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(54) Title: PARTICLE FORMULATION

(57) Abstract: The present inventions relates to combination particle formulations suitable for use in an inhaler formulation comprising a plurality of pharmacologically active ingredients characterized in that the pharmacologically active ingredients are crystalline. The present invention further comprises a particle formulation suitable for use in an inhalation formulation comprising a plurality of pharmacologically active ingredients, for example crystalline pharmacologically active ingredients characterized in that the ratio of the pharmacologically active substances has a distribution of less than $\pm 5\%$ of the target ratio as measured by Impactor testing. Particularly particle formulations prepared from nanoparticles, for example by spray drying of an aqueous suspension of nanoparticles. The invention further comprises methods for making said particle formulations and method of using said particle formulations in therapeutic treatments to achieve co-localisation of agents in the body, particularly when delivered as inhaled formulations to the human airways and lungs.



Particle Formulation

The present inventions relates to combination particle formulations comprising a plurality of pharmacologically active ingredients. Particularly particle formulations prepared from nanoparticles wherein the pharmaceutically active ingredients are crystalline. The invention further comprises methods for making said particle formulations and method of using said particle formulations in therapeutic treatments, particularly when delivered as inhaled formulations to the human airways and lungs.

Nanoparticles are particles with a dimension in the nanometer range. In general, they are of interest because they bridge between bulk materials and atomic or molecular structures. A bulk material tends to have constant physical properties regardless of its size but at the nanoscale size dependent properties are often observed. As particles decrease in size the surface area to volume ratio increases and it is the large relative surface area which often leads to the interesting and sometimes unexpected properties of nanoparticles. Nanoparticles have applications in a number of technologies, for example, semiconductors, textiles and drug delivery systems, such as inhaled therapeutics.

There are currently two inhalable, combination products in dry powder inhaler form on the market: GlaxoSmithkline's (GSK's) Seretide (fluticasone/salmeterol) and AstraZeneca's Symbicort (budesonide/ formoterol). Both are prescribed for asthma and COPD. GSK's Seretide was the first combination inhaled corticosteroid/long-acting beta2-agonist (ICS/LABA) to reach the market and achieved 2008 sales that accounted for 27% of total asthma/COPD drug sales across the seven major markets, with almost \$4.4 billion in the US, \$2.0 billion in the five major European markets, and \$153m in Japan. Symbicort sales have also been substantial since its launch, with 2008 and 2009 sales at US\$2 B and US\$2.3 B respectively.

ICS/LABA combinations are usually prescribed to patients who are not benefiting from low doses of ICS alone and where combination therapy is

regarded as more effective than prescribing the single drug treatment. Prescription of the LABA as a monotherapy has been associated with deterioration in asthma control and an increase in asthma exacerbations (Donohue, 2004), so the combination therapy ensures that LABA is prescribed alongside ICS. Prescribing the combination drugs also ensures better patient compliance and simplification of the disease management process.

A downside of the two combination products currently on the market is that they require twice daily dosing, which re-creates issues with compliance. Drug candidates currently in later stages of development, GlaxoSmithKline's Beyond Advair (currently in Phase III for COPD) and Novartis's mometasone/indacaterol (in Phase II for asthma and COPD), will be once-daily products. These two candidates are expected to take a substantial portion of the market as a result of the differentiating feature of having a favorable dosing regimen in comparison to marketed and other pipeline products. This demonstrates the importance of developing combination products with greater efficacy, leading to better compliance and improved dosing regimen. Other potential combinations that could be developed, and whose need has been highlighted by physicians, include theophylline and corticosteroids for the treatment of asthma/COPD, for which potential reductions in steroid resistance have been identified. Of these combination therapies, potential pharmacological synergy and therapeutic benefits are perceived from co-delivery of the agents to the site of action, with a particular focus on co-deposition in the human lungs.

We have developed particles comprising a plurality of pharmacologically active ingredients, suitable for use for use as therapeutics, particularly useful in inhaled therapeutics.

Thus, according to the first aspect of the invention there is provided a particle formulation suitable for use in an inhalation formulation (including dry powder and pressurized metered dose inhaler systems) comprising a plurality of pharmacologically active ingredients characterized in that the pharmacologically active ingredients are crystalline.

In a further aspect of the invention there is provided a particle formulation suitable for use in an inhalation formulation comprising a plurality of pharmacologically active ingredients, for example crystalline pharmacologically active ingredients characterized in that the ratio of the pharmacologically active substances has a distribution across the particles of less than $\pm 5\%$ of the target ratio as measured by Impactor testing (for example Twin Stage Impinger (TSI) or Next Generation Impactor (NGI)).

In a further aspect of the invention there is provided a particle formulation suitable for use in an inhalation formulation comprising a plurality of pharmacologically active ingredients, for example crystalline pharmacologically active ingredients characterized in that the ratio of the pharmacologically active substances has a distribution across the particles of less than or equal to $\pm 5\%$ of the target ratio as measured by the NGI impactor.

In a further embodiment the ratio in the impactor testing is less than or equal $\pm 4\%$, less than or equal to $\pm 3\%$ or less than or equal to $\pm 2\%$.

The ratios relate to the ratio averaged across all stages of the impactor instrument. In one embodiment the ratios are less than or equal $\pm 5\%$, less than or equal $\pm 4\%$, less than or equal to $\pm 3\%$ or less than or equal to $\pm 2\%$ at each stage of the impactor instrument.

In one embodiment the pharmacologically active ingredients are crystalline. In a further embodiment the pharmacologically active ingredients are amorphous. In a yet further embodiment the pharmacologically active ingredients are a mixture of amorphous and crystalline ingredients. Examples of amorphous ingredients include insulin.

According to a further aspect of the invention there is provided a particle formulation suitable for use in an inhalation formulation comprising a plurality of crystalline pharmacologically active ingredients characterized in that it is formed by spray drying of a nanoparticle formulation, for example an aqueous nanoparticle formulation.

Drug powders used in dry powder inhalers are normally prepared by crystallization followed by micronisation to the optimal particle size range for deep lung delivery. However, this often results in highly cohesive, highly charged and crystallographically defective materials which are difficult to process downstream and can potentially lead to highly variable dose accuracy and poor aerosol performance. In the present invention spray drying of crystalline nanoparticulate formulations offers the capability of generating ultrafine, free flowing, non cohesive dispersible particles which, unlike conventional spray drying that converts a liquid feed, gives a highly crystalline and stable product. Particles of the invention have improved processing properties over prior art particle formulations, including improved bulk density, powder flow, cohesion / adhesion balance and lower surface energies.

Particles of the invention have improved stability over prior art particle formulations, particularly for formulation of compounds which adversely interact in a combination formulation. Adverse interactions include aggregation, chemical decomposition and dimer formation.

In a further embodiment of the invention there is provided a particle formulation comprising a porous aggregate, comprising a plurality of pharmacologically active ingredients, for example crystalline pharmacologically active ingredients.

For the avoidance of doubt formulations of the invention comprise both porous and non-porous formulations. In general, porous formulations of the invention would be expected to occur with an average particle sizes of greater than about 5 μ m.

Porous aggregates may be amorphous or crystalline, for example crystalline porous aggregates. In some aggregates one or more active ingredients are crystalline and the other active ingredient or ingredients are amorphous.

According to a further aspect of the invention there is provided a particle formulation comprising a crystalline porous aggregate, comprising a plurality of pharmacologically active ingredients, characterized in that it is formed by spray

drying of a nanoparticle formulation, for example an aqueous nanoparticle formulation.

According to a further aspect of the invention there is provided a particle formulation comprising a crystalline porous aggregate, comprising a plurality of pharmacologically active ingredients.

According to a further aspect of the invention there is provided a particle formulation comprising an amorphous porous aggregate, comprising a plurality of pharmacologically active ingredients.

In general particles of the invention have a substantially uniform matrix which is not hollow and does not have significantly sized voids.

In one embodiment of the invention the particles of the formulations of the invention have a diameter between 1 μ m to 40 μ m, 1 μ m to 35 μ m, 1 μ m to 20 μ m, for example between 2 μ m to 16 μ m, such as between 2 μ m and 8 μ m or between 2 μ m and 5 μ m. In an alternative embodiments, particles of the formulation comprise particles with a diameter of between 25 μ m and 40 μ m, for example between 30 μ m and 35 μ m.

In a further embodiment of the invention the particles of the formulations of the invention have a diameter between 100nm to 40 μ m, 100nm to 35 μ m, 100nm to 20 μ m, for example between 100nm to 16 μ m, such as between 200nm and 8 μ m, between 100nm and 8 μ m, between 200nm and 8 μ m, between 200nm and 5 μ m, between 100nm and 5 μ m, between 200nm and 2 μ m or 100nM to 2 μ m.

For the avoidance of doubt when a range is expressed as for example between 1 μ m and 40 μ m, this includes 1 μ m and 40 μ m, In addition where values are quoted as a range the top and bottom values includes a tolerance of +/- 10%, for example +/- 5%, for examples +/- 2% and for example +/- 1%.

Porous formulations of the invention are particularly advantageous due to their porous nature which provides favorable aerodynamic characteristics.

Porous formulations of the invention have a small pore size. Small pores sizes are particularly advantageous since there is less potential for moisture ingress and therefore a markedly diminished propensity for moisture-related instability.

Particles have different aerodynamic properties due their shape and density, therefore it is necessary to use a particle size definition that directly relates to how the particle behaves in a fluid such as air. The term "aerodynamic diameter" has been developed by aerosol physicists in order to provide a simple means of categorizing the sizes of particles having different shapes and densities with a single dimension. The aerodynamic diameter is the diameter of a spherical particle having a density of 1 gm/cm^3 that has the same inertial properties [i.e. terminal settling velocity] in air as the particle of interest. The particles of formulations of the invention have a particularly advantageous aerodynamic diameter, for example between about $1\mu\text{m}$ and about $10\mu\text{m}$ or about $1\mu\text{m}$ and about $8\mu\text{m}$. For example between about $1\mu\text{m}$ and about $7\mu\text{m}$, between about $2\mu\text{m}$ and about $7\mu\text{m}$, between about $2\mu\text{m}$ and about $3.5\mu\text{m}$ or about $5\mu\text{m}$ and about $7\mu\text{m}$. For example comprising particles with an aerodynamic diameter of about $6\mu\text{m}$ or about $3\mu\text{m}$.

Formulations of the invention are particularly suitable for combination formulations where one active ingredient is in excess over one or more of the other active ingredients. For example, where one component is less than 10%, less than 5%, less than 2%, less than 1% or less than 0.5% of the active ingredients in the formulation. In two component formulations, for example the components are in the ratio, 1:5, 1:10, 1:20, 1:30, 1:40, 1:50, 1:75, 1:100 or 1:200.

According to a further aspect of the invention there is provided a formulation comprising:

- (i) from about 0.1 parts to about 20 parts of a plurality of pharmacologically active ingredients;
for example:
 - (a) Fluticasane / Salmeterol (Ratio about 10 : about 1);
 - (b) Budesonide / Formoterol (Ratio about 10 : about 0.3);
 - (c) Budesonide / Codisterol (Ratio about 10 : about 0.3); or
 - (d) Ibuprofen / glibenclamide (Ratio about 5 : about 1)
- (ii) about 0.1 parts to about 2 parts of one or more povidone polymers;

- (iii) about 0.01 parts to 1 parts of a surfactant, for example or soya lecithin; and optionally
- (iv) about 0.1 parts to 1 parts of a further surface stabilizer, for example hydroxy propyl methyl cellulose;

According to a further aspect of the invention there is provided a formulation comprising:

- (i) about 15 parts Ibuprofen;
- (ii) about 3 parts glibenclamide ;
- (iii) about 0.5 parts PVP;
- (iv) about 0.5 parts hydroxy propyl methyl cellulose;
- (v) about 0.1 parts sodium lauryl sulfate.

According to a further aspect of the invention there is provided a formulation of the invention comprising:

- (i) about 6 parts fluticasone;
- (ii) about 0.6 parts salmeterol;
- (iii) about containing 0.5 parts PVP; and
- (iv) about 0.1 parts soya lecithin.

Particle formulations of the invention optionally further comprise an additive, for example a surface stabiliser. In general the surface stabiliser is at a low level in the formulation for example less than 16%, such as less than 10%, less than 8%, less than 7%, less than 6%, less than 5% or less than 4% w/w

Suitable surface stabilizers include, but are not limited to, known organic and inorganic pharmaceutical excipients.

Such excipients include various polymers, low molecular weight oligomers, natural products, and surfactants.

Surface stabilizers include nonionic, ionic, anionic, cationic, and zwitterionic surfactants.

In one embodiment the surface stabilizer is selected from one or more of the group consisting of a non-ionic surface stabilizer, an anionic surface stabilizer, a cationic surface stabilizer, a zwitterionic surface stabilizer, and an ionic surface stabilizer.

Examples of surface stabilizers include but are not limited to hydroxypropyl methylcellulose (now known as hypromellose), hydroxypropylcellulose, polyvinylpyrrolidone, sodium lauryl sulfate, dioctylsulfosuccinate, gelatin, casein, lecithin (phosphatides), dextran, gum acacia, cholesterol, tragacanth, stearic acid, benzalkonium chloride, calcium stearate, glycerol monostearate, cetostearyl alcohol, cetomacrogol emulsifying wax, sorbitan esters, polyoxyethylene alkyl ethers (e.g., macrogol ethers such as cetomacrogol 1000), polyoxyethylene castor oil derivatives, polyoxyethylene sorbitan fatty acid esters (e.g., the commercially available Tweens (Registered trademark) such as e.g., Tween 20 (Registered trademark) and Tween 80 (Registered trademark) (ICI Speciality Chemicals)); polyethylene glycols (e.g., Carbowaxes 3550 (Registered trademark) and 934 (Registered trademark) (Union Carbide)), polyoxyethylene stearates, colloidal silicon dioxide, phosphates, carboxymethylcellulose calcium, carboxymethylcellulose sodium, methylcellulose, hydroxyethylcellulose, hypromellose phthalate, noncrystalline cellulose, magnesium aluminum silicate, triethanolamine, polyvinyl alcohol (PVA), 4-(1,1,3,3-tetramethylbutyl)-phenol polymer with ethylene oxide and formaldehyde (also known as tyloxapol, superione, and triton), poloxamers (e.g., Pluronic F68 (Registered trademark) and F108 (Registered trademark) , which are block copolymers of ethylene oxide and propylene oxide); poloxamines (e.g., Tetronic 908 (Registered trademark) , also known as Poloxamine 908 (Registered trademark) , which is a tetrafunctional block copolymer derived from sequential addition of propylene oxide and ethylene oxide to ethylenediamine (BASF Wyandotte Corporation, Parsippany, N.J.)); Tetronic 1508 (Registered trademark) (T-1508) (BASF Wyandotte Corporation), Tritons X-200 (Registered trademark) , which is an alkyl aryl polyether sulfonate (Rohm and Haas); Crodestas F-110 (Registered trademark) , which is a mixture of sucrose stearate and sucrose distearate (Croda Inc.); p-isononylphenoxy-poly-(glycidol), also known as Olin-IOG (Registered trademark) or Surfactant 10-G (Registered trademark) (Olin Chemicals, Stamford, Conn.); Crodestas SL-40 (Registered trademark) (Croda, Inc.); and SA9OHCO, which is $C_{18}H_{37}CH_2(CON(CH_3)-CH_2(CHOH)_4(CH_2OH)_2$

(Eastman Kodak Co.); decanoyl-N-methylglucamide; n-decyl(-D-glucopyranoside; n-decyl(-D-maltopyranoside; n-dodecyl(-D-glucopyranoside; n-dodecyl(-D-maltoside; heptanoyl-N-methylglucamide; n-heptyl(-D-glucopyranoside; n-heptyl(-D-thiogluconoside; n-hexyl(-D-glucopyranoside; nonanoyl-N-methylglucamide; n-nonyl(-D-glucopyranoside; octanoyl-N-methylglucamide; n-octyl(-D-glucopyranoside; octyl(-D-thiogluconoside; PEG-phospholipid, PEG-cholesterol, PEG-cholesterol derivative, PEG-vitamin A, PEG-vitamin E, lysozyme, random copolymers of vinyl pyrrolidone and vinyl acetate, and the like.

Examples of useful cationic surface stabilizers include, but are not limited to, polymers, biopolymers, polysaccharides, cellulose, alginates, phospholipids, and nonpolymeric compounds, such as zwitterionic stabilizers, poly-n-methylpyridinium, anthryl pyridinium chloride, cationic phospholipids, chitosan, polylysine, polyvinylimidazole, polybrene, polymethylmethacrylate trimethylammoniumbromide bromide (PMMTMABr), hexyldesyltrimethylammonium bromide (HDMAB), and polyvinylpyrrolidone-2-dimethylaminoethyl methacrylate dimethyl sulfate.

Other useful cationic stabilizers include, but are not limited to, cationic lipids, sulfonium, phosphonium, and quaternary ammonium compounds, such as stearyltrimethylammonium chloride, benzyl-di(2-chloroethyl)ethylammonium bromide, coconut trimethyl ammonium chloride or bromide, coconut methyl dihydroxyethyl ammonium chloride or bromide, decyl triethyl ammonium chloride, decyl dimethyl hydroxyethyl ammonium chloride or bromide, C12-15dimethyl hydroxyethyl ammonium chloride or bromide, coconut dimethyl hydroxyethyl ammonium chloride or bromide, myristyl trimethyl ammonium methyl sulfate, lauryl dimethyl benzyl ammonium chloride or bromide, lauryl dimethyl (ethenoxy)4 ammonium chloride or bromide, N-alkyl (C12-18)dimethylbenzyl ammonium chloride, N-alkyl (C14-18)dimethyl-benzyl ammonium chloride, N-tetradecyldimethylbenzyl ammonium chloride monohydrate, dimethyl didecyl ammonium chloride, N-alkyl and (C12-14) dimethyl 1-naphthylmethyl ammonium chloride, trimethylammonium halide, alkyl-trimethylammonium salts and dialkyl-

dimethylammonium salts, lauryl trimethyl ammonium chloride, ethoxylated alkyamidoalkyldialkylammonium salt and/or an ethoxylated trialkyl ammonium salt, dialkylbenzene dialkylammonium chloride, N-didecyldimethyl ammonium chloride, N-tetradecyldimethylbenzyl ammonium, chloride monohydrate, N-alkyl(C12-14) dimethyl 1-naphthylmethyl ammonium chloride and dodecyldimethylbenzyl ammonium chloride, dialkyl benzenealkyl ammonium chloride, lauryl trimethyl ammonium chloride, alkylbenzyl methyl ammonium chloride, alkyl benzyl dimethyl ammonium bromide, C12, C15, C17 trimethyl ammonium bromides, dodecylbenzyl triethyl ammonium chloride, poly-diallyldimethylammonium chloride (DADMAC), dimethyl ammonium chlorides, alkyldimethylammonium halogenides, tricetyl methyl ammonium chloride, decyltrimethylammonium bromide, dodecyltriethylammonium bromide, tetradecyltrimethylammonium bromide, methyl trioctylammonium chloride (ALQUAT 336), POLYQUAT, tetrabutylammonium bromide, benzyl trimethylammonium bromide, choline esters (such as choline esters of fatty acids), benzalkonium chloride, stearylkonium chloride compounds (such as stearyltrimonium chloride and distearyldimonium chloride), cetyl pyridinium bromide or chloride, halide salts of quaternized polyoxyethylalkylamines, MIRAPOL and ALKAQUAT (Alkaril Chemical Company), alkyl pyridinium salts; amines, such as alkylamines, dialkylamines, alkanolamines, polyethylenepolyamines, N,N-dialkylaminoalkyl acrylates, and vinyl pyridine, amine salts, such as lauryl amine acetate, stearyl amine acetate, alkylpyridinium salt, and alkylimidazolium salt, and amine oxides; imide azolinium salts; protonated quaternary acrylamides; methylated quaternary polymers, such as poly[diallyl dimethylammonium chloride] and poly-[N-methyl vinyl pyridinium chloride]; and cationic guar.

Such exemplary cationic surface stabilizers and other useful cationic surface stabilizers are described in J. Cross and E. Singer, *Cationic Surfactants: Analytical and Biological Evaluation* (Marcel Dekker, 1994); P. and D. Rubingh (Editor), *Cationic Surfactants: Physical Chemistry* (Marcel Dekker, 1991); and J. Richmond, *Cationic Surfactants: Organic Chemistry*, (Marcel Dekker, 1990).

Nonpolymeric surface stabilizers are any nonpolymeric compound, such as benzalkonium chloride, a carbonium compound, a phosphonium compound, an oxonium compound, a halonium compound, a cationic organometallic compound, a quarternary phosphorous compound, a pyridinium compound, an anilinium compound, an ammonium compound, a hydroxylammonium compound, a primary ammonium compound, a secondary ammonium compound, a tertiary ammonium compound, and quarternary ammonium compounds of the formula $NR_1R_2R_3R_4(+)$.

For compounds of the formula $NR_1R_2R_3R_4(+)$:

- (i) none of R_1 - R_4 are CH_3 ;
- (ii) one of R_1 - R_4 is CH_3 ;
- (iii) three of R_1 - R_4 are CH_3 ;
- (iv) all of R_1 - R_4 are CH_3 ;
- (v) two of R_1 - R_4 are CH_3 , one of R_1 - R_4 is $C_6H_5CH_2$, and one of R_1 - R_4 is an alkyl chain of seven carbon atoms or less;
- (vi) two of R_1 - R_4 are CH_3 , one of R_1 - R_4 is $C_6H_5CH_2$, and one of R_1 - R_4 is an alkyl chain of nineteen carbon atoms or more;
- (vii) two of R_1 - R_4 are CH_3 and one of R_1 - R_4 is the group $C_6H_5(CH_2)_n$, where $n > 1$;
- viii) two of R_1 - R_4 are CH_3 , one of R_1 - R_4 is $C_6H_5CH_2$, and one of R_1 - R_4 comprises at least one heteroatom;
- ix) two of R_1 - R_4 are CH_3 , one of R_1 - R_4 is $C_6H_5CH_2$, and one of R_1 - R_4 comprises at least one halogen;
- (x) two of R_1 - R_4 are CH_3 , one of R_1 - R_4 is $C_6H_5CH_2$, and one of R_1 - R_4 comprises at least one cyclic fragment;
- (xi) two of R_1 - R_4 are CH_3 and one of R_1 - R_4 is a phenyl ring; or
- (xii) two of R_1 - R_4 are CH_3 and two of R_1 - R_4 are purely aliphatic fragments.

Such compounds include, but are not limited to, behenalkonium chloride, benzethonium chloride, cetylpyridinium chloride, behentrimonium chloride, lauralkonium chloride, cetalkonium chloride, cetrimonium bromide, cetrimonium chloride, cethylamine hydrofluoride, chlorallylmethenamine chloride (Quaternium-

15), distearyldimonium chloride (Quaternium-5), dodecyl dimethyl ethylbenzyl ammonium chloride (Quaternium-14), Quaternium-22, Quaternium-26, Quaternium-18 hectorite, dimethylaminoethylchloride hydrochloride, cysteine hydrochloride, diethanolammonium POE (10) oleyl ether phosphate, diethanolammonium POE (3)oleyl ether phosphate, tallow alkonium chloride, dimethyl dioctadecylammoniumbentonite, stearalkonium chloride, domiphen bromide, denatonium benzoate, myristalkonium chloride, laurtrimonium chloride, ethylenediamine dihydrochloride, guanidine hydrochloride, pyridoxine HCl, iofetamine hydrochloride, meglumine hydrochloride, methylbenzethonium chloride, myrtrimonium bromide, oleyltrimonium chloride, polyquaternium-1, procainehydrochloride, cocobetaine, stearalkonium bentonite, stearalkoniumhectonite, stearyl trihydroxyethyl propylenediamine dihydrofluoride, tallowtrimonium chloride, and hexadecyltrimethyl ammonium bromide.

Most of these surface stabilizers are known pharmaceutical excipients and are described in detail in the Handbook of Pharmaceutical Excipients, published jointly by the American Pharmaceutical Association and The Pharmaceutical Society of Great Britain (The Pharmaceutical Press, 2000), specifically incorporated herein by reference.

Povidone polymers are exemplary surface stabilizers for use in formulating an injectable nanoparticulate leukotriene receptor antagonist/corticosteroid formulation.

Povidone polymers, also known as polyvidon(e), povidonum, PVP, and polyvinylpyrrolidone, are sold under the trade names Kollidon (Registered trademark) (BASF Corp.) and Plasdone (Registered trademark) (ISP Technologies, Inc.).

They are polydisperse macromolecular molecules, with a chemical name of 1-ethenyl-2-pyrrolidinone polymers and 1-vinyl-2-pyrrolidinone polymers.

Povidone polymers are produced commercially as a series of products having mean molecular weights ranging from about 10,000 to about 700,000 daltons.

To be useful as a surface modifier for a drug compound to be administered to a mammal, the povidone polymer must have a molecular weight of less than about 40,000 daltons, as a molecular weight of greater than 40,000 daltons would have difficulty clearing the body.

Povidone polymers are prepared by, for example, Reppe's process, comprising: (1) obtaining 1,4-butanediol from acetylene and formaldehyde by the Reppe butadiene synthesis; (2) dehydrogenating the 1,4-butanediol over copper at 2000 to form gamma -butyrolactone; and (3) reacting gamma -butyrolactone with ammonia to yield pyrrolidone.

Subsequent treatment with acetylene gives the vinyl pyrrolidone monomer.

Polymerization is carried out by heating in the presence of H₂O and NH₃.

See The Merck Index, 10th Edition, pp. 7581 (Merck & Co., Rahway, N.J., 1983).

The manufacturing process for povidone polymers produces polymers containing molecules of unequal chain length, and thus different molecular weights.

The molecular weights of the molecules vary about a mean or average for each particular commercially available grade.

Because it is difficult to determine the polymer's molecular weight directly, the most widely used method of classifying various molecular weight grades is by K-values, based on viscosity measurements.

The K-values of various grades of povidone polymers represent a function of the average molecular weight, and are derived from viscosity measurements and calculated according to Fikentscher's formula.

The weight-average of the molecular weight, M_w , is determined by methods that measure the weights of the individual molecules, such as by light scattering.

Exemplary useful commercially available povidone polymers for injectable formulations include, but are not limited to, Plasdone C-15™, Kollidon 12 PF™, Kollidon 17 PF™, Kollidon 25™.and Kollidon 30™.

Example of suitable surface stabilizer compounds include: hydroxyl propyl methyl cellulose (HPMC), carboxymethylcellulose sodium, sodium lauryl sulphate

(SLS) and poly vinyl pyrrolidone (PVP), soy lecithin, polysorbate (20, to 80), Span (20 or 80), dipalmitoylphosphatidylcholine, poloxomers, sodium deoxycholate, sodium docusate, PLA-PEG, Cremophors and Solutol.

Combination formulations of the invention suitable for delivery as inhalation formulations may also be delivered by other routes of administration, for example orally.

Pharmaceutical compositions of the invention may also comprise one or more binding agents, filling agents, lubricating agents, suspending agents, sweeteners, flavoring agents, preservatives, buffers, wetting agents, disintegrants, effervescent agents, and other excipients depending upon the route of administration and the dosage form desired.

Such excipients are well known in the art.

Examples of filling agents are lactose monohydrate, lactose anhydrous, and various starches; examples of binding agents are various celluloses and cross-linked polyvinylpyrrolidone, microcrystalline cellulose, such as Avicel (Registered trademark) PH101 and Avicel (Registered trademark) PH102, microcrystalline cellulose, and silicified microcrystalline cellulose (ProSolv SMCC (Registered Trademark)).

Suitable lubricants, including agents that act on the flowability of the powder to be compressed, are colloidal silicon dioxide, such as Aerosil (Registered trademark) 200, talc, stearic acid, magnesium stearate, calcium stearate, and silica gel.

Examples of sweeteners are any natural or artificial sweetener, such as sucrose, xylitol, sodium saccharin, cyclamate, aspartame, and acesulfame.

Examples of flavoring agents are Magnasweet (Registered trademark) (trademark of MAFCO), bubble gum flavor, and fruit flavors, and the like.

Examples of preservatives are potassium sorbate, methylparaben, propylparaben, benzoic acid and its salts, other esters of parahydroxybenzoic acid such as butylparaben, alcohols such as ethyl or benzyl alcohol, phenolic compounds such as phenol, and quaternary compounds such as benzalkonium chloride.

Suitable diluents include pharmaceutically acceptable inert fillers, such as microcrystalline cellulose, lactose, dibasic calcium phosphate, saccharides, and/or mixtures of any of the foregoing.

Examples of diluents include microcrystalline cellulose, such as Avicel (Registered trademark) PH101 and Avicel (Registered trademark) PH102; lactose such as lactose monohydrate, lactose anhydrous, and Pharmatose (Registered trademark) DCL21; dibasic calcium phosphate such as Emcompress (Registered trademark) ; mannitol; starch; sorbitol; sucrose; and glucose.

Suitable disintegrants include lightly crosslinked polyvinyl pyrrolidone, corn starch, potato starch, maize starch, and modified starches, croscarmellose sodium, cross-povidone, sodium starch glycolate, and mixtures thereof.

Examples of effervescent agents are effervescent couples, such as an organic acid and a carbonate or bicarbonate.

Suitable organic acids include, for example, citric, tartaric, malic, fumaric, adipic, succinic, and alginic acids and anhydrides and acid salts.

Suitable carbonates and bicarbonates include, for example, sodium carbonate, sodium bicarbonate, potassium carbonate, potassium bicarbonate, magnesium carbonate, sodium glycine carbonate, L-lysine carbonate, and arginine carbonate.

Alternatively, only the sodium bicarbonate component of the effervescent couple may be present.

The invention encompasses dry powder aerosols of the formulations of the invention and liquid dispersion aerosols of the formulations of the invention.

In one embodiment of the invention, the aerosol droplets comprising the particulate formulations of the invention for aqueous dispersion aerosols, or the dry powder aggregates comprising the particulate formulations of the invention for dry powder aerosols, have a mass media aerodynamic diameter of less than or equal to about 100 microns.

In other embodiments of the invention, the aerosol droplets comprising the particulate formulations of the invention for aqueous dispersion aerosols, or the

dry powder aggregates comprising the particulate formulations of the invention for dry powder aerosols, have a mass media aerodynamic diameter (MMAD) of (1) about 30 to about 60 microns; (2) about 0.1 to about 10 microns; (3) about 2 to about 6 microns; or (4) less than about 2 microns.

Particles of the invention are particularly advantageous since they have very low levels of components other than the pharmacologically active ingredients. For examples, no other components except for low levels of stabilisers are used in the nanoparticle suspension used to make the particles of the invention.

A pharmacologically active ingredient is any compound which when dosed to an animal or human produces a therapeutically beneficial effect. Pharmaceutically active ingredients may have side effects in addition to the therapeutic benefit.

In one embodiment the pharmacologically active ingredient is one or more of the following classes :corticosteroids such as Inhaled Corticosteroid (ICS) and Long Acting Beta Agonists (LABA), Short Acting Beta Agonists (SABA), Leukotriene Modifiers (LM) and Immunomodulators.

Corticosteroid drugs include betamethasone (Celestone™), budesonide (Entocort™), cortisone (Cortone™), dexamethasone (Decadron™), hydrocortisone (Cortef™), methylprednisolone (Medrol™), prednisolone (Prelone™), prednisone (Cortan™, Deltasone™, Liquid Pred™, Meticorten™, Orasone™, Panasol-S™, Prednicen-M™ and Sterapred™), and triamcinolone (Kenacort™, Kenalog™).

Examples of inhalation corticosteroids include beclomethasone (aerosol, capsules for inhalation, and powder for inhalation); beclomethasone dipropionate HFA (aerosol); budesonide (powder for inhalation and suspension for inhalation); flunisolide (aerosol); and triamcinolone (aerosol).

Example of a leukotriene Modifier include a leukotriene biosynthesis inhibitor, 5-lipoxygenase (5-LO) inhibitor or 5-lipoxygenase activating protein (FLAP) antagonist, such as zileuton; ABT-761; fenleuton; tepoxalin; Abbott-79175; Abbott-85761; N-(5-substituted)-thiophene-2-alkylsulfonamides; 2,6-di-

tert-butylphenolhydrazones; methoxytetrahydropyrans such as Zeneca ZD-2138; the compound SB-210661; a pyridinyl-substituted 2-cyanonaphthalene compound, such as L-739,010; a 2-cyanoquinoline compound, such as L-746,530; indole and/or a quinoline compound, such as MK-591, MK-886 and/or BAY 1005;

Example of leukotriene modifiers also include a receptor antagonist for leukotrienes (LT) B₄, LTC₄, LTD₄, and LTE₄, selected from the group consisting of the phenothiazin-3-1s, such as L-651,392; amidino compounds, such as CGS-25019c; benzoxalamines, such as ontazolast; benzenecarboximidamides, such as BIIL 284/260; and compounds, such as zafirlukast, ablukast, montelukast, pranlukast, verlukast (MK-679), RG-12525, Ro-245913, iralukast (CGP 45715A) and BAY * 7195;

In one embodiment a leukotriene modifiers is selected from zafirlukast, montelukast, and zileuton.

Examples of short acting beta agonists include: salbutamol (albuterol (US name), Ventolin[™]), bitolterol mesylate, fenoterol, hexoprenal in, levosalbutamol (levalbuterol (US name), Xopenex), metaproterenol (Alupent[™]), orciprenaline, pirbuterol (Maxair[™]), procaterol, reproterol, ritodrine and/or terbutaline (Bricanyl[™]).

Examples of long acting beta agonists include: salmeterol (Serevent Diskus) formoterol (Foradil[™], Symbicort[™]), bambuterol, clenbuterol and indacaterol.

Examples of immunomodulators include thiopurines such as 6-mercaptopurine.

Examples of pharmacologically active ingredients suitable for use in formulation of the invention also include:

- (i) non-steroidal anti-inflammatory drugs such as Aspirin (acetylsalicylic acid), Diflunisal, Salsalate, ibuprofen, Naproxen, Fenoprofen, Ketoprofen, Dexketoprofen, Flurbiprofen, Oxaprozin, Loxoprofen, Indomethacin, Sulindac, Etodolac, Ketorolac, Diclofenac, Nabumetone, Piroxicam, Meloxicam, Tenoxicam, Droxicam, Lornoxicam, Isoxicam, Mefenamic acid, Meclofenamic acid, Flufenamic acid and Tolfenamic acid;

- (ii) cyclo-oxygenase-2 inhibitors such as celecoxib, valdecoxib, etoricoxib, parecoxib, rofecoxib);
- (iii) anti-inflammatory agents for example adrenocorticoids, corticosteroids, (e.g., beclomethasone, budesonide, flunisolide, fluticasone, triamcinolone, methylprednisolone, prednisolone, prednisone, hydrocortisone), glucocorticoids, steroids
- (iv) Sulphonyl ureas such as Carbutamide, Acetohexamide, Chlorpropamide, Tolbutamide, Tolazamide, Glipizide, Glliclazide, Glibenclamide (glyburide), Glibornuride, Gliquidone, Glisoxepide, Glyclopamide, and Glimepiride;
- (v) xanthine derivatives such as caffeine, aminophylline, IBMX (3-isobutyl-1-methylxanthine), paraxanthine, pentoxifylline, theobromine, and theophylline;

Suitable pharmacologically active ingredients for formulations of the inventions include any pharmaceutical agent which exists in a crystalline form. Examples include: ibuprofen [(RS)-2-(4-(2-methylpropyl)phenyl)propanoic acid], glibenclamide, theophylline, salmeterol, fluticasone, formoterol, budesonide, beclometasone and carmoterol. For example a combination of ibuprofen and glibenclamide or fluticasone and salmeterol or budesonide and codisterol or budesonide and formoterol.

The term 'about' when used with reference to numerical values refers to a tolerance of +/- 10%, for example +/- 5%, for examples +/- 2% and for example +/- 1%.

The term 'plurality' refers to one or more. In one embodiment the term 'plurality' refers to two or more, for example two or three.

A further embodiment of the invention provides a process for making a particle formulation of the invention comprising:

- (i) providing a plurality of pharmacologically active ingredients as nanoparticles;
- (ii) suspending the nanoparticles in a liquid to form a suspension; for example an aqueous liquid, and
- (iii) forming a particle formulation by spray drying;

and then thereafter if necessary

(a) forming a pharmaceutical composition.

A further embodiment of the invention provides a process for making a particle formulation of the invention comprising:

- (i) mixing a plurality of pharmacologically active compounds,
- (ii) suspending the compounds in a liquid to form a suspension; for example an aqueous liquid,
- (iii) preparing nanoparticles of the pharmacologically active compounds, for example by co-milling; and
- (iv) forming a particle formulation, for example, by spray drying;

and then thereafter if necessary,

(v) forming a pharmaceutical composition.

A further embodiment of the invention provides a process for making a particle formulation of the invention comprising:

- (i) mixing a plurality of pharmacologically active compounds,
- (ii) preparing nanoparticles of the pharmacologically active compounds, for example by co-milling; and
- (iii) preparing a suspension of the nanoparticles, for example an aqueous suspension;
- (iv) forming a particle formulation by spray drying;

and then thereafter if necessary,

(v) forming a pharmaceutical composition.

A further embodiment of the invention provides a process for making a particle formulation of the invention comprising:

- (i) preparing nanoparticles of pharmacologically active compounds, by mixing a plurality of pharmacologically active compounds and co-milling;
- (ii) preparing a suspension of the nanoparticles, for example an aqueous suspension; and
- (iii) forming a particle formulation by spray drying;

and then thereafter if necessary,

(iv) forming a pharmaceutical composition.

In some embodiments of processes of the invention the liquid, for example water comprises further components, for example stabilisers. A stabiliser is any compound which prevents aggregation of the nanoparticles in liquid form. Example of suitable stabilizer compounds include: hydroxyl propyl methyl cellulose (HPMC), sodium lauryl sulphate (SLS) and poly vinyl pyridone (PVP). Example of suitable stabilizer compounds include: hydroxyl propyl methyl cellulose (HPMC), carboxymethylcellulose sodium lauryl sulphate (SLS) and poly vinyl pyrrolidone (PVP), soy lecithin, polysorbate (20, to 80), Span (20 or 80), dipalmitoylphosphatidylcholine, poloxomers, sodium deoxycholate, sodium docusate, PLA-PEG, Cremophors and Solutol.

In one embodiment the stabilisers comprise a povidone polymer and a lecithin. In a further embodiment the stabiliser are selected from a povidone polymer and soy lecithin, for example PVP and soy lecithin. In one embodiment the povidone polymer and lecithin are in the ratio:

- (i) povidone polymer : lecithin in the range about 10 :1 to about 2 : 1, for example about 5 to about 1 or about 4 to about 1 or about 3 to about 1;

In a further embodiment the povidone and lecithin further comprise carboxymethylcellulose (CMC), such as the sodium salt of CMC. In a further embodiment the CMC is present at a ratio compared to the PVP in the range about 10 :1 to about 2 : 1, for example about 5 to about 1 or about 4 to about 1 or about 3 to about 1 and/or at a ratio compared to the lecithin about 3 :1 to about 1 : 3, for example about 2 to about 1 or about 1 to about 1.

The term 'lecithin' refers to a yellow-brownish fatty substances occurring in animal and plant tissues, and in egg yolk, comprising phosphoric acid, choline, fatty acids, glycerol, glycolipids, triglycerides, and phospholipids (e.g., phosphatidylcholine, phosphatidylethanolamine, and phosphatidylinositol) or any combination thereof.

Stabilizers are added to the suspension at a concentration sufficient to prevent aggregation of the nanoparticles. In general in the range 0.1-1%. In one

embodiment one or more of the following stabilizers are added: about 0.5%PVP, about 0.5% HPMC and about 0.1% SLS.

In general, the aqueous suspension contains no other solvents. This has the advantage that there are no residual solvents in the particle formulation of the invention.

In general particles of the formulations of the invention have a diameter between 1 μ m to 10 μ m. Although, as the skilled man will be aware, modification of the spray drying conditions will modify the size of particles formed. For example particles as small as 0.2 μ m and as large as 20 μ m can be formed depending of the requirements of the pharmaceutical formulation for which the particles are intended.

As their name suggests, the nanoparticles used in the practice of the present invention are particles with one dimension in the nanometer (nm) size range, that is, from about 1 to 1,000 nm. Particularly the nanoparticles are in the size range of about about 100 to about 1000 nm, for example in the range about 200 to about 1000 nm, such as particles with an average particle size of about 200 to about 600nm, for example about 200 to about 400, about 200 to about 300 or about 200 to about 250nm. The nanoparticles may have any shape.

The skilled man would be aware of a number of methodologies for making nanoparticles. Each of these methods would produce nanoparticles suitable for using in processes of the invention. For a summary of processes available to make nanoparticles the reader is referred to: An Overview: Nanoparticles. Patel et al International Journal of Pharmaceutical Sciences and Nanotechnology 1(3), 215-220.

Examples of methodologies for making nanoparticles include:

- (i) milling for example using the Dena particle reduction machine, as described in WO 2007/020407,
- (ii) US 2009 /0317504 A1, , Markku Rajala et al.
- (iii) US 7,572, 430 B2, 2009, Joel A, Taube et al

- (iv) Bingbing Jiang, Ling hu, Changyou Gao, Jiacong Shen, 2005. International Journal of Pharmaceutics 304, 220-230 Cristini, F., Delalonde, M., Jousset-Dubien, C., Bataille, B., 2003. Elaboration of ibuprofen microcomposites in supercritical CO₂. Proceedings of the 6th International Symposium on Supercritical Fluids, Brunner G., Kikic I., Perrut M., Edts., pp 1917-1922.
- (v) Subrata Mallicka, Satyanarayan Pattnaika, Kalpana Swaina, Pintu K. Deb, Arindam Sahab, Gaurisankar Ghoshalb and Arijit Mondalb, 2008. Formation of physically stable amorphous phase of ibuprofen by solid state milling with kaolin. European Journal of Pharmaceutics and Biopharmaceutics, Volume 68 (2), 346-351.
- (vi) Vijaykumar, N., Venkateswarlu, V. and Raviraj, P., 2010. Development of oral tablet dosage form incorporating drug nanoparticles, RJPBCS 1(4), Page 952.

In one embodiment, nanoparticles are made using the Dena particle reduction machine, using the following condition:

- (i) RPM of impellor

The impellor of the rig rotates at about 1400 rotations per minute in the clockwise direction.

- (ii) Grinding media

The grinding media used are Yttrium stabilized zirconium beads of size 0.2mm at a volume of 150 mL which enable the production of an average particle size of approximately 250-300nm. The particle diameter can be manipulated by changing the dimensions of the grinding media with larger media (0.4 mm) giving coarser particles and smaller media (0.1 mm or 0.15 mm) giving rise to finer particulates. The volume of grinding media can also be adjusted to modify the efficiency of size reduction, with larger media volumes typically giving rise to smaller particulates. With increased media volumes, the batch size of suspension that can be processed must however be reduced accordingly with some reduction in the solids content of the suspension also necessary to enable free flow of the formulation.

(iii) Batch volumes

Using the Dena DM100 size reduction system, batch volumes ranging from 150 to 500mL can be processed to produce nanoparticles in the desired size range. Larger scale equipment can however be used to produce equivalent sized particles at increased volume.

(iv) Temperature

The heat exchanger attached to the size reduction system enables the temperature of the sample suspensions to be controlled during processing. The water inlet tube is connected into the heat exchanger from a cold water source which allows for efficient heat transfer and cooling of the formulation during processing. During processing the temperature of the sample suspensions are maintained between 15-30°C (Coolant systems can also be used to maintain temperatures at cool levels (<10°C).

(v) Solids content of suspensions

A range of solids contents 2%w/v to 40%w/v can be processed using the Dena size reduction systems, which can be maximized through use of a reduced volume of grinding media.

Formulations of the invention are, in general, prepared by spray drying. The skilled man would be familiar with a number of apparatuses and conditions for spray drying suspensions of particles. Conditions used in spray drying methodologies, used to prepare particles of the invention include:

- (i) An Inlet temp of 70-130°C, for example 120°C;
- (ii) A Flow rate of 400 – 800l/hr, for example 600l/hr; and
- (iii) A Liquid feed rate of 2-10%, for example 5%.

In a further aspect of the invention there is provided a particle formulation produced using a process of the invention.

In a further aspect of the invention there is provided a particle formulation substantially as described herein.

In a further aspect of the invention there is provided a particle formulation produced substantially by a process as described herein.

In a further aspect of the invention there is provided a pharmaceutical composition comprising a particle formulation of the invention in association with one or more pharmaceutical carriers, excipients or diluents. Suitable carriers, excipients or diluents may be selected having regard to the intended mode of administration and standard practice. The pharmaceutical compositions may be for human or animal usage in human and veterinary medicine, preferably for treatment of a condition, disease or disorder as herein defined. Pharmaceutical compositions may be in the form of a dry powder, an aerosol, a spray, a capsule or a tablet.

The compositions of the invention may be in a form suitable for oral use (for example as tablets, lozenges, hard or soft capsules, dispersible powders or granules), for topical use for administration by inhalation (for example as a finely divided powder or a liquid aerosol), for administration by insufflation (for example as a finely divided powder).

The compositions of the invention may be obtained by conventional procedures using conventional pharmaceutical excipients, well known in the art. Thus, compositions intended for oral use may contain, for example, one or more colouring, sweetening, flavouring and/or preservative agents.

Suitable pharmaceutically acceptable excipients for a tablet formulation include, for example, inert diluents such as lactose, sodium carbonate, calcium phosphate or calcium carbonate, granulating and disintegrating agents such as crospovidone, croscarmellose sodium, sodium starch glycollate, corn starch or algenic acid; binding agents such as starch, polyvinylpyrrolidone, or hydroxypropylmethylcellulose; lubricating agents such as magnesium stearate, stearic acid, sodium stearyl fumarate or talc; preservative agents such as ethyl or propyl p-hydroxybenzoate, and anti-oxidants, such as ascorbic acid. Tablet formulations may be uncoated or coated either to modify their disintegration and the subsequent absorption of the active ingredient within the gastrointestinal

tract, or to improve their stability and/or appearance, in either case, using conventional coating agents and procedures well known in the art.

Compositions for oral use may be in the form of hard gelatin capsules in which the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate, mannitol, lactose or kaolin, or as soft gelatin capsules in which the active ingredient is mixed with water or an oil such as peanut oil, liquid paraffin, or olive oil.

Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water generally contain the active ingredient together with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients such as sweetening, flavouring and colouring agents, may also be present.

Compositions for administration by inhalation may be in the form of a conventional pressurised aerosol arranged to dispense the active ingredient either as an aerosol containing finely divided solid. Conventional aerosol propellants such as volatile fluorinated hydrocarbons or hydrocarbons may be used and the aerosol device is conveniently arranged to dispense a metered quantity of active ingredient.

When administered via inhalation the unit dose of the active ingredient may generally be in the range of from 0.1 µg to 10000 µg, 0.1 to 5000 µg, 0.1 to 1000 µg, 0.1 to 500 µg, 0.1 to 200 µg, 0.1 to 200 µg, 0.1 to 100 µg, 0.1 to 50 µg, 5 µg to 5000 µg, 5 to 1000 µg, 5 to 500 µg, 5 to 200 µg, 5 to 100 µg, 5 to 50 µg, 10 to 5000 µg, 10 to 1000 µg, 10 to 500 µg, 10 to 200 µg, 10 to 100 µg, 10 to 50 µg, 20 to 5000 µg, 20 to 1000 µg, 20 to 500 µg, 20 to 200 µg, 20 to 100 µg, 20 to 50 µg, 50 to 5000 µg, 50 to 1000 µg, 50 to 500 µg, 50 to 200 µg, 50 to 100 µg, 100 to 5000 µg, 100 to 1000 µg or 100 to 500 µg.

In formulations to be administered by inhalation, the active ingredient is desirably finely divided, i.e. the particles of active ingredient have a mass median diameter of less 10 µm. In some formulations to be administered by inhalation the finely divided active ingredient may be suspended in a propellant (e.g. a

HFA) with the assistance of a dispersant, such as a C₈-C₂₀ fatty acid or salt thereof, (for example, oleic acid), a bile salt, a phospholipid, an alkyl saccharide, a perfluorinated or polyethoxylated surfactant, or other pharmaceutically acceptable dispersant. Alternatively, the finely divided compound may be coated by another substance.

In one embodiment of the particle formulation of the invention is administered in a dry powder formulation. Dry powder formulations are used in a dry powder inhaler. The inhaler may be a single or a multi dose inhaler, and may be a breath actuated dry powder inhaler.

In dry powder formulations for administration by inhalation the active ingredient is generally formulated in association with carriers/diluents to facilitate accurate dosing from an inhaler. Examples of carriers/diluents that may be used in dry powder formulations include for example, a mono-, di- or polysaccharide, and sugars for example, lactose, glucose, raffinose, melezitose, lactitol, maltitol, trehalose, sucrose, mannitol and starch.

One form of dry powdered formulation comprises fine particles of the active ingredient, coarse particles of carrier/diluent, and optionally small and/or fine particles of carrier/diluent. This form of dry powder formulation is known in the art as an 'Ordered mixture'.

The term coarse carrier /diluent refers to carrier/diluent having a mass median diameter of greater than 25 µm; small carrier /diluent refers to carrier/diluent having a mass median diameter in the range of from 10 µm to 25 µm; and fine carrier/diluent refers to carrier/diluent having a mass median diameter of less than 10 µm. In the context of the present invention mass median diameter is measured by a laser diffraction instrument (e.g. a Malvern MasterSizer 2000).

Another form of dry powder formulation is where the fine particles of the drug are mixed with fine and/or small particles of carrier/diluent, and the mixture of particles agglomerated into spheres, which break up during the inhalation procedure e.g. see US 5,551,489. The spheres may be filled into the drug reservoir of a multidose inhaler, for example, that known as Turbuhaler™ in

which a dosing unit meters the desired dose which is then inhaled by the patient. With this system the active ingredient, with or without a carrier substance, is delivered to the patient.

For further information on formulation the reader is referred to Chapter 25.2 in Volume 5 of Comprehensive Medicinal Chemistry (Corwin Hansch; Chairman of Editorial Board), Pergamon Press 1990.

The amount of active ingredient (typically less than 10 mg for inhalation, but probably less than 600 mg for oral) that is combined with one or more excipients to produce a single dosage form will necessarily vary depending upon the host treated and the particular route of administration. For example, a formulation intended for oral administration to humans will generally contain, for example, from 0.5 mg to 2 g of active agent compounded with an appropriate and convenient amount of excipients which may vary from about 5 to about 98 percent by weight of the total composition. Dosage unit forms will generally contain about 1 mg to about 500 mg of an active ingredient. For further information on Routes of Administration and Dosage Regimes the reader is referred to Chapter 25.3 in Volume 5 of Comprehensive Medicinal Chemistry (Corwin Hansch; Chairman of Editorial Board), Pergamon Press 1990.

In a further aspect of the invention there is provided a particle formulation of the invention for use as a medicament.

In a further aspect of the invention there is provided the use of a formulation of the invention in the prevention or treatment of a respiratory disease, for example asthma or COPD.

In a further aspect of the invention there is provided the use of a formulation of the invention in the manufacture of a medicament for prevention or treatment of a respiratory disease, for example asthma or COPD.

In a further aspect of the invention there is provided a formulation of the invention for the prevention or treatment of a respiratory disease, for example asthma or COPD.

In a further aspect of the invention there is provided a method of treating a

respiratory disease, for example asthma or COPD, said method comprising administering to a subject in need thereof, a formulation of the invention in an amount sufficient to treat the condition.

In a further aspect of the invention there is provided a method of preventing a respiratory disease, for example asthma or COPD, said method comprising administering to a subject in need thereof, a formulation of the invention in an amount sufficient to treat the condition.

Respiratory diseases include: obstructive diseases of the airways including: asthma, including bronchial, allergic, intrinsic, extrinsic, exercise-induced, drug-induced (including aspirin and NSAID-induced) and dust-induced asthma, both intermittent and persistent and of all severities, and other causes of airway hyper-responsiveness; chronic obstructive pulmonary disease (COPD); bronchitis, including infectious and eosinophilic bronchitis; emphysema; bronchiectasis; cystic fibrosis; sarcoidosis; farmer's lung and related diseases; hypersensitivity pneumonitis; lung fibrosis, including cryptogenic fibrosing alveolitis, idiopathic interstitial pneumonias, fibrosis complicating anti-neoplastic therapy and chronic infection, including tuberculosis and aspergillosis and other fungal infections; complications of lung transplantation; vasculitic and thrombotic disorders of the lung vasculature, and pulmonary hypertension; antitussive activity including treatment of chronic cough associated with inflammatory and secretory conditions of the airways, and iatrogenic cough; acute and chronic rhinitis including rhinitis medicamentosa, and vasomotor rhinitis; perennial and seasonal allergic rhinitis including rhinitis nervosa (hay fever); nasal polyposis; acute viral infection including the common cold, and infection due to respiratory syncytial virus, influenza, coronavirus (including SARS) and adenovirus;

The invention is now exemplified by the following non-limiting examples with reference to the following figures.

Figure 1 - shows a twin stage Impinger wherein the following parts are marked: (1) throat, (2) neck tube, (3) Stage I and (4) Stage II.

Figure 2.- shows the average particle size distribution for 15% ibuprofen and : 3% Glibenclamide nano suspension at 5, 20, 30, 45 and 60 minutes after processing using the D100 size reduction system.

Figure 3 - shows a scanning electron micrograph of a spray dried Ibuprofen/Glibenclamide particle formulation of the invention.

Figure 4.- shows a differential scanning calorimetry plots for:
(a) the ibuprofen raw powder;
(b) the Glibenclamide raw powder;
(c) the processed Ibuprofen/Glibenclamide nano suspension; and
(d) the Ibuprofen/Glibenclamide spray dried powder.

Figure 5 - shows the X-ray powder diffraction patterns for;:
(a) the Glibenclamide raw powder;
(b) the ibuprofen raw powder;
(c) the Ibuprofen/Glibenclamide spray dried powder.and
(d) the processed Ibuprofen/Glibenclamide nano suspension;.

Figure 6- shows a DSC plot for;
(a) Salmeterol Raw powder;
(b) Flu:Sal (10:1) spray dried powder; and
(c) Flu Raw powder

Figure 7- shows an X-ray diffraction pattern for:
(a) Salmeterol Raw powder,
(b) Flu Raw powder;
(c) Flu:sal (10:1) physical mixture,; and
(d) Flu:Sal (10:1) spray dried powder

Figure 8 – shows the stage by stage deposition of the Flu:Sal formulation using the NGI test (see Example 3). In the figure the x –axis shows the data for the different stages of the NGI instrument and the Y axis shows percentage normalized mass deposited as a function of recovered dose. In each set of bars the left bar is Flu and the right bar is Sal.

The following abbreviations are used:

DSC	differential scanning calorimetry
flu	fluticasone
FP	fluticasone propionate
gli	glibenclamide .
HPMC	hydroxy propyl methyl cellulose
Ibu	ibuprofen;
PVP	polyvinyl pyrrolidinone
<i>PXRD</i>	<i>Powder X-ray diffraction</i>
sal	salmeterol
SLS	sodium lauryl sulfate
SX	salmeterol xinafoate

In the Examples the following materials were used:

Ibuprofen USP was purchased from Albermarle Europe sprl, (Belgium). Glibenclamide BP/EP was purchased from Anzen Exports, Kolkata, India. Hydroxy propyl methyl cellulose (HPMC) was a gift from Shinetsu, (Japan). Sodium lauryl sulfate (SLS) was purchased from Sigma–Aldrich, USA. Kollidon 30 (PVP K-30) was purchased from BASF (Aktiengesellschaft Ludwigshafen, Germany). Soya lecithin was purchased from Rectapur, BDH, UK. All other materials used were of analytical grade and purchased from established suppliers.

Example 1: Preparation of Ibuprofen/Glibenclamide Particle Formulation

(i) Processing of 15%w/v Ibuprofen : 3%w/v glibenclamide nano-suspension

The two drugs- ibuprofen (a ductile, poorly aqueous soluble drug) and glibenclamide (a potent sulphonyl urea drug) in 5:1 ratio (15%w/w: 3%w/w) were dispersed in an aqueous stabilizer solution containing 0.5%PVP, 0.5%HPMC and 0.1%SLS. The resultant suspension was processed using

the Dena particle size reduction system (DM100, Dena Technologies Ltd, Mapplewell, Barnsley, UK). Samples were collected at 5 minutes, 20, 30, 45 and 60 minutes. For more information on the DM100 particle size reduction machine see: International Patent Application, WO 2007/020407.

(ii) *Particle sizing*

The particle size for sample suspensions collected at time intervals was analysed by Dynamic Light Scattering (DLS) using the nano Zetasizer (Malvern Instruments Ltd, Malvern, UK).

Figure 2 demonstrates the overlayed average particle size distribution profiles for Ibu : Gli nano suspension generated at 5, 20, 30, 45 and 60 minutes using the DM100 size reduction system.

The average particle size determined by nano zetasizer for the Ibu:gli nano-suspension at 5mins was 581nm (represented by the red coloured profile (a) in figure 2) and was further reduced to 224nm at 60mins (represented by pink coloured profile (b) in figure 2).

(iii) *Determination of the active content by HPLC*

The processed suspension was analysed for active content by a modification of a validated HPLC method (US Pharmacopeia 28, NF 23 (2005) pg 991)

A Waters Alliance (Water systems, UK) 2695 separations module with 2487 dual wavelength absorbance detector at 214nm was used with (Vydac Technology Ltd., UK) C-18 silica based 25cmx4.6mmx5µm column. The mobile phase was acetonitrile: water (50:50), with pH of water adjusted to 2.5 using ortho phosphoric acid. The flow rate was set to 1.0mL/min, column temperature set to 30±2°C and the sample temperature set at 20±2°C.

Table 1 demonstrates the concentration of ibuprofen and glibenclamide in the processed nano suspension determined by the HPLC and the ratio of ibu : gli in the nano suspension before spray drying.

Table 1 Concentration of Ibuprofen, Glibenclamide and ibu : gli ratio in the nano suspension

Replicates	Concentration of ibuprofen mg/mL	Concentration of glibenclamide mg/mL	Ratio of ibu : gli in ibu : gli nano suspension (5:1)
1	125.75	25.41	4.94
2	125.09	25.20	4.96
3	126.78	25.46	4.98
Mean	125.87	25.36	4.96

The ratio of Ibu : Gli in the nano suspension when determined by a validated HPLC method was found to be 4.96 : 1. This indicates that the 5:1 ibu : gli ratio was maintained in the nano suspension even after processing using the DM100 size reduction system.

A comparative DSC plot for nano suspension, glibenclamide (gli) raw powder and ibuprofen (ibu) raw powder is given in Figure 4.

(iv) Spray Drying

Spray-drying was carried out using a Büchi 190 Mini Spray Dryer fitted with a two-fluid nozzle and peristaltic pump. The processing parameters comprised an inlet temperature of 120°C, an atomizing air flow rate of 600 l/h and a liquid feed rate of 5%. A resulting outlet temperature of 72°C was observed. The Ibu:Gli suspension was diluted to 1.5% in distilled water and spray dried using the above conditions. The resultant powder produced

by spray-drying was then analysed for active agent content using the same HPLC method described above with associated evaluation by scanning electron microscopy (SEM), X-ray powder diffraction (XRPD) and differential scanning calorimetry (DSC).

(v) *Analysis of particle formulation formed by spray drying*

Scanning electron microscopy (SEM)

Following spray-drying of the nanosuspension, crystalline porous aggregates were formed providing potential for optimal aerodynamic behavior and co-deposition of multiple agents, see Figure 3.

Differential scanning calorimetry (DSC)

A comparative DSC plot for Ibu:gli spray dried powder, nano suspension, glibenclamide (gli) raw powder and ibuprofen (Ibu) raw powder is given in Figure 4.

The DSC plot given in Figure 4 shows the melting transitions of ibuprofen and glibenclamide in the ibu:gli spray dried powder and when isolated from suspension. While the melting endotherm for Ibuprofen is sharp, the melting endotherm for glibenclamide in the spray dried powder is visible as a broad peak which is possibly related to changes in the particle size or through its interaction with ibuprofen which is present in the molten state at temperatures exceeding 80 °C.

X-ray powder diffraction (XRPD)

Overlaid X-ray diffraction patterns for the Ibu:gli nano suspension, Ibu:gli spray dried powder, ibuprofen raw powder and glibenclamide raw powder are given in figure 5.

From the PXRD pattern in Fig. 5, crystalline peaks for ibuprofen in the Ibu:Gli spray dried powder can be observed clearly, though for

glibenclamide the crystalline peaks are of lower intensity owing to the low concentration of the glibenclamide compared to that of Ibuprofen with some additional potential for line broadening through production of ultrafine particles.

Ratio of ibuprofen/Glibenclamide by HPLC

The Ratio of ibuprofen/Glibenclamide in the spray-dried particles by HPLC was analysed using the HPLC method outlined in (iii) above. Table 2 gives the active content and the ratio of Ibuprofen and glibenclamide in the spray dried powder determined by HPLC.

Table 2 Ibuprofen and Glibenclamide active content and ibu : gli ratio in the spray dried powder

Replicates	Active content of ibuprofen (% w/w) Nominal content (78.5% w/w)	Active content of glibenclamide (% w/w) Nominal content (15.77% w/w)	Ratio of ibu : gli in spray dried powder (5:1)
1	74.43	16.52	4.51
2	73.68	16.03	4.59
3	73.19	15.90	4.60
4	74.00	16.08	4.60
5	71.24	15.49	4.60
6	73.36	16.42	4.47
Mean	73.32	16.07	4.56

Replicates	Active content of ibuprofen (% w/w) Nominal content (78.5% w/w)	Active content of glibenclamide (% w/w) Nominal content (15.77% w/w)	Ratio of ibu : gli in spray dried powder (5:1)
SD	1.11	0.37	0.06
Acceptable range (% w/w) $\pm$ 10% of nominal	70.65 – 86.35	14.20 – 17.35	

The active agent content data shows the ratio of ibuprofen : glibenclamide in the spray dried powder for six replicates. The average ratio is 4.56:1, which indicates that even after spray drying the ratio of ibuprofen : glibenclamide is maintained in the spray dried powder, although some losses of ibuprofen have been incurred.

(vi) *Twin-stage impinger analysis*

15.1 mg of the (5:1) spray dried powder was weighed into size 3 inhalation grade HPMC capsules and liberated over 2.7 seconds into the twin stage impinger using the Aerolizer dry powder inhaler device (Novartis GmbH, Switzerland) at an air flow of 90 L/min. 30mL of methanol were added to the lower stage base (Stage-II) and 7mL of methanol were added to the upper stage base (Stage-I) to recover the deposited drugs. See Figure 1.

Samples were collected from the throat, neck tube, upper stage base, lower stage base, capsule+aerolizer device. These samples were then injected in the HPLC to determine the ratio of each active agent on each stage of the impinger using the standard HPLC method described in section (iii) above.

Table 3 gives the ratio of Ibuprofen and glibenclamide deposited on the various stages of the twin-stage impinger.

Table 3 Ratio of Ibu:gli deposited in Twin Stage Impinger

Section of impinger	Ratio of Ibu : gli	Particulate cut-off (µm)
Throat	4.98	
Neck Tube	4.87	Upper stage 7.2
Upper stage base	4.90	
Lower stage tube	4.33	Lower stage 5.2
Lower stage base	4.05	
Average	4.63	
SD	0.41	
RSD (%)	8.91	

The data demonstrates the ratios of the two drugs has typically been maintained following aerosolisation, although the finer material <5.2 microns is slightly richer in glibenclamide than its coarser counterpart. This indicates a potential for substantial co-deposition in respiratory tract.

Conclusion :

- From the results we can conclude that both compounds deposited at approximate ratio of 4 - 5 : 1 across all the stages of the twin stage impinger. Each of these agents was present in a composite particle, which showed signs of crystallinity for each agent.
- Thus the ratio of Ibuprofen : glibenclamide is maintained when delivered by dry powder inhaler.

Example 2: Preparation of Fluticasone/Salmeterol Particle Formulation

A 6.0%: 0.6% fluticasone:salmeterol formulation (i.e. 10:1) with an average particle size of about 300nm was prepared as follows.

(i) Processing of 6%w/v fluticasone : 0.6%w/v salmeterol nano-suspension

Fluticasone and salmeterol in 10:1 ratio (6%w/w: 0.6%w/w) were dispersed in an aqueous stabilizer solution containing 0.5%PVP and 0.1%soya lecithin. The resultant suspension was processed using the Dena particle size reduction machine (DM100, Dena Technologies Ltd, Mapplewell, Barnsley, UK) as described above. Samples were collected at 5 minutes, 35, 50 and 75 minutes.

(ii). Particle sizing

The particle size for sample suspensions collected at time intervals was analysed by Dynamic Light Scattering (DLS) using the nano Zetasizer (Malvern Instruments Ltd, Malvern, UK).

Table-1 gives average particle size for flu : sal nano suspension generated at 5, 35, 50 and 75 minutes using the DM100 size reduction system.

Table-1 Average particle size distribution for 6%flu:0.6%sal nano suspension

Time (mins)	Average particle size (nm)	Poly dispersity Index (pdl)
5	350	0.31
35	263	0.28
50	260	0.26
75	250	0.24

The average particle size determined by nano zetasizer for the flu:sal nano-suspension at 5mins was 350nm and was further reduced to 250nm at 75mins. The poly dispersity index was 0.31 and 0.24 respectively.

(iii). Determination of the active content by HPLC and Spray-drying

The processed suspension was analysed for active content by HPLC method. A Waters Alliance (Water systems, UK) 2695 separations module with 2487 dual wavelength absorbance detector at 228nm was used with (Vydac Technology

Ltd., UK) C-18 silica based 25cmx4.6mmx5 μ m column. The mobile phase was methanol:0.6% aqs ammonium acetate (75:25). The flow rate was set to 1.0ml/minute, column temperature set to 40 $\pm$ 2°C and the sample temperature set at 20 $\pm$ 2°C.

Table-2 demonstrates the concentration of fluticasone and salmeterol in the processed nano suspension determined by the HPLC and the ratio of flu : sal in the nano suspension before spray drying.

Table-2 Concentration of fluticasone, salmeterol and flu : sal ratio in the nano suspension

Replicates	Concentration of fluticasone mg/mL	Concentration of salmeterol mg/mL	Ratio of flu : sal in flu : sal nano suspension (10:1)
1	38.57	4.12	9.36
2	50.09	5.24	9.56
3	50.34	5.04	9.99
Mean			9.63:1

The ratio of flu:sal in the nano suspension when determined by a validated HPLC method was found to be 9.63 : 1. This indicates that the 10:1 flu:sal ratio is maintained in the nano suspension even after processing using the DM100 size reduction system.

(iv) Spray Drying

The suspension was then spray-dried as described above.

(v) Determination of the active content in Spray-dried powder

The resultant spray dried powder produced by spray-drying the nano-suspension was then analysed for active agent content using the same HPLC method.

Table-3 demonstrates the concentration of fluticasone and salmeterol in the spray dried powder determined by the HPLC and the ratio of flu : sal in the spray dried powder.

Table-3 Concentration of fluticasone, salmeterol and flu : sal ratio in the spray dried powder

Replicates	Concentration of fluticasone mg/mL	Concentration of salmeterol mg/mL	Ratio of flu : sal in flu : sal nano suspension (10:1)
1	0.6365	0.0644	9.88
2	0.5992	0.0616	9.73
3	0.6021	0.0618	9.74
Mean			9.78:1

(vi) *Twin-stage impinger analysis*

15.2 mg of the Flu:Sal (10:1) spray dried powder was weighed in size 3 HPMC capsule and liberated over 2.7 seconds into the twin stage impinger using the aerolizer at an air flow of 90 L/min. 30mL of methanol were added to the lower stage base (Stage-II), 7mL of methanol were added to the upper stage base (Stage-I).

Samples were collected from the throat, neck tube, upper stage base, lower stage base, capsule + aerolizer. These samples were then injected in the HPLC for determining the ratio using a standard HPLC method.

Table-1 gives the %deposition (%D) of fluticasone and **Table-2** gives the %deposition of Salmeterol on the twin stage impinger.

Table-1

FLU-%D		
SAMPLES	CONC	% D
Throat	3.01	38.63
Neck Tube	1.20	15.38
Upper stage base	0.51	6.52
Lower stage tube	0.52	6.67
Lower stage base	0.01	0.14
Capsule + Aerolizer	2.54	32.66
TOTAL	7.78	100

Table-2

SAL-%D		
SAMPLES	CONC	% D
Throat	0.31	26.35
Neck Tube	0.11	9.03
Upper stage base	0.05	4.04
Lower stage tube	0.05	4.31
Lower stage base	0.05	4.34
Capsule + Aerolizer	0.62	51.92
TOTAL	1.19	100

The tables indicate that the fluticasone and salmeterol gave approximately the same %deposition across the different sections of the twin stage impinger. It is probable that the fine particle mass would be improved if an optimal dry powder formulation incorporating a carrier particle was used. The ratio of the two compounds deposited across all sections of twin stage including the residual levels in the device was 9 : 1.

(vii) Thermal analysis:

Figure -1 gives the differential thermal analysis (DSC) plot for the Salmeterol raw powder, Fluticasone raw powder and flu_sal spray dried powder.

Though there is no definite endothermic peak for Salmeterol in the flu:sal (10:1) spray dried powder, the crystallinity is maintained even after spray drying.

(viii) Powder X-ray diffraction

Figure-2 gives the X-ray diffraction comparison plot for salmeterol raw powder, fluticasone raw powder, fluticasone : salmeterol (10:1) mixture (two compounds mixed physically) and fluticasone: salmeterol spray dried powder.

From the X-ray diffraction plot we can see that the crystallinity is maintained for the fluticasone:salmeterol spray dried powder.

Conclusion:

Both the compounds flu:sal deposited at approximate ratio of 10 : 1 across all the stages of the twin stage impinger. Thus the ratio of flu:sal is maintained when delivered by dry powder inhaler. The DSC and the PXRD results showed that the crystallinity is maintained even after spray drying.

Example 3 Measurement of the consistency of the ratio of drug components in the Fluticasone/Salmeterol Particle Formulation

Experiments were performed using a New Generation Impactor (NGI) (Copley Scientific Ltd., Nottingham, UK) See Marple, et al (2003) Journal of Aerosol Medicine 16, 283-99; Marple, et al (2003) Journal of Aerosol Medicine (2003) 16, 301-24; Marple et al (2004) Journal of Aerosol Medicine 17, 335-43.

Combination particles of FP/SX were formulated into a drug-only pMDI (pressurized metered dose inhaler) with HFA 134a (1,1,1,2-tetrafluoroethane) such that the nominal dose of FP was 250 mcg and SX was 25 mcg. A 50 µl valve was employed to dispense the formulation.

Testing was performed using a Next Generation Impactor (NGI), which was connected to a vacuum pump (GE Motors). Prior to testing, the cups of the NGI cups were coated with 1 % v/v silicone oil in hexane to eliminate particle bounce.

For each experiment, three actuations of the can were discharged into the NGI at 30 L.min⁻¹ as per pharmacopieal guidelines.

European Pharmacopoeia (Ph.Eur.) Section 2.9.18 of Supplement 5.1 of the 5th Edition, September 16th, 2004.

Following aerosolization, the NGI apparatus was dismantled and the actuator and each part of the NGI was washed down into known volumes of HPLC mobile phase. The mass of drug deposited on each part of the NGI was determined by HPLC as described above. This protocol was repeated three times for the can, following which, the fine particle dose (FPD) and fine particle fraction of the targeted delivered amount (FPF_{TDA}) were determined.

Results (see Figure 8)

	Emitted Dose ($\mu\text{g} \pm$ S.D.)	Fine Particle Dose ($\mu\text{g} \pm$ S.D.)	FPF_{TDA} (%)	MMAD $\pm$ GSD
FP	213.2 (3.2)	99.1 (1.7)	39.6 (2.1)	2.8 (2.0)
SX	24.4 (1.9)	11.0 (1.3)	43.9 (1.8)	2.8 (2.0)

The data of the stage by stage deposition shows evidence of co-delivery of both actives on all stages including the actuator, mouthpiece and throat. In addition, the MMAD is small and more importantly the same for both drugs. Therefore, these data conclude that crystalline combination particles are aerosolized efficiently from a metered dose inhaler.

Claims

1. A particle formulation suitable for use in an inhalation formulation comprising a plurality of pharmacologically active ingredients characterized in that the pharmacologically active ingredients are crystalline.
2. A particle formulation according to Claim 1 characterized in that the ratio of the pharmacologically active substances has a distribution of less than $\pm 5\%$ of the target ratio as measured by Impactor testing .
3. A particle formulation according to Claim 1 or Claim 2 further comprising at least one stabilizer.
4. A particle formulation according to Claim 3 wherein the stabiliser comprises one of more of hydroxyl propyl methyl cellulose, carboxymethylcellulose sodium, sodium lauryl sulphate, poly vinyl pyrrolidone soy lecithin, polysorbate (20, to 80), Span (20 or 80) dipalmitoylphosphatidylcholine, poloxomers, sodium deoxycholate, sodium docusate, PLA-PEG, cremophors and solutol.
5. A particle formulation according to Claim 4 wherein the stabiliser comprises one of more of poly vinyl pyrrolidone, hydroxyl propyl methyl cellulose, soy lecithin and sodium lauryl sulphate.
6. A particle formulation according to any one of the preceding Claims wherein the particles have a diameter of 100nm to 40 μ m.
7. A particle formulation according to any one of the preceding claims characterized in that it is formed by spray drying of a nanoparticle formulation.

8. A formulation according to Claim 1 comprising:
 - (i) from about 0.1 to about 20% of a plurality of pharmacologically active ingredients;
 - (ii) about 0.1% to about 2% of one or more povidone polymers;
 - (iii) about 0.01 to 1% of a surfactant; and optionally
 - (iv) about 0.1% to 1% of a further surface stabilizer;
9. A particle formulation according to any one of the preceding claims wherein the pharmacologically active ingredient is one or more of the following classes :Inhaled Corticosteroid (ICS) and Long Acting Beta Agonist (LABA), Short Acting Beta Agonists (SABA), Leukotriene Modifiers (LM) and Immunomodulators.
10. A particle formulation according to any one of the preceding claims wherein the pharmacologically active ingredient is selected from ibuprofen, glibenclamide, theophylline, salmeterol, fluticasone, formoterol, budesonide, beclometasone and carmeterol.
11. A particle formulation according to any one of the preceding claims wherein the pharmacologically active ingredients comprise ibuprofen and glibenclamide or fluticasone and salmeterol.
12. A pharmaceutical composition comprising a particle formulation according to any one of the preceding claims.
13. A pharmaceutical composition according to Claim 12 where the pharmaceutical composition is selected from a dry powder, an aerosol, a spray, a capsule or a tablet.

14. A particle formulation according to any one of Claims 1 to 11 or a pharmaceutical composition according to Claim 12 or Claim 13 for use in therapy.
15. A particle formulation according to any one of Claims 1 to 11 or a pharmaceutical composition according to Claim 12 or Claim 13 for use in the treatment of a respiratory disease.
15. A process for the formation of a particle formulation according to any one of Claims 1 to 10 comprising:
 - (i) mixing a plurality of pharmacologically active compounds,
 - (ii) preparing nanoparticles of the pharmacologically active compounds by co-milling;
 - (iii) preparing a suspension of the nanoparticles, and
 - (iv) forming a particle formulation by spray drying;and then thereafter if necessary,
 - (v) forming a pharmaceutical composition.

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Figure 1

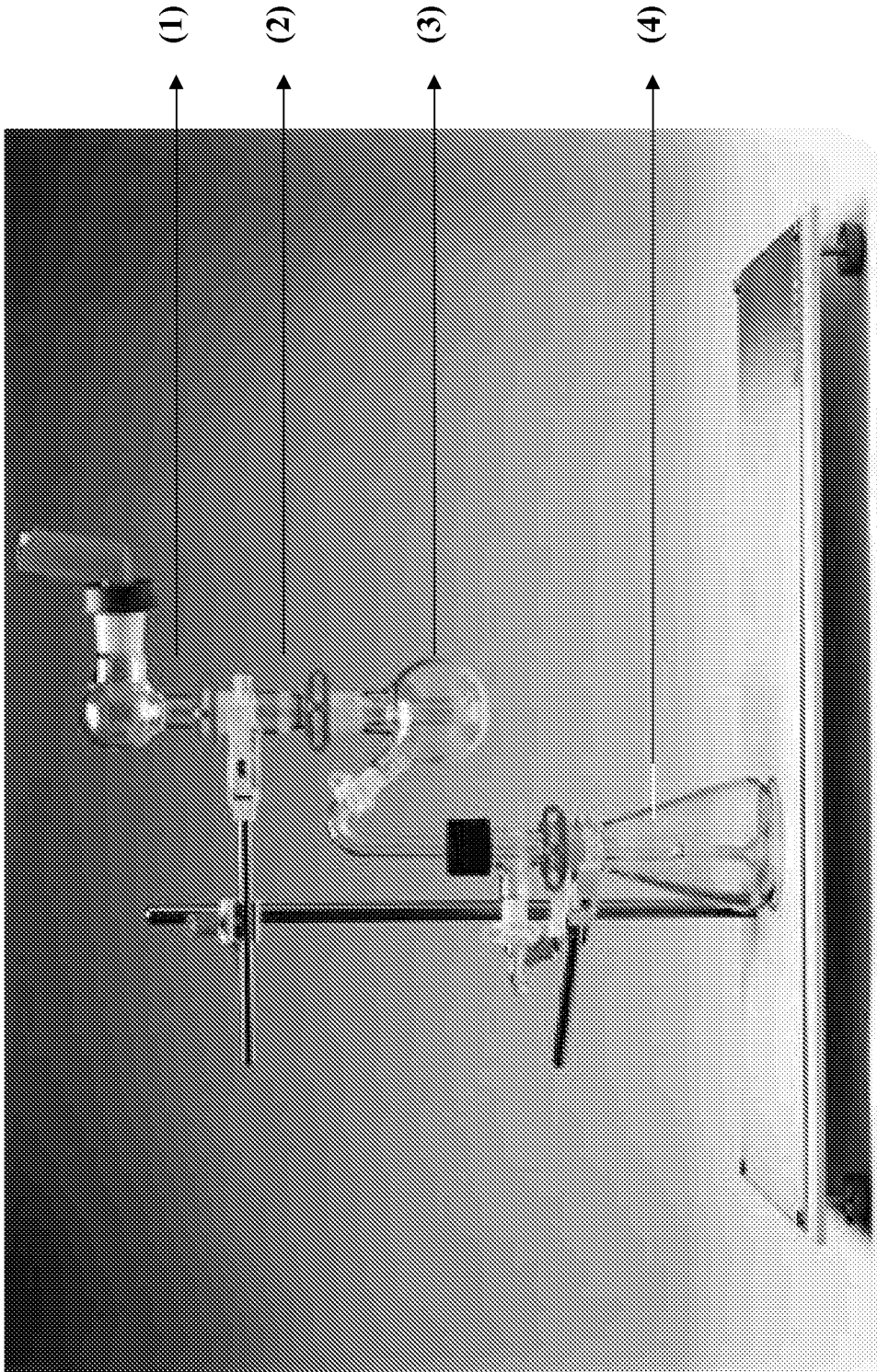


Figure 2

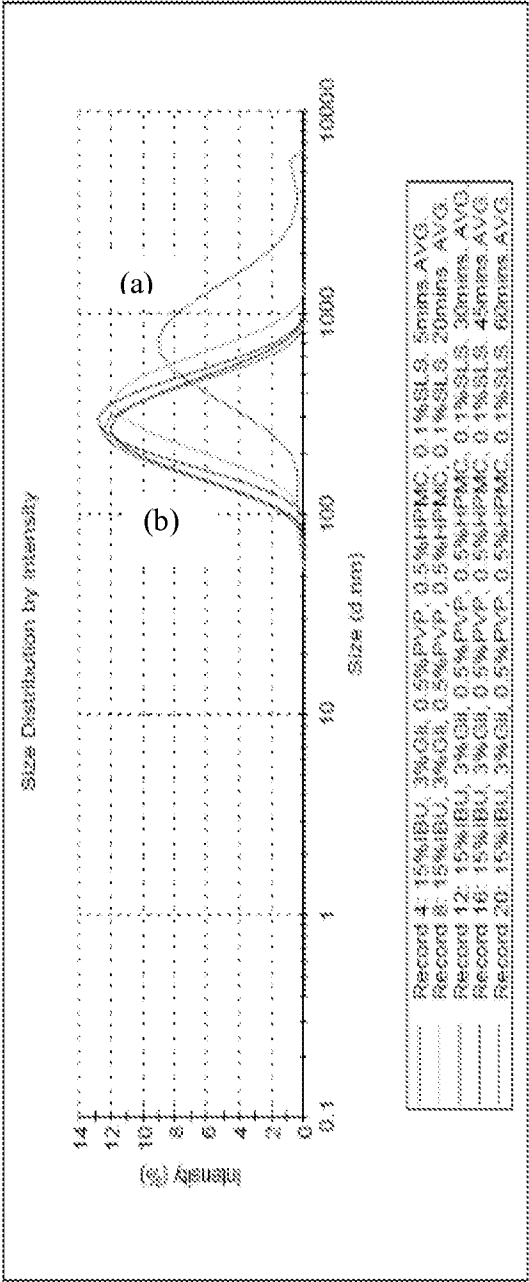


Figure 3

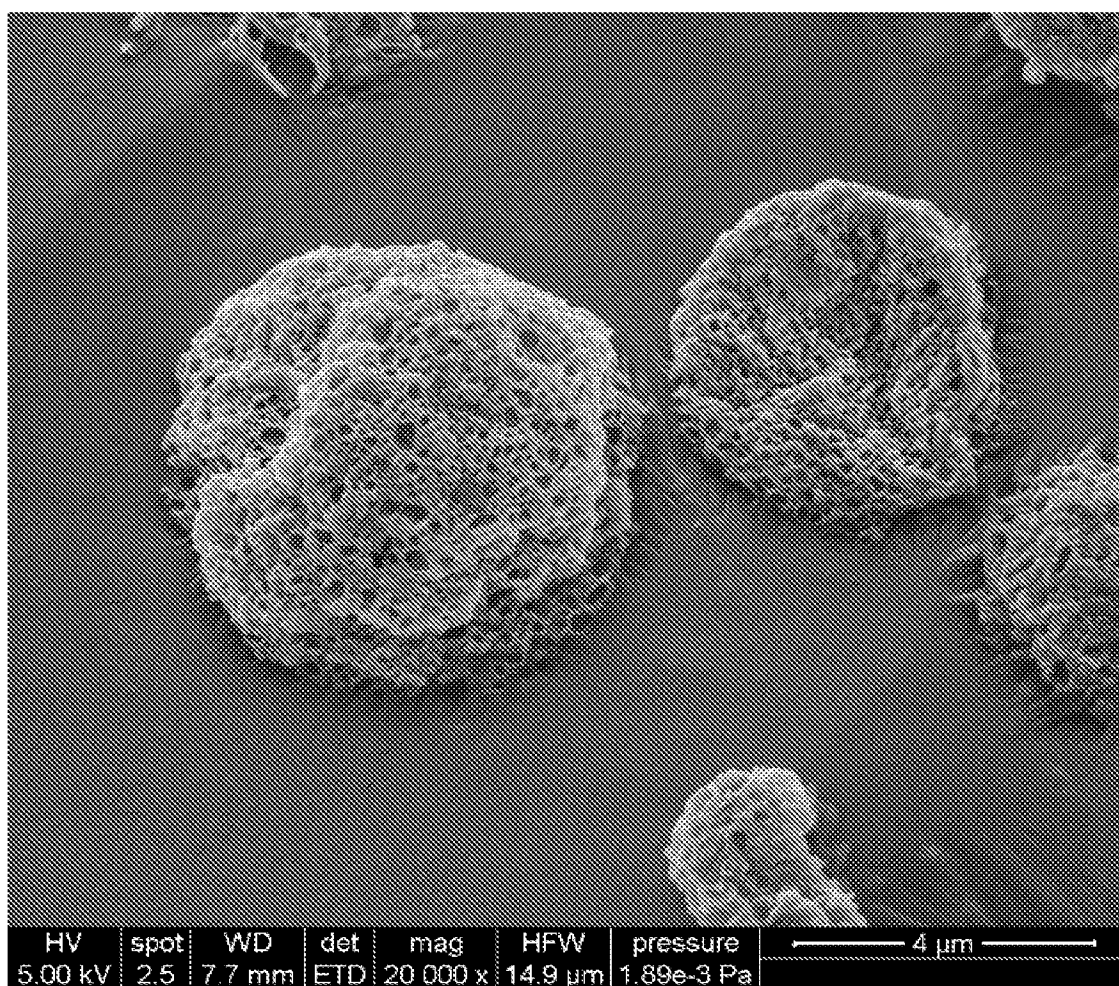


Figure 4

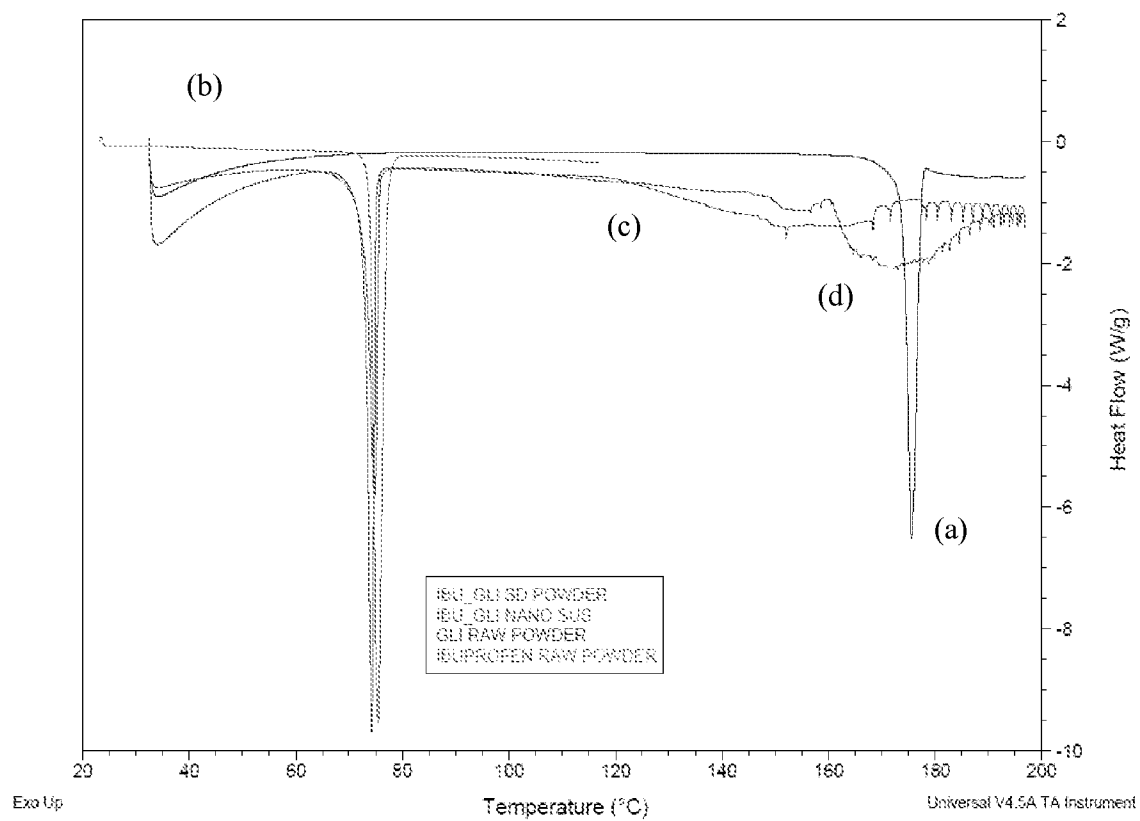


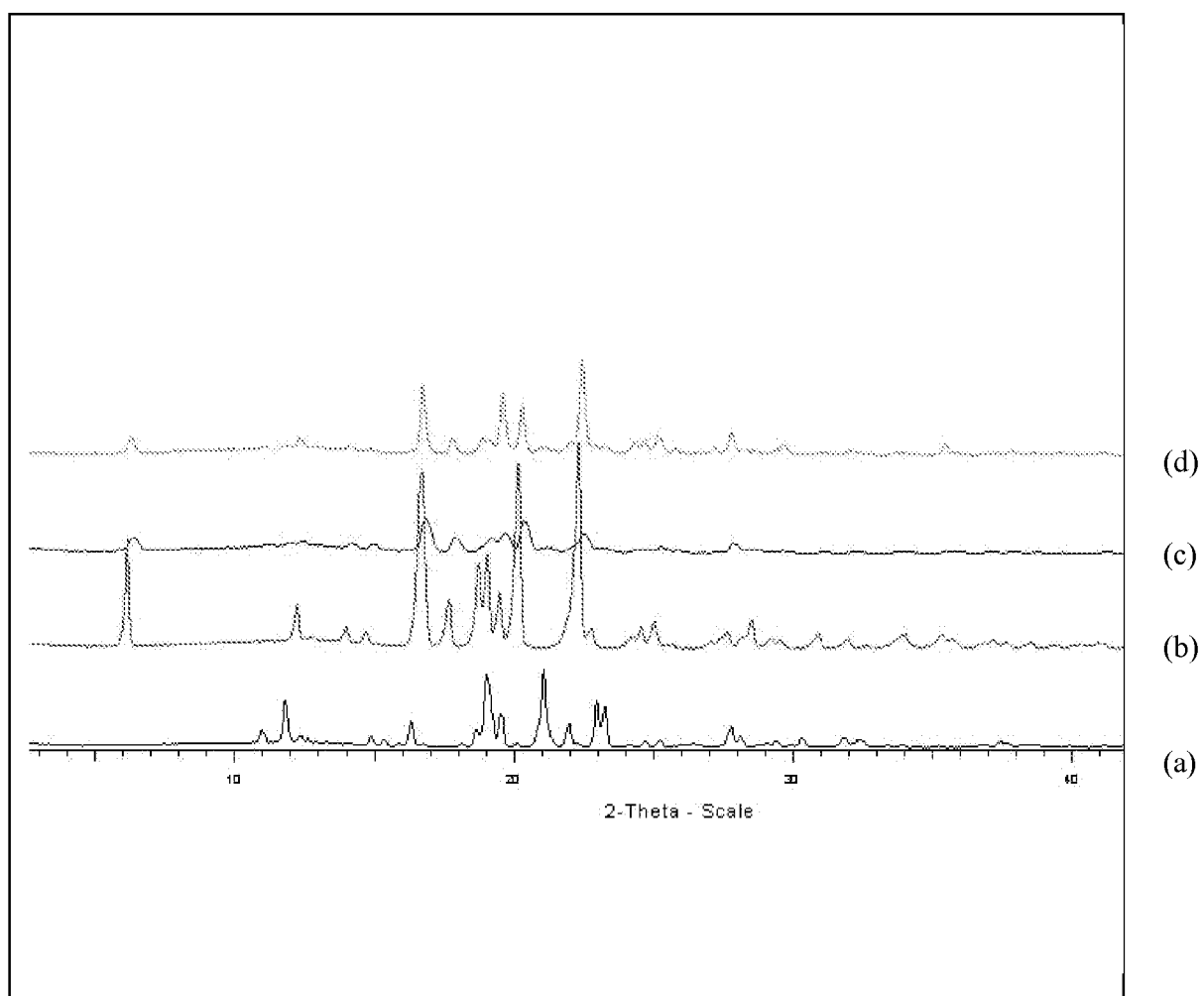
Figure 5

Figure 6

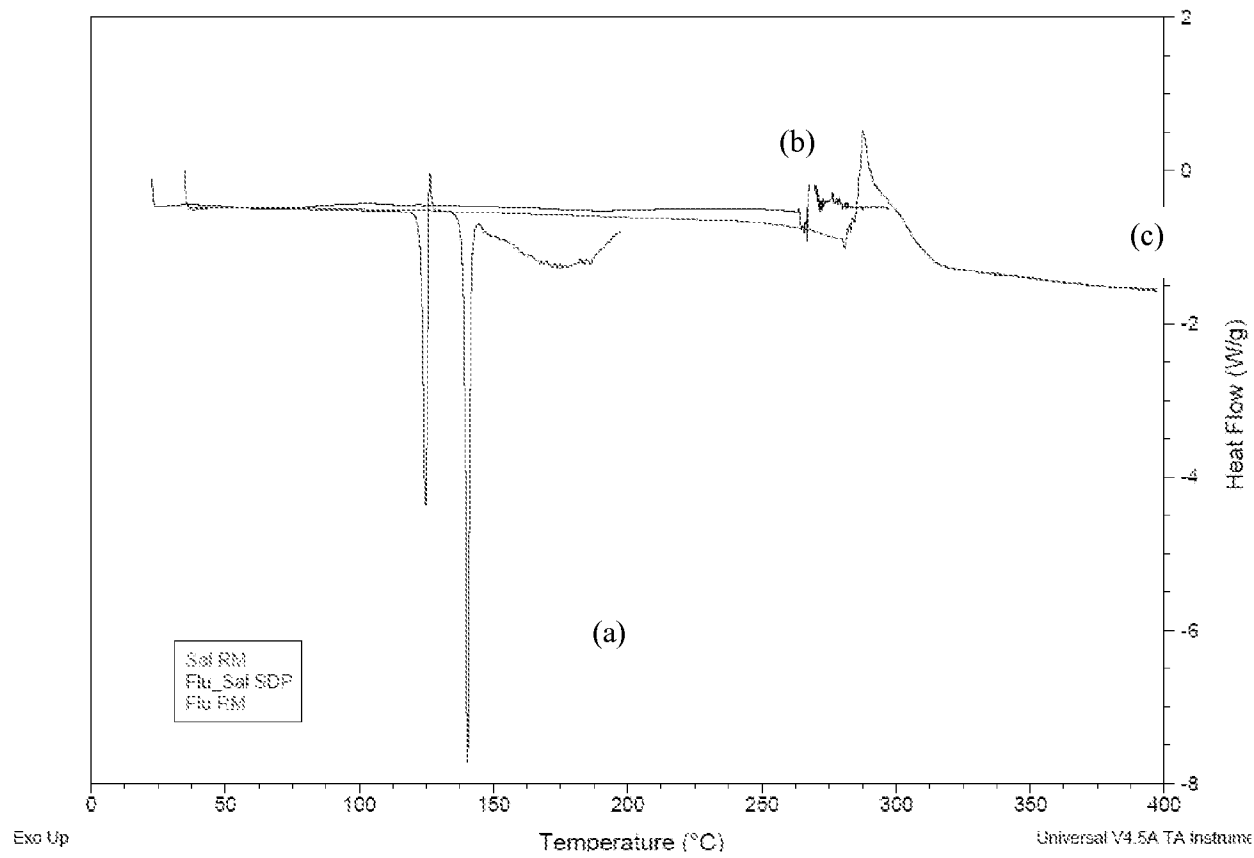


Figure 7

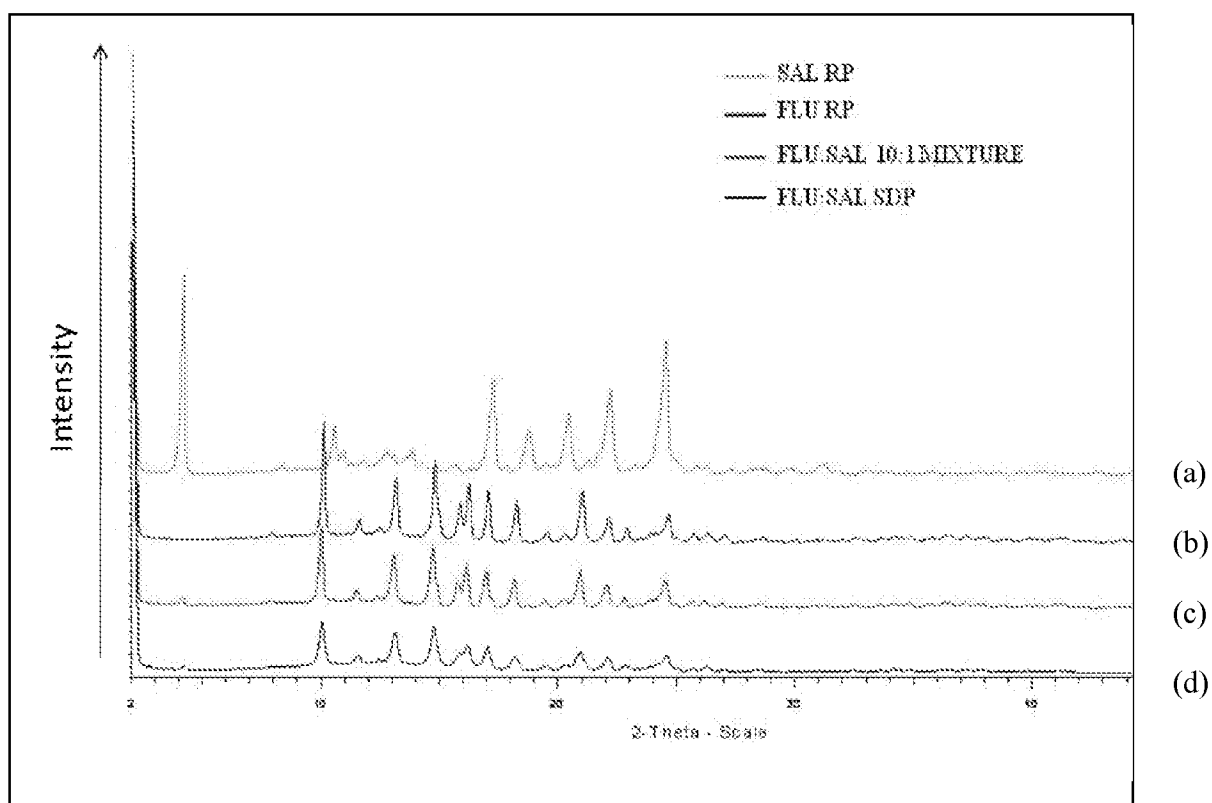


Figure 8

