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WO-A1-98/35800
WO-A1-2011/140307
WO-A2-01/78693
US-A1- 2011 184 088
US-A1- 2011 294 987
"composite", The Free Dictionary , Retrieved from the Internet: URL:<http://www.thefreedictionary.com/composite> [retrieved on 2009-06-12]
"composite", AskOxford.com - Compact Oxford English Dictionary , Retrieved from the Internet: URL:http://www.askoxford.com/concise_oed/composite?view=uk [retrieved on 2009-06-12]

DESCRIPTION

[0001] The present invention relates to particles and to methods of making particles. In particular, the invention relates to pharmaceutical compositions comprising composite excipient particles as defined in claim 1. It is known to administer to patients drugs in the form of fine particles. For example, in pulmonary administration a particulate medicament composition is inhaled by the patient. Pulmonary administration is particularly suitable for medicaments which are intended to cure or alleviate respiratory conditions such as asthma and for medicaments which are not suitable for oral ingestion such as certain biological macromolecules. Known devices for the administration of drugs to the respiratory system include pressurised metered dose inhalers (pMDI's) and dry powder inhalers (DPI's).

[0002] In order that the particles be carried deep into the lungs, the particles must be very fine, for example having a mass median aerodynamic diameter of less than $10\mu\text{m}$.

[0003] Such small particles are, however, thermodynamically unstable due to their high surface area to volume ratio, which provides significant excess surface free energy and encourages particles to agglomerate. In the inhaler, agglomeration of small particles and adherence of particles to the walls of the inhaler are problems that result in the active particles leaving the inhaler as large agglomerates or being unable to leave the inhaler and remaining adhered to the interior of the inhaler.

[0004] In an attempt to improve that situation, dry powders for use in dry powder inhalers often include particles of an excipient material mixed with the fine particles of active material. Such particles of excipient material may be coarse, for example, having mass median aerodynamic diameters greater than $90\mu\text{m}$, (such coarse particles are referred to as carrier particles) or they may be fine.

[0005] The step of dispersing the active particles from other active particles and from the carrier particles, if present, to form an aerosol of fine active particles for inhalation is significant in determining the proportion of the dose of active material which reaches the desired site of absorption in the lungs. In order to improve the efficiency of that dispersal it is known to include in the composition additive materials. Such additive materials are thought to reduce the attractive forces between the particles thereby promoting their dispersal.

[0006] WO 96/23485 discloses powders for inhalation comprising carrier particles and an additive material for the promotion of the dispersal of the active particles from the carrier particles. The use of gentle milling of carrier particles of diameter 90 to $125\mu\text{m}$ in order to remove surface asperities which are suggested to be sites of high surface energy at which active particles can be bound so tightly to the carrier particles that they are not released upon actuation of the inhaler is also disclosed. In some cases the carrier particles are gently milled in the presence of the additive material. However, in all cases, the milling treatment is a gentle one such that the size of the carrier particles is not substantially changed.

[0007] The present invention provides a pharmaceutical composition comprising composite excipient particles, each composite excipient particle comprising a particle of an excipient material and additive material applied to the surface of that particle of excipient material, the composite excipient particles having a mass median aerodynamic diameter of not more than 50 μm determined using an impinger, wherein the additive material is in the form of a coating on the surfaces of the particles of excipient material, and wherein the composition consists essentially of the composite excipient particles, particles of active material, and optionally a flavouring agent.

[0008] The additive material is an material which, when included in a dry powder formulation for inhalation, promotes the dispersal of the particles, particularly the active particles, to form an aerosol upon actuation of the inhaler. Additive materials and dry powder formulations containing the additive materials are disclosed in WO 96/23485 . The additive materials are, in particular, suitable for promoting the release (upon actuation of the inhaler) of the active particles from carrier particles when a dry powder comprising active particles, carrier particles and additive material is administered via a dry powder inhaler.

[0009] It will be understood that the additive material will be a different material to the excipient material.

[0010] It has been found that the milling of the particles of excipient material in the presence of an additive material produces significantly smaller particles and/or requires less time and less energy than the equivalent process carried out in the absence of the additive material. Using the method of the invention, it has been possible to produce composite excipient particles which have a mass median aerodynamic (MMAD) or a volume median diameter (VMD) of less than 1 μm . It is often not possible to make such small particles by other milling methods. Furthermore, when the composite excipient particles are included in a pharmaceutical composition the additive material promotes the dispersal of the active particles on administration of that composition to the patient, for example, via actuation of a dry powder inhaler device. ("Actuation of a dry powder inhaler device" refers to the process during which a dose of the powder is removed from its rest position in the inhaler device, usually by a patient inhaling. That step takes place after the powder has been loaded into the dry powder inhaler device ready for use.) The degree of that promotion of dispersal has been found to be enhanced in comparison to a composition made by simple blending of similar sized particles of excipient material with additive material. This is believed to be because the method of the invention produces improved distribution of the additive material on the surfaces of the excipient particles.

[0011] The particles of excipient material may comprise more than 50% by weight of excipient material, preferably more than 80% by weight, more preferably more than 95% by weight of excipient material. The particles of excipient material preferably consists essentially of excipient material.

[0012] The composite excipient particles are particles of excipient material which have, upon their surfaces, an amount of the additive material. That amount of additive material may be very small, for example, in the case where the additive material is present as a solution which is removed after the milling step leaving only a residue of additive material upon the surface of the active or excipient particles.

[0013] The additive material is in the form of a coating on the surfaces of the particles of excipient material. The coating may be a discontinuous coating.

[0014] The word "milling" as used herein refers to any mechanical process which applies sufficient force to the particles of excipient material that it is capable of breaking coarse particles (for example, particles of mass median aerodynamic diameter greater than 100 μ m) down to fine particles of mass median aerodynamic diameter not more than 50 μ m. For example, the milling step may be one which if the excipient particles were replaced with the same weight of lactose having a MMAD of between 150 and 200 μ m would be capable of reducing the MMAD of that lactose to below 50 μ m. It has been found that processes which do not apply that degree of force are not effective in the method of the invention. It is believed that is because that degree of force is required to separate the individual particles of excipient material such that effective mixing and effective application of the additive material to the surfaces of those particles is achieved. It should be understood, however, that in the case where the particles of excipient material are already fine, for example, having a mass median aerodynamic diameter below 60 μ m prior to the milling step, the size of those particles may not be significantly reduced. The important thing is that the milling process applies a sufficiently high degree of force or energy to the particles.

[0015] A wide range of milling devices and conditions are suitable for use in the method of the invention. The selection of appropriate milling conditions, for example, intensity of milling and duration, to provide the required degree of force will be within the ability of the skilled person who will understand how to arrange those milling conditions such that the milling is capable of breaking down coarse particles, as mentioned above. Ball milling is a preferred method. Alternatively, a high pressure homogeniser may be used in which a fluid containing the particles is forced through a valve at high pressure producing conditions of high shear and turbulence. Shear forces on the particles, impacts between the particles and machine surfaces or other particles and cavitation due to acceleration of the fluid may all contribute to the fracture of the particles. Such homogenisers may be more suitable than ball mills for use in large scale preparations of the composite excipient particles. Suitable homogenisers include the EmulsiFlex high pressure homogeniser which is capable of pressure up to 4000 Bar, Niro Soavi high pressure homogenisers (capable of pressures up to 2000 Bar), and the Microfluidics Microfluidiser (maximum pressure 2750 Bar). The milling step may, alternatively, involve an agitator bead mill, for example, the DYNO-mill (Willy A. Bachofen AG, Switzerland) or the Netzsch high energy media mill. The Mechano-Fusion system (Hosokawa Micron Ltd) and the Hybridizer (Nara) are also suitable for use with the invention. Other possible milling devices include air jet mills, pin mills, hammer mills, knife mills and ultracentrifugal mills. Preferably, the milling process is a sealed process, preventing the escape of the additive

material as fine particles or as a vapour. Jet milling may be used but in some cases additive material can be lost from the jet mill, for example, when the additive material is of very small particles, e.g. less than 1 μm in diameter.

[0016] Where the excipient material is in the form of coarse particles prior to the milling step their size will be substantially reduced during the milling step.

[0017] The mass median aerodynamic diameter of the particles of excipient material may be substantially reduced during the milling step. More preferably the mass median aerodynamic diameter (MMAD) of the particles of excipient material is reduced 10%, advantageously by at least 20%, preferably by at least 50%, more preferably by at least 70% during the milling step.

[0018] After the milling step, the mass median aerodynamic diameter of the composite excipient particles is not more than 50 μm , advantageously not more than 20 μm , more preferably not more than 15 μm and especially preferably not more than 10 μm . Furthermore, 90% by weight of the composite excipient particles may have a diameter of less than 50 μm , advantageously less than 20 μm , more preferably less than 15 μm and especially preferably less than 10 μm . The mass median aerodynamic diameter of the composite excipient particles will, in general not be less than 0.1 μm .

[0019] The milling step may be carried out in a closed vessel, for example in a ball mill. The use of a closed vessel prevents loss of ultrafine particles or vapour of the additive material which has been found to occur in jet milling or other open processes. The milling may be dry, that is to say, there is no liquid present and the mixture to be milled is in the form of a dry particulate. Preferably, the milling is wet, that is, the milling step is carried out in the presence of a liquid. The liquid medium may be aqueous or non-aqueous, high or low volatility and of any solid content as long as it does not dissolve the excipient particles to any significant degree and its viscosity is not so high that it prevents motion of the balls. The additive material is preferably not dissolved in the liquid but is present in the form of particles. However, the additive material may be soluble in the liquid medium in which case it will be present as a solution during the milling step and will adsorb to the particle surfaces. The presence of a liquid medium helps to prevent compacting of the particles of excipient material on the walls of the vessel and may also allow the more even spreading of the additive material on the surface of the particles of excipient material as compared to dry milling. Preferably, the method also comprises the step of removing the liquid after the milling step. That may be accomplished by sieving followed by spray drying, or by evaporation of the liquid (followed by milling, if necessary, to break up large aggregates or cakes of material or by freeze drying). Preferably, the liquid is removed by spray drying.

[0020] As mentioned above, the composite excipient particles produced after the milling step may be of a suitable size for use in a pharmaceutical composition, for example, a powder or suspension for inhalation. However, it may also be desirable for the composite excipient particles to be smaller than that and to have after the milling step an agglomeration step in which the particles of excipient material are agglomerated to form agglomerated particles. In

that way agglomerates of a size tailored to the requirement may be produced. Preferably, the agglomeration step is a spray drying step. The spray drying conditions may be selected to produce droplets having a desired size in the range of $1000\mu\text{m}$ to $0.5\mu\text{m}$. The size of the agglomerates produced will depend largely on the concentration of the composite excipient particles in the spray feed and the droplet size. Other materials, for example, binders may be included in the spray feed. Where the milling step is wet milling, the suspension or slurry may be spray dried directly after the milling step. Agglomeration may also be conducted in a fluid bed dryer or granulator.

[0021] The optimum amount of additive material will depend on the chemical composition and other properties of the additive material and upon the nature of the excipient material. In general, the amount of additive material in the composite particles will be not more than 60% by weight, based on the weight of the excipient material. However, it is thought that for most additive materials the amount of additive material should be in the range of 40% to 0.25%, preferably 30% to 0.5%, more preferably 20% to 2%, based on the total weight of the additive material and the excipient material being milled. In general, the amount of additive material is at least 0.01% by weight based on the total weight of the additive material and the excipient material being milled.

[0022] Where additive material is lost in the process, for example, as particles carried away in the filtrate when a liquid milling medium is filtered off, it may be necessary to add more additive material at the start of the milling step than is desired in the composite excipient particles.

[0023] Advantageously the additive material is an anti-adherent material and will tend to decrease the cohesion between the composite excipient particles and between the composite excipient particles and any other particles present in the pharmaceutical composition.

[0024] Advantageously the additive material is an anti-friction agent (glidant) and will give better flow of the pharmaceutical composition in, for example, a dry powder inhaler which will lead to a better dose reproducibility.

[0025] Where reference is made to an anti-adherent material, or to an anti-friction agent, the reference is to include those materials which are able to decrease the cohesion between the particles, or which will tend to improve the flow of powder in an inhaler, even though they may not usually be referred to as anti-adherent material or an anti-friction agent. For example, leucine is an anti-adherent material as herein defined and is generally thought of as an anti-adherent material but lecithin is also an anti-adherent material as herein defined, even though it is not generally thought of as being anti-adherent, because it will tend to decrease the cohesion between the composite excipient particles and between the composite excipient particles and any other particles present in the pharmaceutical composition.

[0026] Advantageously, the additive material consists of physiologically acceptable material.

[0027] The additive material may include a combination of one or more materials.

[0028] It will be appreciated that the chemical composition of the additive material is of particular importance. Preferably, the additive material is a naturally occurring animal or plant substance.

[0029] Advantageously, the additive material includes one or more compounds selected from amino acids and derivatives thereof, and peptides and polypeptides having molecular weight from 0.25 to 1000Kda, and derivatives thereof. Amino acids, peptides or polypeptides and derivatives of peptides and polypeptides are both physiologically acceptable and give acceptable release of the active particles on inhalation.

[0030] It is particularly advantageous for the additive material to comprise an amino acid. The additive material may comprise one or more of any of the following amino acids: leucine, isoleucine, lysine, valine, methionine, phenylalanine. The additive may be a salt or a derivative of an amino acid, for example aspartame or acesulfame K. Preferably, the additive particles consist substantially of an amino acid, more preferably of leucine, advantageously L-leucine. The D- and DL-forms may also be used. As indicated above, leucine has been found to give particularly efficient dispersal of the active particles on inhalation.

[0031] The additive material may include one or more water soluble substances. This helps absorption of the substance by the body if the additive reaches the lower lung. The additive material may include dipolar ions, which may be zwitterions.

[0032] Alternatively, the additive material may comprise a phospholipid or a derivative thereof. Lecithin has been found to be a good material for the additive material.

[0033] Preferably, the additive material comprises a metal stearate, or a derivative thereof, for example, sodium stearyl fumarate or sodium stearyl lactylate. Advantageously, the additive material comprises a metal stearate. For example, magnesium stearate, calcium stearate, sodium stearate or lithium stearate. Preferably, the additive material comprises magnesium stearate.

[0034] The additive material may include or consist of one or more surface active materials, in particular materials that are surface active in the solid state, which may be water soluble, for example lecithin, in particular soya lecithin, or substantially water insoluble, for example solid state fatty acids such as oleic acid, lauric acid, palmitic acid, stearic acid, erucic acid, behenic acid, or derivatives (such as esters and salts) thereof such as glyceryl behenate. Specific examples of such materials are: phosphatidylcholines, phosphatidylglycerols and other examples of natural and synthetic lung surfactants; Liposomal formulations; lauric acid and its salts, for example, sodium lauryl sulphate, magnesium lauryl sulphate; triglycerides such as Dynsan 118 and Cutina HR; and sugar esters in general.

[0035] Other possible additive materials include talc, titanium dioxide, aluminium dioxide, silicon dioxide and starch.

[0036] The additive material preferably comprises one or more materials selected from the group consisting of amino acids, lecithins, phospholipids and metal stearates (especially magnesium stearate).

[0037] It should be understood that, whilst the above discussion of the additive material has related primarily to the use of those additive materials in pharmaceutical compositions for dry powder inhalers, the composite excipient particles of the present invention are suitable for use in any pharmaceutical composition which requires the dispersal of small particles of active material into an aerosol cloud. The composite excipient particles are therefore especially suitable for use in pharmaceutical compositions which are administered as an aerosol or cloud. Such compositions include powders for dry powder inhalers, suspensions for use in pressurised metered dose inhalers.

[0038] The terms "active particles" and "particles of active material" are used interchangeably herein. The active particles referred to throughout the specification will comprise one or more pharmacologically active agents. The active particles advantageously consist essentially of one or more pharmacologically active agents. Suitable pharmacologically active agents may be materials for therapeutic and/or prophylactic use. Active agents which may be included in the formulation include those products which are usually administered orally by inhalation for the treatment of disease such as respiratory disease, for example, β -agonists.

[0039] The active particles may comprise at least one β_2 -agonist, for example one or more compounds selected from terbutaline, salbutamol, salmeterol and formoterol. If desired, the active particles may comprise more than one of those active agents, provided that they are compatible with one another under conditions of storage and use. Preferably, the active particles are particles of salbutamol sulphate. References herein to any active agent are to be understood to include any physiologically acceptable derivative. In the case of the β_2 -agonists mentioned above, physiologically acceptable derivatives include especially salts, including sulphates.

[0040] The active particles may be particles of ipatropium bromide.

[0041] The active particles may include a steroid, which may be beclometasone dipropionate or may be fluticasone. The active principle may include a cromone which may be sodium cromoglycate or nedocromil. The active principle may include a leukotriene receptor antagonist.

[0042] The active particles may include a carbohydrate, for example heparin.

[0043] The active particles may advantageously comprise a therapeutically active agent for systemic use being advantageously capable of being absorbed into the circulatory system via the lungs. For example, the active particles may comprise peptides or polypeptides or proteins such as DNase, leukotrienes or insulin (including substituted insulins and pro-insulins),

cyclosporin, interleukins, cytokines, anti-cytokines and cytokine receptors, vaccines (including influenza, measles, 'anti-narcotic' antibodies, meningitis) growth hormone, leuprolide and related analogues, interferons, desmopressin, immunoglobulins, erythropoietin, calcitonin and parathyroid hormone. The pharmaceutical compositions of the invention may in particular have application in the administration of insulin to diabetic patients, thus avoiding the normally invasive administration techniques used for that agent.

[0044] The composite excipient particles of the invention may advantageously be for use in pain relief. Non-opioid analgesic agents that may be included as pain relief agents are, for example, alprazolam, amitriptyline, aspirin, baclofen, benzodiazepines, bisphosphonates, caffeine, calcitonin, calcium-regulating agents, carbamazepine, clonidine, corticosteroids, dantrolene, dexamethasone, disodium pamidronate, ergotamine, flecainide, hydroxyzine, hyoscine, ibuprofen, ketamine, lignocaine, lorazepam, methotrimeprazine, methylprednisolone, mexiletine, mianserin, midazolam, NSAIDs, nimodipine, octreotide, paracetamol, phenothiazines, prednisolone, somatostatin. Suitable opioid analgesic agents are: alfentanil hydrochloride, alphaprodine hydrochloride, anileridine, bezitramide, buprenorphine hydrochloride, butorphanol tartrate, carfentanil citrate, ciramadol, codeine, dextromoramide, dextropropoxyphene, dezocine, diamorphine hydrochloride, dihydrocodeine, dipipanone hydrochloride, enadoline, eptazocine hydrobromide, ethoheptazine citrate, ethylmorphine hydrochloride, etorphine hydrochloride, fentanyl citrate, hydrocodone, hydromorphone hydrochloride, ketobemidone, levomethadone hydrochloride, levomethadyl acetate, levorphanol tartrate, meptazinol hydrochloride, methadone hydrochloride, morphine, nalbuphine hydrochloride, nicomorphine hydrochloride, opium, hydrochlorides of mixed opium alkaloids, papaveretum, oxycodone, oxymorphone hydrochloride, pentamorphone, pentazocine, pethidine hydrochloride, phenazocine hydrobromide, phenoperidine hydrochloride, piconadol hydrochloride, piritramide, propiram fumarate, remifentanil hydrochloride, spiradoline mesylate, sufentanil citrate, tilidate hydrochloride, tonazocine mesylate, tramadol hydrochloride, trefentanil. Illustrative of the application of the invention in relation to formulations for pain relief are formulations containing composite particles comprising fentanyl citrate as analgesic or comprising agents for the treatment of migraine, for example, dihydroergotamine mesylate.

[0045] The composite particles could also be used in formulations for the local administration of agents, for example, for anti cancer activity, anti-virals, antibiotics, muscle relaxants, antidepressants, antiepileptics or vaccines.

[0046] The term excipient as used herein refers to any solid, generally pharmaceutically inert material which is acceptable for inclusion in pharmaceutical formulations. The excipient material may be composed of one or more materials selected from sugar alcohols; polyols, for example sorbitol, mannitol and xylitol, and crystalline sugars, including monosaccharides and disaccharides; inorganic salts such as sodium chloride and calcium carbonate; organic salts such as sodium lactate; and other organic compounds such as urea, polysaccharides, for example starch and its derivatives; oligosaccharides, for example cyclodextrins and dextrans. Advantageously the excipient material is a crystalline sugar, for example, a monosaccharide

such as glucose or arabinose, or a disaccharide such as maltose, saccharose, dextrose or lactose. Preferably, the excipient material is of lactose.

[0047] The invention also provides composite excipient particles for use in a pharmaceutical composition, preferably a pharmaceutical composition for inhalation, more preferably a powder for a dry powder inhaler.

[0048] The invention further provides composite excipient particles for use in a pharmaceutical composition each composite excipient particle comprising a particle of an excipient material and additive material on the surface of that particle of excipient material, the composite excipient particles having a mass median aerodynamic diameter of less than $20\mu\text{m}$. Preferably, the composite excipient particles have a MMAD of not more than $15\mu\text{m}$, advantageously not more than $10\mu\text{m}$ and more preferably not more than $5\mu\text{m}$. Furthermore, 90% by weight of the composite excipient particles may have a diameter of less than $50\mu\text{m}$, advantageously less than $20\mu\text{m}$, more preferably less than $15\mu\text{m}$, more advantageously less than $10\mu\text{m}$ and especially advantageously less than $5\mu\text{m}$.

[0049] It will be understood that persons skilled in the art are able to convert in an approximate manner between mass, volume, aerodynamic, surface, number based and other diameters.

[0050] MMAD is determined using an impinger, for example, a multi-stage liquid impinger. Volume median diameters and measurements of the proportion of particles having a diameter less than a certain value may be determined by the Malvern laser light scattering method.

[0051] The invention provides a pharmaceutical composition comprising composite excipient particles. Preferably, the pharmaceutical composition is a dry powder and is suitable for use in a dry powder inhaler. Such pharmaceutical compositions comprise essentially only the composite excipient particles and active particles and optionally flavouring agents.

[0052] Where the pharmaceutical composition is a powder for use in a dry powder inhaler the composite excipient particles are preferably present in an amount of at least 1%, more preferably at least 5%, advantageously at least 10% and most preferably at least 20% by weight based on the combined weights of the composite excipient particles and the active particles. The composite excipient particles will preferably be present in an amount of not more than 95%, more preferably not more than 90% and especially advantageously not more than 70% based on the combined weights of the composite excipient particles and the active particles.

[0053] The pharmaceutical composition may comprise a propellant and be suitable for use in a pressurised metered dose inhaler.

[0054] The disclosure also provides the use of an additive material as a milling aid in the milling of particles of an excipient material. The term milling aid should be understood to refer

to a substance which reduces the amount of energy required to mill the particles of excipient material.

[0055] Embodiments of the invention will now be described for the purposes of illustration only.

[0056] Evaluation of the fine particle fraction of multi-stage liquid impinger (MSLI) was carried out in accordance with method given in European Pharmacopoeia, Supplement 2000, Section 2.9.18.

[0057] Evaluation of the fine particle fraction using a twin stage liquid impinger (TSI) was carried out in accordance with the method of WO 96/23485 pages 29 to 33. The method is also described in the European Pharmacopoeia referred to above and in J. Pharm. Pharmacol, 1987, 39, 966-972).

[0058] All percentages are by weight unless indicated otherwise.

Composite Excipient Particles

Method 1

[0059] 98g of Microfine (MMAD approximately 8 μ m) lactose (manufactured by Borculo) was placed in a stainless steel milling vessel. 300g of stainless steel milling balls varying from 10 to 3mm diameter were added. 2g of additive material was added and the vessel was located in a Retsch S100 Centrifugal Mill. The powder was milled for 30 minutes at 580 rpm and was then sieved to remove the milling balls. Each of the following additive materials were used in turn: magnesium stearate, calcium stearate, sodium stearate, lithium stearate, stearic acid, stearylamine, soya lecithin, sodium stearyl fumarate, L-leucine, 1-iso-leucine, oleic acid, starch, diphosphatidyl choline, behenic acid, glyceryl behenate and sodium benzoate. Pharmaceutically acceptable fatty acids and derivatives, waxes and oils may also be used (where those materials are sticky, they should be used at levels where their stickiness does not inhibit the flow of the powder).

Method 2

[0060] 95g of Microfine lactose (Borculo) was placed in a ceramic milling vessel (manufactured by the Pascall Engineering Company). 5g of additive material and the ceramic milling balls were added. The ball mill was tumbled at 60 rpm for 5 hours. This was repeated a number of times with the amount of additive material varied as a percentage of the lactose from 0.25 to 20%. Additive materials used were L-leucine and magnesium stearate.

[0061] The powder was recovered by sieving to remove the milling balls.

Method 3

[0062] Experiments were performed to produce co-processed powders of fine lactose and additive material (L-leucine) in a Gem-T jet mill. Quantities of L-leucine were varied from 0.5 to 10% based on the weight of the lactose. Lactoses used included Lactochem Regular (having a broad distribution of particle sizes over 1-200 μ m) and Microfine (Borculo). The mill was operated normally.

Method 4

[0063] Method 3 was repeated using magnesium stearate in place of L-leucine.

Method 5

[0064] The experiments of Methods 3 and 4 were repeated using a Retsch ZM100 Ultra-Centrifugal Mill.

Method 6

[0065] Leucine was micronised in a jet mill and blended with Microfine lactose (Borculo) in a high shear mixer (Morphy Richards food processor) or in a Retsch ZM100 Ultra-Centrifugal mill. Quantities of L-leucine were varied from 0.5 to 10% based on the weight of the lactose.

[0066] Methods 3, 5 and 6 (where leucine is used) are less favoured methods, as the powders frequently performed only slightly better than with equivalent powders comprising unmodified lactoses. This is believed to be because the mills used were not sealed allowing the leucine to escape as fine particles or as vapour. In method 4, (using magnesium stearate, which is not as volatile as leucine), the powders performed well.

[0067] It was observed in some cases that when ball milling according to Methods 1 and 2, a fine powder was not produced. Instead the powder was compacted on the walls of the mill by the action of the mill. That inhibited the milling action and prevented the preparation of the composite excipient particles. That problem occurred particularly when certain additive materials were used, in cases where the additive material was present in small proportions (typically <2%), in cases where the milling balls were relatively small (typically <3mm), in cases where the milling speed was too slow and where the starting lactose was too fine. To prevent

this occurring it is advantageous to mill in a liquid medium. The liquid medium reduces the tendency to compaction, assists the dispersal of additive material with lactose and improves any milling action.

Method 7

[0068] 2g leucine with 98g of ultra-fine micronised lactose (mass median diameter approximately $3\mu\text{m}$) was placed in a stainless steel milling vessel. 300g of stainless steel milling balls varying from 10 to 3mm diameter were added. The vessel was located in a Retsch S100 Centrifugal Mill. The powder was milled for 10 minutes at 580 rpm and was found to have compacted on the sides of the vessel, and consequently co-milling was not possible. Compaction also occurred when magnesium stearate was used as additive material. Sufficient cyclohexane was added to the vessel to create a loose paste and the co-milling was continued successfully in that liquid medium. The excipient powder was recovered by drying the paste, milling the powder for 2 minutes and sieving.

Method 8

[0069] 10g of Microfine lactose (Borculo) was combined with 1g of sodium stearate and 10cm³ cyclohexane. 50g of 5mm balls were added and the mixture was milled for 90 minutes. The powder was recovered by leaving the paste in a fume hood overnight to evaporate the cyclohexane and then ball milling for 1 minute. Powders having lecithin, PVP, Span 80, magnesium stearate and leucine in place of sodium stearate were prepared by this method. Quantities of additive material were usually 10% by weight based on weight of lactose but were also varied from 1% to 60%. The experiments were also repeated using dichloromethane as liquid medium.

Method 9

[0070] 47.5g of Sorbalac 400 (Meggle) was combined with 2.5g of magnesium stearate and 50cm³ dichloromethane. 620g 3mm stainless steel balls were added to the mixture and the mixture was milled in a 250cm³ stainless steel pot at 500 rpm for 90 minutes in a Retsch S100 Centrifugal mill.

[0071] The excipient powder was recovered by drying the paste, milling the powder for 2 minutes and sieving to remove the steel balls.

[0072] This method was repeated using leucine in place of magnesium stearate.

Pharmaceutical Compositions comprising composite excipient particles

Composition 1

[0073] 0.9g of composite excipient particles made by method 2 containing 5% 1-leucine in Microfine lactose was blended with 0.6g of micronised budesonide by hand in a mortar. This blending could also be performed, for example, in a high shear blender, or in a ball mill or in a centrifugal mill. The resulting powder may be used in an inhaler directly, although in this example a sample of this powder was blended with a coarse carrier lactose (355 to 600 μ m) by tumbling in order to improve the powder flow properties (not according to the invention). The powder was fired from a Cyclohaler at a flow rate of 60 litre per minute in a multi-stage liquid impinger. The fine particle fraction (<5 μ m) was 45%.

Composition 2

(not according to the invention)

[0074] 1g of micronised salbutamol sulphate was added to 1g of composite excipient particles made by method 1 containing 2% lecithin, and to 8g of a coarse carrier lactose. The mixture was tumbled for 30 minutes at 42 rpm. The resulting power was fired from a Cyclohaler at a flow rate of 60 litres per minute into a twin-stage impinger, giving a fine particle fraction (<5 microns) of about 44%. A similar example with a 2% leucine precursor gave a fine particle fraction (<5 μ m) of 52%.

Composition 3

(not according to the invention)

[0075] The wet milled composite excipient particles have given particularly good results.

[0076] 0.5g of micronised salbutamol sulphate was added to 0.5g of composite excipient particles made by method 7 containing 10% magnesium stearate, and to 4g of a coarse carrier lactose. This was tumbled for 30 minutes at 62 rpm. The resulting powder was fired from a Cyclohaler at a flow rate of 60 litres per minute into a twin-stage impinger, giving a fine particle fraction (<5 μ m) of 57%. The experiment was repeated using composite excipient particles containing 20% magnesium stearate and similar results were obtained.

Composition 4

(not according to the invention)

[0077] 0.5g of micronised salbutamol sulphate, 0.25g of g of composite excipient particles made by method 7 containing 10% magnesium stearate, 0.25g of g of composite excipient particles made by method 7 containing 10% leucine, and 4g of a coarse carrier lactose were all combined. The mixture was tumbled for 30 minutes at 62 rpm. The resulting powder was fired from a Cyclohaler at a flow rate of 60 litres per minute into a twin-stage impinger, giving a fine particle fraction ($<5\mu\text{m}$) of ~65%.

Composition 5

(not according to the invention)

[0078] 0.5g of micronised salbutamol sulphate, 0.25g of composite excipient particles made by method 7 containing 10% lecithin, 0.25g of composite excipient particles made by method 7 containing 10% leucine, and 4g of a coarse carrier lactose were combined. The mixture was tumbled for 30 minutes at 62 rpm. The resulting powder was fired from a Cyclohaler at a flow rate of 60 litres per minute into a twin-stage impinger, giving a fine particle fraction ($<5\mu\text{m}$) of 68%.

Composition 6

(not according to the invention)

[0079] 0.5g of micronised salbutamol sulphate, 0.25g of composite excipient particles powder made by method 7 containing 10% lecithin, and 0.25g of g of composite excipient particles powder made by method 7 containing 10% sodium stearate, and 4g of a coarse carrier lactose were combined. The mixture was tumbled for 30 minutes at 62 rpm. The resulting powder was fired from a Cyclohaler at a flow rate of 60 litres per minute into a twin-stage impinger, giving a fine particle fraction ($<5\mu\text{m}$) of 65%.

Composition 7

(not according to the invention)

[0080] 0.25g micronised Fentanyl citrate, 5g of composite excipient particles made by method 9 and 44.75g of Primalac (Meggles) 355-600µm sieve fraction lactose were combined in a Turbula mixer for 30 minutes at 60 rpm. The resulting powder was fired from a Cyclohaler at a flow rate of 90 litres min⁻¹ into a multistage liquid impinger giving a fine particle fraction (<5µm) of approximately 50%.

Composition 8

(not according to the invention)

[0081] Composition 7 was repeated using double quantities of each material and replacing fentanyl citrate with micronised budesonide. The fine particle fraction was approximately 50%.

Composition 9

(not according to the invention)

[0082] Composition 8 was repeated using micronised dihydroergatamine mesylate in place of the budesonide. The fine particle fraction was approximately 60%.

[0083] It has been found to be particularly favourable to use a 355 to 600µm sieve fraction of Primalac as the coarse carrier lactose. Segregation has not been observed in those formulations, even those comprising 10 and 20% magnesium stearate (i.e. up to 2% in the final composition).

[0084] When milling excipient material, it has been found to be preferable to use a large number of fine milling balls, rather than fewer heavy balls. The finer balls perform a more efficient co-milling action. Preferably the balls have a diameter of 5mm or less, advantageously 2mm or less. Liquid media are preferred which do not dissolve the excipient material and which evaporate rapidly and fully, for example non-aqueous liquids such as cyclohexane, ethanol, isopropanol or dichloromethane. Liquid media are preferred which are non flammable, for example dichloromethane and fluorinated hydrocarbons, especially fluorinated hydrocarbons which are suitable for use as propellants in inhalers.

[0085] A particularly preferred method is milling using a high pressure homogeniser, as this

reduces contamination as compared to ball milling, for example, where the collisions between the balls may produce contaminants.

[0086] In the wet milling process, the additive material appears to confer several advantages: it allows the milling process to be more efficient, with smaller particles produced and compaction reduced, the particles may be stabilised in suspension, and on drying, the ternary agent remains as a coating around the particles which may aid dispersion, and may modify the subsequent dissolution characteristics of the particle.

[0087] When the active material is a protein, the milling may be preceded by lyophilisation (freeze drying) of the protein either pure or in combination with an additive material and/or a polymeric stabiliser. The freeze drying may make them more brittle and more easily milled. The milling may need to be conducted under cryogenic (cold) conditions to increase the brittleness of the material.

REFERENCES CITED IN THE DESCRIPTION

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Patent documents cited in the description

- WO9623485A **[0006]** **[0008]** **[0057]**

Non-patent literature cited in the description

- J. Pharm. Pharmacol, 1987, vol. 39, 966-972 **[0057]**

Patentkrav

1. Farmaceutisk sammensætning, der omfatter sammensatte excipientspartikler, hvor hver sammensatte excipientspartikel
5 omfatter en partikel af et excipientsmateriale og additivmateriale, der er påført på overfladen af partiklen af excipientsmateriale, hvilke sammensatte excipientspartikler har en massebaseret median aerodynamisk diameter på ikke mere end 50 µm bestemt ved anvendelse af en impinger, hvor
10 additivmaterialet er i form af en belægning på overfladerne af partiklerne af excipientsmateriale, og hvor sammensætningen i det væsentlige består af de sammensatte excipientspartikler, partikler af aktivt materiale og eventuelt et smagsstof.
- 15 2. Farmaceutisk sammensætning ifølge krav 1, hvor de sammensatte excipientspartikler har en massebaseret median aerodynamisk diameter på ikke mere end 20 µm bestemt ved anvendelse af en impinger.
- 20 3. Farmaceutisk sammensætning ifølge krav 1, hvor de sammensatte excipientspartikler har en massebaseret median aerodynamisk diameter på ikke mere end 15 µm bestemt ved anvendelse af en impinger.
- 25 4. Farmaceutisk sammensætning ifølge krav 1, hvor de sammensatte excipientspartikler har en massebaseret median aerodynamisk diameter på ikke mere end 10 µm bestemt ved anvendelse af en impinger.
- 30 5. Farmaceutisk sammensætning ifølge et hvilket som helst af kravene 1 til 4, hvor excipientsmaterialet er et krystallinsk sukker.
6. Farmaceutisk sammensætning ifølge et hvilket som helst af
35 ovennævnte krav, hvor additivmaterialet omfatter en aminosyre.
7. Farmaceutisk sammensætning ifølge et hvilket som helst af kravene 1 til 5, hvor additivmaterialet omfatter et

phospholipid.

8. Farmaceutisk sammensætning ifølge et hvilket som helst af
kravene 1 til 5, hvor additivmaterialet omfatter en
5 metalstearat.

9. Farmaceutisk sammensætning ifølge et hvilket som helst af
ovennævnte krav, som er et tørt pulver, der er egnet til
anvendelse i en tørpulverinhalator.
10

10. Farmaceutisk sammensætning ifølge et hvilket som helst af
kravene 1 til 8, som omfatter et drivmiddel og er egnet til
anvendelse i en dosis-inhalationsspray.

15 11. Tørpulverinhalator, der omfatter en farmaceutisk
sammensætning ifølge et hvilket som helst af kravene 1 til 9.

12. Dosis-inhalationsspray, der omfatter en farmaceutisk
sammensætning ifølge krav 10.