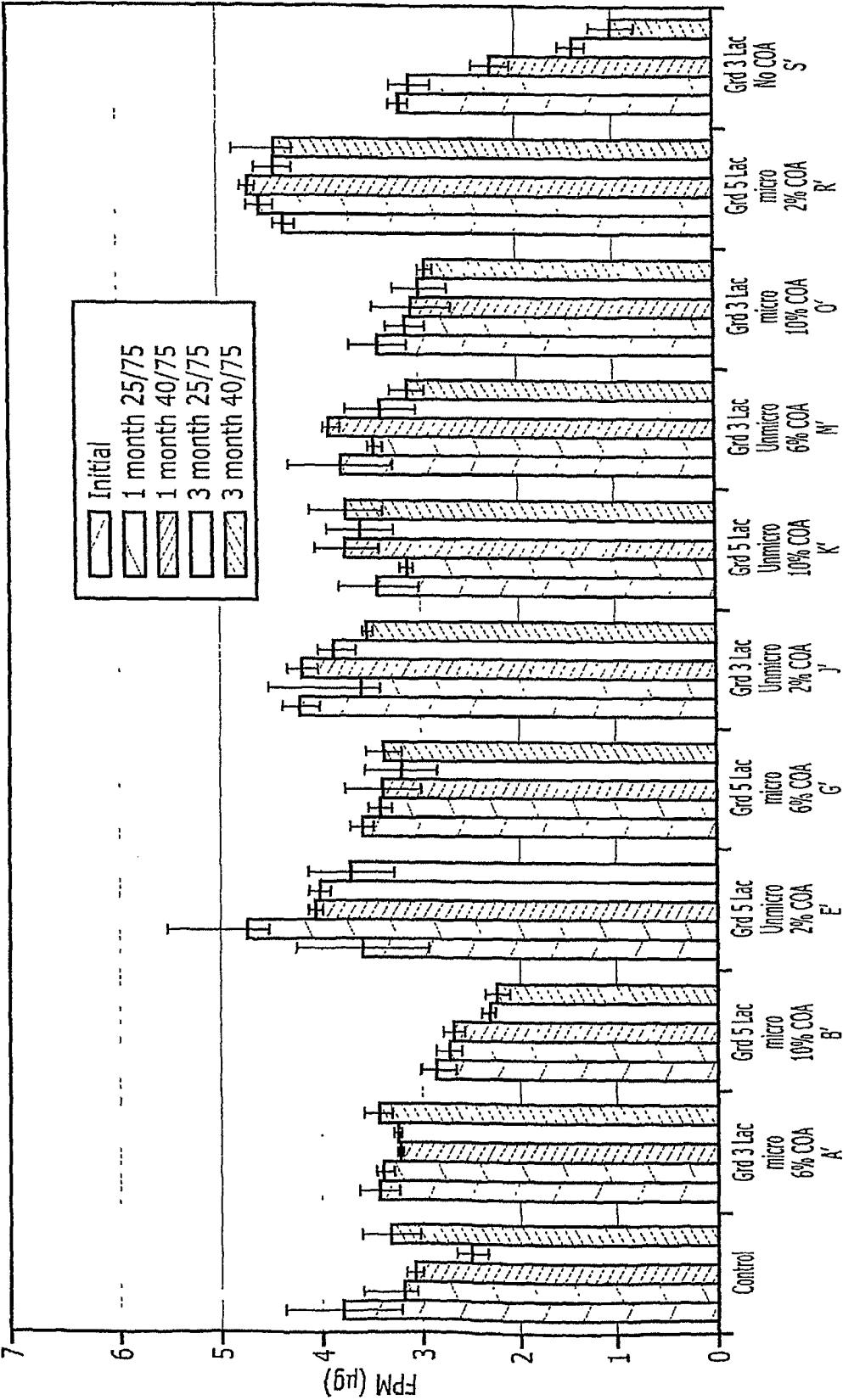


Figure 13

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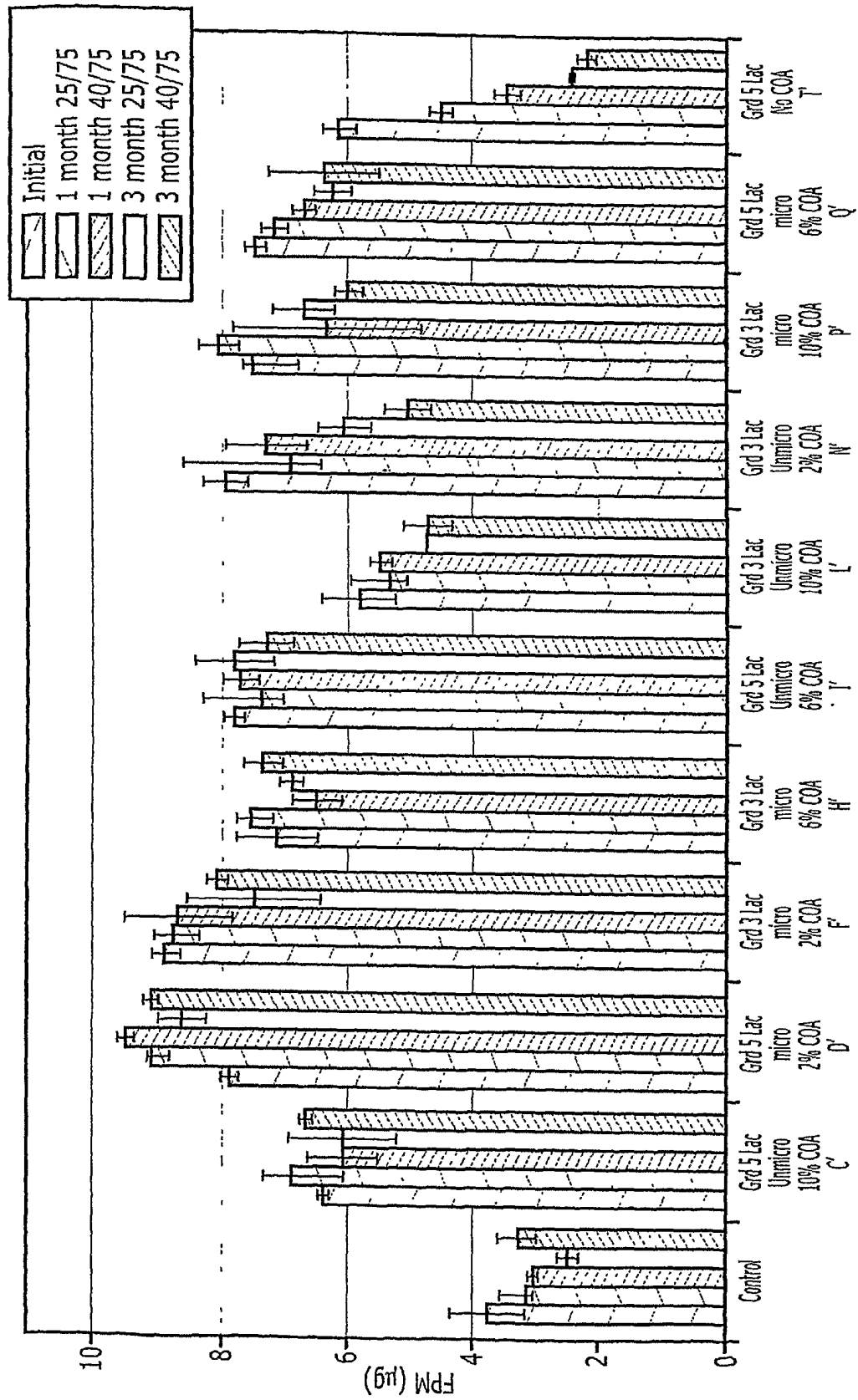


Figure 14

15/22

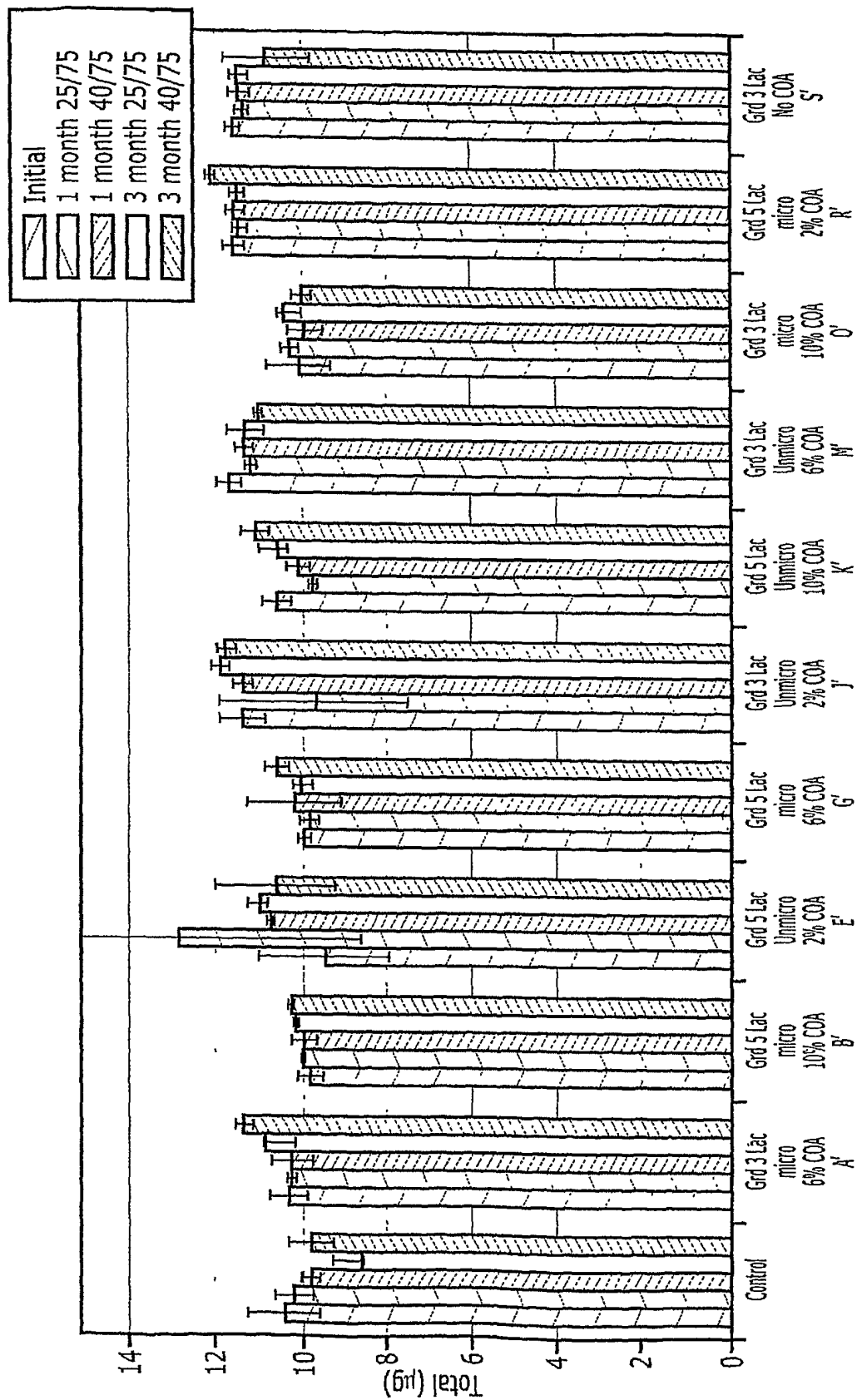


Figure 15

16/22

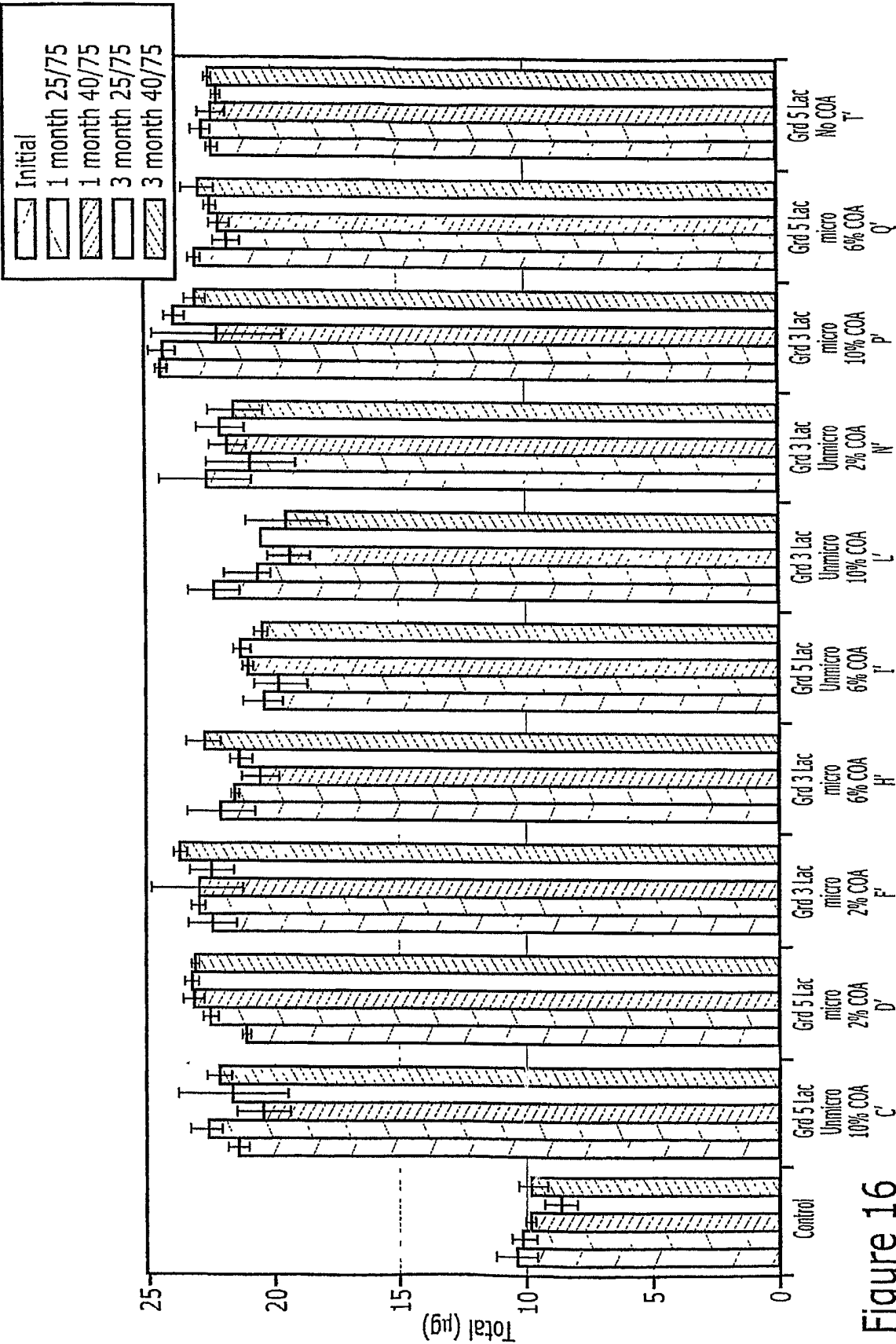


Figure 16

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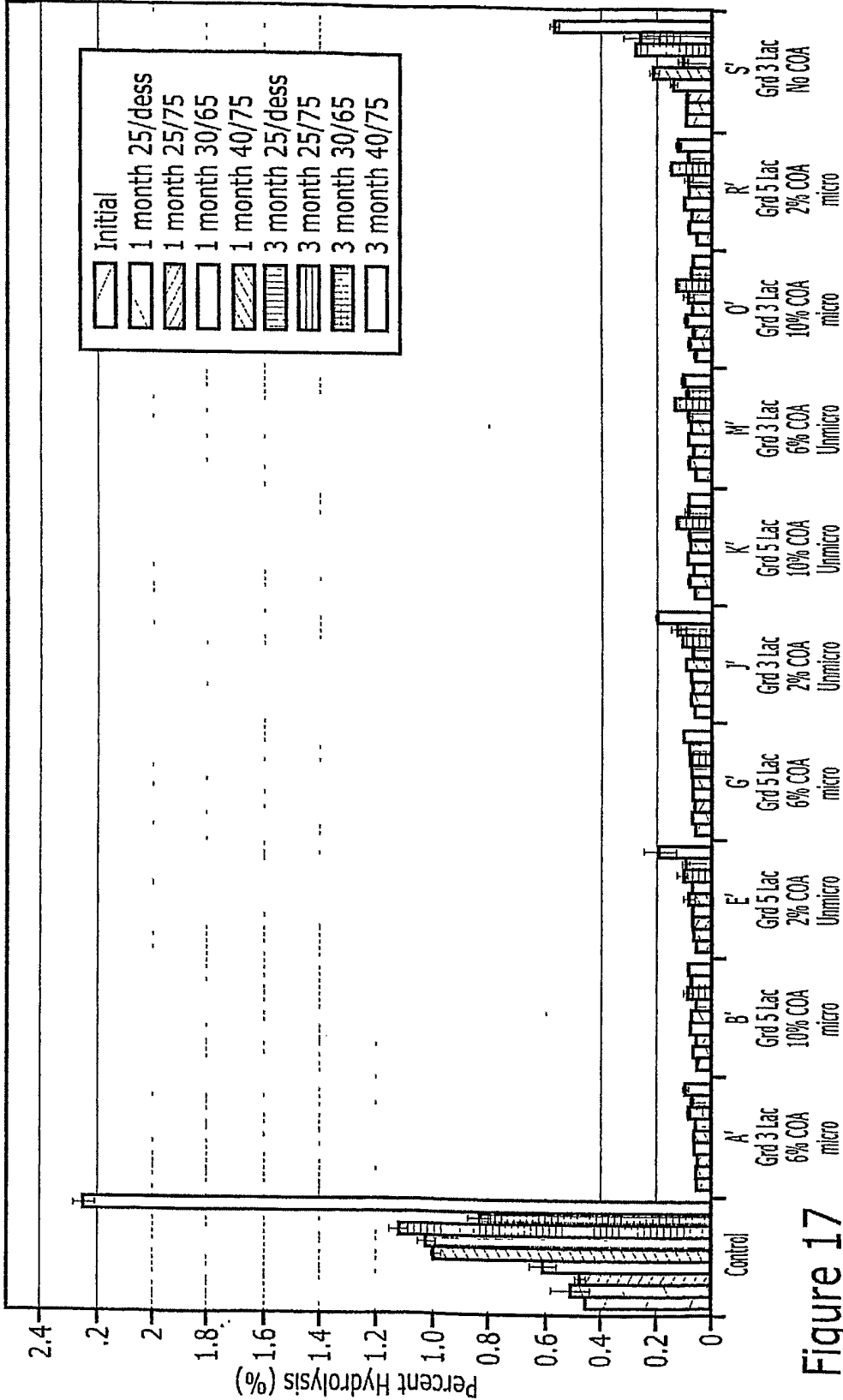


Figure 17

18/22

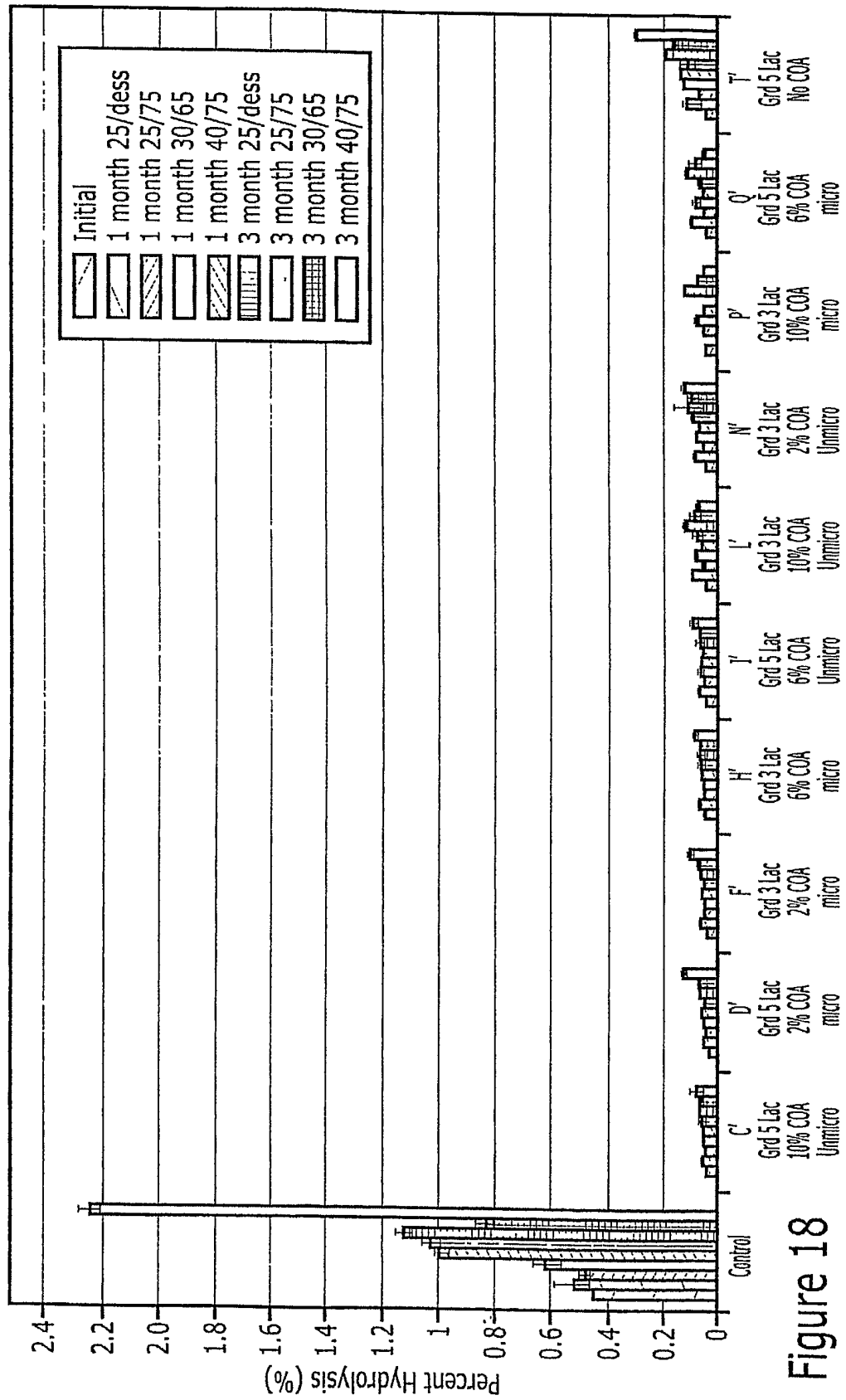


Figure 18

19/22

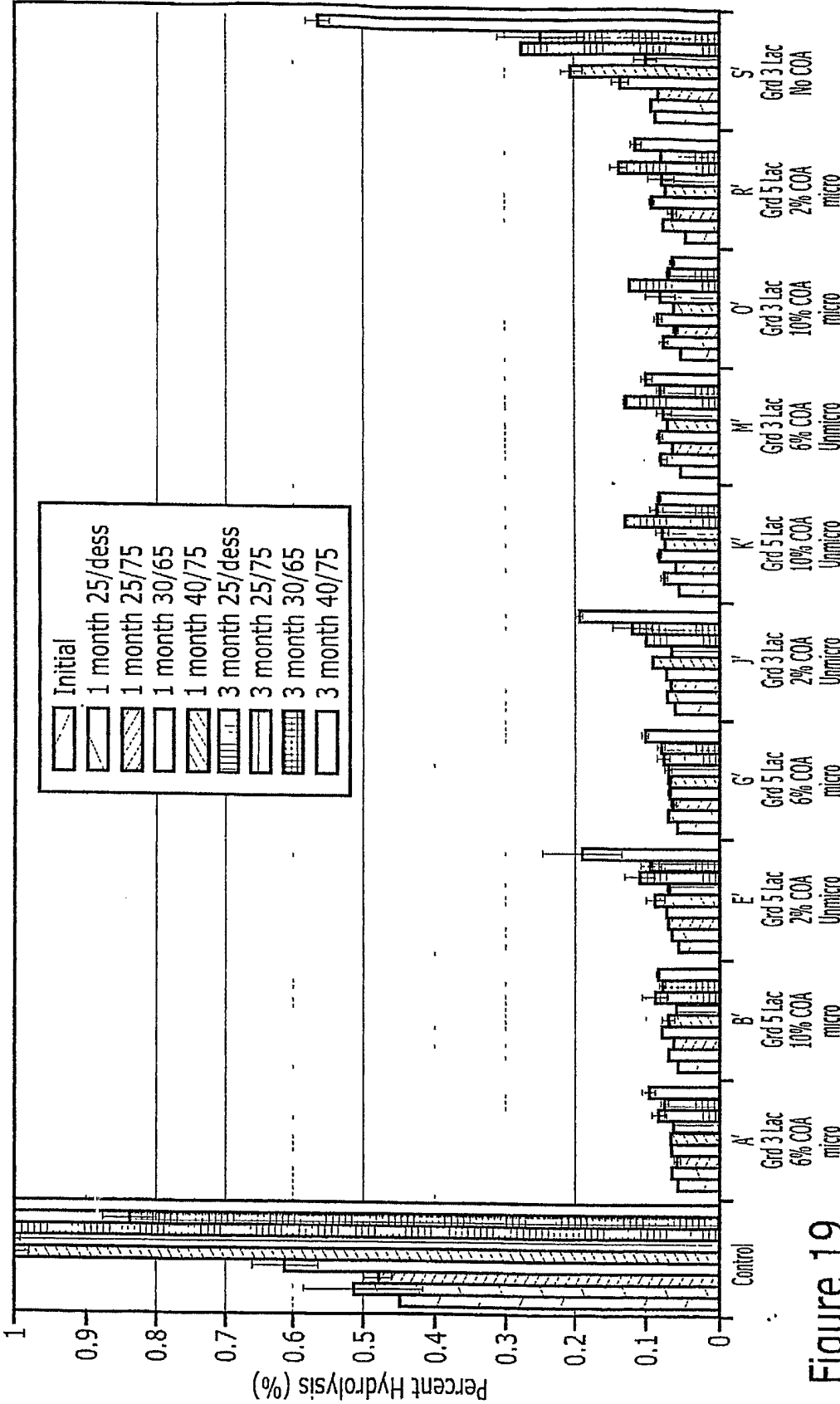


Figure 19

20/22

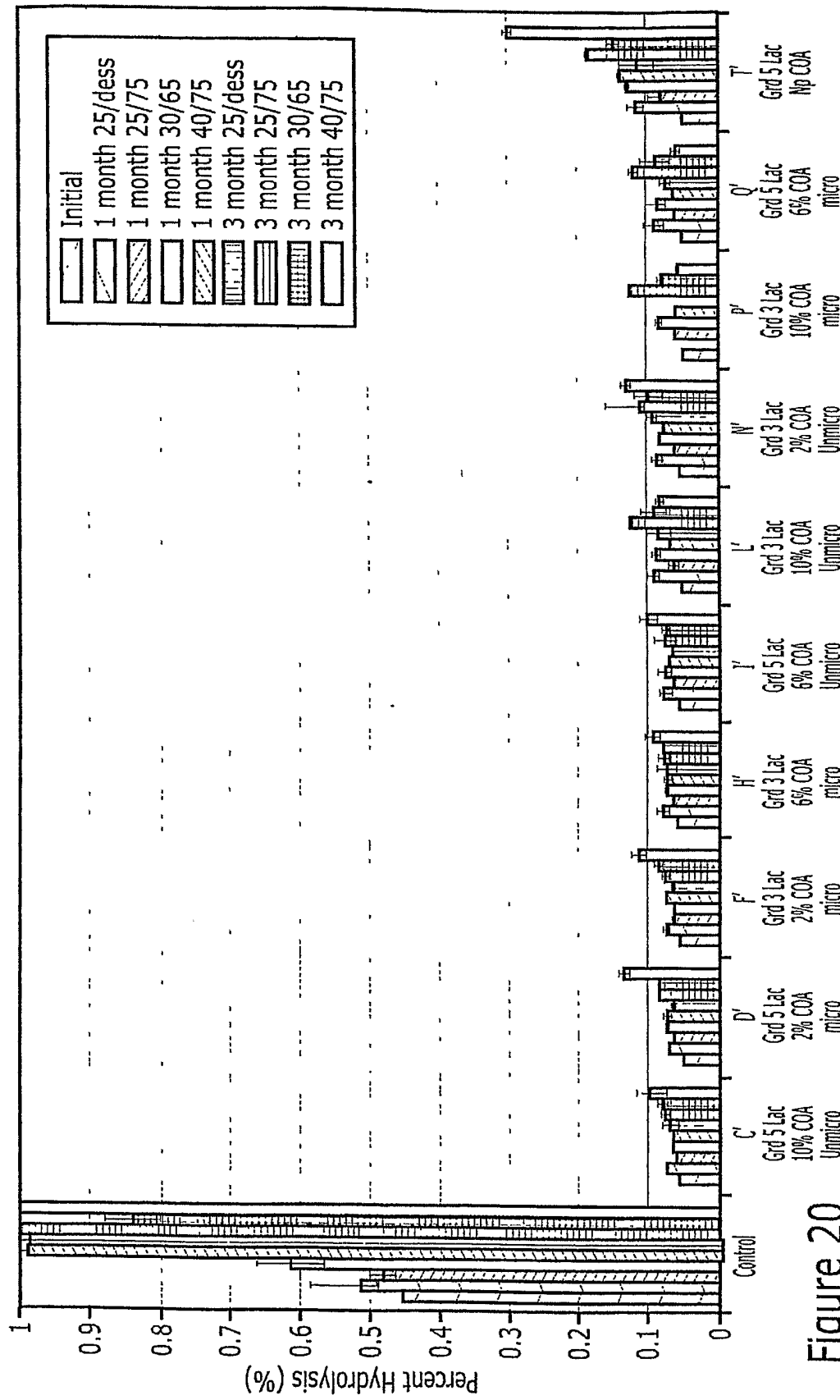


Figure 20

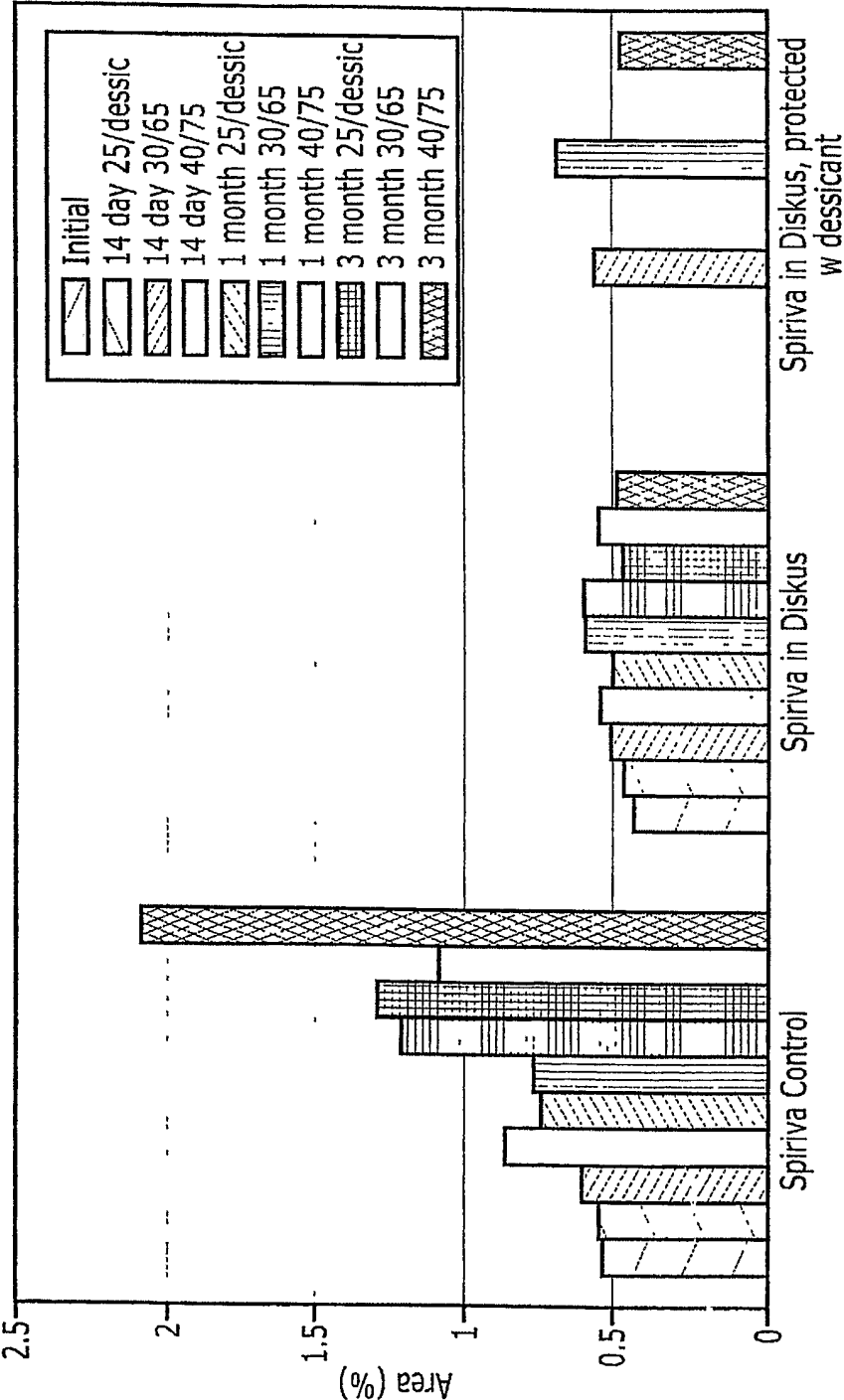


Figure 21

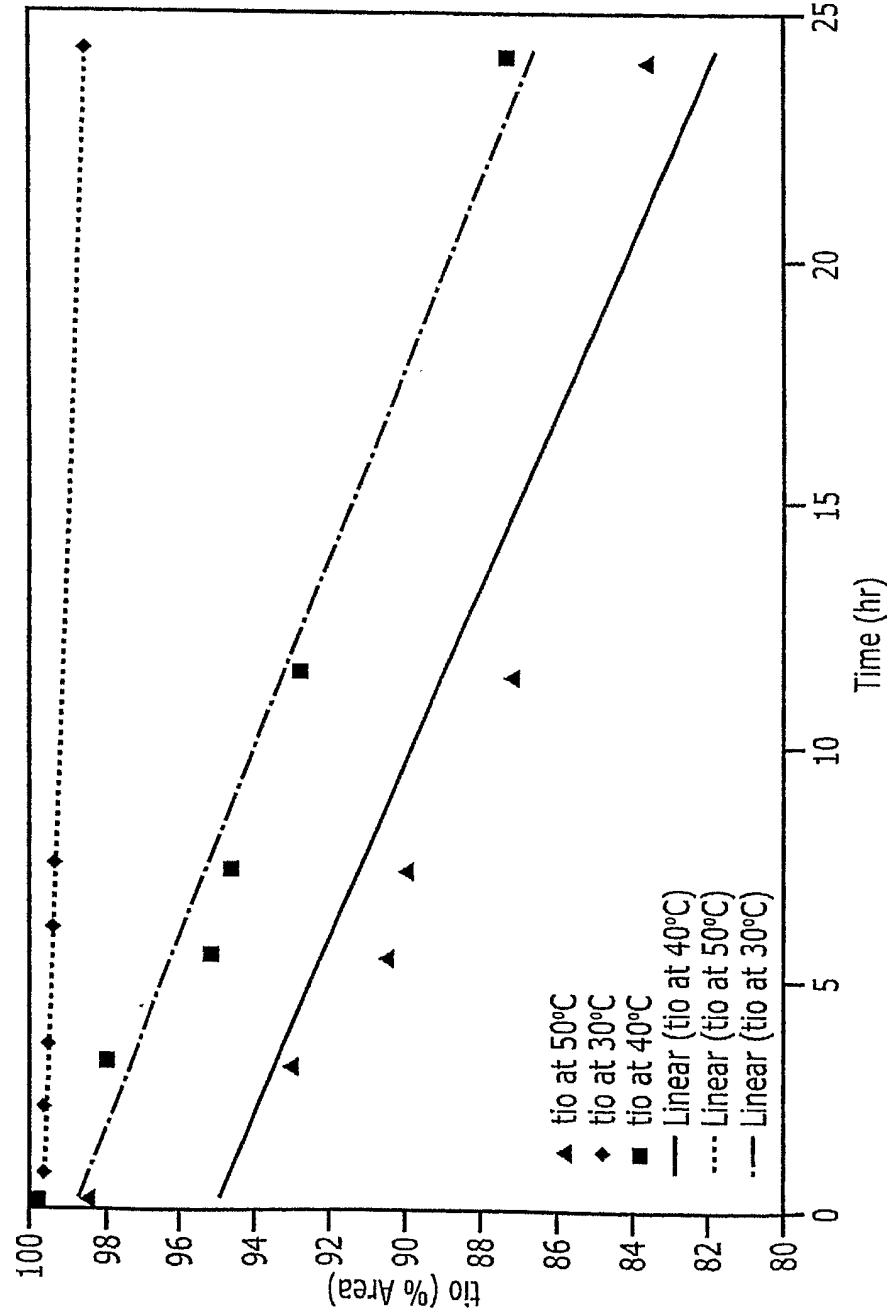


Figure 22