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(54) Title: TAURINE COMPOSITIONS SUITABLE FOR INHALATION

(57) Abstract: The invention discloses spray-dried compositions for inhalation and methods for preparing such powder compositions. The compositions of the invention are produced by spray-drying taurine under conditions that (i) retain the physical and chemical stability of the composition during spray drying and upon storage, (ii) protect the powder composition from aggregation and (iii) provide particles suitable for aerosolisation.



## TAURINE COMPOSITIONS SUITABLE FOR INHALATION

Description

- 5 The present invention relates to stable materials, compositions comprising such materials suitable for inhalation and methods for preparing such compositions.

Background of the Invention

- 10 The process of spray drying has been widely used in the production of pharmaceuticals since the 1940s (Corrigan, 1995). The food industry also commonly employs spray drying to produce food products demonstrating enhanced stability and suitable for long term storage (Sliwinski et al., 2004). Spray drying is a one step process used to convert a liquid based feedstock (such as a solution, suspension or emulsion) into a dried powder form by atomizing the feedstock in droplets, into a hot drying-medium, typically air or nitrogen. The process provides enhanced control over particle size, size distribution, particle shape, density, purity and structure. As formulators are able to control these parameters so precisely, spray drying as a possible method for formulating dry powder compositions intended for pulmonary delivery has also been investigated in recent years (WO 96/321 94).

Spray drying active pharmaceutical ingredients (API) or biological material suitable for inhalation normally requires the presence of stabilizing excipients and/or diluents.

- 25 The *de-facto* spray drying excipient of choice is often Mannitol as it possesses many advantageous properties. Mannitol will readily dry in a crystalline state, is water soluble and is considered non-hygroscopic as it picks up less than 1% moisture at relative humidity as high as 70% (Handbook of Pharmaceutical Excipients, 6<sup>th</sup> Edition, R.C. Rowe). In addition it can pick up 10% of mass in water at humidity's >70%RH. However despite mannitol's attractive stabilizing capabilities, it is a tussive agent and will induce coughing when administered via the pulmonary route.

- As an alternative choice excipient, trehalose is often used for spray drying compositions. Trehalose (α-D-glucopyranosyl- α-D-glucopyranoside) is a naturally occurring, non-reducing disaccharide which was initially found to be associated with the prevention of desiccation damage in certain plants and animals which can dry out without damage and can revive when rehydrated. Trehalose however does not spray

dry completely crystalline and will instead form an amorphous matrix. This amorphous matrix is hygroscopic and will readily absorb water. Spray-dried trehalose therefore  
40 suffers from physical stability issues, principally particle agglomeration, resulting in loss of primary particle size and aerosol performance characteristics.

Thus a need still exists for materials such as excipients for preparing stable inhalable compositions which exhibit excellent aerosolisation properties and demonstrate very  
45 low levels of agglomeration. Ideally, such excipients will spray dry in a crystalline form and will possess various favourable attributes such as low toxicity (with no cough induced side effects), low hygroscopicity, high melting point, with very low moisture content (advantageous for long term storage).

## 50 Summary of the Invention

The invention relates to a method for preparing conditioned taurine, the method comprising a conditioning step, optionally a spray drying step, to produce taurine that:  
55 (a) demonstrates no significant net change in the  $D_{90}$  ( $\pm 20\%$ ) after 7 days of ambient storage; and  
(b) have a particle size ( $D_{90}$ ) of  $<20\mu\text{m}$ , but more preferably  $<10\mu\text{m}$  after 7 days of ambient storage,  
optionally and preferably in which a method zwitterionic neutralisation is facilitated during spray drying of the taurine.

60 The invention also relates to conditioned taurine, obtained or obtainable by the method of the invention and to a composition comprising conditioned taurine, such as a dry powder composition suitable for inhalation.

65 The invention further relates to a method for preparing conditioned taurine the method comprising drying solubilised taurine, optionally by spray drying with one or more of the following parameters:  
(a) the pH of the feedstock to be spray dried is acidic e.g. less than pH 5, preferably equal to or less than pH 4, such as about pH 4;  
70 (b) wherein the feedstock concentration is between 0.1% and 10%, more preferably between 1% and 5%;  
(c) the feedstock temperature is between  $0.1^\circ\text{C}$  and  $100^\circ\text{C}$ , more preferably between  $20^\circ\text{C}$  and  $70^\circ\text{C}$ ;

(d) the outlet temperature is between 50°C and 120°C, more preferably between 60°C and 100°C;

(e) the  $T_{(solid:gas)}$  ratio is between  $2.000 \times 10^{-6}$  and  $2.750 \times 10^{-3}$ .

The invention also relates to a container comprising:

- (a) conditioned taurine; or
- (b) a composition comprising conditioned taurine.

The invention also relates to a method for preparing conditioned taurine, the method being a multi-step process, in one embodiment a two-step process, and in one further embodiment a one step process such as spray drying.

### Figures

FIGURE 1 is a response plot of modelled residual results versus actual data. The boxed area highlights the 8 conditioned taurine batches.

FIGURE 2 is a variability chart showing how the 8 conditioned taurine batches span the whole theoretical operating range for spray dryers. The conditioned taurine batches are shown as a function of the  $T_{(solid:gas)}$  ratios.

FIGURE 3 is a plot showing the relationship of conditioned taurine batches which obey a quadratic relationship with the  $D_{90}$  of the PSD after 7 days ( $R^2=0.91$  Prob> F 0.0031).

FIGURE 4 is a TGA (thermo-gravimetric analysis) graph depicting the weight loss mean as a percentage at the initial time point, T=0 for 24 samples of spray-dried taurine.

FIGURE 5 is a TGA (thermo-gravimetric analysis) graph depicting the weight loss mean as a percentage at the 7 day time point, T=7 days for 24 samples of spray-dried taurine.

FIGURE 6 is a DSC (differential scanning calorimetry) graph depicting a sample of spray-dried taurine.

FIGURE 7 depicts the pKa profile of taurine.

FIGURE 8 depicts the pH profile and isoelectric point of taurine.

FIGURE 9 lists the joint factor tests indicating significance of all variables.

FIGURE 10 is a graph depicting the PSD (particle size distribution) for a spray-dried  
115 trehalose/leucine/salbutamol powder composition obtained by spray-drying under  
Process A conditions where  $T=0$ .

FIGURE 11 is a graph depicting the PSD (particle size distribution) for a spray-dried  
trehalose/leucine/salbutamol powder composition obtained by spray-drying under  
120 Process A, stored under ambient sealed conditions where  $T=24$  hours.

FIGURE 12 is a graph depicting the PSD (particle size distribution) for a spray-dried  
taurine/leucine/salbutamol powder composition obtained by spray-drying under Process  
B conditions where  $T=0$ .

125 FIGURE 13 is a graph depicting the PSD (particle size distribution) for a spray-dried  
taurine/leucine/salbutamol powder composition obtained by spray-drying under Process  
B, stored under ambient sealed conditions where  $T=24$  hours.

130 FIGURE 14 is a graph depicting the PSD (particle size distribution) for a spray-dried  
trehalose/leucine/salbutamol powder composition obtained by spray-drying under  
Process B conditions where  $T=0$ .

FIGURE 15 is a graph depicting the PSD (particle size distribution) for a spray-dried  
135 trehalose/leucine/salbutamol powder composition obtained by spray-drying under  
Process B, stored under ambient sealed conditions where  $T=24$  hours.

FIGURE 16 is a graph depicting the PSD (particle size distribution) for a spray-dried  
taurine/leucine/salbutamol powder composition obtained by spray-drying under Process  
140 B, stored open at  $25^{\circ}\text{C}/50\%\text{RH}$ , where  $T=24$  hours.

#### Detailed description of the invention

145 Taurine or 2-aminoethanesulfonic acid is an organic acid that is ubiquitous in the human  
body, constituting 0.1% w/w of its total weight (EFSA Response Letter, EFSA-Q-2007-  
113, 2009). It has been shown to be tolerable in excess of  $1000\text{mg kg}^{-1}\text{ day}^{-1}$  by the

EFSA with no indications of inhalation toxicity or intolerability. Taurine has exceptionally low moisture sorption characteristics and is thus considered non-hygroscopic as it does not take up any water at a relative humidity of between 0% and 100%. It is also soluble in water, is not considered a tussive agent and when spray-dried, produces particles with very low moisture content (less than 1% w/w, more preferably less than 0.5% w/w).

Taurine is a versatile molecule with various important biological functions, including: antioxidation; conjugation of bile acids; modulation of calcium signalling; osmoregulation and membrane stabilization. Taurine is also regularly used as a dietary supplement and as an ingredient in energy drinks.

Although there is little evidence in the literature of taurine being utilised as an active pharmaceutical ingredient, it has been described for the treatment of cardiac failure, and a taurine based composition has been disclosed in the treatment of asthma and various other respiratory failures (WO 92/17170). In the latter example, the taurine based composition was administered by pulmonary inhalation as an aerosolised solution.

Spray drying taurine to create inhalable taurine particles that do not agglomerate has proven surprisingly challenging.

In the present invention we have determined spray drying taurine under certain conditions can result in particle agglomeration over 1 to 7 days resulting in a loss of primary particles and negligible aerosol performance.

However, under certain conditions taurine can be produced which is suitable for inhalation use, and does not display such agglomeration. Such taurine is referred to as conditioned taurine herein, and in one aspect is made by the methods of the invention as disclosed herein, although other methods can be used. Conditioned taurine is suitably taurine that demonstrates no significant net change in the  $D_{90}$  ( $\pm 20\%$ ) after 7 days of ambient storage and has a particle size ( $D_{90}$ ) of  $<20\mu\text{m}$ , but more preferably  $<10\mu\text{m}$  after 7 days of ambient storage.

Provided herein is also a likely basis for the agglomeration of taurine which permits conditioned taurine to be produced by spray drying and other methods, the basis referred to herein as the zwitterionic neutralisation theory.

**Definitions**

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It will be understood that particular embodiments described herein are shown by way of illustration and not as limitations of the invention. The principal features of this invention can be employed in various embodiments without departing from the scope of the invention. Those skilled in the art will recognise, or be able to ascertain using no more than routine study, numerous equivalents to the specific procedures described herein. Such equivalents are considered to be within the scope of this invention and are covered by the claims.

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195

The term "Taurine" is intended to encompass salt forms or counterion formulations of taurine as well as isolated stereoisomers (e.g. D-Taurine or L-Taurine) and mixtures of stereoisomers. Derivatives and intermediates of taurine (e.g. hypotaurine) are also encompassed.

The term "Raw Taurine" refers to commercially available pure taurine.

200

The term "Processed Taurine" refers to taurine that has been spray-dried using spray drying conditions with resulting taurine particles tending to agglomerate (i.e. demonstrate a net change in the  $D_{90}$  (> 20%) after 7 days of ambient storage) and have a particle size ( $D_{90}$ ) of >20 $\mu\text{m}$  after 7 days of ambient storage.

205

The term "Conditioned Taurine" refers to taurine that has been prepared to obtain taurine particles that demonstrate very low levels of agglomeration (i.e. demonstrate no significant net change in the  $D_{90}$  ( $\pm$  20%) after 7 days of ambient storage) and remain as aerosolisable primary particles e.g. where particles have a particle size ( $D_{90}$ ) of <20 $\mu\text{m}$ , but more preferably <10 $\mu\text{m}$  after 7 days of ambient storage.

210

The term "Leucine" is intended to encompass salt forms or counterion formulations of leucine as well as isolated stereoisomers (e.g. D-Leucine or L-Leucine) and mixtures of stereoisomers. Derivatives and intermediates of leucine are also encompassed.

215

The term "Agglomerate" or "Agglomeration" refers to the process whereby particles cohere to one another to create particle clusters, which demonstrate larger particle dimensions.

The term "Aerosolised" or "Aerosolisable" refers to particles, which when dispensed from a dry powder inhalation device, will remain suspended in the inhaler's gas stream for an

220 amount of time suitable for at least a portion of the particles to be inhaled by the patient, thereby reaching the patients lungs.

The term "Process Parameters" refers specifically to spray drying parameters such as: drying gas flow rate; atomisation gas flow rate; feedstock pumping rate; outlet temperature;  
225 feedstock temperature; feedstock concentration and feedstock pH and buffer/acid type.

The term " $D_{10}$ " refers to the size in microns below which 10% of the particles reside on a volume basis.

230 The term " $D_{50}$ " refers to the size in microns above or below which 50% of the particles reside on a volume basis.

The term " $D_{90}$ " refers to the size in microns below which 90% of the particles reside on a volume basis.  
235

The term "Inhalation" or "Inhalable" refers to particles that are suitable for pulmonary administration. Such particles typically have a mean aerodynamic particle size of less than  $10\mu\text{m}$ , more preferably less than  $5\mu\text{m}$  and most preferably less than  $3.5\mu\text{m}$ .

240 The term "Process A" refers to a preferred spray drying process for producing optimal trehalose particles suitable for inhalation using in one embodiment the Niro spray dryer.

The term "Process B" refers to a preferred spray drying process for producing optimal taurine particles, namely conditioned taurine particles suitable for inhalation using in one  
245 embodiment the Niro spray dryer.

The term "Ambient Conditions" refers to material sealed and stored at room temperature at about  $20^{\circ}\text{C} \pm 2.0^{\circ}\text{C}$  in the laboratory.

250 The term "Medicament" refers to pharmaceutical active agents or bioactive material. Medicament may also refer to combinations of pharmaceutical agents, combinations of bioactive material or combinations of pharmaceutical agent and bioactive material.

The term "Container" refers to either a bulk storage container, such as a multi-dose reservoir  
255 for a dry powder inhaler, or unit dose containers such as a capsule or a blister. The capsule may be formed from various materials e.g. gelatine, cellulose derivatives such as



hydroxypropyl methylcellulose (HPMC) or hydroxypropylcellulose (HPC), starch, starch derivatives, chitosan or synthetic plastics, while the blister may be provided in the form of a blister pack or blister strip.

260

The term "Passive Device" refers to a dry powder inhaler device in which a patient's breathe is the only source of gas which provides the motive force in the device.

265

The term "Active Device" refers to a dry powder inhaler device in which a source of compressed gas or an alternative energy source is used to provide the motive force in the device.

270

The term "Glass Transition Temperature", which is represented by the symbol  $T_g$ , refers to the temperature at which a composition changes from a glassy or vitreous state to a syrup or rubbery state.  $T_g$  is generally determined using differential scanning calorimetry (DSC).

The term " $T_{(solid:gas)}$  ratio" refers to the mass of taurine per volume of drying gas per unit time in the spray dryer.

275

### **General Statements**

280

As used in this specification and the claim(s), the use of the word "a" or "an" when used in conjunction with the term "comprising" in the claim(s) and/or the specification may mean "one", but it is also consistent with the meaning of "one or more", "at least one", and "one or more than one". The use of the term "or" in the claim(s) is used to mean "and/or" unless explicitly indicated to refer to alternatives only or the alternatives are mutually exclusive, although the disclosure supports a definition that refers to only alternatives and "and/or".

285

As used in this specification and claim(s), the words "comprising" (and any form of comprising, such as "comprise" and "comprises"), "having" (and any form of having, such as "have" and "has"), "including" (and any form of including, such as "includes" and "include") or "containing" (and any form of containing, such as "contains" and "contain") are inclusive or open-ended and do not exclude additional, unrecited elements or method steps.

290

The term "any combinations thereof" as used herein refers to all permutations and mixtures of the listed items preceding the term. For example, "A, B, C, or any combinations thereof" is intended to include at least one of: A, B, C, AB, AC, BC, or ABC, and if order is important in a particular context, also BA, CA, CB, CBA, BCA, ACB, BAC, or CAB. Continuing with this example, expressly included are mixtures that contain repeats of one or more items or terms, such as BB, AAA, BBC, AAABCCCC, CBBAAA, CABABB, and so forth. The skilled

295 artisan will understand that typically there 525 is no limit on the number of items or terms in any mixture, unless otherwise apparent from the context.

All publications and patent applications mentioned in the specification are indicative of the level of skill of those skilled in the art to which this invention pertains. All publications and  
300 patent applications are herein incorporated by reference to the same extent as if each individual publication or patent application was specifically and individually indicated to be incorporated by reference.

### Detailed Description

305

#### **Process**

The invention relates to, inter alia, a method for preparing taurine, the method comprising a conditioning step, wherein taurine is produced in the form of particles that:

- 310 (a) demonstrate no significant net change in the  $D_{90}(\pm 20\%)$  after 7 days of ambient storage; and  
(b) have a particle size ( $D_{90}$ ) of  $<20\mu m$ , but more preferably  $<10\mu m$  after 7 days of ambient storage,  
optionally and preferably in which a method zwitterionic neutralisation is facilitated during  
315 drying of the taurine.

As taurine is a zwitterionic compound, it is believed that the sulphur-hydyl group of the taurine becomes ionised (oxidation) with the proton being added to the amine group (reduction), in the feedstock of a spray drying approach, and retains a charge even after  
320 drying. This leads to the material relaxing on storage which is believed to be the charged groups neutralising resulting in a conformational structural change. This conformational change causes agglomeration of the particles in the dry state, leading to a significant reduction in the aerosol performance. It is believed the neutralisation has a vitrification intermediate phase, which is the cause of the agglomeration.

325

In one aspect facilitation of zwitterionic neutralisation is the prevention or minimising of ionic interaction between the sulphur-hydyl group of the taurine and the amine group, such as the use of conditions that minimise or prevent reduction of the amine group and/or oxidation of the sulphur-hydyl group.

330

Further, we have demonstrated in the examples herein that predictive models can be generated that allow modulation of the spray drying parameters consistent with this theory to allow conditioned taurine as defined herein to be produced.

335 Parameters that affect the zwitterionic neutralisation process include:

- Drying Gas flow rate
- Atomisation gas flow rate
- Feedstock pumping rate
- 340 • Outlet temperature
- Feedstock temperature
- Feedstock concentration
- Feedstock pH and buffer/acid type

Thus in one aspect of the invention any one or more of the above parameters may be varied  
 345 to allow conditioned taurine to be produced, and the invention relates to a method for spray drying taurine, wherein one or more or all of these properties are controlled to produce conditioned taurine, optionally wherein a model using one or more or all parameters is used to predict appropriate parameters for the production of conditioned taurine.

350 In in one embodiment of the invention the taurine is spray dried.

In in one embodiment of the invention the pH of the feedstock to be spray dried is acidic e.g. less than pH 5 in one embodiment equal to or less than pH 4, such as about pH 4.

355 In a further aspect of the invention the feedstock concentration is between 0.1 % and 10%, in one embodiment between 1% and 5%.

In another aspect of the invention the feedstock temperature is between 0.1 °C and 100°C, in one embodiment between 20°C and 70°C.

360

In still a further aspect of the invention the outlet temperature is between 50°C and 120°C, in one embodiment between 60°C and 100°C.

In another aspect of the invention the  $T_{(SO_2:gas)}$  ratio is between  $2.000 \times 10^{-6}$  and  $2.750 \times 10^{-3}$ .

365

The production of conditioned taurine can be confirmed by:

(a) no significant net change in the  $D_{90}$  ( $\pm 20\%$ ) after 7 days of ambient storage; and

(b) a particle size ( $D_{90}$ ) of  $<20\mu\text{m}$ , but more preferably  $<10\mu\text{m}$  after 7 days of ambient storage following the drying process.

370

In a further aspect of the invention raw commercially available taurine may be comminuted to reduce particle size before any processing to produce conditioned taurine as described herein. Particle size reduction is preferably to form a particle of size less than  $20\mu\text{m}$  in diameter, in one embodiment less than  $10\mu\text{m}$  in diameter.

375

Comminution can be achieved through various processes in isolation, for example media milling or jet milling (micronisation).

380

Conditioning is the process of allowing charge neutralisation induced, for example following the comminution step.

385

For the avoidance of doubt the conditioning of taurine may be carried out by spray drying but other techniques may also be used to produce conditioned taurine, such as fluid bed conditioning. Fluid bed conditioning is considered a one-step conditioning process but would additionally require a separate comminution step and so a preferred method to achieve both the conditioned step and the comminution step simultaneously, repeatably and more economically is to use spray drying.

390

The method of preparing conditioned taurine may therefore involve a multi-step process, or in one embodiment a two-step process or in one further embodiment a one-step process such as spray drying.

395

Spray drying solubilises the taurine raw material and produces smaller particles through atomisation, which in this sense, due to the size reduction, is considered as comminuted.

400

In a further aspect of the present invention, the conditioned taurine is made by a spray drying method comprising: providing a feedstock comprising raw taurine in an aqueous solution or suspension, and spray drying the feedstock under conditions to create particles that demonstrate no significant net change in the  $D_{90}$  ( $\pm 20\%$ ) after 7 days of ambient storage; and have a particle size ( $D_{90}$ ) of  $<20\mu\text{m}$ , but more preferably  $<10\mu\text{m}$  after 7 days of ambient storage.

**Product**

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The invention relates to conditioned taurine obtained or obtainable using the method of the invention, and to compositions comprising such taurine per se.

410

For example, the invention relates to a composition comprising conditioned taurine, such as a dry powder composition suitable for inhalation.

In in one embodiment the conditioned taurine is substantially in crystalline form, with at least 95% of the taurine or more having a crystalline form

415

In in one embodiment of the invention, the conditioned taurine is present in an amount less than 99.9% by weight based on the dry weight of the composition e.g. less than 98.5%, less than 90%, less than 80%, less than 70%, less than 60%, less than 50%, less than 40%, less than 30%, less than 20%, less than 10%, less than 5%, less than 2.5% by weight based on the dry weight of the composition.

420

In a further embodiment of the invention, taurine has a moisture content of less than 2% by weight, optionally less than 1% by weight, optionally less than 0.5% by weight of conditioned taurine.

425

***Compositions and other elements***

In another embodiment of the present invention, the conditioned taurine is both suitable for use as, and for use as an excipient, carrier or diluent in a pharmaceutical composition.

430

The taurine of the invention may be prepared in combination with other components, such as drugs or excipients, for example in a co-spray dried process.

435

In in one embodiment the taurine may be dried, e.g. co-spray dried with leucine in an aqueous solution or suspension, wherein the aqueous solution or suspension is spray dried under conditions to produce a composition comprising conditioned taurine and leucine suitable for inhalation.

440

In in one embodiment the spray-dried composition comprising leucine will comprise leucine present in an amount less than 10% by weight based on the dry weight of the composition e.g. less than 9%, less than 8%, less than 7%, less than 6%, less than 5%, in one

embodiment less than 4%, in one embodiment less than 3%, in one embodiment less than 2% by weight based on the dry weight of the composition.

In a further in one embodiment of the present invention, a composition comprising taurine may also comprise an additive material such as a so-called force control agent. A force control agent is an agent which reduces the cohesion between fine particles within the powder composition. Suitable force control agents include amino acids, metal stearates such as magnesium stearate, phospholipids, lecithin, colloidal silicon dioxide and sodium stearyl fumarate. In one embodiment the force control agent is magnesium stearate.

Amino acids which are suitable for use in the present invention include alanine, leucine, isoleucine, lysine, valine, methionine or phenylalanine. In one embodiment the amino acid is leucine. The inclusion of these amino acids improves the aerosol performance of the composition.

In yet a further embodiment of the present invention, the amino acid, in one embodiment leucine, is present in an amount less than 10% by weight based on the dry weight of the composition e.g. less than 9%, less than 8%, less than 7%, less than 6%, less than 5%, in one embodiment less than 4%, in one embodiment less than 3%, in one embodiment less than 2% by weight based on the dry weight of the composition.

In still a further embodiment of the present invention, the amino acid is predominately present on the surface of the conditioned taurine. Without wishing to be bound by theory this may result from the amino acid's hydrophobic and surface active properties.

### **Actives**

In yet a further aspect of the present invention, the composition further comprises a medicament or a combination of medicaments selected from the following:

**1) Adrenergic agonists** such as, for example, amphetamine, apraclonidine, bitolterol, clonidine, colterol, dobutamine, dopamine, ephedrine, epinephrine, ethylnorepinephrine, fenoterol, formoterol, guanabenz, guanfacine, hydroxyamphetamine, isoetharine, isoproterenol, isotharine, mephenterine, metaraminol, methamphetamine, methoxamine, methpentermine, methyl dopa, methylphenidate, metaproterenol, metaraminol, mitodrine, naphazoline, norepinephrine, oxymetazoline, pemoline, phenylephrine, phenylethylamine, phenylpropanolamine, pirbuterol, prenalterol, procaterol, propylhexedrine, pseudoephedrine,

ritodrine, salbutamol, salmeterol, terbutaline, tetrahydrozoline, tramazoline, tyramine and xylometazoline.

480 2) **Adrenergic antagonists** such as, for example, acebutolol, alfuzosin, atenolol, betaxolol, bisoprolol, bopindolol, bucindolol, bunazosin, butyrophenones, carteolol, carvedilol, celiprolol, chlorpromazine, doxazosin, ergot alkaloids, esmolol, haloperidol, indoramin, ketanserin, labetalol, levobunolol, medroxalol, metipranolol, metoprolol, nebivolol, nadolol, naftopidil, oxprenolol, penbutolol, phenothiazines, phenoxybenzamine, phentolamine, 485 pindolol, prazosin, propafenone, propranolol, sotalol, tamsulosin, terazosin, timolol, tolazoline, trimazosin, urapidil and yohimbine.

3) **Adrenergic neurone blockers** such as, for example, bethanidine, debrisoquine, guabenzan, guanadrel, guanazodine, guanethidine, guanoclor and guanozan.

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4) **Drugs for treatment of addiction**, such as, for example, buprenorphine.

5) **Drugs for treatment of alcoholism**, such as, for example, disulfiram, naloxone and naltrexone.

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6) **Drugs for Alzheimer's disease management**, including acetylcholinesterase inhibitors such as, for example, donepezil, galantamine, rivastigmine and tacrin.

7) **Anaesthetics** such as, for example amethocaine, benzocaine, bupivacaine,

500 hydrocortisone, ketamine, lignocaine, methylprednisolone, prilocaine, proxymetacaine, ropivacaine and tyrothricin.

8) **Angiotensin converting enzyme inhibitors** such as, for example, captopril, cilazapril, enalapril, fosinopril, imidapril hydrochloride, lisinopril, moexipril hydrochloride, perindopril, 505 quinapril, ramipril andtrandolapril.

9) **Angiotensin receptor blockers**, such as, for example, candesartan, cilxetil, eprosartan, irbesartan, losartan, medoxomil, olmesartan, telmisartan and valsartan.

10) **Antiarrhythmics** such as, for example, adenosine, amidodarone, disopyramide, flecainide 510 acetate, lidocaine hydrochloride, mexiletine, procainamide, propafenone and quinidine.

11) **Antibiotic and antibacterial agents** (including the beta-lactams, fluoroquinolones, ketolides, macrolides, sulphonamides and tetracyclines) such as, for example, aclarubicin,

amoxicillin, amphotericin, azithromycin, aztreonam, chlorhexidine, clarithromycin,  
 515 clindamycin, colistimethate, dactinomycin, dirithromycin, doripenem, erythromycin,  
 fusafungine, gentamycin, metronidazole, mupirocin, natamycin, neomycin, nystatin,  
 oleandomycin, pentamidine, pimaricin, probenecid, roxithromycin, sulphadiazine and  
 triclosan.

520 **12) Anti-clotting agents** such as, for example, abciximab, acenocoumarol, alteplase,  
 aspirin, bemparin, bivalirudin, certoparin, clopidogrel, dalteparin, danaparoid, dipyridamole,  
 enoxaparin, epoprostenol, eptifibatide, fondaparin, heparin (including low molecular weight  
 heparin), heparin calcium, lepirudin, phenindione, reteplase, streptokinase, tenecteplase,  
 tinzaparin, tirofiban and warfarin.

525 **13) Anticonvulsants** such as, for example, GABA analogs including tiagabine and  
 vigabatrin; barbiturates including pentobarbital; benzodiazepines including alprazolam,  
 chlordiazepoxide, clobazam, clonazepam, diazepam, flurazepam, lorazepam, midazolam,  
 oxazepam and zolazepam; hydantoins including phenytoin; phenyltriazines including  
 lamotrigine; and miscellaneous anticonvulsants including acetazolamide, carbamazepine,  
 530 ethosuximide, fosphenytoin, gabapentin, levetiracetam, oxcarbazepine, piracetam,  
 pregabalin, primidone, sodium valproate, topiramate, valproic acid and zonisamide.

**14) Antidepressants** such as, for example, tricyclic and tetracyclic antidepressants  
 including amineptine, amitriptyline (tricyclic and tetracyclic amitriptyline), amoxapine,  
 535 butriptyline, cianopramine, clomipramine, demexiptiline, desipramine, dibenzepin,  
 dimetacrine, dosulepin, dothiepin, doxepin, imipramine, iprindole, levoprotiline, lofepramine,  
 maprotiline, melitracen, metapramine, mianserin, mirtazapine, nortriptyline, opipramol,  
 propizepine, protriptyline, quinupramine, setiptiline, tianeptine and trimipramine; selective  
 serotonin and noradrenaline reuptake inhibitors (SNRIs) including clovoxamine, duloxetine,  
 540 milnacipran and venlafaxine; selective serotonin reuptake inhibitors (SSRIs) including  
 citalopram, escitalopram, femoxetine, fluoxetine, fluvoxamine, ifoxetine, milnacipran,  
 nomifensine, oxaprotiline, paroxetine, sertraline, sibutramine, venlafaxine, viquiline and  
 zimeldine; selective noradrenaline reuptake inhibitors (NARIS) including demexiptiline,  
 desipramine, oxaprotiline and reboxetine; noradrenaline and selective serotonin reuptake  
 545 inhibitors (NASSAs) including mirtazapine; monoamine oxidase inhibitors (MAOIs) including  
 amiflamine, brofaromine, clorgyline,  $\alpha$ -ethyltryptamine, etoperidone, iproclozide, iproniazid,  
 isocarboxazid, mebanazine, medifoxamine, moclobemide, nialamide, pargyline, phenelzine,  
 pheniprazine, pirlindole, procarbazine, rasagiline, safrazine, selegiline, toloxatone and  
 tranylcypromine; muscarinic antagonists including benactyzine and dibenzepin; azaspiro-  
 550 nes including buspirone, gepirone, ipsapirone, tandospirone and tiaspirone; and other



antidepressants including acetaphenazine, ademetionine, S-adenosylmethionine, adrafinil, amesergide, amineptine, amperozide, benactyzine, benmoxine, binedaline, bupropion, carbamazepine, caroxazone, cericlamine, cotinine, fezolamine, flupentixol, idazoxan, kitanserin, levoprotiline, lithium salts, maprotiline, medifoxamine, methylphenidate, metralindole, minaprine, nefazodone, nisooxetine, nomifensine, oxaflozane, oxitriptan, phenylhydrazine, rolipram, roxindole, sibutramine, teniloxazine, tianeptine, tofenacin, trazadone, tryptophan, viloxazine and zalospirone.

**15) Anticholinergic agents** such as, for example, atropine, benztropine, biperiden, cyclopentolate, glycopyrrolate, hyoscine, ipratropium bromide, orphenadine hydrochloride, oxitropium bromide, oxybutinin, pirenzepine, procyclidine, propantheline, propiverine, telenzepine, tiotropium, trihexyphenidyl, tropicamide and tropium.

**16) Antidiabetic agents** such as, for example, pioglitazone, rosiglitazone and troglitazone.

**17) Antidotes** such as, for example, deferoxamine, edrophonium chloride, flumazenil, nalmeferene, naloxone, and naltrexone.

**18) Anti-emetics** such as, for example, alizapride, azasetron, benzquinamide, bestahistine, bromopride, buclizine, chlorpromazine, cinnarizine, clebopride, cyclizine, dimenhydrinate, diphenhydramine, diphenidol, domperidone, dolasetron, dronabinol, droperidol, granisetron, hyoscine, lorazepam, metopimazine, metopimazine, nabilone, ondansetron, palonosetron, perphenazine, prochlorperazine, promethazine, scopolamine, triethylperazine, trifluoperazine, trifluorpromazine, trimethobenzamide and tropisetron.

**19) Antihistamines** such as, for example, acrivastine, astemizole, azatadine, azelastine, brompheniramine, carbinoxamine, cetirizine, chlorpheniramine, cinnarizine, clemastine, cyclizine, cyproheptadine, desloratadine, dexmedetomidine, diphenhydramine, doxylamine, fexofenadine, hydroxyzine, ketotifen, levocabastine, loratadine, mizolastine, promethazine, pyrilamine, terfenadine and trimetopazine.

**20) Anti-infective agents** such as, for example, antivirals (including nucleoside and non-nucleoside reverse transcriptase inhibitors and protease inhibitors) including aciclovir, adefovir, amantadine, cidofovir, efavirenz, famciclovir, foscarnet, ganciclovir, idoxuridine, indinavir, inosine pranobex, lamivudine, nelfinavir, nevirapine, oseltamivir, palivizumab, penciclovir, pleconaril, ribavirin, rimantadine, ritonavir, rupintrivir, saquinavir, stavudine, valaciclovir, zalcitabine, zanamivir, zidovudine and interferons; AIDS adjunct agents

including dapsone; aminoglycosides including tobramycin; antifungals including amphotericin, caspofungin, clotrimazole, econazole nitrate, fluconazole, itraconazole, ketoconazole, miconazole, nystatin, terbinafine and voriconazole; anti-malarial agents including quinine; antituberculosis agents including capreomycin, ciprofloxacin, ethambutol, meropenem, piperacillin, rifampicin and vancomycin; beta-lactams including cefazolin, cefmetazole, cefoperazone, cefoxitin, cephacetrile, cephalixin, cephaloglycin and cephaloridine; cephalosporins, including cephalosporin C and cephalothin; cephamycins such as cephamycin A, cephamycin, cephamycin C, cephapirin and cephradine; leprostatics such as clofazimine; penicillins including amoxicillin, ampicillin, amylpenicillin, azidocillin, benzylpenicillin, carbenicillin, carfecillin, carindacillin, clometocillin, cloxacillin, cyclacillin, dicloxacillin, diphenicillin, heptylpenicillin, hetacillin, metampicillin, methicillin, nafcillin, 2-pentenylpenicillin, penicillin N, penicillin *o*, penicillin S and penicillin V; quinolones including ciprofloxacin, clinafloxacin, difloxacin, grepafloxacin, norfloxacin, ofloxacin and temafloxacin; tetracyclines including doxycycline and oxytetracycline; miscellaneous anti-infectives including linezolid, trimethoprim and sulfamethoxazole.

**21) Anti-neoplastic agents** such as, for example, droloxifene, tainoxifen and toremifene.

**22) Antiparkinsonian drugs** such as, for example, amantadine, andropinirole, apomorphine, baclofen, benserazide, biperiden, benztropine, bromocriptine, budipine, cabergoline, carbidopa, eliprodil, entacapone, eptastigmine, ergoline, galanthamine, lazabemide, levodopa, lisuride, mazindol, memantine, mofegiline, orphenadrine, trihexyphenidyl, pergolide, piribedil, pramipexole, procyclidine, propentofylline, rasagiline, remacemide, ropinerole, selegiline, spheramine, terguride and tolcapone.

**23) Antipsychotics** such as, for example, acetophenazine, alizapride, amisulpride, amoxapine, amperozide, aripiprazole, benperidol, benzquinamide, bromperidol, buramate, butaclamol, butaperazine, carphenazine, carpipramine, chlorpromazine, chlorprothixene, clocapramine, clomacran, clopenthixol, clospirazine, clothiapine, clozapine, cyamemazine, droperidol, flupenthixol, fluphenazine, fluspirilene, haloperidol, loxapine, melperone, mesoridazine, metofenazate, molindrone, olanzapine, penfluridol, pericyazine, perphenazine, pimozide, pipamerone, piperacetazine, pipotiazine, prochlorperazine, promazine, quetiapine, remoxipride, risperidone, sertindole, spiperone, sulpiride, thioridazine, thiothixene, trifluoperidol, trifluopromazine, trifluoperazine, ziprasidone, zotepine and zuclopenthixol; phenothiazines including aliphatic compounds, piperidines and piperazines; thioxanthenes, butyrophenones and substituted benzamides.

625 **24) Antirheumatic** agents such as, for example, diclofenac, heparinoid, hydroxychloroquine and methotrexate, leflunomide and teriflunomide.

**25) Anxiolytics** such as, for example, adinazolam, alpidem, alprazolam, alseroxlon, amphenidone, azacyclonol, bromazepam, bromisovalum, buspirone, captodiamine,  
630 capuride, carbcloral, carbromal, chloral betaine, chlordiazepoxide, clobenzepam, enciprazine, flesinoxan, flurazepam, hydroxyzine, ipsapiraone, lesopitron, loprazolam, lorazepam, loxapine, mecloqualone, medetomidine, methaqualone, methprylon, metomidate, midazolam, oxazepam, propranolol, tandospirone, trazadone, Zolpidem and zopiclone.

635 **26) Appetite stimulants** such as, for example, dronabinol.

**27) Appetite suppressants** such as, for example, fenfluramine, phentermine and sibutramine; and anti-obesity treatments such as, for example, pancreatic lipase inhibitors, serotonin and norepinephrine re-uptake inhibitors, and anti-anorectic agents.

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**28) Benzodiazepines** such as, for example, alprazolam, bromazepam, brotizolam, chlordiazepoxide, clobazam, clonazepam, clorazepate, demoxepam, diazepam, estazolam, flunitrazepam, flurazepam, halazepam, ketazolam, loprazolam, lorazepam, lormetazepam, medazepam, midazolam, nitrazepam, nordazepam, oxazepam, prazepam, quazepam,  
645 temazepam and triazolam.

**29) Bisphosphonates** such as, for example, alendronate sodium, sodium clodronate, etidronate disodium, ibandronic acid, pamidronate disodium, isedronate sodium, tiludronic acid and zoledronic acid.

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**30) Blood modifiers** such as, for example, cilostazol and dipyridamol, and blood factors.

**31) Cardiovascular agents** such as, for example, acebutalol, adenosine, amiloride, amiodarone, atenolol, benazepril, bisoprolol, bumetanide, candesartan, captopril, clonidine,  
655 diltiazem, disopyramide, dofetilide, doxazosin, enalapril, esmolol, ethacrynic acid, flecanide, furosemide, gemfibrozil, ibutilide, irbesartan, labetalol, losartan, lovastatin, metolazone, metoprolol, mexiletine, nadolol, nifedipine, pindolol, prazosin, procainamide, propafenone, propranolol, quinapril, quinidine, ramipril, sotalol, spironolactone, telmisartan, tocainide, torsemide, triamterene, valsartan and verapamil.

660 **32) Calcium channel blockers** such as, for example, amlodipine, bepridil, diltiazem, felodipine, flunarizine, gallopamil, isradipine, lacidipine, lercanidipine, nicardipine, nifedipine, nimodipine and verapamil.

**33) Central nervous system stimulants** such as, for example, amphetamine, brucine, 665 caffeine, dexfenfluramine, dextroamphetamine, ephedrine, fenfluramine, mazindol, methyphenidate, modafmil, pemoline, phentermine and sibutramine.

**34) Cholesterol-lowering drugs** such as, for example, acipimox, atorvastatin, ciprofibrate, colestipol, colestyramine, bezafibrate, ezetimibe, fenofibrate, fluvastatin, gemfibrozil, 670 ispaghula, nicotinic acid, omega-3 triglycerides, pravastatin, rosuvastatin and simvastatin.

**35) Drugs for cystic fibrosis** management such as, for example, *Pseudomonas aeruginosa* infection vaccines (eg Aerugen<sup>TM</sup>), alpha 1-antitrypsin, amikacin, cefadroxil, denufosal, duramycin, glutathione, mannitol, and tobramycin.

675

**36) Diagnostic agents** such as, for example, adenosine and aminohippuric acid.

**37) Dietary supplements** such as, for example, melatonin and vitamins including vitamin E.

680 **38) Diuretics** such as, for example, amiloride, bendroflumethiazide, bumetanide, chlortalidone, cyclopenthiazide, furosemide, indapamide, metolazone, spironolactone and torasemide.

**39) Dopamine agonists** such as, for example, amantadine, apomorphine, bromocriptine, 685 cabergoline, lisuride, pergolide, pratinipexole and ropinerole.

**40) Drugs for treating erectile dysfunction**, such as, for example, apomorphine, apomorphine diacetate, moxisylyte, phentolamine, phosphodiesterase type 5 inhibitors, such as sildenafil, tadalafil, vardenafil and yohimbine.

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**41) Gastrointestinal agents** such as, for example, atropine, hyoscyamine, famotidine, lansoprazole, loperamide, omeprazole and rebeprazole.

**42) Hormones and analogues** such as, for example, cortisone, epinephrine, estradiol, 695 insulin, Ostabolin-C, parathyroid hormone and testosterone.

**43) Hormonal drugs** such as, for example, desmopressin, lanreotide, leuprolide, octreotide, pegvisomant, protirelin, salcotonin, somatropin, tetracosactide, thyroxine and vasopressin.

700 **44) Hypoglycaemics** such as, for example, sulphonylureas including glibenclamide, gliclazide, glimepiride, glipizide and gliquidone; biguanides including metformin; thiazolidinediones including pioglitazone, rosiglitazone, nateglinide, repaglinide and acarbose.

705 **45) Immunoglobulins.**

**46) Immunomodulators** such as, for example, interferon (e.g. interferon beta-1a and interferon beta-1b) and glatiramer.

710 **47) Immunosuppressives** such as, for example, azathioprine, cyclosporin, mycophenolic acid, rapamycin, sirolimus and tacrolimus.

**48) Mast cell stabilizers** such as, for example, cromoglycate, iodoxamide, nedocromil, ketotifen, tryptase inhibitors and pemirolast.

715

**49) Drugs for treatment of migraine headaches** such as, for example, almotriptan, alperopride, amitriptyline, amoxapine, atenolol, clonidine, codeine, coproxamol, cyproheptadine, dextropropoxyphene, dihydroergotamine, diltiazem, doxepin, ergotamine, eletriptan, fluoxetine, frovatriptan, isometheptene, lidocaine, lisinopril, lisuride, loxapine, 720 methysergide, metoclopramide, metoprolol, nadolol, naratriptan, nortriptyline, oxycodone, paroxetine, pizotifen, pizotyline, prochlorperazine, propranolol, propoxyphene, protriptyline, rizatriptan, sertraline, sumatriptan, timolol, tolfenamic acid, tramadol, verapamil, zolmitriptan, and nonsteroidal anti-inflammatory drugs.

725 **50) Drugs for treatment of motion sickness** such as, for example, diphenhydramine, promethazine and scopolamine.

**51) Mucolytic agents** such as N-acetylcysteine, ambroxol, amiloride, dextrans, heparin, desulphated heparin, low molecular weight heparin and recombinant human DNase.

730

**52) Drugs for multiple sclerosis management** such as, for example, bencyclane, methylprednisolone, mitoxantrone and prednisolone.

**53) Muscle relaxants** such as, for example, baclofen, chlorzoxazone, cyclobenzaprine, methocarbamol, orphenadrine, quinine and tizanidine.

**54) NMDA receptor antagonists** such as, for example, memantine.

**55) Nonsteroidal anti-inflammatory agents** such as, for example, aceclofenac, acetaminophen, alminoprofen, amfenac, amin~prop~loam, ixetrine, aspirin, benoxaprofen, bromfenac, bufexamac, carprofen, celecoxib, choline, cinchophen, cinmetacin, clometacin, clopiac, diclofenac, diclofenac sodium, diflunisal, etheizamide, etodolac, etoricoxib, fenoprofen, flurbiprofen, ibuprofen, indomethacin, indoprofen, ketoprofen, ketorolac, loxoprofen, mazipredone, meclofenamate, mefenamic acid, meloxicam, nabumetone, naproxen, nimesulide, parecoxib, phenylbutazone, piroxicam, piroprofen, rofecoxib, salicylate, sulindac, tiaprofenic acid, tolafenamate, tolmetin and valdecoxib.

**56) Nucleic-acid medicines** such as, for example, oligonucleotides, decoy nucleotides, antisense nucleotides and other gene-based medicine molecules.

**57) Opiates and opioids** such as, for example, alfentanil, allylprodine, alphaprodine, anileridine, benzylmorphine, bezitramide; buprenorphine, butorphanol, carbiphen, cipramadol, clonitazene, codeine, codeine phosphate, dextromoramide, dextropropoxyphene, diamorphine, dihydrocodeine, dihydromorphine, diphenoxylate, dipipanone, fentanyl, hydromorphone, L-alpha acetyl methadol, levorphanol, lofentanil, loperamide, meperidine, meptazinol, methadone, metopon, morphine, nalbuphine, nalorphine, oxycodone, papaveretum, pentazocine, pethidine, phenazocine, pholcodeine, remifentanil, sufentanil, tramadol, and combinations thereof with an anti-emetic.

**58) Ophthalmic** preparations such as, for example, betaxolol and ketotifen.

**59) Osteoporosis preparations** such as, for example, alendronate, estradiol, estropitate, raloxifene and risedronate.

**60) Other analgesics** such as, for example, apazone, benzpiperylon, benzydamine, caffeine, cannabinoids, clonixin, ethoheptazine, flupirtine, nefopam, orphenadrine, pentazocine, propacetamol and propoxyphene.

**61) Other anti-inflammatory agents** such as, for example, B-cell inhibitors, p38 MAP kinase inhibitors and TNF inhibitors.

**62) Phosphodiesterase inhibitors** such as, for example, non-specific phosphodiesterase inhibitors including theophylline, theobromine, IBMX, pentoxifylline and papaverine; phosphodiesterase type 3 inhibitors including bipyridines such as milrinone, amrinone and olprinone; imidazolones such as piroximone and enoximone; imidazolines such as imazodan and 5-methyl-imazodan; imidazo-quinoxalines; and dihydropyridazinones such as indolidan and LY 181 512 (5-(6-oxo-1,4,5,6-tetrahydro-pyridazin-3-yl)-1,3-dihydro-indo-2-one); dihydroquinolinone compounds such as cilostamide, cilostazol, and vesnarinone; motapizone; phosphodiesterase type 4 inhibitors such as cilomilast, etazolate, rolipram, oglemilast, roflumilast, ONO 6126, tolafentrine and zardaverine, and including quinazolinones such as nitraquazone and nitraquazone analogs; xanthine derivatives such as denbufylline and arofylline; tetrahydropyrimidones such as atizoram; and oxime carbamates such as filaminast; and phosphodiesterase type 5 inhibitors including sildenafil, zaprinast, vardenafil, tadalafil, dipyridamole, and the compounds described in WO 01/19802, particularly (S)-2-(2-hydroxymethyl-1-pyrrolidinyl)-4-(3-chloro-4-methoxybenzylamino)-5-[N-(2-pyrimidinyl methyl)carbamoyl] pyrimidine, 2-(5,6,7,8-tetrahydro-1,7-naphthyridin-7-yl)-4-(3-chloro-4-methoxybenzylamino)-5-[N-(2-morpholinoethyl)carbamoyl]-pyrimidine, and (S)-2-(2-hydroxymethyl-1-pyrrolidinyl)-4-(3-chloro-4-methoxybenzylamino)-5-[N-(1,3,5-trimethyl-4-pyrazolyl)carbamoyl]-pyrimidine).

**63) Potassium channel modulators** such as, for example, cromakalim, diazoxide, glibenclamide, levcromakalim, minoxidil, nicorandil and pinacidil.

**64) Prostaglandins** such as, for example, alprostadil, dinoprostone, epoprostanol and misoprostol.

**65) Respiratory agents and agents for the treatment of respiratory diseases** including bronchodilators such as, for example, the  $\beta_2$ -agonists bambuterol, bitolterol, broxaterol, carmoterol, clenbuterol, fenoterol, formoterol, vilanterol, indacaterol, levalbuterol, metaproterenol, orciprenaline, picumeterol, pirbuterol, procaterol, reproterol, rimiterol, salbutamol, salmeterol, terbutaline and the like; inducible nitric oxide synthase (iNOS) inhibitors; the antimuscarinics ipratropium, ipratropium bromide, oxitropium, tiotropium, glycopyrrolate and the like; the xanthines aminophylline, theophylline and the like; adenosine receptor antagonists, cytokines such as, for example, interleukins and interferons; cytokine antagonists and chemokine antagonists including cytokine synthesis inhibitors, endothelin receptor antagonists, elastase inhibitors, integrin inhibitors, leukotriene receptor antagonists, prostacyclin analogues, and ablukast, ephedrine, epinephrine, fenleuton, iloprost, iralukast,

isoetharine, isoproterenol, montelukast, ontazolast, pranlukast, pseudoephedrine, sibenadet, tepoxalin, verlukast, zafirlukast and zileuton.

810

**66) Sedatives and hypnotics** such as, for example, alprazolam, butalbital, chlordiazepoxide, diazepam, estazolam, flunitrazepam, flurazepam, lorazepam, midazolam, temazepam, triazolam, zaleplon, Zolpidem, and zopiclone.

815

**67) Serotonin agonists** such as, for example, 1-(4-bromo-2,5-dimethoxyphenyl)-2-aminopropane, buspirone, m-chlorophenylpiperazine, cisapride, ergot alkaloids, gepirone, 8-hydroxy-(2-N,N-dipropylamino)-tetraline, iprasterone, lysergic acid diethylamide, 2-methyl serotonin, mezacopride, sumatriptan, tiaproterone, trazodone and zacopride.

820

**68) Serotonin antagonists** such as, for example, amitriptyline, azatadine, chlorpromazine, clozapine, cyproheptadine, dexfenfluramine, R(+)-α-(2,3-dimethoxyphenyl)-1-[2-(4-fluorophenyl)ethyl]-4-piperidine-methanol, laseteron, fenclonine, fenfluramine, granisetron, ketanserine, methysergide, metoclopramide, mianserine, ondansetron, risperidone, ritanserine, trimethobenzamide and tropisetron.

825

**69) Steroid drugs** such as, for example, alcometasone, beclomethasone, beclomethasone dipropionate, betamethasone, budesonide, butixocort, ciclesonide, clobetasol, deflazacort, diflucortolone, desoxymethasone, dexamethasone, fludrocortisone, flunisolide, fluocinolone, fluometholone, fluticasone, fluticasone propionate, hydrocortisone, methylprednisolone, mometasone, nandrolone decanoate, neomycin sulphate, prednisolone, rimesolone, rofleponide, triamcinolone and triamcinolone acetonide.

830

**70) Sympathomimetic** drugs such as, for example, adrenaline, dexamfetamine, dipiridine, dobutamine, dopamine, dopexamine, isoprenaline, noradrenaline, phenylephrine, pseudoephedrine, tramazoline and xylometazoline.

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**71) Nitrates** such as, for example, glyceryl trinitrate, isosorbide dinitrate and isosorbide mononitrate.

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**72) Skin and mucous membrane agents** such as, for example, bergapten, isotretinoin and methoxsalen.

**73) Smoking cessation aids** such as, for example, bupropion, nicotine and varenicline.



845 **74) Drugs for treatment of Tourette's syndrome** such as, for example, pimozide.

**75) Drugs for treatment of urinary tract infections** such as, for example, darifenicin, oxybutynin, propantheline bromide and tolteridine.

850 **76) Vaccines.**

**77) Drugs for treating vertigo** such as, for example, betahistine and meclizine.

**78) Therapeutic proteins and peptides** such as acylated insulin, glucagon, glucagon-like peptides, exendins, insulin, insulin analogues, insulin aspart, insulin detemir, insulin glargine, insulin glulisine, insulin lispro, insulin zinc, isophane insulins, neutral, regular and insoluble insulins, protamine zinc insulin, antibodies and antibody fragments.

**79) Anticancer agents** such as, for example, anthracydines, doxorubicin, idarubicin, epirubicin, methotrexate, taxanes, paclitaxel, docetaxel, cisplatin, vinca alkaloids, vincristine and 5-fluorouracil.

**80) Pharmaceutically acceptable salts or derivatives** of any of the foregoing.

865 It should be noted that medicaments listed above under a particular indication or class may also find utility in other indications. A plurality of medicaments can be employed in the practice of the present invention. A drug delivery system according to the invention may also be used to deliver combinations of two or more different medicaments.

870 In one embodiment of the invention the medicament or combination of medicaments are suitable for the treatment of a respiratory disorder. In one embodiment the respiratory disorder is asthma or COPD.

In one embodiment the pharmaceutically active material is selected from a long-acting muscarinic antagonist and/or long-acting beta-adrenoceptor agonist and/or an inhaled corticosteroid.

In one embodiment the medicament is selected from budesonide, formoterol fumarate dihydrate, tiotropium, fluticasone propionate, salmeterol xinafoate, vilanterol trifenate, umeclidinium bromide, glycopyrronium bromide or indacaterol maleate.

In one embodiment the pharmaceutically active material is glycopyrronium bromide. In one embodiment the pharmaceutically active material is a combination of glycopyrronium bromide and indacaterol maleate.

885

In one embodiment the medicament is selected from budesonide and formoterol fumarate dehydrate. In one embodiment the medicament is selected from fluticasone propionate and salmeterol xinafoate. In one embodiment the medicament is selected from fluticasone propionate and vilanterol trifenate. In one embodiment the medicament is selected from umeclidinium bromide and vilanterol trifenate.

890

### ***Containers and inhalation devices***

895 It is another aim of the present invention to provide a container comprising conditioned taurine or a composition comprising conditioned taurine. Containers which are suitable for use in the present invention include either a bulk storage container, such as a multi-dose reservoir for a dry powder inhaler, or unit dose containers such as a capsule or a blister. The capsule may be formed from various materials e.g. gelatine, cellulose derivatives such as 900 hydroxypropyl methylcellulose (HPMC) or hydroxypropylcellulose (HPC), starch, starch derivatives, chitosan or synthetic plastics, while the blister may be provided in the form of a blister pack or blister strip.

Containers which are also considered suitable for use in the present invention include pMDI 905 canisters.

### ***Administration***

In a further aspect of the present invention, the conditioned taurine or a composition 910 comprising conditioned taurine, suitable for inhalation, are preferably administered via a dry powder inhaler (DPI). In a dry powder inhaler, the dose to be administered is stored in the form of a non-pressurized dry powder and, on actuation of the inhaler the particles of the powder are expelled from the device in the form of a cloud of finely dispersed particles that may be inhaled by the patient.

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Dry powder inhalers can be "passive" devices in which the patient's breath is the only source of gas which provides a motive force in the device. Examples of "passive" dry powder inhaler devices include the Rotahaler™ and Discus/Diskhaler™, the Monohaler™, the GyroHaler™

Turbuhaler™ and Novolizer™. Alternatively, "active" devices may be used, in which a source of compressed gas or alternative energy source is used. Examples of suitable active devices include Aspirair™ and the active inhaler device produced by Nektar Therapeutics (as covered by US Patent No. 6,257,233).

It is generally considered that different compositions perform differently when dispensed using passive and active type inhalers. Passive devices create less turbulence within the device and the powder particles are moving more slowly when they leave the device. This leads to some of the metered dose remaining in the device and, depending on the nature of the composition, less de-agglomeration upon actuation. However, when the slow moving cloud is inhaled, less deposition in the throat is often observed. In contrast, active devices create more turbulence when they are activated. This results in more of the metered dose being extracted from the blister or capsule and better de-agglomeration as the powder is subjected to greater shear forces. However, the particles leave the device moving faster than with passive devices and this can lead to an increase in throat deposition.

Particular "passive" dry powder inhalers that may be mentioned herein are "passive" dry powder inhalation devices that are described in WO 2010/086285. Particularly, "active" dry powder inhalers that may be mentioned herein are referred to as Aspirair® inhalers and are described in more detail in WO 2001/00262, WO 2002/07805, WO 2002/89880 and WO 2002/89881. It should be appreciated, however, that conditioned taurine or a composition comprising conditioned taurine of the present invention can be administered with either passive or active inhaler devices.

In another aspect of the present invention, the conditioned taurine or a composition comprising conditioned taurine, suitable for inhalation, are preferably administered via a spray or aerosol device, such as a pressurised metered dose inhaler (pMDI). The composition (whether in solution or suspension) may be for pulmonary, nasal, buccal or topical administration, but preferably for pulmonary inhalation.

The pMDI is dependent upon the propulsive force of a propellant system used in its manufacture to dispense the composition from the device in a form that may be inhaled by a patient. The propellant generally comprises a mixture of liquefied hydrofluorocarbons (HFAs) which are selected to provide the desired vapour pressure and stability of the formulation. Propellants HFA 227 (1,1,1,2,3,3,3-heptafluoropropane) and HFA 134a (1,1,1,2-tetrafluoroethane) or mixtures thereof are currently the most widely used propellants in aerosol formulations for inhalation administration.

Additional embodiments of the invention include the following:

Conditioned taurine suitable for inhalation.

960

Conditioned taurine which is crystalline.

Conditioned taurine as an inhalation excipient.

965 A pharmaceutical composition comprising conditioned taurine.

A pharmaceutical composition comprising conditioned taurine further comprising an amino acid. The amino acid may be selected from the group consisting of alanine, leucine, isoleucine, lysine, valine, methionine or phenylalanine, in one embodiment leucine. The leucine may be present in an amount less than 10%, less than 9%, less than 8%, less than 7%, less than 6%, less than 5%, less than 4%, less than 3%, less than 2%, less than 1% by weight based on the dry weight of the composition.

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A pharmaceutical composition comprising conditioned taurine further comprising a medicament or combinations of medicaments.

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A pharmaceutical composition of the invention wherein the taurine and at least one other component are co-spray-dried using the spray drying conditions effective to produce conditioned taurine.

980

A pharmaceutical composition of the invention suitable for inhalation.

A pharmaceutical composition of the invention wherein the conditioned taurine acts as an excipient, carrier or diluent.

985

A pharmaceutical composition of the invention where the amino acid is located on the surface of the conditioned taurine.

Conditioned taurine made by a spray-drying method comprising:

990

- (a) providing a feedstock comprising raw taurine in an aqueous solution or suspension;
- and

(b) spray-drying the feedstock under conditions to create particles that demonstrate no significant net change in the  $D_{90}$  ( $\pm 20\%$ ) after 7 days of ambient storage and have a particle size ( $D_{90}$ ) of  $<20\mu\text{m}$ , but more preferably  $<10\mu\text{m}$  after 7 days of ambient storage.

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A further embodiment of the invention is a method for preparing conditioned taurine comprising:

(a) providing a feedstock comprising raw taurine in an aqueous solution or suspension; and

1000

(b) spray-drying the feedstock under conditions to create particles that demonstrate no significant net change in the  $D_{90}$  ( $\pm 20\%$ ) after 7 days of ambient storage and have a particle size ( $D_{90}$ ) of  $<20\mu\text{m}$ , but more preferably  $<10\mu\text{m}$  after 7 days of ambient storage.

A further embodiment is a method of the invention wherein the pH of the feedstock is between pH 1 and pH 7, in one embodiment between pH 3 and pH 5.

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A further embodiment is a method of the invention wherein the pH of the feedstock is acidic e.g. less than pH 5, in one embodiment equal to or less than pH4, such as about pH4.

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A further embodiment is a method of the invention wherein the feedstock concentration of taurine is between 0.1% and 10%, in one embodiment between 1% and 5%.

A further embodiment is a method of the invention wherein the feedstock concentration of taurine is less than 5%, such as less than 4%, such as less than 3%, such as less than 2%, such as about 1%.

1015

A further embodiment is a method of the invention wherein the feedstock temperature is between  $0.1^{\circ}\text{C}$  and  $100^{\circ}\text{C}$ , in one embodiment between  $20^{\circ}\text{C}$  and  $70^{\circ}\text{C}$ .

1020

A further embodiment is a method of the invention wherein the feedstock temperature is less than  $70^{\circ}\text{C}$ , such as less than  $60^{\circ}\text{C}$ , such as less than  $50^{\circ}\text{C}$ , such as less than  $40^{\circ}\text{C}$  such as less than  $30^{\circ}\text{C}$ .

A further embodiment is a method of the invention wherein the outlet temperature of the spray drying apparatus is between  $50^{\circ}\text{C}$  and  $120^{\circ}\text{C}$ , in one embodiment between  $60^{\circ}\text{C}$  and  $100^{\circ}\text{C}$ .

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A further embodiment is a method of the invention wherein the outlet temperature is less than 100°C, in one embodiment less than 90°C, in one embodiment less than 80°C, still in  
1030 one embodiment less than 70°C, such as about 60°C.

A further embodiment is a method of the invention wherein the  $T_{(solid, gas)}$  ratio is between  $2.00 \times 10^{-6}$  and  $2.75 \times 10^{-3}$ .

1035 A further embodiment is a method of the invention for preparing conditioned taurine wherein the conditioned taurine particles have a particle size ( $D_{90}$ ) that remain below 20µm after 7 days of ambient storage post spray drying.

A further embodiment is a method of the invention used to make a composition comprising  
1040 taurine which further comprises an amino acid, e.g. selected from the group consisting of alanine, leucine, isoleucine, lysine, valine, methionine or phenylalanine, in one embodiment leucine.

A further embodiment is a method of the invention used to make a composition comprising  
1045 taurine which further comprises a medicament or combinations of medicaments.

A further embodiment is a container comprising:

- (a) conditioned taurine; or
- (b) a composition comprising conditioned taurine

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The container may be a reservoir for a dry powder inhaler, a blister or a capsule. In one embodiment the container is a blister such as a foil blister.

Conditioned taurine having a moisture content of less than 2% by weight, optionally less  
1055 than 1% by weight, optionally less than 0.5% by weight of conditioned taurine.

Optionally the composition further comprises leucine and a medicament or combinations of medicaments. The composition may be a powder.

1060

Examples

1065 The following examples are provided to illustrate the invention but should not be construed as limiting the invention.

Example 1 - Experimental Spray Drying Strategy*Zwitterionic Hypothesis:*

1070 As taurine is a zwitterionic compound, it is believed that the sulphur-hydryl group of the taurine becomes ionised (oxidation) with the proton being added to the amine group (reduction), in the feedstock and retains a charge even after drying. This leads to the material relaxing on storage which is believed to be the charged groups neutralising resulting in a conformational structural change. This conformational change causes agglomeration of

1075 the particles in the dry state, leading to a significant reduction in the aerosol performance. It is believed the neutralisation has a vitrification intermediate phase, which is the cause of the agglomeration (See FIGURE 7).

*Materials:*

1080 Raw taurine was obtained from Sigma-Aldrich Chemicals (The old brickyard, New road, Gillingham, Dorset, SP8 4XT). Sodium Hydroxide, hydrochloric acid and citric acid were obtained from Fisher Scientific (Bishop Meadow Road, Loughborough, LE1 1 5RG).

*Spray Drying Strategy:*

1085 The Taurine spray drying process was investigated by producing 24 batches with varying process and formulation parameters (factors). These were:

- Drying Gas flow rate
- Atomisation gas flow rate
- Feedstock pumping rate
- 1090 • Outlet temperature
- Feedstock temperature
- Feedstock concentration
- Feedstock pH and buffer/acid type

These process and formulation parameters (factors) examined also affect the zwitterionic neutralisation process and the hypothesis behind them are discussed below. The values for

1095 the extremes and centre points (levels) for each of the factors were determined on well documented physical design limits for spray dryers.

1100

*Drying gas flow rate Parameters and Rationale:***a) Definition of the operation Range**

The drying gas flow rates range were determined as being just high enough to maintain particles in the airstream during drying while allowing a particle to have sufficient residence time in the drying chamber to complete drying. A significant enough velocity is required to maintain curvilinear flow through the equipment and prevent premature deposition of the particles in the drying chamber of transfer conduit before collection and classification in the cyclone. If the drying gas is too high, then the velocity of the particles will be too high to have sufficient time in the drying gas for complete evaporation of all of the water from the feedstock to occur, resulting in high residual moisture (often >5.0%w/w). If particles have high residual moisture, then they are liable to agglomerate strongly through capillary forces and if partial dissolution occurs, then solid bridging will occur. For this investigation and for the VSD equipment, the lower limit is defined as 12.0 Kg.Hr<sup>-1</sup> and the upper limit defined as 15.0Kg.Hr<sup>-1</sup> and the centre point was defined as 13.5 Kg.Hr<sup>-1</sup>.

**b) Impact and Effect on the Zwitterionic Neutralisation**

The drying gas is believed to affect the neutralisation process of the taurine's sulphur-hydryl group, impacting the physical stability. A lower drying gas flow, results in a lower drying gas velocity, which in turn lowers the velocity of droplets and resultant particles. The lower velocity causes a slower rate of evaporation and results in a longer time period for charge neutralisation, giving particles more stable form, preventing the storage agglomeration that has been observed.

*Atomisation gas flow rate Parameters and Rationale:***a) Definition of the operation Range**

The atomisation gas flow rate range was chosen to reflect the lowest limit where particles of inhalation size range for a given nozzle are produced. The upper limit defined as giving dry particles and no significant decrease in the D<sub>50</sub> of the resultant particles, at a given drying gas flow rate. At higher atomisation flow rates, droplets/particles possess too high velocity and therefore low residence time in the drying chamber, resulting in particles with high residual moisture (often >5.0% w/w). If particles have high residual moisture, then they are liable to agglomeration. In extreme case, too high atomisation gas causes collisions between droplets before complete drying, leading to agglomerates being formed. For this investigation and for the VSD equipment, the lower limit is defined as 12.0 L.min<sup>-1</sup> and the upper limit defined as 18.0 L.min<sup>-1</sup>, the centre point was defined as 15.0 L.min<sup>-1</sup>.



**b) Impact and Effect on the Zwitterionic Neutralisation**

The atomisation gas flow rate has been shown to have an impact on the physical stability of spray dried taurine. One theory attributed to this mechanism is that there is a high degree of interaction of the atomising gas, with the liquid, not just to form small and uniform droplets, but to catalyse the neutralisation of the zwitterionic charges, potentially through oxidation of the sulphur-hydryl group of taurine.

Feedstock Pumping Rate Parameters and Rationale:**a) Definition of the operation Range**

The feedstock pumping rates range was chosen to reflect the lowest limit where the production rate of product was high enough to obtain sufficient material for analysis in a reasonable amount of time. While lower rates can be achieved, too low a feedrate would take an unreasonable amount of time to produce a batch and would have commercial limitations. The upper level was defined as the feedrate at which, for a given drying and atomisation gas flow rate, the particles produced were not effectively dried due to oversaturation of the drying gas resulting in particles with high residual moisture (often >5.0% w/w). If particles have high residual moisture, then they are liable to agglomeration. For this investigation and for the VSD equipment, the lower limit is defined as 1.5ml.min<sup>-1</sup> and the upper limit defined as 4.5ml.min<sup>-1</sup>, the centre point was defined as 3.0ml.min<sup>-1</sup>.

**b) Impact and Effect on the Zwitterionic Neutralisation**

The feed rate controls the amount of feedstock in the drying chamber per unit time. Therefore, the feed rate has a direct effect on the drying capacity of the gas through altering the saturation concentration of water, which in turn alters the drying kinetics of the system and resultant particles. A low feed rate would have a larger drying capacity margin for the drying gas resulting in faster drying and thus potentially leading to less physically stable particles.

Outlet Temperature Parameters and Rationale:**a) Definition of the operation Range**

The outlet temperature range was chosen to reflect the lowest temperature at which dry particles (often <5.0% w/w moisture) are collected (for the centre-point values of feedstock flow rate, atomisation gas and drying gas flow rates). The upper temperature was defined as the boiling point of water, above which the kinetic rate of evaporation only slightly increases. For this investigation and for the VSD equipment, the lower limit is defined as 60°C and the upper limit defined as 100°C, the centre point was defined as 80°C.

**b) Impact and Effect on the Zwitterionic Neutralisation**

The outlet temperature defines the thermal gradient across the drying chamber and thus has a subsequent impact on the drying rate. As discussed for the drying gas rationale, a longer  
1175 time to evaporate the water and form a particle results in a longer time to allow charge neutrality and the conformational change to occur.

*Feed stock Temperature Parameters and Rationale:***a) Definition of the operation Range**

1180 The feedstock temperature range was determined as being as low as room temperature, essentially 20°C, with the highest temperature where vapour was being produced resulting in variable concentrations of the feedstock being established throughout the run. With this in mind, 70°C was chosen.

**b) Impact and Effect on the Zwitterionic Neutralisation**

1185 The temperature of the feedstock during spray drying will also be investigated to access how the temperature affects the pKa of the sulphur-hydryl group. Theoretically, an increase in the temperature could increase the pKa of the sulphur-hydryl group from the current relatively low 1.49 (henderson-hasselbalch(1908)). This would mean that less acidification and shorter drying times could be required to achieve the same level of physical stability at lower  
1190 temperatures. In addition, adding heat to the feedstock increases the thermal energy in the atomised droplet which leads to a smaller thermal gradient and may increase the droplet drying kinetics to allow a particle to be dried quicker. As discussed in previous sections, it is hypothesised that the increased drying rate leads to a shorter time for charge neutralisation and thus physical instability on storage.

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*Feedstock Concentration Parameters and Rationale:***a) Definition of the operation Range**

The feedstock concentration range was chosen as it will affect the drying kinetics and resultant size/density of the produced particles. A minimum of 1.0% w/v is often used to give  
1200 an efficient production rate, while having acceptable PSD span. Above 5.0% w/v, the particle size increases above the inhalation size range for most 2 fluid nozzles. Therefore, the lower concentration was defined as 1.0% w/v and the upper range defined as 5.0% w/v. The centre point was defined as 2.5% w/v.

**b) Impact and Effect on the Zwitterionic Neutralisation**

1205 The concentration of the feedstock could have several impacts on the drying kinetics and resultant particle stability. As taurine's sulphur-hydryl group is a strong acid, increasing the concentration of taurine would mean a reduction in the pH. At a certain concentration, the

taurine would generate sufficient protons to establish itself at its isoelectric point. This is not so simple if one considers a drying droplet, which alters the concentration as water is lost.

1210 Therefore, the initial pH might not necessarily be the optimum.

Feedstock Solution pH and buffer/acid type Parameters and Rationale

1215 The pH of the feedstock and the acid used to modify the pH is believed to affect the taurine stability via the zwitterionic theory and driving the molecule to the isoelectric point when in the feedstock solution. Acidifying the solution should allow the taurine to neutralise the sulphur-hydryl groups charge by reaching the molecules isoelectric point, which is calculated to be at pH 4.0 (See FIGURE 8). The type of acid to do this may be important too. If the acid boils at too a low a boiling point, or is an azeotrope, the conjugate base and associated proton will be removed in the drying process before the particle is dried and charge 1220 neutralisation capability will be lost. But the acid and thus its residual conjugate base must be pharmaceutically acceptable as a salt forming agent, have a strong enough dissociation constant (pKa) to require very small effective concentrations to be effective and a high melting/boiling point to not be lost during drying prematurely.

1225 Therefore, although the values for limits and operation space defined in this investigation are specific to the VSD spray dryer, the experimental strategy can be said to cover the complete operation space for spray drying that can be translated and transposed onto any spray dryer model at any scale where these physical limits and constraints exist.

1230 *Batch Preparation:*

24 raw taurine samples were dissolved in an appropriate amount of Milli-Q water and sonicated. The pH of each sample was adjusted accordingly. The prepared feedstock solutions were separately spray-dried using a VSD spray-drier with a 0.5mm, two-fluid nozzle using various combinations of the process and formulation parameters summarised 1235 in Table 1.

1240

Batch	Drying Gas	Outlet Temperature	Feed Rate	Feedstock Temperature	Feedstock Concentration	Buffer	PH	Atomisation Flow Rate
1	15	100	4.5	70	1	Citrate	4.0	15
2	13.5	80	4.5	70	1	N/A	5.5	12
3	13.5	100	1.5	45	2.5	N/A	5.5	15
4	15	100	3	20	1	N/A	5.5	12
5	12	80	3	20	1	HCl	4.0	18
6	12	100	3	45	5	Citrate	4.0	12
7	13.5	60	1.5	45	1	NaOH	7.0	18
8	15	60	3	70	2.5	NaOH	7.0	12
9	13.5	60	4.5	20	2.5	Citrate	4.0	18
10	13.5	80	3	70	5	Citrate	4.0	18
11	15	100	4.5	45	5	HCl	4.0	18
12	12	60	3	45	2.5	N/A	5.5	18
13	15	80	3	20	5	NaOH	7.0	15
14	13.5	100	3	70	2.5	HCl	4.0	15
15	12	60	1.5	70	1	HCl	4.0	12
16	15	80	4.5	45	2.5	HCl	4.0	12
17	12	60	4.5	70	5	N/A	5.5	15
18	15	60	1.5	45	1	Citrate	4.0	15
19	13.5	60	1.5	20	5	HCl	4.0	15
20	12	80	1.5	20	2.5	Citrate	4.0	12
21	12	80	4.5	45	1	NaOH	7.0	15
22	13.5	100	4.5	20	5	NaOH	7.0	12
23	15	80	1.5	70	5	N/A	5.5	18
24	12	100	1.5	70	2.5	NaOH	7.0	18

**Table 1 summaries the various combinations of the process and formulation parameters analysed**

1245

*(i) Particle Size Distribution Analysis:*

Particle size distributions of the 24 sample batches were measured by laser diffraction using a Sympatec HELOS and RODOS particle size analyser and ASPIROS dispersion unit (0.5bar dispersion). A focal length corresponding to R4 lens was used and each batch sample was run in triplicate in order to determine the average particle size. In this instance, the D<sub>90</sub> for each batch sample was derived from the diffraction data using in-built Sympatec software (WINDOX 5.0).

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1255

Out of the 24 sample batches analysed, only 8 sample batches (Table 2) were identified as forming conditioned taurine and demonstrated a particle size distribution of  $D_{90} < 10.0 \mu\text{m}$ .

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Sample	PSD R4 $D_{90}$ Mean ( $\mu\text{m}$ ) T=0	PSD R4 $D_{90}$ Mean ( $\mu\text{m}$ ) T=7days
11	7.42	8.90
13	8.30	8.79
15	4.82	5.80
16	8.19	8.44
17	7.89	8.17
19	7.86	7.91
20	6.51	7.34
23	6.62	6.89

Table 2 summarises the PSD ( $D_{90}$ ) R4 lens at T=0 and T=7 days

Table 2, highlights the change in the  $D_{90}$  using the R4 lens, from initial (T=0) to the 7 day time point (T=7 days). All 8 samples show a small increase ( $\pm 20\%$ ) in the  $D_{90}$  between the initial and 7 day time point and consequently the absence of any agglomeration.

1265

FIGURE 1, which depicts a model response plot for all 24 sample batches produced, similarly demonstrates that only 8 have an acceptable PSD profile after 7 days of storage. Statistical analysis reveals that the model was highly significant with an  $R^2=1.00$  and significant P value of  $p<0.05$ , meaning the null hypothesis is rejected and that the parameters modelled are significantly affecting the agglomeration potential of the taurine. The parameters that govern the production of conditioned taurine are feedstock concentration, feedstock pumping rate, drying gas flow rate and second/third order interactions between them.

1275

The joint factor tests indicate from the p-values calculated (see FIGURE 9), that all the factors tested are significant.

Taurine can be produced in a form for inhalation that meets the particle size criteria and particle size stability provided the spray drying process is carefully controlled. The control of the parameters is used to allow zwitterionic neutralisation during drying, to prevent this occurring during storage resulting in agglomeration and loss of primary particles. The data verifies the hypothesis that zwitterionic neutralisation is the most likely mechanism responsible for agglomeration in the solid state and that all of the process and formulation parameters tested in this investigation have an impact on this process.

1285

While the model and analysis are specific to the VSD, the full operation space of the dryers capability has been mapped. Therefore, it can be inferred that inhalation taurine produced on any spray dryer and at any scale will exhibit the same dependence on all the parameters and leverages, which control the neutralisation of the zwitterionic charge. It would be straightforward, for any person skilled in the art to map the operation space of a spray dryer and achieve a similar model, with the same level of interdependence of the factors on the production of conditioned taurine.

(ii) *Calculating the Ratio of taurine dried per unit time during spray drying*

It has been determined that the inter-relationship between these parameters (feedstock concentration, feedstock pumping rate and drying gas flow rate) can be explained using the following expression, which calculates the amount of taurine being dried versus the amount of drying gas present, per unit time.

$$T_{Solid:Gas} = \frac{(C_F \times R_F)}{V_{DG}}$$

Where:

$T_{Solid:Gas}$  = Mass of taurine per volume of drying gas per unit time (AU)

$C_F$  = Feedstock Concentration (g mL<sup>-1</sup>)

$R_F$  = Feedrate (mL min<sup>-1</sup>)

$V_{DG}$  = Volume of Drying Gas (g min<sup>-1</sup>)

It has been determined by experiment that processed taurine and conditioned taurine products can be produced by spray drying when the  $T_{(solid:gas)}$  ratios are between  $2.000 \times 10^{-6}$

(smallest ratio) and  $2.750 \times 10^{-3}$  (largest ratio). The use of a more acidic feedstock is also a significant factor (though not essential) and allows a wider operation window of parameters to be used in the production of conditioned taurine.

Furthermore, to demonstrate that the calculated ratios are applicable to any open loop spray dryer, extrapolations to the Niro spray dryer are shown as exemplification:

- Smallest ratio =  $3.529 \times 10^{-6}$

- Largest ratio =  $2.118 \times 10^{-3}$

These calculated ratios fall within the range of the VSD spray dryer ratios.

1320 FIGURE 2 depicts a visual variability chart showing the spread of the acceptable batches (i.e. conditioned taurine) produced as a function of the  $T_{\text{solid:Gas}}$  ratios and indicates the relatively even spread across the theoretically operation range for the VSD spray dryer. Furthermore, the theoretical Niro spray dryer parameters are also seen to fall within the VSD operational range.

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FIGURE 3 demonstrates the strong relationship of the conditioned taurine batches which obeys a quadratic relationship with the  $D_{90}$  of the PSD after 7 days. Therefore, a batch of any inhalable PSD that is stable i.e. conditioned can be made on any spray dryer at any scale using the quadratic equation defined below. Rearranging the equation will give an

1330 appropriate t-ratio which can then be used to select the appropriate drying gas, feed rate and concentration for that dryer based on its functional operation parameter ranges.

$$D_{90} \text{ (Mm)} = A + BX - CX^2$$

1335 Where:

X = T-Ratio

A = 6.8

B = 3450.4

C = 6230437.9

1340

(Hi) *Thermogravimetric Analysis:*

Thermogravimetric analysis (TGA) determines the changes in sample weight in relation to change in temperature. This technique is used to examine the weight loss due to the removal of water upon heating and gives an assessment of the moisture content of the spray dried taurine samples.

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Equipment	Perkin Elmer TGA 5000
Starting Temperature	25°C
End Temperature	200°C
Heating Rate	10°C/min <sup>-1</sup>

Table 3 summarises the equipment and method used

1350 FIGURE 4 illustrates the moisture content for each sample at the initial time point, T=0. All samples were below 0.2% w/w moisture.

FIGURE 5 illustrates the moisture content for each sample at the 7 day time point, T=7. All samples were below 0.2% w/w moisture, with the exception of sample batch 21 which

1355 measured 0.45% w/w moisture. In some instances the results obtained gave a negative

weight loss. This was attributed to the balance drift in conjunction with the very small weight loss experienced and these results were subsequently reported as a zero-weight loss.

1360 Spray drying raw taurine, irrespective of the spray drying conditions used, resulted in spray-dried taurine demonstrating very low moisture content (0.2% w/w in comparison to spray-dried trehalose, which is typically between 3% and 5% w/w). Furthermore, there was no significant change in moisture content during storage.

*(iv) Differential Scanning Calorimetry*

1365 Differential Scanning Calorimetry (DSC) is a thermo-analysis technique in which the difference in the amount of heat required to increase the temperature of a sample and reference is measured as a function of temperature. This technique is used to assess the glass Transition temperatures ( $T_g$ ) and melting characteristics of the spray-dried samples.

1370 FIGURE 6 illustrates a DSC graph depicting spray-dried taurine, exemplified with sample 2 data.

1375 A glass transition temperature was not observed for any of the samples analysed, indicating that, irrespective of the spray drying conditions used, a transition from an amorphous form to crystalline does not occur, therefore the samples are produced in the crystalline form. The majority of samples examined demonstrated a melting point at approximately 333°C, with the lowest observed melting point seen at approximately 325°C.

1380



Example 2*Materials:*

Raw taurine and L-Leucine were obtained from Sigma-Aldrich Chemicals (The old brickyard, New road, Gillingham, Dorset, SP8 4XT). Trehalose was obtained from Ferro Pfanstiehl and Salbutamol sulphate was obtained from Cambrex Pharmaco.

*Preparation of Salbutamol Sulphate/Taurine OR Trehalose/L-Leucine Samples:*

Salbutamol sulphate (1% w/w), raw taurine OR trehalose (98.5% w/w) and L-Leucine (0.5% w/w) samples were dissolved in Milli-Q-water (800ml) and sonicated. The prepared feedstock solutions were separately spray-dried using the Niro Mobile Minor X3000 with a 0.5mm, two-fluid nozzle, according to the parameters outlined below in Table 4 and 5:

Sample	Parameters	Storage	Time Point	PSD		
				D <sub>10</sub>	D <sub>50</sub>	D <sub>90</sub>
Tre/Leu/Sal	Process A		0	0.73	1.65	3.44
		Ambient	24h	0.82	2.27	245.71
		25°C/50%RH	24h	NA	NA	NA
Tau/Leu/Sal	Process B		0	0.75	1.75	3.86
		Ambient	24h	0.75	1.74	3.80
		25°C/50%RH	24h	0.76	1.79	4.03
Tre/Leu/Sal	Process B		0	0.72	1.59	3.20
		Ambient	24h	0.94	75.80	279.99
		25°C/50%RH	24h	NA	NA	NA

Table 4 Summarises the PSD R4 lens at T=0 and T=24

Process A is a spray drying process using appropriate spray drying conditions specific to the Niro Mobile Minor X3000 for producing optimal trehalose particles suitable for inhalation. It should be noted that these conditions can be modified by a person skilled in the art to ensure that trehalose particles suitable for inhalation are produced regardless of the spray drying machine used.

Process B is a spray drying process using appropriate spray drying conditions specific to the Niro Mobile Minor X3000 for producing optimal taurine particles, namely conditioned taurine, suitable for inhalation. These conditions can also be modified depending on the spray drying machine used.

Component	Process Parameters	Conditions Used	
		Process A	Process B
Drying Gas	Pressure	30+/-5.0 mm Wg <sup>-1</sup>	
	Outlet Temperature	90.0°C+/-3.0°C	60.0°C+/-3.0°C
	Inlet Temperature	160.0°C+/-3.0°C	120.0°C+/-3.0°C
Feedstock	Temperature	20.0°C+/-5.0°C	50.0°C+/-5.0°C
	Concentration	2.5% w/v	
Atomisation Gas	Flow Rate	150+/-10 L min <sup>-1</sup>	200+/-10 L min <sup>-1</sup>
	Pressure	1.6+/-0.2 bar	3.9+/-0.2 bar

**Table 5 summarises the spray drying parameters for Process A and Process B**

Table 4 demonstrates that storage of Tre/Leu/Sal samples, processed under either "A" or "B" conditions and stored at 25°C/50%RH resulted in extreme agglomeration (represented by an N/A) due to an uptake of moisture resulting in total physical loss of primary particles e.g. agglomeration induced through amorphous crystallisation. Only Tau/Leu/Sal samples (FIGURE 16) stored at 25°C/50%RH (process B) resulted in measurable PSD values. Furthermore these values ( $D_{10}$ ,  $D_{50}$  and  $D_{90}$ ) were all  $<10\mu\text{m}$ .

### Example 3

#### Preparation of Glycopyrronium bromide/Taurine/L-leucine Samples:

Glycopyrronium bromide (1.0%w/w), raw taurine (96.5%w/w) and L-leucine (2.5%w/w) samples were dissolved in Milli-Q water (60ml) and sonicated. The prepared feedstock solution was spray dried using a laboratory spray dryer using a 0.5mm, two fluid nozzle, 48.0L · min<sup>-1</sup> atomisation flow rate, 25.5kg · hr<sup>-1</sup> drying gas flow rate, 60.0°C outlet temperature and 5.0g · min<sup>-1</sup> feed rate. Spray drying parameters identified as appropriate for producing taurine particles suitable for inhalation.

#### Preparation of Glycopyrronium bromide/Trehalose/L-leucine Samples:

Glycopyrronium bromide (1.0%w/w), raw trehalose dihydrate (89.0%w/w in the dried product) and L-leucine (10.0%w/w) samples were dissolved in Milli-Q water (100mL) and sonicated. The prepared feedstock solution was spray dried using a laboratory spray dryer using a 0.5mm, two fluid nozzle, 42.0L · min<sup>-1</sup> atomisation flow rate, 18.0kg · hr<sup>-1</sup> drying gas flow rate, 70.0°C outlet temperature and 2.0g · min<sup>-1</sup> feed rate. Spray drying parameters identified as appropriate for producing taurine particles suitable for inhalation.

### Conditioning of Samples

The taurine based formulation was stored in an open jar at ambient conditions overnight to condition the samples prior to analysis.

1440 The trehalose based formulation was stored in a sealed jar under low humidity (<5%RH) prior to analysis.

Each formulation was assessed for PSD, KF and assay/content at the initial time point. For the taurine sample this corresponds to the powder after storage in an open jar at ambient  
1445 conditions overnight. For trehalose this corresponds to the powder after storage overnight in a sealed jar under low humidity (<5%RH).

Each formulation was then assessed for PSD and drug content after 24 hours storage open at a constant relative humidity (%RH) of 53%RH and 23±3°C.

1450

Particle Size distribution (PSD)

Particle size distributions of the samples were measured by laser diffraction using a Sympatec HELOS and RODOS particle size analyser and ASPIROS dispersion unit (LObar dispersion). A focal length corresponding to R4 lens was used and each batch sample was  
1455 run in triplicate in order to determine the average particle size. In this instance, the D<sub>90</sub> for each batch sample was derived from the diffraction data using in built Sympatec software (WINDOX 5.0).

Moisture Content by Karl Fischer (KF)

1460 Karl Fischer (KF) analysis is used to assess the water content of solid formulations using the Metrohm 774 Oven Sample Processor and 756KF Coulometer. The solid formulations were heated to a set temperature of 120.0°C and titrated using the coulometer until no water is remaining in the sample. 10mg of each powder was weighed and the samples assessed. This was performed on both the taurine and trehalose based formulations.

1465

Aerosol Performance Testing

The Fast Screening Impactor (FSI) was used to assess the aerosolisation properties of the powder. Each formulation was assessed using gravimetric analysis, which involved filling a blister with the formulation (12.5±1.0mg) and firing into the FSI. The mass of the powder  
1470 evacuated from the blister and the mass collected on the fine fraction collector filter paper can then be calculated to evaluate how well the formulation is aerosolised. Water was used as the diluent for the insert.

1475

Drug Content Assay

The drug content of the taurine and trehalose based formulations were assessed using High Performance Liquid Chromatography (HPLC) at the initial time point and after 24 hours to assess the chemical stability of the formulations.

All data is summarised in table 6.

Formulation/ Condition	Time point	Mean D10 ( $\mu\text{m}$ )	Mean D50 ( $\mu\text{m}$ )	Mean D90 ( $\mu\text{m}$ )	Drug Assay (% Nominal)	% FPF <5 $\mu\text{m}$ t = 0	KF (%w/w)
Trehalose/ glycopyrronium bromide	Initial	0.73	1.65	3.43	103.1	70.2	2.59
	24 hours at 53%RH	No result - solid compact formed, mechanical force required to break up compact			91.2		
	27 days at ambient						
Taurine/ glycopyrronium bromide	Initial	0.76	1.79	4.02	100.7	40.3	0.41
	24hours at 53%RH	0.77	1.87	4.27	98.6		
	27 days at ambient	0.77	1.85	4.23			

Table 6 Summarises the data for glycopyrronium bromide T=0, 24 hours and 27 days

Table 6 demonstrates that both taurine and trehalose based formulations are aerosolisable and respirable at the initial time point.

After 24 hours storage at 53%RH the trehalose formulation has agglomerated and is no longer respirable, a PSD assessment was not able to be performed due to the formation of a solid compact. Additionally, the drug content dropped from 103% of nominal to 91% of nominal, indicating this is not chemically stable. Whereas, after 24 hours storage at 53%RH the taurine formulation has remained respirable ( $D_{90}<10\mu\text{m}$ ), and is chemically stable. After 27days storage at ambient conditions the taurine particles remain respirable and aerosolisable.

Example 4*Preparation of Salbutamol sulphate/Taurine/L-leucine Samples:*

- 1500 Salbutamol sulphate (1.0%w/w), raw taurine (96.5%w/w) and L-leucine (2.5%w/w) samples were dissolved in Milli-Q water (60ml) and sonicated. The prepared feedstock solution was spray dried using a spray dryer using a 0.5mm, two fluid nozzle, 48.0L·min<sup>-1</sup> atomisation flow rate, 25.5kg·hr<sup>-1</sup> drying gas flow rate, 60.0°C outlet temperature and 5.0g·min<sup>-1</sup> feed rate. Spray drying parameters identified as appropriate for producing taurine particles suitable for
- 1505 inhalation.
- The taurine based formulation was stored in an open jar at ambient conditions overnight to condition the samples.
- The formulation was assessed for PSD, KF and assay/content at the initial time point.
- The formulation was then assessed for PSD and drug content after 24 hours storage open at
- 1510 a constant relative humidity (%RH) of 53%RH and 23±3°C.

Particle Size distribution (PSD)

- Particle size distributions of the samples were measured by laser diffraction using a Sympatec HELOS and RODOS particle size analyser and ASPIROS dispersion unit (LObar
- 1515 dispersion). A focal length corresponding to R4 lens was used and each batch sample was run in triplicate in order to determine the average particle size. In this instance, the D<sub>90</sub> for each batch sample was derived from the diffraction data using in built Sympatec software (WINDOX 5.0).

1520 Moisture Content by Karl Fischer (KF)

Karl Fischer (KF) analysis is used to assess the water content of solid formulations using the Metrohm 774 Oven Sample Processor and 756KF Coulometer. The solid formulations were heated to a set temperature of 120.0°C and titrated using the coulometer until no water is remaining in the sample. 10mg of each powder was weighed and the samples assessed.

1525

Aerosol Performance Testing

- The Fast Screening Impactor (FSI) was used to assess the aerosolisation properties of the powder. Each formulation was assessed using gravimetric analysis, which involved filling a blister with the formulation (12.5±1.0mg) and firing into the FSI. The mass of the powder
- 1530 evacuated from the blister and the mass collected on the fine fraction collector filter paper can then be calculated to evaluate how well the formulation is aerosolised. Water was used as the diluent for the insert.

Drug Content Assay

1535 The drug content of the taurine based formulation was assessed using High Performance Liquid Chromatography (HPLC) at the initial time point and after 24 hours to assess the chemical stability of the formulation.

All data is summarised in Table 7.

Formulation / Condition	Time point	Mean D10 ( $\mu\text{m}$ )	Mean D50 ( $\mu\text{m}$ )	Mean D90 ( $\mu\text{m}$ )	Drug Assay (% Nominal)	% FPF <5 $\mu\text{m}$ t = 0	KF (%w/w)
Taurine, Salbutamol sulphate	Initial	0.77	1.87	4.26	97.9	42.0	0.5
	24 hours at 53%RH	0.78	1.92	4.38	99.4		
	26 days at ambient	0.78	1.92	4.38			

1540

Table 7 Summarises the data for salbutamol sulphate T=0 and T=24 hours

Table 7 demonstrates that the taurine based formulation is aerosolisable and respirable at the initial time point. After 24 hours storage at 53%RH the taurine formulation remains respirable ( $D_{90} < 10\mu\text{m}$ ) and chemically stable. After 26 days at storage at ambient conditions

1545 the taurine formulation remains respirable and aerosolisable.

Example 5*Preparation of Sumatriptan succinate/Taurine/L-leucine Samples:*

1550 Sumatriptan succinate (1.0%w/w), raw taurine (96.5%w/w) and L-leucine (2.5%w/w) samples were dissolved in Milli-Q water (60ml) and sonicated. The prepared feedstock solution was spray dried using a spray dryer using a 0.5mm, two fluid nozzle,  $48.0\text{L} \cdot \text{min}^{-1}$  atomisation flow rate,  $25.5\text{kg} \cdot \text{hr}^{-1}$  drying gas flow rate,  $60.0^\circ\text{C}$  outlet temperature and  $5.0\text{g} \cdot \text{min}^{-1}$  feed rate. Spray drying parameters identified as appropriate for producing taurine

1555 particles suitable for inhalation.

The taurine based formulation was stored in an open jar at ambient conditions overnight to condition the samples.

The formulation was assessed for PSD, KF and assay/content at the initial time point.

1560 The formulation was then assessed for PSD and drug content after 24 hours storage open at a constant relative humidity (%RH) of 53%RH and 23±3°C.

Particle Size distribution (PSD)

1565 Particle size distributions of the samples were measured by laser diffraction using a Sympatec HELOS and RODOS particle size analyser and ASPIROS dispersion unit (IObar dispersion). A focal length corresponding to R4 lens was used and each batch sample was run in triplicate in order to determine the average particle size. In this instance, the D<sub>90</sub> for each batch sample was derived from the diffraction data using in built Sympatec software (WINDOX 5.0).

1570 Moisture Content by Karl Fischer (KF)

Karl Fischer (KF) analysis is used to assess the water content of solid formulations using the Metrohm 774 Oven Sample Processor and 756KF Coulometer. The solid formulations were heated to a set temperature of 120.0°C and titrated using the coulometer until no water is remaining in the sample. 10mg of each powder was weighed and the samples assessed.

1575

Aerosol Performance Testing

The Fast Screening Impactor (FSI) was used to assess the aerosolisation properties of the powder. Each formulation was assessed using gravimetric analysis, which involved filling a blister with the formulation (12.5±1.0mg) and firing into the FSI. The mass of the powder  
1580 evacuated from the blister and the mass collected on the fine fraction collector filter paper can then be calculated to evaluate how well the formulation is aerosolised. Water was used as the diluent for the insert.

Drug Content Assay

1585 The drug content of the taurine based formulations was assessed using ultraviolet (U.V.) analysis at the initial time point and after 24 hours to assess the chemical stability of the formulation.

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Formulation/ Condition	Time point	Mean D10 ( $\mu\text{m}$ )	Mean D50 ( $\mu\text{m}$ )	Mean D90 ( $\mu\text{m}$ )	Drug Assay (% Nominal)	% FPF <5 $\mu\text{m}$ t = 0	KF
Taurine, Sumatriptan succinate	Initial	0.77	1.89	4.31	97.0	53.9	0.48
	24 hours at 53%RH	0.78	1.94	4.43	93.8		
	26 days at ambient	0.78	1.92	4.39			

Table 8 Summarises the data for sumatriptan succinate T=0 and T=24 hours

1600 Table 8 demonstrates that the taurine based formulation is aerosolisable and respirable at the initial time point, with sumatriptan succinate present. After 24 hours storage at 53%RH the taurine formulation remains aerosolisable and respirable ( $D_{90}<10\mu\text{m}$ ) and chemically intact. After 26 days at storage at ambient conditions the taurine formulation remains respirable and aerosolisable.

1605

### Dose ranging study

#### *Preparation of Salbutamol sulphate/Taurine/L-leucine Samples:*

Salbutamol sulphate, raw taurine and L-leucine samples were dissolved in the ratios detailed  
 1610 in Milli-Q water (60mL) and sonicated. The prepared feedstock solution was spray dried using a spray dryer using a 0.5mm, two fluid nozzle,  $48.0\text{L}\cdot\text{min}^{-1}$  atomisation flow rate,  $25.5\text{kg}\cdot\text{hr}^{-1}$  drying gas flow rate,  $60.0^\circ\text{C}$  outlet temperature and  $5.0\text{g}\cdot\text{min}^{-1}$  feed rate. Spray drying parameters identified as appropriate for producing taurine particles suitable for inhalation.

1615

The taurine based formulation was stored in an open jar at ambient conditions overnight to condition the samples.

The formulations were assessed for PSD, KF and assay/content at the initial time point.



1620 The formulations was then assessed for PSD and drug content after 24 hours storage open at a constant relative humidity (%RH) of 53%RH and 23±3°C.

Formulation/ Condition	Time point	Mean D10 (µm)	Mean D50 (µm)	Mean D90 (µm)	% FPF <5µm	Drug Assay (% Nominal)	KF
Taurine 96.5%w/w, leucine 2.5%w/w, drug 1.0%w/w	Initial	0.77	1.87	4.26	42.0	97.9	0.5
	24 hours At 53%RH	0.78	1.92	4.38		99.4	
Taurine 87.5%w/w, Leucine 2.5%w/w, drug 10.0%w/w	Initial	0.88	2.55	5.92	35.1	96.8	1.45
	60 hours At 53%RH	0.96	2.93	6.52		97.8	
Taurine 79.95%w/w, Leucine 2.5%w/w, drug 17.55%w/w	Initial	1.02	3.21	6.93	39	97.7	1.27
	24 hours At 53%RH	1.01	3.23	12.06		97.2	
Taurine 77.0%w/w, Leucine 2.5%w/w, drug 20.5%w/w	Initial	1.26	3.87	7.75	33	97.0	0.15
	24 hours At 53%RH	2.38	5.4	94.59		99.6	
Taurine 73.1%w/w, Leucine 2.5%w/w, drug 24.4%w/w	Initial	3.15	7.06	80.64	25	95.3	
	24 hours At 53%RH	2.8	6.74	86.62		95.9	

Table 9 Formulation composition and data for salbutamol sulphate at a range of compositions T=0 and T=24 hours

Table 9 shows that as the taurine concentration in the formulation decreases and the drug concentration increases the physically stabilising influence of taurine begins to diminish.

1630 There is no agglomeration of the powder when left at ambient overnight and at 53%RH (21±3°C) for 24 hours at taurine concentrations of 96.5%w/w and 87.5%w/w. A small amount of agglomeration is observed (n=1 rep) at 79.95%w/w taurine concentration. A larger amount of agglomeration is observed at taurine concentrations above 77.0%w/w.

#### Example 6, pMDI

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#### Preparation of Salbutamol sulphate/Taurine/L-leucine Samples:

1640 Salbutamol sulphate, raw taurine and L-leucine samples were dissolved in the ratios detailed in Table 10. Milli-Q water (60mL) and sonicated. The prepared feedstock solution was spray dried using a spray dryer using a 0.5mm, two fluid nozzle, 48.0L·min<sup>-1</sup> atomisation flow rate, 25.5kg·hr<sup>-1</sup> drying gas flow rate, 60.0°C outlet temperature and 5.0g·min<sup>-1</sup> feed rate. Spray drying parameters identified as appropriate for producing taurine particles suitable for inhalation.

The taurine based formulation was stored in an open jar at ambient conditions overnight to condition the samples.

1645

#### Preparation of Salbutamol/ Taurine/L-leucine Metered Dose Inhalers:

1650 Formulations as listed in table 10 were weighed into 19mL Presspart aluminium canisters. A Bepak 357 50µL valve was crimped onto the cannister. P134a propellant was subsequently filled through the valve using a Pamasol pressure fill system. The filled can was placed into a Bepak Actuator with nominal orifice size of 0.42mm.

#### Emitted Dose

1655 Prior to testing the MDI canister was placed in a Branson 8510 model sonic bath for five minutes. Dose Uniformity Sampling Apparatus (DUSA) with a testing flow rate of 28.3L·min<sup>-1</sup> was used to assess the emitted dose from the MDI. Ten actuations from the MDI were fired into individual DUSA. The DUSA tubes were rinsed with fixed volumes of diluent to recover the salbutamol sulphate. Samples were analysed using High Performance Liquid Chromatography (HPLC). The mean emitted dose was calculated as the average recovery from ten DUSA.

1660

#### Particle Size Distribution of Emitted Dose

1665 Prior to testing the MDI canister was placed in a Branson 8510 model sonic bath for five minutes. The Next Generation Impactor (NGI) with a testing flow rate of  $30\text{L} \cdot \text{min}^{-1}$  was used to assess the particle size distribution of the emitted dose from the MDI. Two actuations from the MDI were fired into the NGI. The MDI actuator, NGI throat and stages were washed with fixed volumes of diluent to recover the salbutamol sulphate. Samples were analysed using High Performance Liquid Chromatography (HPLC). The Impactor Sized Mass (ISM, the sum of the recovered dose on stages 2 to the micro orifice collector of the NGI) was calculated as a function of the emitted dose (i.e. the ratio between the ISM and the sum of the ISM, throat and stage 1 deposition expressed as a percentage). The Mass Median Aerodynamic Diameter was determined.

#### 1675 Drug Content Assay

The drug content of the salbutamol sulphate in propellant in the MDI canister was determined. Canisters were submersed in liquid nitrogen to freeze propellant. An incision made in the valve shoulder allowed the propellant to sublime as the MDI equilibrated to room temperature. The canister and valve were rinsed with fixed volumes of diluent to recover the salbutamol sulphate. Samples were analysed using High Performance Liquid Chromatography (HPLC).

#### Particle Size Distribution (PSD) - Prior to use in MDI preparation

1685 Approximately 10mg of formulation was dispersed in 0.2% lecithin in iso-octane and sonicated for 3 minutes using a sonic probe. The sample was left to rest for 5 minutes then analysed for particle size distribution using the Malvern Mastersizer 2000, with a pump speed of 3000rpm and an obscuration of 5-10%. 6 measurements were taken for each sample and the mean  $D_{10}$ ,  $D_{50}$  and  $D_{90}$  determined using the built in Malvern software.

#### 1690 Particle Size Distribution (PSD) - After use in MDI preparation

Prior to testing the MDI canister was placed in a Branson 8510 model sonic bath for five minutes. Canisters were submersed in liquid nitrogen to freeze propellant. An incision made in the valve shoulder allowed the propellant to sublime as the MDI equilibrated to room temperature. Formulation was manually recovered from the canister. Approximately 10mg of formulation was dispersed in 0.2% lecithin in iso-octane and sonicated for 3 minutes using a sonic probe. The sample was left to rest for 5 minutes then analysed for particle size distribution using the Malvern Mastersizer 2000, with a pump speed of 3000rpm and an obscuration of 5-10%. 6 measurements were taken for each sample and the mean  $D_{10}$ ,  $D_{50}$  and  $D_{90}$  determined using the built in Malvern software.

1700 Visual inspection of MDI suspensions

Formulations as listed in table 11 were weighed into plastic coated clear glass canisters. A continuous flow valve was crimped onto the canister. P134a propellant was subsequently filled through the valve using a Pamasol pressure fill system. Prior to testing the MDI canister was placed in a Branson 8510 model sonic bath for five minutes. Each canister was shaken for ten seconds and placed in front of a black background. Photographs were taken at 5 second intervals. Visual comparison of the photographs versus a clear glass canister allowed determination of the time where the majority of the formulation was no longer in suspension. No creaming was visible for any of the suspensions.

Formulation/ Condition	Formulation per canister (mg)	HFA 134a per canister (mg)
Taurine 87.5%w/w, Leucine 2.5%w/w, Salbutamol Sulphate 10.0%w/w	120	14700
Taurine 73.1%w/w, Leucine 2.5%w/w, Salbutamol Sulphate 24.4%w/w	48	14700
Taurine 90%w/w, Salbutamol Sulphate 10.0%w/w	120	14700
Taurine 100%w/w	48	14700

1710 **Table 10 Formulation composition for salbutamol sulphate in a range of MDI compositions**

Formulation/ Condition	Formulation per canister (mg)	HFA 134a per canister (mg)
Taurine 87.5%w/w, Leucine 2.5%w/w, Salbutamol Sulphate 10.0%w/w	60	7350
Taurine 73.1%w/w, Leucine 2.5%w/w, Salbutamol Sulphate 24.4%w/w	24	7350
Taurine 90%w/w, Salbutamol Sulphate 10.0%w/w	60	7350
Taurine 100%w/w	24	7350

**Table 11 Formulation composition for salbutamol sulphate in a range of MDI composition**

Formulation/ Condition	Mean D10 Pre MDI ( $\mu\text{m}$ )	Mean D50 Pre MDI ( $\mu\text{m}$ )	Mean D90 Pre MDI ( $\mu\text{m}$ )	Mean D10 Ex MDI ( $\mu\text{m}$ )	Mean D50 Ex MDI ( $\mu\text{m}$ )	Mean D90 Ex MDI ( $\mu\text{m}$ )	Emitted Dose Mean ( $\mu\text{g}$ ) (RSD, %)	Visible Suspension Duration (s)	Impactor Sized Mass (% of Emitted Dose)	MMAD ( $\mu\text{m}$ )	Drug Assay (% Nominal)
Taurine 87.5%w/w, Leucine 2.5%w/w, Salbutamol Sulphate 10.0%w/w	1.0	2.9	6.5	1.0	2.9	6.6	50.0 (32.2)	15	33.9	7.10	102
Taurine 73.1%w/w, Leucine 2.5%w/w, Salbutamol Sulphate 24.4%w/w	1.2	5.8	36.0	1.1	5.7	15.0	81.3 (13.0)	>120	13.5	Not Determined	102
Taurine 90%w/w, Salbutamol Sulphate 10.0%w/w	1.0	3.5	7.4	1.0	3.8	7.8	46.3 (12.0)	20	33.8	7.39	100
Taurine 100%w/w	1.1	2.9	5.9	1.1	2.8	5.5		15			

Table 12 Formulation composition for salbutamol sulphate in a range of MDI compositions

**Claims****1715**

I A method for preparing conditioned taurine, the method comprising a conditioning step, optionally a spray drying step, to produce taurine that:  
(a) demonstrates no significant net change in the  $D_{90}$  ( $\pm 20\%$ ) after 7 days of ambient storage; and

**1720**

(b) have a particle size  $D_{90}$  of  $<20\mu\text{m}$ , but more preferably  $<10\mu\text{m}$  after 7 days of ambient storage;  
optionally and preferably in which a method zwitterionic neutralisation is facilitated during drying of the taurine.

**1725**

2 Conditioned taurine obtained or obtainable by the method of claim 1.

3 The conditioned taurine according to claim 2, which is suitable for inhalation.

4 The conditioned taurine according to claim 2, which is at least 95% crystalline.

**1730**

5 A composition comprising conditioned taurine, such as a dry powder composition suitable for inhalation.

6 A composition according to claim 5, further comprising an amino acid.

**1735**

7 A composition according to claim 5 or 6, wherein the amino acid is selected from the group consisting of alanine, leucine, isoleucine, lysine, valine, methionine or phenylalanine.

**1740**

8 A composition according to claim 5 or 6, wherein the amino acid is leucine.

9 A composition according to claim 8, wherein the leucine is present in an amount less than 10% by weight based on the dry weight of the composition.

**1745**

10 A composition according to any one of claims 5 to 9, further comprising a medicament.

II A composition according to claim 10 in which the medicament is selected from budesonide, formoterol fumarate dihydrate, tiotropium, fluticasone propionate, salmeterol

**1750** xinafoate, vilanterol trifenate, umecldinium bromide, glycopyrronium bromide or indacaterol maleate.

12. A composition according to any one of claims 5 to 9, further comprising combinations of medicaments.

**1755**

13. A composition according to claim 12 in which the combination of medicaments is selected from budesonide and formoterol fumarate dehydrate, fluticasone propionate and salmeterol xinafoate, fluticasone propionate and vilanterol trifenate, or umecldinium bromide and vilanterol trifenate.

**1760**

14. A composition according to any one of claims 5 to 13 in the form of a dry powder.

15. A method for preparing conditioned taurine, the method comprising drying solubilised taurine, optionally by spray drying with one or more of the following

**1765** parameters:

(a) the pH of the feedstock to be spray dried is acidic e.g. less than pH 5, preferably equal to or less than pH 4, such as about pH 4;

(b) wherein the feedstock concentration is between 0.1% and 10%, more preferably between 1% and 5%;

**1770** (c) the feedstock temperature is between 0.1 °C and 100 °C, more preferably between 20 °C and 70 °C;

(d) the outlet temperature is between 50 °C and 120 °C, more preferably between 60 °C and 100 °C;

(e) the T(solid:gas) ratio is between  $2.00 \times 10^{-6}$  and  $2.75 \times 10^{-3}$ .

**1775**

16. A method for preparing conditioned taurine, the method comprising drying solubilised taurine, optionally by spray drying with one or more of the following parameters:

(a) the pH of the feedstock to be spray dried is less than pH 4;

**1780** (b) wherein the feedstock concentration is between 1% and 5%;

(c) the feedstock temperature is between 20 °C and 70 °C;

(d) the outlet temperature is between 60 °C and 100 °C;

(e) the T<sub>(solid:gas)</sub> ratio is between  $2.00 \times 10^{-6}$  and  $2.75 \times 10^{-3}$ .

**1785** 17. A container comprising:

(a) conditioned taurine; or

(b) a composition comprising conditioned taurine.

18. A container according to claim 17 which is the reservoir for a dry powder inhaler,  
1790 a blister or a capsule.

19. A method for preparing conditioned taurine, the method comprising a one-step  
process such as spray drying.

1795



## AMENDED CLAIMS

received by the International Bureau on 20 Aout 2014 (20.08.2014)

**Claims**

- 1 A method for preparing conditioned taurine, the method comprising a conditioning step, a spray drying step, to produce taurine that:
  - (a) demonstrates no significant net change in the  $D_{90}$  ( $\pm 20\%$ ) after 7 days of ambient storage; and
  - (b) have a particle size  $D_{90}$  of  $<20\mu\text{m}$ , but more preferably  $<10\mu\text{m}$  after 7 days of ambient storage;
- 2 Conditioned taurine obtained or obtainable by the method of claim 1.
- 3 The conditioned taurine according to claim 2, which is suitable for inhalation.
- 4 The conditioned taurine according to claim 2, which is at least 95% crystalline.
- 5 A composition comprising conditioned taurine, a dry powder composition suitable for inhalation, wherein the dry powder composition is prepared by spray drying.
- 6 A composition according to claim 5, further comprising an amino acid.
- 7 A composition according to claim 5 or 6, wherein the amino acid is selected from the group consisting of alanine, leucine, isoleucine, lysine, valine, methionine or phenylalanine.
- 8 A composition according to claim 5 or 6, wherein the amino acid is leucine.
- 9 A composition according to claim 8, wherein the leucine is present in an amount less than 10% by weight based on the dry weight of the composition.
- 10 A composition according to any one of claims 5 to 9, further comprising a medicament.
- 11 A composition according to claim 10 in which the medicament is selected from budesonide, formoterol fumarate dihydrate, tiotropium, fluticasone propionate, salmeterol xinafoate, vilanterol trifenate, umecclidinium bromide, glycopyrronium bromide or indacaterol maleate.
12. A composition according to any one of claims 5 to 9, further comprising combinations of medicaments.

13. A composition according to claim 12 in which the combination of medicaments is selected from budesonide and formoterol fumarate dehydrate, fluticasone propionate and salmeterol xinafoate, fluticasone propionate and vilanterol trifenate, or umeclidinium bromide and vilanterol trifenate.

14. A composition according to any one of claims 5 to 13 in the form of a dry powder.

15. A method for preparing conditioned taurine, the method comprising drying solubilised taurine, by spray drying with one or more of the following parameters:

(a) the pH of the feedstock to be spray dried is acidic e.g. less than pH 5, preferably equal to or less than pH 4, such as about pH 4;

(b) wherein the feedstock concentration is between 0.1% and 10%, more preferably between 1% and 5%;

(c) the feedstock temperature is between 0.1 °C and 100°C, more preferably between 20°C and 70°C;

(d) the outlet temperature is between 50°C and 120°C, more preferably between 60°C and 100°C;

(e) the  $T_{(solid:gas)}$  ratio is between  $2.00 \times 10^{-6}$  and  $2.75 \times 10^{-3}$ .

16. A method for preparing conditioned taurine, the method comprising drying solubilised taurine, by spray drying with one or more of the following parameters:

(a) the pH of the feedstock to be spray dried is less than pH 4;

(b) wherein the feedstock concentration is between 1% and 5%;

(c) the feedstock temperature is between 20°C and 70°C;

(d) the outlet temperature is between 60°C and 100°C;

(e) the  $T_{(solid:gas)}$  ratio is between  $2.00 \times 10^{-6}$  and  $2.75 \times 10^{-3}$ .

17. A container comprising:

(a) conditioned taurine; or

(b) a composition comprising conditioned taurine;

wherein the dry powder composition is prepared by spray drying.

18. A container according to claim 17 which is the reservoir for a dry powder inhaler, a blister or a capsule.

19. A method for preparing conditioned taurine, the method comprising a one-step spray drying process .

Figures

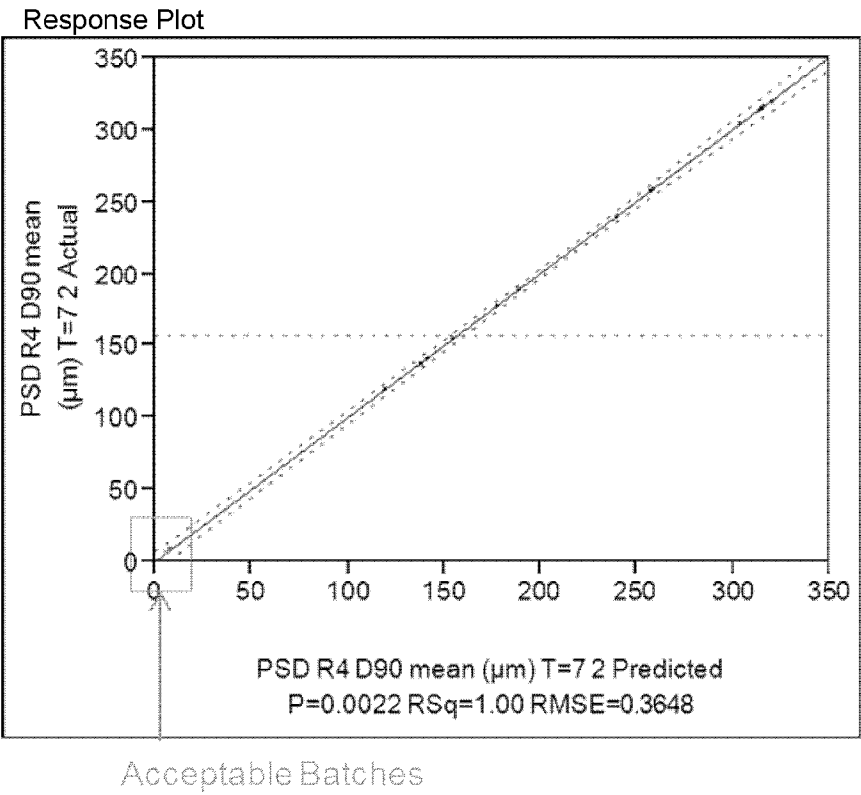


FIG. 1

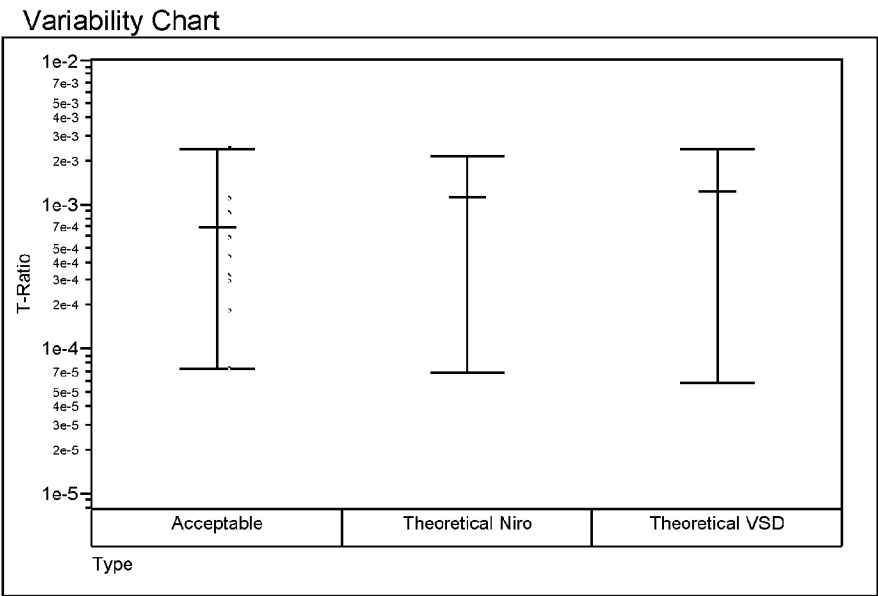


FIG. 2

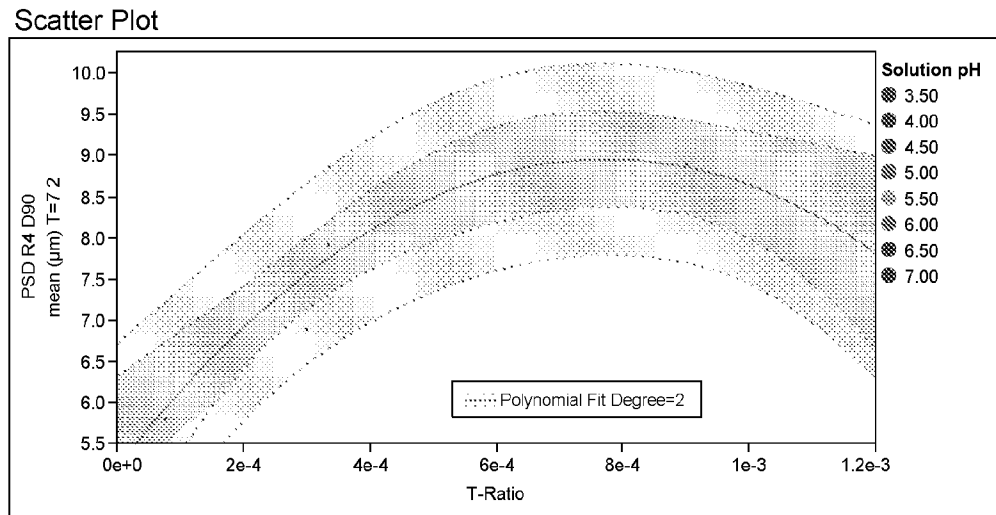


FIG. 3

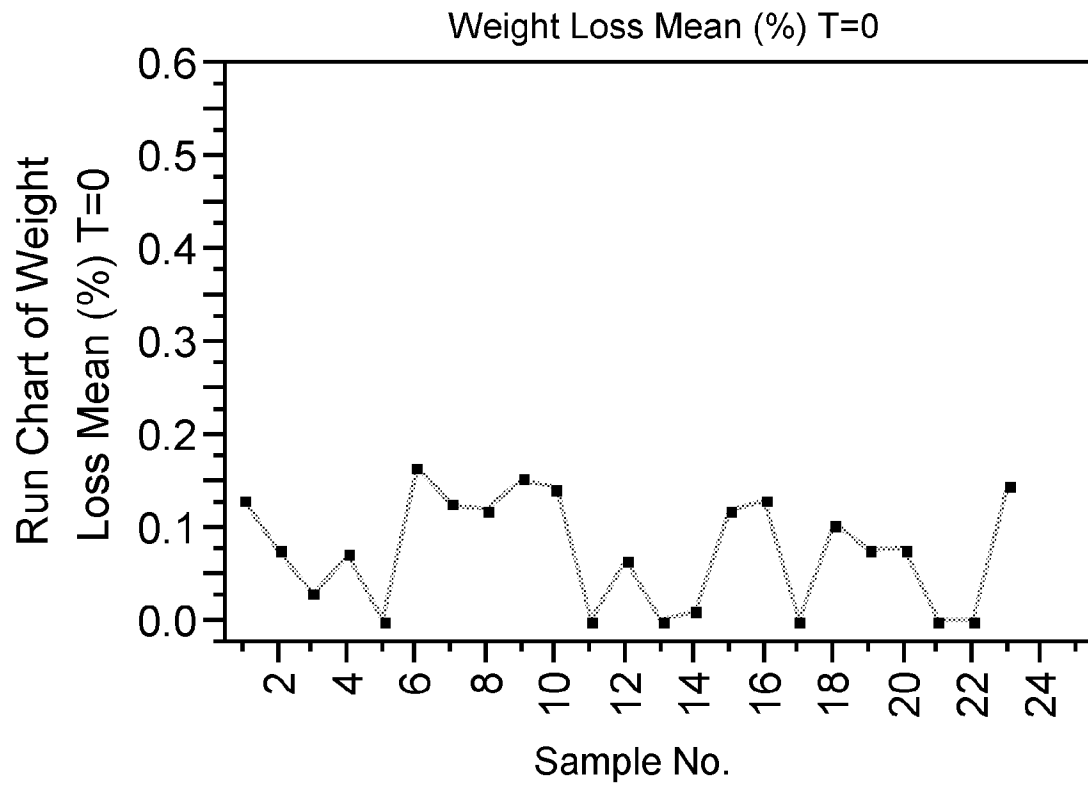


FIG. 4

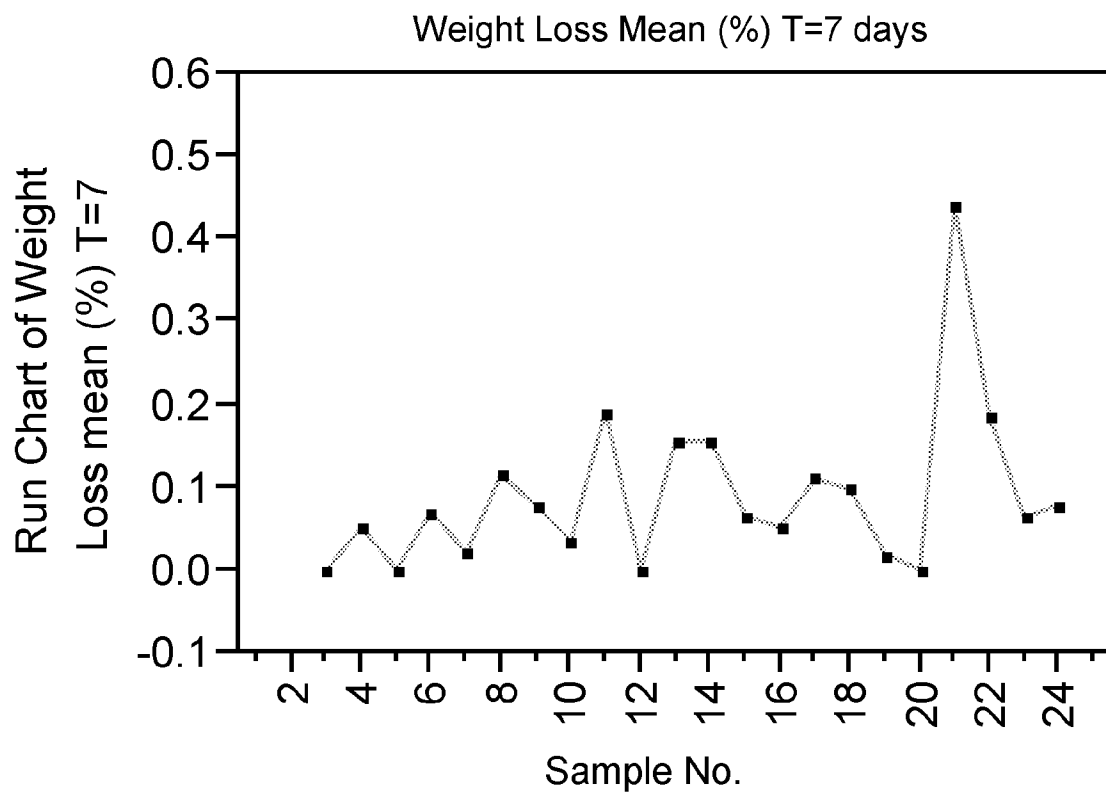


FIG. 5

## DSC

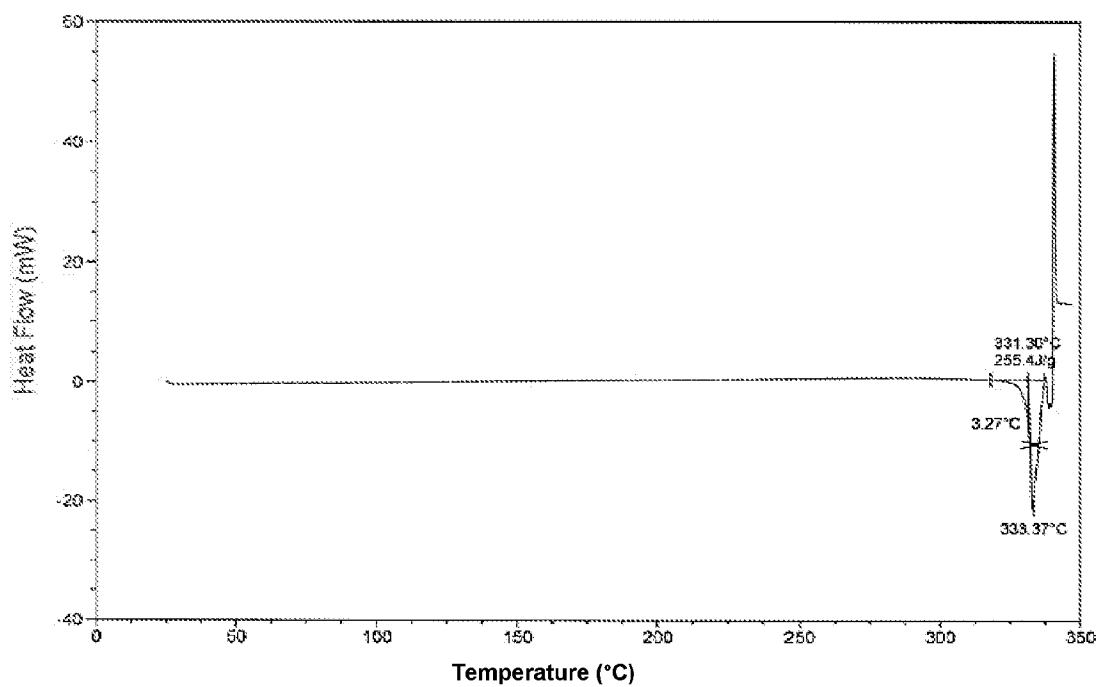


FIG. 6

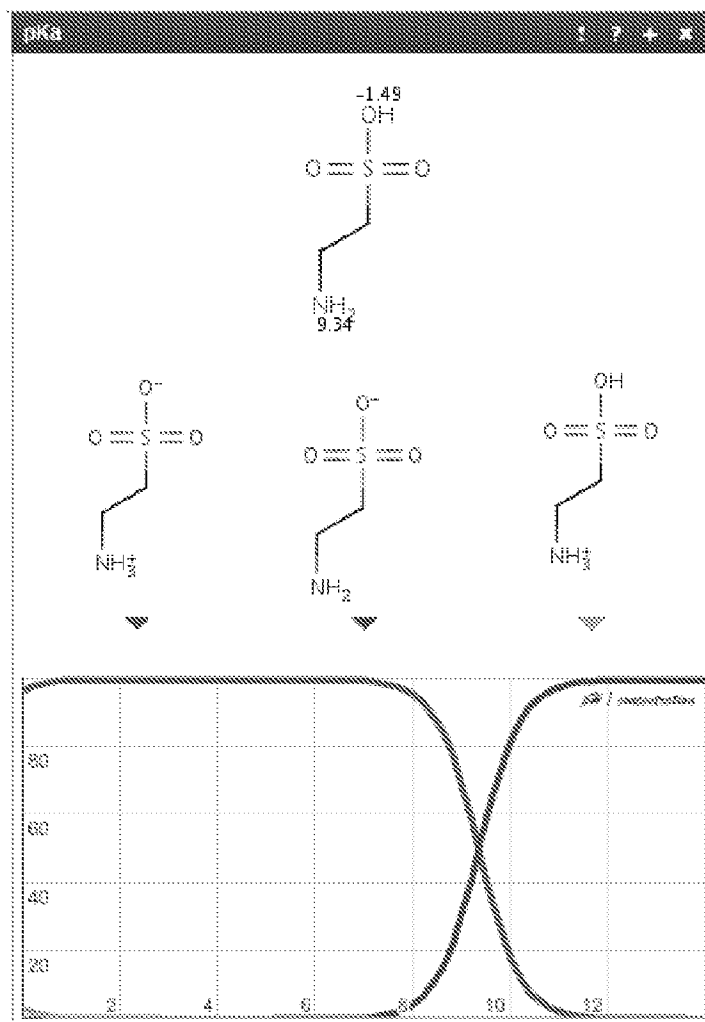


FIG. 7

pH profile and isoelectric point of taurine

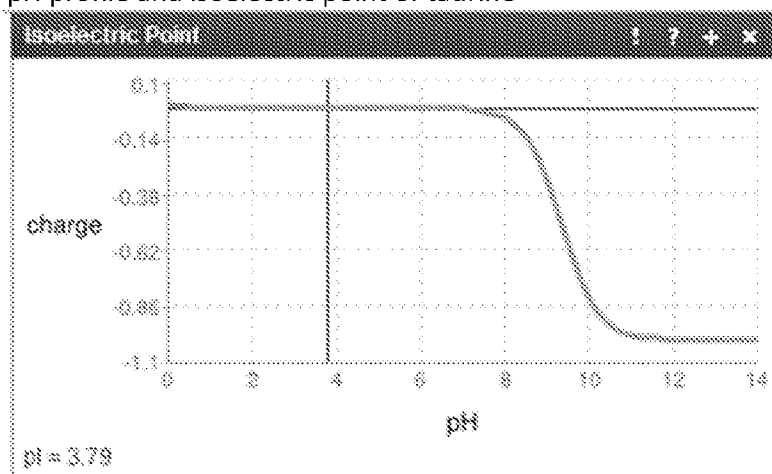


FIG. 8

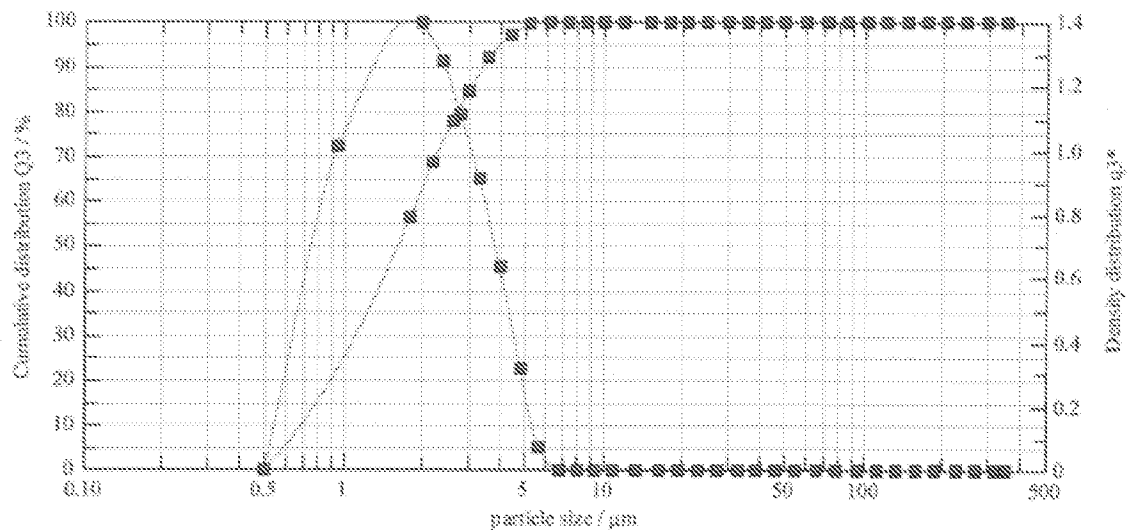


**Joint Factor Tests**

Term	DF	Sum of Squares	F Ratio	Prob > F
Feedstock Concentration (%w/v)	4	10665.73	20032.44	0.0053*
Drying Gas (kg/hr)	4	35688.84	67030.96	0.0029*
Outlet Temperature (°C)	6	219933.88	275387.3	0.0015*
Feedrate (g/min)	5	82431.94	123859.3	0.0022*
Feedstock Temperature (°C)	5	128944.38	193747.2	0.0017*
Solution pH	5	80610.74	121122.8	0.0022*
Atomisation Flow Rate (l/min)	6	200972.45	251645.0	0.0015*

**FIG. 9**

PSD – Tre/Leu/Sal - Process A – Initial Time Point, T=0 hours:

**FIG. 10**

PSD – Tre/Leu/Sal - Process A - Stored under ambient sealed conditions - T=24 hours:

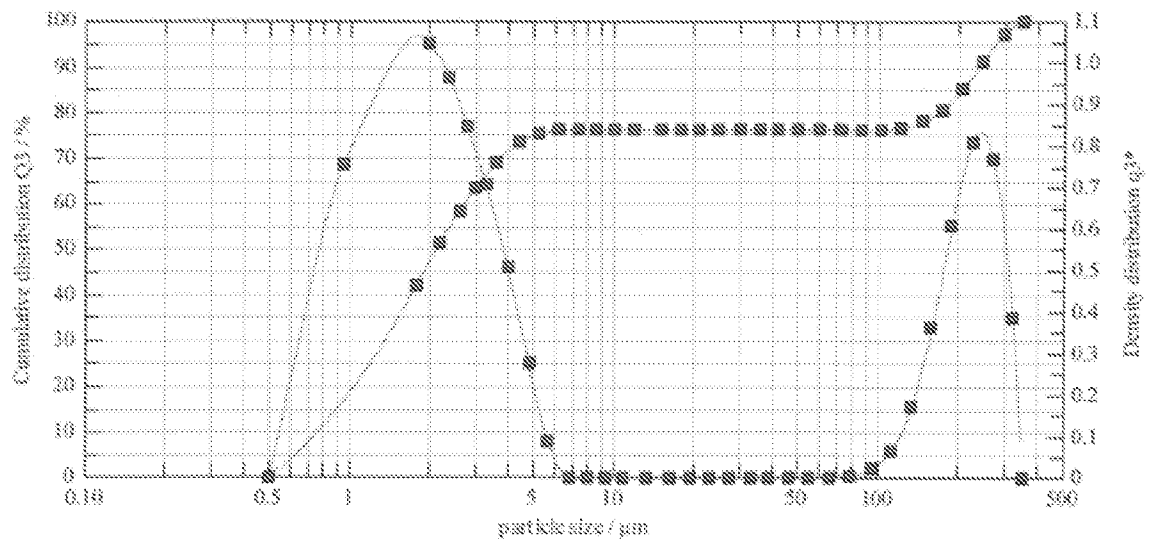


FIG. 11

PSD – Tau/Leu/Sal - Process B – Initial Time Point, T=0 hours:

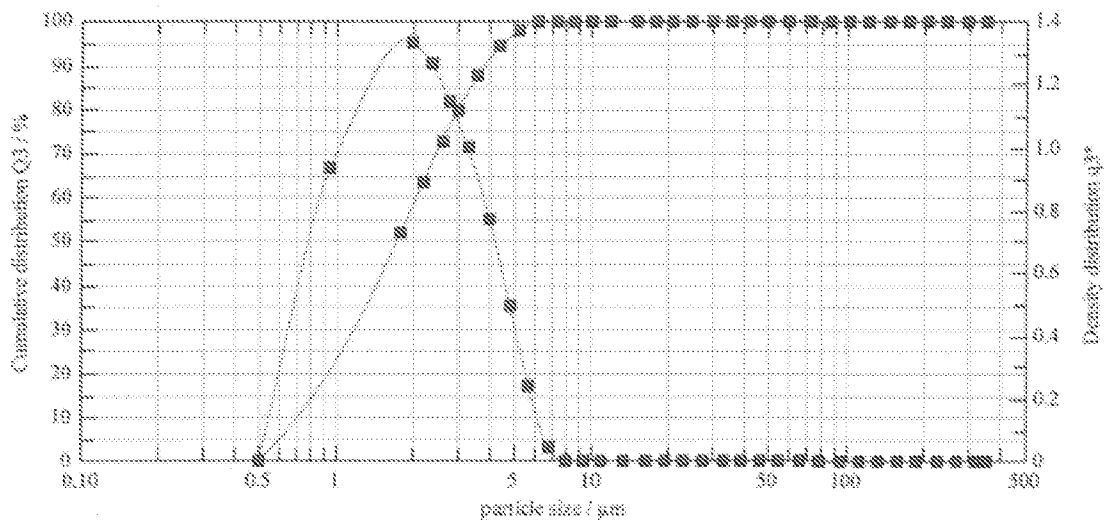


FIG. 12

PSD – Tau/Leu/Sal - Process B - Stored under ambient sealed conditions - T=24 hours:

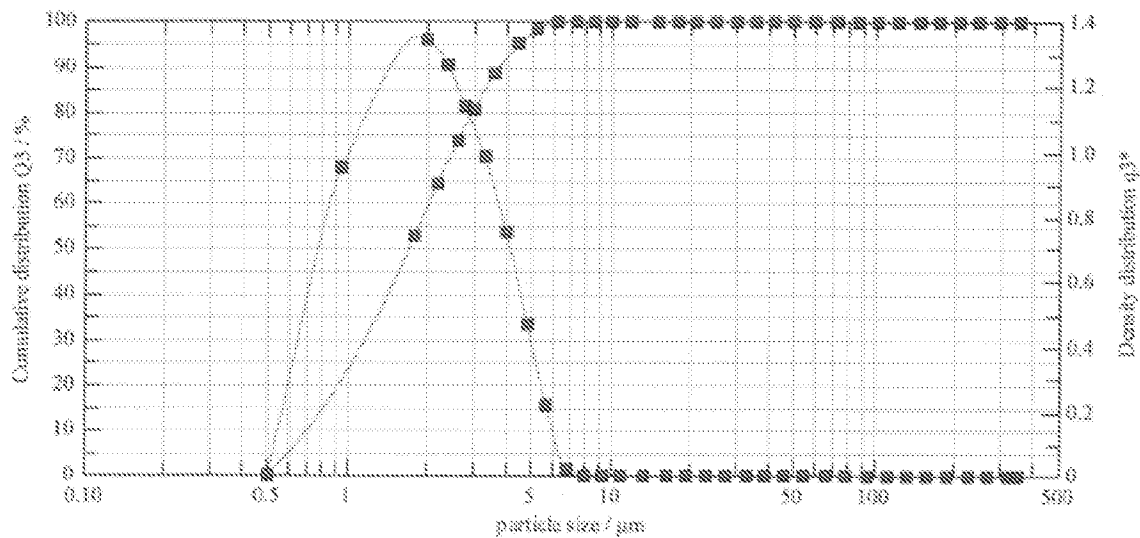


FIG. 13

PSD – Tre/Leu/Sal - Process B – Initial Time Point, T=0 hours:

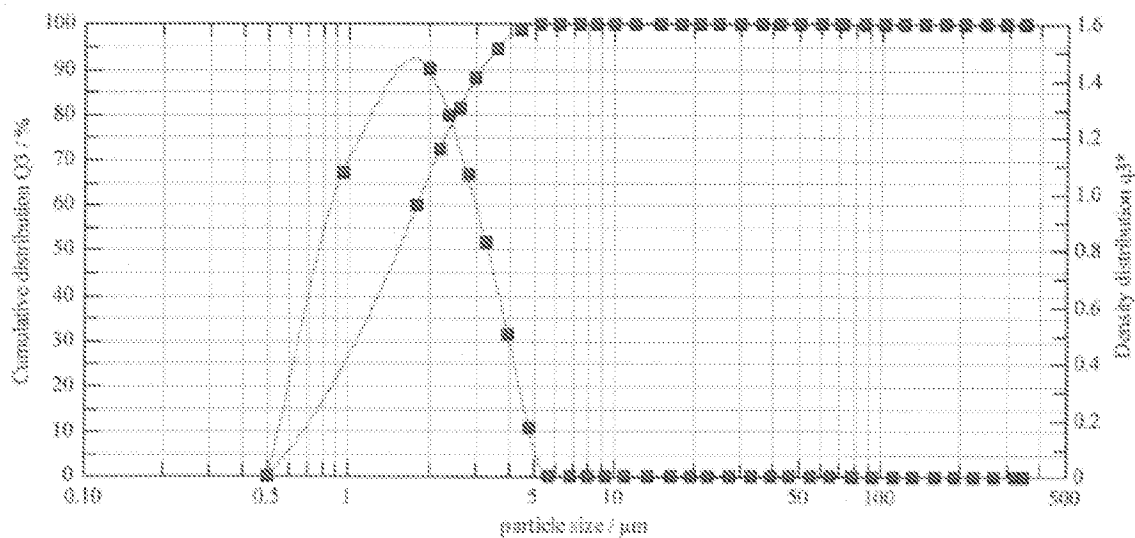


FIG. 14

PSD – Tre/Leu/Sal - Process B - Stored under ambient sealed conditions - T=24 hours:

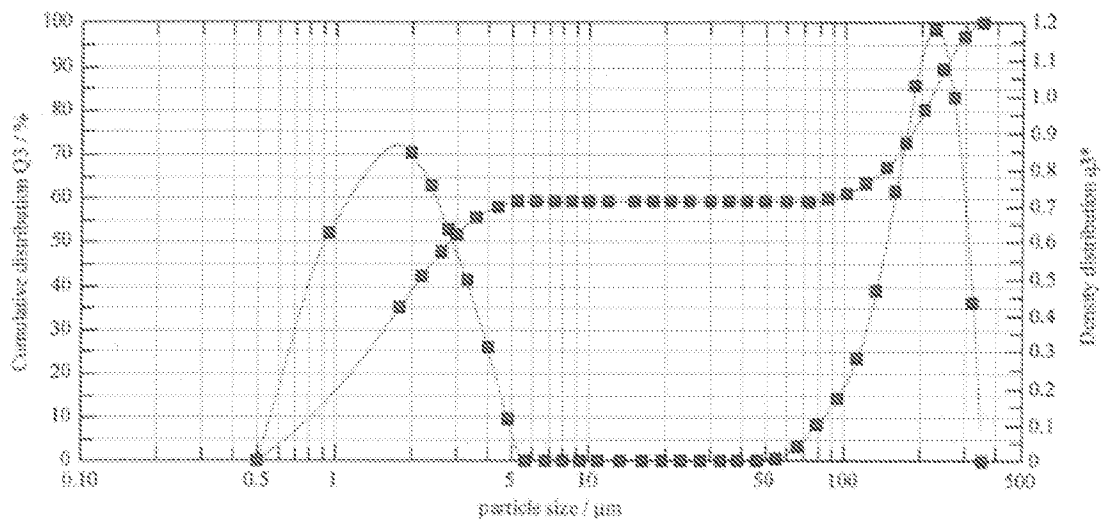


FIG. 15

PSD – Tau/Leu/Sal - Process B – Stored open at 25°C/50%RH - T=24 hours

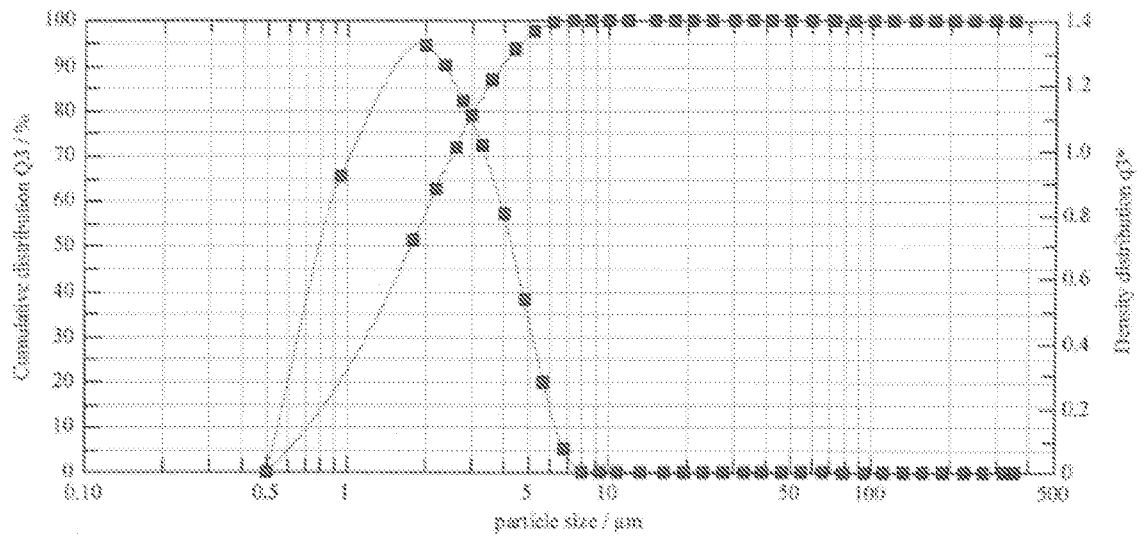


FIG. 16

## INTERNATIONAL SEARCH REPORT

International application No

PCT/GB2014/050953

A. CLASSIFICATION OF SUBJECT MATTER		
INV.	A61K9/00 A61K31/4045	A61K47/20 C07C309/14
	A61K9/16 A61P11/00	A61K31/137 A61K31/40
ADD.		
According to International Patent Classification (IPC) or to both national classification and IPC		
B. FIELDS SEARCHED		
Minimum documentation searched (classification system followed by classification symbols)		
A61K C07C		
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched		
Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)		
EPO-Internal , BIOSIS, CHEM ABS Data, EMBASE, COMPENDEX, WPI Data		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	KUDO S ET AL: "Producti on of fine organi c crystal line parti cles by usi ng milli segmented flow crystal lizer" , JOURNAL OF CHEMICAL ENGINEERING OF JAPAN 2012 SOCIETY OF CHEMICAL ENGINEERS, JAPAN JPN , vol . 45, no. 4, 2012 , pages 305-309 , XP009178283 , DOI : 10.1252/JCEJ.11WE168 page 308; figures 5, 6 page 306, col umn 2 ----- -/- .	1-5 , 14-17 , 19
<input checked="" type="checkbox"/> Further documents are listed in the continuation of Box C. <input checked="" type="checkbox"/> See patent family annex.		
* Special categories of cited documents :		
"A" document defining the general state of the art which is not considered to be of particular relevance		
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"O" document referring to an oral disclosure, use, exhibition or other means		
"P" document published prior to the international filing date but later than the priority date claimed		
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention		
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone		
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art		
"&" document member of the same patent family		
Date of the actual completion of the international search		Date of mailing of the international search report
4 June 2014		25/06/2014
Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016		Authorized officer  Kol Imannsberger, M

## INTERNATIONAL SEARCH REPORT

International application No

PCT/GB2014/050953

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
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Information on patent family members

International application No

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