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PROVISIONAL SPECIFICATION

Invention Title: A Novel Formulation of Diclofenac

The invention is described in the following statement:

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A Novel Formulation of Diclofenac

Field of the Invention

The present invention relates to methods for producing particles of diclofenac using dry milling processes as well as compositions comprising diclofenac, medicaments produced using diclofenac in particulate form and/or compositions, and to methods of treatment of an animal, including man, using a therapeutically effective amount of diclofenac administered by way of said medicaments.

Background

Poor bioavailability is a significant problem encountered in the development of compositions in the therapeutic, cosmetic, agricultural and food industries, particularly those materials containing a biologically active material that is poorly soluble in water at physiological pH. An active material's bioavailability is the degree to which the active material becomes available to the target tissue in the body or other medium after systemic administration through, for example, oral or intravenous means. Many factors affect bioavailability, including the form of dosage and the solubility and dissolution rate of the active material.

In therapeutic applications, poorly and slowly water-soluble materials tend to be eliminated from the gastrointestinal tract before being absorbed into the circulation. In addition, poorly soluble active agents tend to be disfavored or even unsafe for intravenous administration due to the risk of particles of agent blocking blood flow through capillaries.

It is known that the rate of dissolution of a particulate drug will increase with increasing surface area. One way of increasing surface area is decreasing particle size. Consequently, methods of making finely divided or sized drugs have been studied with a view to controlling the size and size range of drug particles for pharmaceutical compositions.

For example, dry milling techniques have been used to reduce particle size and hence influence drug absorption. However, in conventional dry milling the limit of fineness is reached generally in the region of about 100 microns (100,000 nm), at which point material cakes on the milling chamber and prevents any further diminution of particle size. Alternatively, wet grinding may be employed to reduce particle size, but flocculation restricts the lower particle size limit to approximately 10 microns (10,000 nm). The wet milling process, however, is prone to contamination, thereby leading to a bias in the pharmaceutical art against wet milling. Another alternative milling technique, commercial airjet milling, has provided particles ranging in average size from as low as about 1 to about 50 microns (1,000-50,000 nm).

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There are several approaches currently used to formulate poorly soluble active agents. One approach is to prepare the active agent as a soluble salt. Where this approach cannot be employed, alternate (usually physical) approaches are employed to improve the solubility of the active agent. Alternate approaches generally subject the active agent to physical conditions that change the agent's physical and or chemical properties to improve its solubility. These include process technologies such as micronization, modification of crystal or polymorphic structure, development of oil based solutions, use of co-solvents, surface stabilizers or complexing agents, micro-emulsions, supercritical fluid and production of solid dispersions or solutions. More than one of these processes may be used in combination to improve formulation of a particular therapeutic material. Many of these approaches commonly convert a drug into an amorphous state, which generally leads to a higher dissolution rate. However, formulation approaches that result in the production of amorphous material are not common in commercial formulations due to concerns relating to stability and the potential for material to re-crystallize.

These techniques for preparing such pharmaceutical compositions tend to be complex. By way of example, a principal technical difficulty encountered with emulsion polymerization is the removal of contaminants, such as unreacted monomers or initiators (which may have undesirable levels of toxicity), at the end of the manufacturing process.

Another method of providing reduced particle size is the formation of pharmaceutical drug microcapsules, which techniques include micronizing, polymerisation and co-dispersion. However, these techniques suffer from a number of disadvantages including at least the inability to produce sufficiently small particles such as those obtained by milling, and the presence of co-solvents and/or contaminants such as toxic monomers which are difficult to remove, leading to expensive manufacturing processes.

Over the last decade, intense scientific investigation has been carried out to improve the solubility of active agents by converting the agents to ultra fine powders by methods such as milling and grinding. These techniques may be used to increase the dissolution rate of a particulate solid by increasing the overall surface area and decreasing the mean particle size.

US Patent 6,634,576 discloses examples of wet-milling a solid substrate, such as a pharmaceutically active compound, to produce a "synergetic co-mixture".

International Patent Application PCT/AU2005/001977 (Nanoparticle Composition(s) and Method for Synthesis Thereof) describes, *inter alia*, a method comprising the step of contacting a precursor compound with a co-reactant under mechanochemical synthesis conditions wherein a solid-state chemical reaction between the precursor compound and the co-reactant produces therapeutically active nanoparticles dispersed in a carrier matrix. Mechanochemical synthesis, as discussed in International Patent Application

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PCT/AU2005/001977, refers to the use of mechanical energy to activate, initiate or promote a chemical reaction, a crystal structure transformation or a phase change in a material or a mixture of materials, for example by agitating a reaction mixture in the presence of a milling media to transfer mechanical energy to the reaction mixture, and includes without limitation "mechanochemical activation", "mechanochemical processing", "reactive milling", and related processes.

International Patent Application PCT/AU2007/000910 (Methods for the preparation of biologically active compounds in nanoparticulate form) describes, *inter alia*, a method for dry milling raloxifene with lactose and NaCl which produced nanoparticulate raloxifene without significant aggregation problems.

One limitation of many of the prior art processes is that they are not suitable for commercial scale milling. The present invention provides methods for overcoming the problems identified by the prior art by providing a milling process which provides particles with increased surface area, yet can also be scaled up to a commercial scale.

One example of a therapeutic area where this technology could be applied in is the area of acute pain management. Many pain medications such as diclofenac are commonly prescribed as pain relief for chronic pain. As a result they are commonly taken on a daily basis to maintain an effective therapeutic level. Diclofenac is a poorly water soluble drug so dissolution and absorbtion to the body is slow. So a method such as the present invention which provides for improved dissolution, will likely provide much faster absorption resulting in a more rapid onset of the therapeutic effect. By using a method such as the present invention, which provides faster absorption, a drug such as diclofenac, could be used more readily to treat acute pain as well as chronic pain.

Although the background to the present invention is discussed in the context of improving the bioavailability of materials that are poorly or slowly water soluble, the applications of the methods of the present invention are not limited to such, as is evident from the following description of the invention.

Further, although the background to the present invention is largely discussed in the context of improving the bioavailability of therapeutic or pharmaceutical compounds, the applications of the methods of the present invention are clearly not limited to such. For example, as is evident from the following description, applications of the methods of the present invention include but are not limited to: nutraceutical and nutritional compounds, complementary medicinal compounds, veterinary therapeutic applications and agricultural chemical applications, such as pesticide, fungicide or herbicide.

Furthermore an application of the current invention would be to materials which contain a biologically active compound such as, but not limited to a therapeutic or pharmaceutical compound, a nutraceutical or nutrient, a complementary medicinal product such as active

components in plant or other naturally occurring material, a veterinary therapeutic compound or an agricultural compound such as a pesticide, fungicide or herbicide. Specific examples would be the spice turmeric that contains the active compound curcumin, or flax seed that contains the nutrient ALA an omega 3 fatty acid. As these specific examples indicate this invention could be applied to, but not limited to, a range of natural products such as seeds, cocoa and cocoa solids, coffee, herbs, spices, other plant materials or food materials that contain a biologically active compound. The application of this invention to these types of materials would enable greater availability of the active compound in the materials when used in the relevant application. For example where material subject to this invention is orally ingested the active would be more bioavailable.

Summary of the Invention

In one aspect the present invention is directed to the unexpected finding that particles of a biologically active material can be produced by dry milling processes at commercial scale. In one surprising aspect the particle size produced by the process is equal to or less than 2000nm. In another surprising aspect the particle size produced by the process is equal to or less than 1000nm. In another surprising aspect the crystallinity of the active material is unchanged or not substantially changed. In a preferred embodiment the present invention is directed to the unexpected finding that particles of diclofenac can be produced by dry milling processes at commercial scale.

Thus in a first aspect the invention comprises a method producing a composition, comprising the steps of dry milling a solid biologically active material and a millable grinding matrix in a mill comprising a plurality of milling bodies, for a time period sufficient to produce particles of the biologically active material dispersed in an at least partially milled grinding material.

In one preferred embodiment, the average particle size, determined on a particle number basis, is equal to or less than a size selected from the group 2000 nm, 1900 nm, 1800nm, 1700nm, 1600nm, 1500nm, 1400nm, 1300nm, 1200 nm, 1100nm, 1000nm, 900nm, 800nm, 700nm, 600nm, 500nm, 400 nm, 300nm, 200nm and 100 nm. Preferably, the average particle size is equal to or greater than 25nm.

In another preferred embodiment, the particles have a median particle size, determined on a particle volume basis, equal or less than a size selected from the group 2000 nm, 1900 nm, 1800nm, 1700nm, 1600nm, 1500nm, 1400nm, 1300nm, 1200 nm, 1100nm, 1000nm, 900nm, 800nm, 700nm, 600nm, 500nm, 400 nm, 300nm, 200nm and 100 nm. Preferably, the median particle size is equal to or greater than 25nm. Preferably, the percentage of particles, on a particle volume basis, is selected from the group consisting of: less than 2000nm (% < 2000 nm) is selected from the group 50 %, 60%, 70%, 80%, 90%, 95% and 100 %; less than 1000nm (% < 1000 nm) is selected from the group 50 %, 60%, 70%, 80%,

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90%, 95% and 100 %; less than 500nm (% < 500 nm) is selected from the group 0%, 10%, 20%, 30%, 40%, 50 %, 60%, 70%, 80%, 90%, 95% and 100 %; less than 300nm (% < 300 nm) is selected from the group 0%, 10%, 20%, 30%, 40%, 50 %, 60%, 70%, 80%, 90%, 95% and 100 %; and less than 200nm (% < 200 nm) is selected from the group 0%, 10%, 20%, 30%, 40%, 50 %, 60%, 70%, 80%, 90%, 95% and 100 %.

In another preferred embodiment, the crystallinity profile of the biologically active material is selected from the group consisting of: at least 50% of the biologically active material is crystalline, at least 60% of the biologically active material is crystalline, at least 70% of the biologically active material is crystalline, at least 75% of the biologically active material is crystalline, at least 85% of the biologically active material is crystalline, at least 90% of the biologically active material is crystalline, at least 95% of the biologically active material is crystalline and at least 98% of the biologically active material is crystalline. More preferably, the crystallinity profile of the biologically active material is substantially equal to the crystallinity profile of the biologically active material before the material was subjected to the method as described herein.

In another preferred embodiment, the amorphous content of the biologically active material is selected from the group consisting of: less than 50% of the biologically active material is amorphous, less than 40% of the biologically active material is amorphous, less than 30% of the biologically active material is amorphous, less than 25% of the biologically active material is amorphous, less than 15% of the biologically active material is amorphous, less than 10% of the biologically active material is amorphous, less than 5% of the biologically active material is amorphous and less than 2% of the biologically active material is amorphous. Preferably, the biologically active material has no significant increase in amorphous content after subjecting the material to the method as described herein.

In another preferred embodiment, the milling time period is a range selected from the group consisting of: between 10 minutes and 2 hours, between 10 minutes and 90 minutes, between 10 minutes and 1 hour, between 10 minutes and 45 minutes, between 10 minutes and 30 minutes, between 5 minutes and 30 minutes, between 5 minutes and 20 minutes, between 2 minutes and 10 minutes, between 2 minutes and 5 minutes, between 1 minutes and 20 minutes, between 1 minute and 10 minutes, and between 1 minute and 5 minutes.

In another preferred embodiment, the milling medium is selected from the group consisting of: ceramics, glasses, polymers, ferromagnetics and metals. Preferably, the milling medium is steel balls having a diameter selected from the group consisting of: between 1 and 20 mm, between 2 and 15 mm and between 3 and 10 mm. In another preferred embodiment, the milling medium is zirconium oxide balls having a diameter selected from the group consisting of: between 1 and 20 mm, between 2 and 15 mm and between 3 and 10 mm. Preferably, the dry milling apparatus is a mill selected from the group consisting of: attritor mills (horizontal

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or vertical), nutating mills, tower mills, pearl mills, planetary mills, vibratory mills, eccentric vibratory mills, gravity-dependent-type ball mills, rod mills, roller mills and crusher mills. Preferably, the milling medium within the milling apparatus is mechanically agitated by 1, 2 or 3 rotating shafts. Preferably, the method is configured to produce the biologically active material in a continuous fashion.

Preferably, the total combined amount of biologically active material and grinding matrix in the mill at any given time is equal to or greater than a mass selected from the group consisting of: 200 grams, 500 grams, 1 kg, 2kg, 5kg, 10kg, 20kg, 30kg, 50kg, 75kg, 100kg, 150kg, 200kg. Preferably, the total combined amount of biologically active material and grinding matrix is less than 2000kg.

Preferably, the biologically active material is selected from the group consisting of: diclofenac or a derivative or salt thereof.

In another preferred embodiment, the grinding matrix is a single material or is a mixture of two or more materials in any proportion. Preferably, the single material or a mixture of two or more materials is selected from the group consisting of: mannitol, sorbitol, Isomalt, xylitol, maltitol, lactitol, erythritol, arabitol, ribitol, glucose, fructose, mannose, galactose, anhydrous lactose, lactose monohydrate, sucrose, maltose, trehalose, maltodextrins, dextrin, Inulin, dextrates, polydextrose, starch, wheat flour, corn flour, rice flour, rice starch, tapioca flour, tapioca starch, potato flour, potato starch, other flours and starches, milk powder, skim milk powders, other milk solids and dreviatives, soy flour, soy meal or other soy products, cellulose, microcystalline cellulose, microcystalline cellulose based co-blended materials, pregelatinized (or partially) starch, HPMC, CMC, HPC, citric acid, tartaric acid, malic acid, maleic acid fumaric acid, ascorbic acid, succinic acid, sodium citrate, sodium tartrate, sodium malate, sodium ascorbate, potassium citrate, potassium tartrate, potassium malate, sodium acetate, potassium ascorbate, sodium carbonate, potassium carbonate, magnesium carbonate, sodium bicarbonate, potassium bicarbonate, calcium carbonate, dibasic calcium phosphate, tribasic calcium phosphate, sodium sulfate, sodium chloride, sodium metabisulphite, sodium thiosulfate, ammonium chloride, glauber's salt, ammonium carbonate, sodium bisulfate, magnesium sulfate, potash alum, potassium chloride, sodium hydrogen sulfate, sodium hydroxide, crystalline hydroxides, hydrogen carbonates, ammonium chloride, methylamine hydrochloride, ammonium bromide, silica, thermal silica, alumina, titanium dioxide, talc, chalk, mica, kaolin, bentonite, hectorite, magnesium trisilicate, clay based materials or aluminium silicates, sodium lauryl sulfate, sodium stearyl sulfate, sodium cetyl sulfate, sodium cetostearyl sulfate, sodium docusate, sodium deoxycholate, N-lauroylsarcosine sodium salt, glyceryl monostearate , glycerol distearate glyceryl palmitostearate, glyceryl behenate, glyceryl caprylate, glyceryl oleate, benzalkonium chloride, CTAB, CTAC, Cetrimide, cetylpyridinium chloride, cetylpyridinium bromide,

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benzethonium chloride, PEG 40 stearate, PEG 100 stearate, poloxamer 188, , poloxamer 338, poloxamer 407 polyoxyl 2 stearyl ether, polyoxyl 100 stearyl ether, polyoxyl 20 stearyl ether, polyoxyl 10 stearyl ether, polyoxyl 20 cetyl ether, polysorbate 20, polysorbate 40, polysorbate 60, polysorbate 61, polysorbate 65, polysorbate 80, polyoxyl 35 castor oil, polyoxyl 40 castor oil, polyoxyl 60 castor oil, polyoxyl 100 castor oil, polyoxyl 200 castor oil, polyoxyl 40 hydrogenated castor oil, polyoxyl 60 hydrogenated castor oil, polyoxyl 100 hydrogenated castor oil, polyoxyl 200 hydrogenated castor oil, cetostearyl alcohol, macrogel 15 hydroxystearate, sorbitan monopalmitate, sorbitan monostearate, sorbitan trioleate, sucrose palmitate, sucrose stearate, sucrose distearate, sucrose laurate, glycocholic acid, sodium glycholate, cholic acid, soidum cholate, sodium deoxycholate, deoxycholic acid, sodium taurocholate, taurocholic acid, sodium taurodeoxycholate, taurodeoxycholic acid, soy lecithin, phosphatidylcholine, phosphatidylethanolamine, phosphatidylserine, phosphatidylinositol, PEG4000, PEG6000, PEG8000, PEG10000, PEG20000, alkyl naphthalene sulfonate condensate/Lignosulfonate blend, calcium dodecylbenzene sulfonate, sodium dodecylbenzene sulfonate, diisopropyl naphthaenesulphonate, erythritol distearate, naphthalene sulfonate formaldehyde condensate, nonylphenol ethoxylate (poe-30), tristyrylphenol ethoxylate, polyoxyethylene (15) tallowalkylamines, sodium alkyl naphthalene sulfonate, sodium alkyl naphthalene sulfonate condensate, sodium alkylbenzene sulfonate, sodium isopropyl naphthalene sulfonate, sodium methyl naphthalene formaldehyde sulfonate, sodium n-butyl naphthalene sulfonate, tridecyl alcohol ethoxylate (poe-18), triethanolamine isodecanol phosphate ester, triethanolamine tristyrylphosphate ester, tristyrylphenol ethoxylate sulfate, bis(2-hydroxyethyl)tallowalkylaminés. Preferably, the concentration of the single (or first) material is selected from the group consisting of: 5 - 99 % w/w, 10 - 95 % w/w, 15 - 85 % w/w, of 20 – 80% w/w, 25 - 75 % w/w, 30 - 60% w/w, 40 - 50% w/w. Preferably, the concentration of the second or subsequent material is selected from the group consisting of: 5 - 50 % w/w, 5 - 40 % w/w, 5 - 30 % w/w, of 5 – 20% w/w, 10 - 40 % w/w, 10 -30% w/w, 10 -20% w/w, 20 - 40% w/w, or 20 - 30% w/w or if the second or subsequent material is a surfactant or water soluble polymer the concentration is selected from 0.1 -10 % w/w, 0.1 -5 % w/w, 0.1 -2.5 % w/w, of 0.1 – 2% w/w, 0.1 -1 %, 0.5 -5% w/w, 0.5 -3% w/w, 0.5 -2% w/w, 0.5 – 1.5%, 0.5 -1 % w/w, of 0.75 – 1.25 % w/w, 0.75 -1% and 1% w/w.

Preferably, the grinding matrix is selected from the group consisting of:

(a) lactose monohydrate or lactose monohydrate combined with a material selected from the group consisting of: sodium pentane sulfate; sodium octadecyl sulfate; Brij700; Brij76; sodium n-lauroyl sacrosine; lecithin; docusate sodium; polyoxyl-40-stearate; Aerosil R972 fumed silica; sodium lauryl sulfate or other alkyl sulfate surfactants with a chain length between C5 to C18; calcium carbonate; malic

acid; tartaric acid; trisodium citrate dehydrate; D,L-Malic acid; Xylitol; Poloxamer 407; Poloxamer 338; Poloxamer 188; Polyvinyl pyrrolidone; lactose anhydrous; mannitol; microcrystalline cellulose; sodium lauryl sulfate and polyethylene glycol 40 stearate; sodium lauryl sulfate and polyethylene glycol 100 stearate; sodium lauryl sulfate and PEG 3000; sodium lauryl sulphate and PEG 6000; sodium lauryl sulfate and Brij700; sodium lauryl sulfate and Poloxamer 407; sodium lauryl sulfate and Poloxamer 338 and sodium lauryl sulfate and Poloxamer 188.

(b) lactose anhydrous or lactose anhydrous combined with a material selected from the group consisting of: sodium pentane sulfate; sodium octadecyl sulfate; Brij700; Brij76; sodium n-lauroyl sacrosine; lecithin; docusate sodium; polyoxyl-40-stearate; Aerosil R972 fumed silica; sodium lauryl sulfate or other alkyl sulfate surfactants with a chain length between C5 to C18; calcium carbonate; malic acid; tartaric acid; trisodium citrate dehydrate; D,L-Malic acid; Xylitol; Polyvinyl pyrrolidone; lactose monohydrate; mannitol; microcrystalline cellulose; sodium lauryl sulfate and polyethylene glycol 40 stearate, sodium lauryl sulfate and polyethylene glycol 100 stearate, sodium lauryl sulfate and PEG 3000, sodium lauryl sulphate and PEG 6000, sodium lauryl sulfate and Brij700, sodium lauryl sulfate and Poloxamer 407, sodium lauryl sulfate and Poloxamer 338, sodium lauryl sulfate and Poloxamer 188; Poloxamer 407, Poloxamer 338 and Poloxamer 188.

(c) mannitol or mannitol combined with a material selected from the group consisting of: sodium pentane sulfate; sodium octadecyl sulfate; Brij700; Brij76; sodium n-lauroyl sacrosine; lecithin; docusate sodium; polyoxyl-40-stearate; Aerosil R972 fumed silica; sodium lauryl sulfate or other alkyl sulfate surfactants with a chain length between C5 to C18; calcium carbonate; malic acid; tartaric acid; trisodium citrate dehydrate; D,L-Malic acid; Xylitol; Polyvinyl pyrrolidone; lactose monohydrate; microcrystalline cellulose; lactose anhydrous; sodium lauryl sulfate and polyethylene glycol 40 stearate, sodium lauryl sulfate and polyethylene glycol 100 stearate, sodium lauryl sulfate and PEG 3000, sodium lauryl sulphate and PEG 6000, sodium lauryl sulfate and Brij700, sodium lauryl sulfate and Poloxamer 407, sodium lauryl sulfate and Poloxamer 338, sodium lauryl sulfate and Poloxamer 188; Poloxamer 407, Poloxamer 338 and Poloxamer 188.

(d) tartaric acid or tartaric acid combined with a material selected from the group consisting of: sodium pentane sulfate; sodium octadecyl sulfate; Brij700; Brij76; sodium n-lauroyl sacrosine; lecithin; docusate sodium; polyoxyl-40-stearate; Aerosil R972 fumed silica; sodium lauryl sulfate or other alkyl sulfate surfactants with a chain length between C5 to C18; calcium carbonate; malic acid; trisodium

citrate dehydrate; D,L-Malic acid; Xylitol; Polyvinyl pyrrolidone; lactose monohydrate; microcrystalline cellulose; lactose anhydrous; mannitol; sodium lauryl sulfate and polyethylene glycol 40 stearate, sodium lauryl sulfate and polyethylene glycol 100 stearate, sodium lauryl sulfate and PEG 3000, sodium lauryl sulphate and PEG 6000, sodium lauryl sulfate and Brij700, sodium lauryl sulfate and Poloxamer 407, sodium lauryl sulfate and Poloxamer 338, sodium lauryl sulfate and Poloxamer 188; Poloxamer 407, Poloxamer 338 and Poloxamer 188.

(e) Xylitol or Xylitol combined with a material selected from the group consisting of: sodium pentane sulfate; sodium octadecyl sulfate; Brij700; Brij76; sodium n-lauroyl sacrosine; lecithin; docusate sodium; polyoxyl-40-stearate; Aerosil R972 fumed silica; sodium lauryl sulfate or other alkyl sulfate surfactants with a chain length between C5 to C18; calcium carbonate; malic acid; tartaric acid; trisodium citrate dehydrate; D,L-Malic acid; Polyvinyl pyrrolidone; lactose monohydrate; microcrystalline cellulose; lactose anhydrous; mannitol; sodium lauryl sulfate and polyethylene glycol 40 stearate, sodium lauryl sulfate and polyethylene glycol 100 stearate, sodium lauryl sulfate and PEG 3000, sodium lauryl sulphate and PEG 6000, sodium lauryl sulfate and Brij700, sodium lauryl sulfate and Poloxamer 407, sodium lauryl sulfate and Poloxamer 338, sodium lauryl sulfate and Poloxamer 188; Poloxamer 407, Poloxamer 338 and Poloxamer 188.

(f) microcrystalline cellulose or microcrystalline cellulose combined with a material selected from the group consisting of: sodium pentane sulfate; sodium octadecyl sulfate; Brij700; Brij76; sodium n-lauroyl sacrosine; lecithin; docusate sodium; polyoxyl-40-stearate; Aerosil R972 fumed silica; sodium lauryl sulfate or other alkyl sulfate surfactants with a chain length between C5 to C18; calcium carbonate; malic acid; tartaric acid; trisodium citrate dehydrate; D,L-Malic acid; polyvinyl pyrrolidone; lactose monohydrate; xylitol; lactose anhydrous; mannitol sodium lauryl sulfate and polyethylene glycol 40 stearate, sodium lauryl sulfate and polyethylene glycol 100 stearate, sodium lauryl sulfate and PEG 3000, sodium lauryl sulphate and PEG 6000, sodium lauryl sulfate and Brij700, sodium lauryl sulfate and Poloxamer 407, sodium lauryl sulfate and Poloxamer 338, sodium lauryl sulfate and Poloxamer 188; Poloxamer 407, Poloxamer 338 and Poloxamer 188.

(g) Kaolin combined with a material selected from the group consisting of: sodium pentane sulfate; sodium octadecyl sulfate; Brij700; Brij76; sodium n-lauroyl sacrosine; lecithin; docusate sodium; polyoxyl-40-stearate; Aerosil R972 fumed silica; sodium lauryl sulfate or other alkyl sulfate surfactants with a chain length

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between C5 to C18; calcium carbonate; malic acid; tartaric acid; trisodium citrate dehydrate; D,L-Malic acid; polyvinyl pyrrolidone; lactose monohydrate; xylitol; lactose anhydrous; mannitol; microcrystalline cellulose; sodium lauryl sulfate and polyethylene glycol 40 stearate, sodium lauryl sulfate and polyethylene glycol 100 stearate, sodium lauryl sulfate and PEG 3000, sodium lauryl sulphate and PEG 6000, sodium lauryl sulfate and Brij700, sodium lauryl sulfate and Poloxamer 407, sodium lauryl sulfate and Poloxamer 338, sodium lauryl sulfate and Poloxamer 188; Poloxamer 407, Poloxamer 338, Poloxamer 188, alkyl naphthalene sulfonate condensate/Lignosulfonate blend; Calcium Dodecylbenzene Sulfonate (Branched); Diisopropyl naphthaenesulphonate; erythritol distearate; linear and branched dodecylbenzene sulfonic acids; Naphthalene Sulfonate Formaldehyde Condensate; nonylphenol ethoxylate; POE-30; Phosphate Esters, Tristyrylphenol Ethoxylate, Free Acid; Polyoxyethylene (15) tallowalkylamines; sodium alkyl naphthalene sulfonate; sodium alkyl naphthalene sulfonate condensate; sodium alkylbenzene sulfonate; sodium isopropyl naphthalene sulfonate; Sodium Methyl Naphthalene; Formaldehyde Sulfonate; sodium salt of n-butyl naphthalene sulfonate; tridecyl alcohol ethoxylate, POE-18; Triethanolamine isodecanol phosphate ester; Triethanolamine tristyrylphosphate ester; Tristyrylphenol Ethoxylate Sulfate; Bis(2-hydroxyethyl)tallowalkylamines.

(h) Talc combined with a material selected from the group consisting of: sodium pentane sulfate; sodium octadecyl sulfate; Brij700; Brij76; sodium n-lauroyl sacrosine; lecithin; docusate sodium; polyoxyl-40-stearate; Aerosil R972 fumed silica; sodium lauryl sulfate or other alkyl sulfate surfactants with a chain length between C5 to C18; calcium carbonate; malic acid; tartaric acid; trisodium citrate dehydrate; D,L-Malic acid; polyvinyl pyrrolidone; lactose monohydrate; xylitol; lactose anhydrous; mannitol; microcrystalline cellulose; sodium lauryl sulfate and polyethylene glycol 40 stearate, sodium lauryl sulfate and polyethylene glycol 100 stearate, sodium lauryl sulfate and PEG 3000, sodium lauryl sulphate and PEG 6000, sodium lauryl sulfate and Brij700, sodium lauryl sulfate and Poloxamer 407, sodium lauryl sulfate and Poloxamer 338, sodium lauryl sulfate and Poloxamer 188; Poloxamer 407, Poloxamer 338, Poloxamer 188, alkyl naphthalene sulfonate condensate/Lignosulfonate blend; Calcium Dodecylbenzene Sulfonate (Branched); Diisopropyl naphthaenesulphonate; erthritol distearate; linear and branched dodecylbenzene sulfonic acids; Naphthalene Sulfonate Formaldehyde Condensate; nonylphenol ethoxylate, POE-30; Phosphate Esters, Tristyrylphenol Ethoxylate, Free Acid; Polyoxyethylene (15) tallowalkylamines; sodium alkyl naphthalene sulfonate; sodium alkyl naphthalene sulfonate condensate; sodium

alkylbenzene sulfonate; sodium isopropyl naphthalene sulfonate; Sodium Methyl Naphthalene; Formaldehyde Sulfonate; sodium salt of n-butyl naphthalene sulfonate; tridecyl alcohol ethoxylate, POE-18; Triethanolamine isodecanol phosphate ester; Triethanolamine tristyrylphosphate ester; Tristyrylphenol Ethoxylate Sulfate; Bis(2-hydroxyethyl)tallowalkylamines.

Preferably, the grinding matrix is selected from the group consisting of: a material considered to be 'Generally Regarded as Safe' (GRAS) for pharmaceutical products; a material considered acceptable for use in an agricultural formulation; and a material considered acceptable for use in a veterinary formulation.

In another preferred embodiment, a milling aid or combination of milling aids is used. Preferably, the milling aid is selected from the group consisting of: colloidal silica, a surfactant, a polymer, a stearic acid and derivatives thereof. Preferably, the surfactant is selected from the group consisting of: polyoxyethylene alkyl ethers, polyoxyethylene stearates, polyethylene glycols (PEG), poloxamers, poloxamines, sarcosine based surfactants, polysorbates, aliphatic alcohols, alkyl and aryl sulfates, alkyl and aryl polyether sulfonates and other sulfate surfactants, trimethyl ammonium based surfactants, lecithin and other phospholipids, bile salts, polyoxyethylene castor oil derivatives, polyoxyethylene sorbitan fatty acid esters, Sorbitan fatty acid esters, Sucrose fatty acid esters, alkyl glucopyranosides, alkyl maltopyranosides, glycerol fatty acid esters, Alkyl Benzene Sulphonic Acids, Alkyl Ether Carboxylic Acids, Alkyl and aryl Phosphate esters, Alkyl and aryl Sulphate esters, Alkyl and aryl Sulphonic acids, Alkyl Phenol Phosphates esters, Alkyl Phenol Sulphates esters, Alkyl and Aryl Phosphates, Alkyl Polysaccharides, Alkylamine Ethoxylates, Alkyl-Naphthalene Sulphonates formaldehyde condensates, Sulfosuccinates, lignosulfonates, Ceto-Oleyl Alcohol Ethoxylates, Condensed Naphthalene Sulphonates, Dialkyl and Alkyl Naphthalene Sulphonates, Di-alkyl Sulphosuccinates, Ethoxylated nonylphenols, Ethylene Glycol Esters, Fatty Alcohol Alkoxylates, Hydrogenated tallowalkylamines, Mono-alkyl Sulphosuccinamates, Nonyl Phenol Ethoxylates, Sodium Oleyl N-methyl Taurate, Tallowalkylamines, linear and branched dodecylbenzene sulfonic acids

Preferably, the surfactant is selected from the group consisting of: sodium lauryl sulfate, sodium stearyl sulfate, sodium cetyl sulfate, sodium cetostearyl sulfate, sodium docusate, sodium deoxycholate, N-lauroylsarcosine sodium salt, glyceryl monostearate , glycerol distearate glyceryl palmitostearate, glyceryl behenate, glyceryl caprylate, glyceryl oleate, benzalkonium chloride, CTAB, CTAC, Cetrimide, cetylpyridinium chloride, cetylpyridinium bromide, benzethonium chloride, PEG 40 stearate, PEG 100 stearate, poloxamer 188, , poloxamer 338, poloxamer 407 polyoxyl 2 stearyl ether, polyoxyl 100 stearyl ether, polyoxyl 20 stearyl ether, polyoxyl 10 stearyl ether, polyoxyl 20 cetyl ether, polysorbate 20,

polysorbate 40, polysorbate 60, polysorbate 61, polysorbate 65, polysorbate 80, polyoxyl 35 castor oil, polyoxyl 40 castor oil, polyoxyl 60 castor oil, polyoxyl 100 castor oil, polyoxyl 200 castor oil, polyoxyl 40 hydrogenated castor oil, polyoxyl 60 hydrogenated castor oil, polyoxyl 100 hydrogenated castor oil, polyoxyl 200 hydrogenated castor oil, cetostearyl alcohol, macrogel 15 hydroxystearate, sorbitan monopalmitate, sorbitan monostearate, sorbitan trioleate, Sucrose Palmitate, Sucrose Stearate, Sucrose Distearate, Sucrose laurate, Glycocholic acid, sodium Glycholate, Cholic Acid, Soidum Cholate, Sodium Deoxycholate, Deoxycholic acid, Sodium taurocholate, taurocholic acid, Sodium taurodeoxycholate, taurodeoxycholic acid, soy lecithin, phosphatidylcholine, phosphatidylethanolamine, phosphatidylserine, phosphatidylinositol, PEG4000, PEG6000, PEG8000, PEG10000, PEG20000, alkyl naphthalene sulfonate condensate/Lignosulfonate blend,Calcium Dodecylbenzene Sulfonate, Sodium Dodecylbenzene Sulfonate,Diisopropyl naphthaenesulphonate, erythritol distearate, Naphthalene Sulfonate Formaldehyde Condensate, nonylphenol ethoxylate (poe-30), Tristyrylphenol Ethoxylate, Polyoxyethylene (15) tallowalkylamines, sodium alkyl naphthalene sulfonate, sodium alkyl naphthalene sulfonate condensate, sodium alkylbenzene sulfonate, sodium isopropyl naphthalene sulfonate, Sodium Methyl Naphthalene Formaldehyde Sulfonate, sodium n-butyl naphthalene sulfonate, tridecyl alcohol ethoxylate (poe-18), Triethanolamine isodecanol phosphate ester, Triethanolamine tristyrylphosphate ester, Tristyrylphenol Ethoxylate Sulfate, Bis(2-hydroxyethyl)tallowalkylamines.

Preferably the polymer is selected from the list of: polyvinylpyrrolidones (PVP), polyvinylalcohol, acrylic acid based polymers and copolymers of acrylic acid

Preferably, the milling aid has a concentration selected from the group consisting of: 0.1 -10 % w/w, 0.1 -5 % w/w, 0.1 -2.5 % w/w, of 0.1 – 2% w/w, 0.1 -1 %, 0.5 -5% w/w, 0.5 -3% w/w, 0.5 -2% w/w, 0.5 – 1.5%, 0.5 -1 % w/w, of 0.75 – 1.25 % w/w, 0.75 -1% and 1% w/w.

In another preferred embodiment of the invention, a facilitating agent is used or combination of facilitating agents is used. Preferably, the facilitating agent is selected from the group consisting of: surfactants, polymers, binding agents, filling agents, lubricating agents, sweeteners, flavouring agents, preservatives, buffers, wetting agents, disintegrants, effervescent agents, agents that may form part of a medicament, including a solid dosage form or a dry powder inhalation formulation and other material required for specific drug delivery. Preferably, the facilitating agent is added during dry milling. Preferably, the facilitating agent is added to the dry milling at a time selected from the group consisting of: with 1-5 % of the total milling time remaining, with 1-10 % of the total milling time remaining, with 1-20 % of the total milling time remaining, with 1-30 % of the total milling time remaining, with 2-5% of the total milling time remaining, with 2-10% of the total milling time remaining, with 5-20% of the total milling time remaining and with 5-20% of the total milling

time remaining. Preferably, the disintegrant is selected from the group consisting of: crosslinked PVP, cross linked carmellose and sodium starch glycolate. Preferably, the facilitating agent is added to the milled biologically active material and grinding matrix and further processed in a mechanofusion process. Mechanofusion milling causes mechanical energy to be applied to powders or mixtures of particles in the micrometre and nanometre range.

The reasons for including facilitating agents include, but are not limited to providing better dispersibility, control of agglomeration, the release or retention of the active particles from the delivery matrix. Examples of facilitating agents include, but are not limited to stearic acid, magnesium stearate, calcium stearate, sodium stearyl fumarate, sodium stearyl lactylate, zinc stearate, sodium stearate or lithium stearate, other solid state fatty acids such as oleic acid, lauric acid, palmitic acid, erucic acid, behenic acid, or derivatives (such as esters and salts), Amino acids such as leucine, isoleucine, lysine, valine, methionine, phenylalanine, aspartame or acesulfame K. In a preferred aspect of manufacturing this formulation the facilitating agent is added to the milled mixture of biologically active material and co-grinding matrix and further processed in another milling device such as Mechnofusion, Cyclomixing, or impact milling such as ball milling, jet milling, or milling using a high pressure homogeniser, or combinations thereof. In a highly preferred aspect the facilitating agent is added to the milling of the mixture of biologically active material and co-grinding matrix as some time before the end of the milling process.

In another preferred embodiment, diclofenac is milled with lactose monohydrate and alkyl sulfates. Preferably diclofenac is milled with lactose monohydrate and sodium lauryl sulfate. Preferably diclofenac is milled with lactose monohydrate and sodium octadecyl sulfate. In another preferred embodiment, Diclofenac is milled with lactose monohydrate, alkyl sulfates and another surfactant or polymers. Preferably diclofenac is milled with lactose monohydrate, sodium lauryl sulfate and polyether sulfates. Preferably diclofenac is milled with lactose monohydrate, sodium lauryl sulfate and polyethylene glycol 40 stearate. Preferably diclofenac is milled with lactose monohydrate, sodium lauryl sulfate and polyethylene glycol 100 stearate. Preferably diclofenac is milled with lactose monohydrate, sodium lauryl sulfate and a poloxamer. Preferably diclofenac is milled with lactose monohydrate, sodium lauryl sulfate and poloxamer 407. Preferably diclofenac is milled with lactose monohydrate, sodium lauryl sulfate and poloxamer 338. Preferably diclofenac is milled with lactose monohydrate, sodium lauryl sulfate and poloxamer 188. Preferably diclofenac is milled with lactose monohydrate, sodium lauryl sulfate and a solid polyethylene glycol. Preferably diclofenac is milled with lactose monohydrate, sodium lauryl sulfate and polyethylene glycol 6000. Preferably diclofenac is milled with lactose monohydrate, sodium lauryl sulfate and polyethylene glycol 3000. In another preferred embodiment, Diclofenac is

milled with lactose monohydrate and polyether sulfates. Preferably diclofenac is milled with lactose monohydrate and polyethylene glycol 40 stearate Preferably diclofenac is milled with lactose monohydrate and polyethylene glycol 100 stearate In another preferred embodiment diclofenac is milled with lactose monohydrate and polyvinyl-pyrrolidine. Preferably diclofenac is milled with lactose monohydrate and polyvinyl-pyrrolidone with an approximate molecular weight of 30,000-40,000. In another preferred embodiment, diclofenac is milled with lactose monohydrate and alkyl sulfonates. Preferably diclofenac is milled with lactose monohydrate and docusate sodium. In another preferred embodiment, diclofenac is milled with lactose monohydrate and a surfactant. Preferably diclofenac is milled with lactose monohydrate and lecithin. Preferably diclofenac is milled with lactose monohydrate and sodium n-lauroyl sarcosine. Preferably diclofenac is milled with lactose monohydrate and polyoxyethylene alkyl ether surfactants. Preferably diclofenac is milled with lactose monohydrate and PEG 6000. In another preferred formulation diclofenac is milled with lactose monohydrate and silica. Preferably diclofenac is milled with lactose monohydrate and Aerosil R972 fumed silica. In another preferred embodiment, diclofenac is milled with with lactose monohydrate, tartaric acid and sodium lauryl sulfate. In another preferred embodiment, diclofenac is milled with with lactose monohydrate, sodium bicarbonate and sodium lauryl sulfate. In another preferred embodiment, diclofenac is milled with lactose monohydrate, potassium bicarbonate and sodium lauryl sulfate.In another preferred embodiment, diclofenac is milled with mannitol and alkyl sulfates. Preferably diclofenac is milled with mannitol and sodium lauryl sulfate. Preferably diclofenac is milled with mannitol and sodium octadecyl sulfate. In another preferred embodiment, Diclofenac is milled with mannitol, alkyl sulfates and another surfactant or polymers. Preferably diclofenac is milled with mannitol, sodium lauryl sulfate and polyether sulfates. Preferably diclofenac is milled with mannitol, sodium lauryl sulfate and polyethylene glycol 40 stearate. Preferably diclofenac is milled with mannitol, sodium lauryl sulfate and polyethylene glycol 100 stearate. Preferably diclofenac is milled with mannitol, sodium lauryl sulfate and a poloxamer. Preferably diclofenac is milled with mannitol, sodium lauryl sulfate and poloxamer 407. Preferably diclofenac is milled with mannitol, sodium lauryl sulfate and poloxamer 338. Preferably diclofenac is milled with mannitol, sodium lauryl sulfate and poloxamer 188. Preferably diclofenac is milled with mannitol, sodium lauryl sulfate and a solid polyethylene glycol. Preferably diclofenac is milled with mannitol, sodium lauryl sulfate and polyethylene glycol 6000. Preferably diclofenac is milled with mannitol, sodium lauryl sulfate and polyethylene glycol 3000. In another preferred embodiment, Diclofenac is milled with mannitol and polyether sulfates. Preferably diclofenac is milled with mannitol and polyethylene glycol 40 stearate Preferably diclofenac is milled with mannitol and polyethylene glycol 100 stearate In another preferred embodiment diclofenac is milled with

mannitol and polyvinyl-pyrrolidine. Preferably diclofenac is milled with mannitol and polyvinyl-pyrrolidone with an approximate molecular weight of 30,000-40,000. In another preferred embodiment, diclofenac is milled with mannitol and alkyl sulfonates. Preferably diclofenac is milled with mannitol and docusate sodium. In another preferred embodiment, diclofenac is milled with mannitol and a surfactant. Preferably diclofenac is milled with mannitol and lecithin. Preferably diclofenac is milled with mannitol and sodium n-lauroyl sarcosine. Preferably diclofenac is milled with mannitol and polyoxyethylene alkyl ether surfactants. Preferably diclofenac is milled with mannitol and PEG 6000. In another preferred formulation diclofenac is milled with mannitol and silica. Preferably diclofenac is milled with mannitol and Aerosil R972 fumed silica. In another preferred embodiment, diclofenac is milled with with mannitol, tartaric acid and sodium lauryl sulfate. In another preferred embodiment, diclofenac is milled with with mannitol, sodium bicarbonate and sodium lauryl sulfate. In another preferred embodiment, diclofenac is milled with mannitol, potassium bicarbonate and sodium lauryl sulfate.

In a second aspect the invention comprises a biologically active material produced by the method described herein and composition comprising the biologically active material as described herein. Preferably, the average particle size, determined on a particle number basis, is equal to or less than a size selected from the group 2000 nm, 1900 nm, 1800nm, 1700nm, 1600nm, 1500nm, 1400nm, 1300nm, 1200 nm, 1100nm, 1000nm, 900nm, 800nm, 700nm, 600nm, 500nm, 400 nm, 300nm, 200nm and 100 nm. Preferably, the average particle size is equal to or greater than 25nm. Preferably, the particles have a median particle size, determined on a particle volume basis, equal or less than a size selected from the group 2000 nm, 1900 nm, 1800nm, 1700nm, 1600nm, 1500nm, 1400nm, 1300nm, 1200 nm, 1100nm, 1000nm, 900nm, 800nm, 700nm, 600nm, 500nm, 400 nm, 300nm, 200nm and 100 nm. Preferably, the median particle size is equal to or greater than 25nm. Preferably, the percentage of particles, on a particle volume basis, is selected from the group consisting of: less than 2000nm (% < 2000 nm) is selected from the group 50 %, 60%, 70%, 80%, 90%, 95% and 100 %; less than 1000nm (% < 1000 nm) is selected from the group 50 %, 60%, 70%, 80%, 90%, 95% and 100 %; less than 500nm (% < 500 nm) is selected from the group 0%, 10%, 20%, 30%, 40%, 50 %, 60%, 70%, 80%, 90%, 95% and 100 %; less than 300nm (% < 300 nm) is selected from the group 0%, 10%, 20%, 30%, 40%, 50 %, 60%, 70%, 80%, 90%, 95% and 100 %; and less than 200nm (% < 200 nm) is selected from the group 0%, 10%, 20%, 30%, 40%, 50 %, 60%, 70%, 80%, 90%, 95% and 100 %.

Preferably, the crystallinity profile of the biologically active material is selected from the group consisting of: at least 50% of the biologically active material is crystalline, at least 60% of the biologically active material is crystalline, at least 70% of the biologically active material is crystalline, at least 75% of the biologically active material is crystalline, at least 85% of the

biologically active material is crystalline, at least 90% of the biologically active material is crystalline, at least 95% of the biologically active material is crystalline and at least 98% of the biologically active material is crystalline. Preferably, the crystallinity profile of the biologically active material is substantially equal to the crystallinity profile of the biologically active material before the material was subject to the method described herein. Preferably, the amorphous content of the biologically active material is selected from the group consisting of: less than 50% of the biologically active material is amorphous, less than 40% of the biologically active material is amorphous, less than 30% of the biologically active material is amorphous, less than 25% of the biologically active material is amorphous, less than 15% of the biologically active material is amorphous, less than 10% of the biologically active material is amorphous, less than 5% of the biologically active material is amorphous and less than 2% of the biologically active material is amorphous. Preferably, the biologically active material has had no significant increase in amorphous content following subjecting the material to the method as described herein.

In one preferred embodiment, the invention comprises compositions comprising the biologically active ingredient together with a grinding matrix, a mixture of grinding matrix materials, milling aids, mixtures of milling aids, facilitating agents and/or mixtures of facilitating agents as described herein, in concentrations and ratios as described herein under the methods of the invention.

In a third aspect the invention comprises a pharmaceutical composition comprising a biologically active material produced by the method described herein and compositions described herein. Preferably, the invention comprises pharmaceutical compositions comprising the biologically active ingredient together with a grinding matrix, a mixture of grinding matrix materials, milling aids, mixtures of milling aids, facilitating agents and/or mixtures of facilitating agents as described herein, in concentrations and ratios as described herein under the methods of the invention. Preferably, the average particle size, determined on a particle number basis, is equal to or less than a size selected from the group 2000 nm, 1900 nm, 1800nm, 1700nm, 1600nm, 1500nm, 1400nm, 1300nm, 1200 nm, 1100nm, 1000nm, 900nm, 800nm, 700nm, 600nm, 500nm, 400 nm, 300nm, 200nm and 100 nm. Preferably, the average particle size is equal to or greater than 25nm. Preferably, the particles have a median particle size, determined on a particle volume basis, equal or less than a size selected from the group 2000 nm, 1900 nm, 1800nm, 1700nm, 1600nm, 1500nm, 1400nm, 1300nm, 1200 nm, 1100nm, 1000nm, 900nm, 800nm, 700nm, 600nm, 500nm, 400 nm, 300nm, 200nm and 100 nm. Preferably, the median particle size is equal to or greater than 25nm. Preferably, the percentage of particles, on a particle volume basis, is selected from the group consisting of: less than 2000nm (% < 2000 nm) is selected from the group 50 %, 60%, 70%, 80%, 90%, 95% and 100 %; less than 1000nm (% < 1000 nm) is

selected from the group 50 %, 60%, 70%, 80%, 90%, 95% and 100 %; less than 500nm (% < 500 nm) is selected from the group 0%, 10%, 20%, 30%, 40%, 50 %, 60%, 70%, 80%, 90%, 95% and 100 %; less than 300nm (% < 300 nm) is selected from the group 0%, 10%, 20%, 30%, 40%, 50 %, 60%, 70%, 80%, 90%, 95% and 100 %; and less than 200nm (% < 200 nm) is selected from the group 0%, 10%, 20%, 30%, 40%, 50 %, 60%, 70%, 80%, 90%, 95% and 100 %. Preferably, the composition has a T_{max} less than that of the equivalent conventional composition administered at the same dosage, wherein the composition comprises diclofenac. Preferably, the composition has a C_{max} greater than that of the equivalent conventional composition administered at the same dosage, wherein the composition comprises diclofenac. Preferably, the composition has an AUC greater than that of the equivalent conventional composition administered at the same dosage, wherein the composition comprises diclofenac.

In a fourth aspect the invention comprises a method of treating a human in need of such treatment comprising the step of administering to the human an effective amount of a pharmaceutical composition as described herein.

In a fifth aspect, the invention comprises the use of a pharmaceutical composition as described herein in the manufacture of a medicament for the treatment of a human in need of such treatment.

In a sixth aspect the invention comprises a method for manufacturing a pharmaceutical composition as described herein comprising the step of combining a therapeutically effective amount of a biologically active material prepared by a method described herein or a composition as described herein, together with a pharmaceutically acceptable carrier to produce a pharmaceutically acceptable dosage form.

In a seventh aspect the invention comprises a method for manufacturing a veterinary product comprising the step of combining a therapeutically effective amount of the biologically active material prepared by a method as described herein or a composition as described herein, together with an acceptable excipient to produce a dosage form acceptable for veterinary use.

In an eighth aspect the invention comprises a method for manufacturing of a pharmaceutical formulation comprising the step of combining an effective amount of the biologically active material prepared by a method described herein together with acceptable excipients to produce a formulation that can deliver a therapeutically effective amount of active to the pulmonary or nasal area. Such a formulation could be, but is not limited to a dry powder formulation for oral inhalation to the lungs or a formulation for nasal inhalation. Preferably the method for manufacturing such a formulation uses lactose, mannitol, sucrose, sorbitol, xylitol or other sugars or polyols as the co-grinding matrix together with surfactant such as, but not limited to lecithin, DPPC (dipalmitoyl phosphatidylcholine), PG (phosphatidylglycerol),

dipalmitoyl phosphatidyl ethanolamine (DPPE), dipalmitoyl phosphatidylinositol (DPPI) or other phospholipid. The particle size of the material produced by the invention disclosed herein results in the materials being readily aerosolized and suitable for methods of delivery to a subject in need thereof, including pulmonary and nasal delivery methods.

While the method of the present invention has particular application in the preparation of poorly water-soluble biologically active materials, the scope of the invention is not limited thereto. For example, the method of the present invention enables production of highly water-soluble biologically active materials. Such materials may exhibit advantages over conventional materials by way of, for example, more rapid therapeutic action or lower dose. In contrast, wet grinding techniques utilizing water (or other comparably polar solvents) are incapable of being applied to such materials, as the particles dissolve appreciably in the solvent.

Other aspects and advantages of the invention will become apparent to those skilled in the art from a review of the ensuing description.

Brief Description of the Drawings

Figure 1: The PSD of 12 w/w % indomethacin Spex milled with lactose monohydrate without and with 1% alkyl sulfate surfactants (example 1a) as measured with the Malvern Mastersizer. The graph is a frequency (volume %) versus size (in micron)

Figure 2: The PSD of 12 w/w % indomethacin 110 ml attritor milled with lactose monohydrate without and with 1% SLS (example 1b) as measured with the Malvern Mastersizer. The graph is a frequency (volume %) versus size (in micron)

Figure 3: The PSD of 12 w/w % indomethacin Spex milled with lactose monohydrate without and with 1% polyoxyethylene alkyl ether surfactants (example 2a) as measured with the Malvern Mastersizer. The graph is a frequency (volume %) versus size (in micron)

Figure 4: The PSD of 12 w/w % indomethacin 110 ml attritor milled with lactose monohydrate without and with 1% Brij700 (example 2b) as measured with the Malvern Mastersizer. The graph is a frequency (volume %) versus size (in micron)

Figure 5: The PSD of 12 w/w % indomethacin Spex milled with lactose monohydrate without and with other surfactants (example 3a) as measured with the Malvern Mastersizer. The graph is a frequency (volume %) versus size (in micron)

Figure 6: The PSD of 10 w/w % indomethacin Spex milled with lactose monohydrate without and with other surfactants or additives (example 3b) as measured with the Malvern Mastersizer. The graph is a frequency (volume %) versus size (in micron)

Figure 7: The PSD of 20 w/w % indomethacin Spex milled with lactose monohydrate and 1% SLS and also milled with the invidual components (example 4) as measured with the Malvern Mastersizer. The graph is a frequency (volume %) versus size (in micron)

Figure 8: The PSD of 20 w/w % diclofenac Spex milled with lactose monohydrate and 1% SLS and also milled with the invidual components (example 5) as measured with the Malvern Mastersizer. The graph is a frequency (volume %) versus size (in micron)

Figure 9: The PSD of 20 w/w % diclofenac in mannitol Spex milled without surfactant, with 1% SLS and with 1%_sodium octadecyl sulfate (example 6a) as measured with the Malvern Mastersizer. The graph is a frequency (volume %) versus size (in micron)

Figure 10: The PSD of 10 w/w % diclofenac in mannitol milled in the Siebtechnik mill with 1% SLS (example 6b) as measured with the Malvern Mastersizer. The graph is a frequency (volume %) versus size (in micron)

Figure 11: The PSD of 35 w/w% naproxen acid in lactose monohydrate Spex milled without (A), with (B) 1 w/w% of the surfactant polyoxyl-40-stearate and with (C) 1 w/w% sodium lauryl sulfate as measured with a Malvern Mastersizer (Example 7 a). The graph is a frequency (volume %) versus size (in micron).

Figure 12: The PSD of 35 w/w% naproxen acid in lactose monohydrate with 1w/w % SLS at larger scale milled with an attritor (A) and a simoloyer (B) mill as measured with a Malvern Mastersizer (example 7 b). The graph is a frequency (volume %) versus size (in micron).

Figure 13: The PSD of 40 w/w% naproxen acid in lactose monohydrate with (A) and without (B) 1 w/w% of the surfactant polyoxyl-40-stearate after Spex milling as measured with a Malvern Mastersizer (example 7c). The graph is a frequency (volume %) versus size (in micron).

Figure 14: The PSD of 35 w/w% naproxen acid in mannitol Spex milled without (A) and with (B) 1 w/w% SLS as measured with a Malvern Mastersizer (example 8a). The graph is a frequency (volume %) versus size (in micron).

Figure 15: The PSD of 35 w/w% naproxen acid in mannitol with 1w/w % SLS milled with an attritor (A) and a simoloyer (B) mill as measured with a Malvern Mastersizer (example 8 b). The graph is a frequency (volume %) versus size (in micron).

Figure 16: The PSD of 30 w/w% naproxen acid in mannitol spex milled without (A) and with (B) 1w/w% of the surfactant SLS as measured with a Malvern Mastersizer (example 8c). The graph is a frequency (volume %) versus size (in micron).

Figure 17: The PSD of 30 w/w% naproxen acid in mannitol 1S attritor milled without (A) and with (B) 1w/w% of the surfactant SLS as measured with a Malvern Mastersizer (example 8d). The graph is a frequency (volume %) versus size (in micron).

Figure 18: The PSD of 20 w/w% meloxicam attritor milled in lactose monohydrate with 3 w/w % SLS (A) and in lactose monohydrate only (B). The graph is a frequency (volume %) versus size (in micron).

Figure 19: The PSD of 20 w/w% meloxicam attritor milled in mannitol with 3 w/w % SLS (A) and in mannitol only (B). The graph is a frequency (volume %) versus size (in micron).

Figure 20: The PSD of 30 w/w% naproxen acid in lactose monohydrate (A), in lactose monohydrate with 20 w/w% Trisodium Citrate Dihydrate (B), and in trisodium citrate dihydrate (C) after spex milling as measured with a Malvern Mastersizer (example 11a). The graph is a frequency (volume %) versus size (in micron).

Figure 21: The PSD of 30 w/w% naproxen acid Spex milled in lactose monohydrate with 20 w/w% calcium carbonate (A), and in calcium carbonate (B) as measured with a Malvern Mastersizer (Example 11b). The graph is a frequency (volume %) versus size (in micron).

Figure 22: The PSD after Spex milling of 25 w/w% naproxen acid in lactose anhydrous with 20 w/w% xylitol (A), and in xylitol (B) as measured with a Malvern Mastersizer (example 12a). The graph is a frequency (volume %) versus size (in micron).

Figure 23: The PSD after Spex milling of 25 w/w% naproxen acid in lactose anhydrous with 20 w/w% malic acid (A), and in malic acid (B) as measured with a Malvern Mastersizer (example 12 b). The graph is a frequency (volume %) versus size (in micron).

Figure 24: The PSD after Spex milling of 25 w/w% naproxen acid in lactose anhydrous with 20 w/w% trisodium citrate dihydrate (A), and in trisodium citrate dihydrate (B) as measured with a Malvern Mastersizer (example 12 c). The graph is a frequency (volume %) versus size (in micron).

Figure 25: The Particle size distribution of 13 w/w % indomethacin in lactose monohydrate milled at 100 gram scale with and without 1% SLS and with and without tartaric acid (example 13a) as measured with the Malvern Mastersizer. The graph is a frequency (volume %) versus size (in micron)

Figure 26: The Particle size distribution of 13 w/w % indomethacin in lactose monohydrate milled at one kilogram scale with 1% SLS and with tartaric acid (example 13b) as measured with the Malvern Mastersizer. The graph is a frequency (volume %) versus size (in micron)

Figure 27: The Particle size distribution of 15 w/w % diclofenac in lactose monohydrate and 1% SLS milled at 350 gram scale with and without tartaric acid (example 14) as measured with the Malvern Mastersizer. The graph is a frequency (volume %) versus size (in micron)

Figure 28: The PSD of 10 w/w % Halosulfuron -Methyl Spex milled with lactose monohydrate without (A) and with (B) 1% lecithin (example 15) as measured with the Malvern Mastersizer. The graph is a frequency (volume %) versus size (in micron).

Figure 29: The PSD of 10 w/w % Metsulfuron -Methyl Spex milled with lactose monohydrate without (A) and with (B) 1% SLS (example 16) as measured with the Malvern Mastersizer. The graph is a frequency (volume %) versus size (in micron).

Figure 30: The PSD of 10 w/w % Tribenuran -Methyl Spex milled with lactose monohydrate without (A) and with (B) 1% Brij 700 (example 17) as measured with the Malvern Mastersizer. The graph is a frequency (volume %) versus size (in micron).

Figure 31: The PSD of 10 w/w % sulfur Spex milled with lactose monohydrate without (A) and with (B) 1% SLS (example 18) as measured with the Malvern Mastersizer. The graph is a frequency (volume %) versus size (in micron).

Figure 32: The PSD of 10 w/w % Mancozeb Spex milled with lactose monohydrate (example 19) as measured with the Malvern Mastersizer. The graph is a frequency (volume %) versus size (in micron).

Figure 33: The PSD of 30 w/w% Metaxalone Spex milled in lactose monohydrate with (A) and without (B) 1 w/w% of Poloxamer 407 and of only unmilled Metaxalone (C) as measured with a Malvern Mastersizer (Example 20). The graph is a frequency (volume %) versus size (in micron).

Figure 34: The PSD of attritor milled powders of (A) 43 w/w% Metaxalone with 1 w/w% SLS, and of (B) 50 w/w% Metaxalone with 2 w/w% SLS, 2w/w% pluronic 407 and 20 w/w% sodium bicarbonate both in lacotse monohydrate (Example 21) as measured with a Malvern Mastersizer. The graph is a frequency (volume %) versus size (in micron).

Figure 35: The Dissolution profile shows the average of three measurements of A) milled metaxalone, B) unmilled metaxalone and C) a commercial tablet of metaxalone, Skelaxin® (Example 21) using 0.01 M HCL in an USP1-dissolution apparatus.

Figure 36: The PSD of 35 w/w % Naproxen Acid milled with the 750 ml 1S attritor in Mannitol with (A) 1% SLS, (B) 1% SLS and 1% POE 40 sterate, and (C) 1% SLS and 1% PEG 3000 (example 22) as measured with the Malvern Mastersizer. The graph is a frequency (volume %) versus size (in micron).

Figure 37: The PSD of 12 w/w % Indomethacin milled with the 750 ml 1S attritor in lactose monohydrate with (A) 1% SLS, (B) 1% SLS and 1% Pluronic F127, (C) 1% SLS and 1% POE 40 Sterate (example 23) as measured with the Malvern Mastersizer. The graph is a frequency (volume %) versus size (in micron).

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Detailed Description of the Invention

General

Those skilled in the art will appreciate that the invention described herein is susceptible to variations and modifications other than those specifically described. It is to be understood that the invention includes all such variations and modifications. The invention also includes all of the steps, features, compositions and materials referred to or indicated in the specification, individually or collectively and any and all combinations or any two or more of the steps or features.

The present invention is not to be limited in scope by the specific embodiments described herein, which are intended for the purpose of exemplification only. Functionally equivalent products, compositions and methods are clearly within the scope of the invention as described herein.

The invention described herein may include one or more ranges of values (e.g. size, concentration etc). A range of values will be understood to include all values within the range, including the values defining the range, and values adjacent to the range that lead to the same or substantially the same outcome as the values immediately adjacent to that value which defines the boundary to the range.

The entire disclosures of all publications (including patents, patent applications, journal articles, laboratory manuals, books, or other documents) cited herein are hereby incorporated by reference. Inclusion does not constitute an admission is made that any of the references constitute prior art or are part of the common general knowledge of those working in the field to which this invention relates.

Throughout this specification, unless the context requires otherwise, the word "comprise" or variations, such as "comprises" or "comprising" will be understood to imply the inclusion of a stated integer, or group of integers, but not the exclusion of any other integers or group of integers. It is also noted that in this disclosure, and particularly in the claims and/or paragraphs, terms such as "comprises", "comprised", "comprising" and the like can have the meaning attributed to it in US Patent law; e.g., they can mean "includes", "included", "including", and the like.

"Therapeutically effective amount" as used herein with respect to methods of treatment and in particular drug dosage, shall mean that dosage that provides the specific pharmacological response for which the drug is administered in a significant number of subjects in need of such treatment. It is emphasized that "therapeutically effective amount," administered to a particular subject in a particular instance will not always be effective in treating the diseases described herein, even though such dosage is deemed a "therapeutically effective amount"

by those skilled in the art. It is to be further understood that drug dosages are, in particular instances, measured as oral dosages, or with reference to drug levels as measured in blood.
The term "inhibit" is defined to include its generally accepted meaning which includes prohibiting, preventing, restraining, and lowering, stopping, or reversing progression or severity, and such action on a resultant symptom. As such the present invention includes both medical therapeutic and prophylactic administration, as appropriate.
The term "biologically active material" is defined to mean a biologically active compound or a substance which comprises a biologically active compound. In this definition, a compound is generally taken to mean a distinct chemical entity where a chemical formula or formulas can be used to describe the substance. Such compounds would generally, but not necessarily be identified in the literature by a unique classification system such as a CAS number. Some compounds may be more complex and have a mixed chemical structure. For such compounds they may only have an empirical formula or be qualitatively identified. A compound would generally be a pure material, although it would be expected that up to 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90% of the substance could be other impurities and the like. Examples of biologically active compounds are, but not limited to, pharmaceutical actives, and analogs, homologs and first order derivatives thereof. A substance that contains a biologically active compound is any substance which has as one of its components a biologically active compound. Examples of substances containing biologically active compounds are, but not limited to, pharmaceutical formulations and products.
Any of the terms, "biological(ly) active", "active", "active material" shall have the same meaning as biologically active material.
The term "grinding matrix" is defined as any inert substance that a biologically active material can or is combined with and milled. The terms "co-grinding matrix" and "matrix" are interchangeable with "grinding matrix".

Particle Size

There are a wide range of techniques that can be utilized to characterize the particle size of a material. Those skilled in the art also understand that almost all these techniques do not physically measure the actually particle size, as one might measure something with a ruler, but measure a physical phenomena which is interpreted to indicate a particle size. As part of the interpretation process some assumptions need to be made to enable mathematical calculations to be made. These assumptions deliver results such as an equivalent spherical particle size, or a hydrodynamic radius.
Amongst these various methods, two types of measurements are most commonly used. Photon correlation spectroscopy (PCS), also known as 'dynamic light scattering' (DLS) is

commonly used to measure particles with a size less than 10 micron. Typically this measurement yields an equivalent hydrodynamic radius often expressed as the average size of a number distribution. The other common particle size measurement is laser diffraction which is commonly used to measure particle size from 100 nm to 2000 micron. This technique calculates a volume distribution of equivalent spherical particles that can be expressed using descriptors such as the median particle size or the % of particles under a given size.

Those skilled in the art recognize that different characterization techniques such as photon correlation spectroscopy and laser diffraction measure different properties of a particle ensemble. As a result multiple techniques will give multiple answers to the question, "what is the particle size." In theory one could convert and compare the various parameters each technique measures, however, for real world particle systems this is not practical. As a result the particle size used to describe this invention will be given as two different sets of values that each relate to these two common measurement techniques, such that measurements could be made with either technique and then evaluated against the description of this invention.

For measurements made using a photo correlation spectroscopy instrument, or an equivalent method known in the art, the term "number average particle size" is defined as the average particle diameter as determined on a number basis.

For measurements made using a laser diffraction instrument, or an equivalent method known in the art, the term "median particle size" is defined as the median particle diameter as determined on an equivalent spherical particle volume basis. Where the term median is used, it is understood to describe the particle size that divides the population in half such that 50 % of the population is greater than or less than this size. The median particle size is often written as D50, D(0.50) or D[0.5]. As used herein D50, D(0.50) or D[0.5] shall be taken to mean 'median particle size'.

Another commonly used way of describing a particle size distribution measured by laser diffraction, or an equivalent method known in the art, is to describe what % of a distribution is under or over a nominated size. The term "percentage less than" also written as "%<" is defined as the percentage, by volume, of a particle size distribution under a nominated size - for example the % < 1000 nm. The term "percentage greater than" also written as "%>" is defined as the percentage, by volume, of a particle size distribution over a nominated size - for example the % > 1000 nm.

The particle size used to describe this invention should be taken to mean the particle size as measured at or shortly before the time of use. For example, the particle size is measured 2 months after the material is subject to the milling method of this invention. In a preferred form, the particle size is measured at a time selected from the group consisting of: 1 day

after milling, 2 days after milling, 5 days after milling, 1 month after milling, 2 months after milling, 3 months after milling, 4 months after milling, 5 months after milling, 6 months after milling, 1 year after milling, 2 years after milling, 5 years after milling.

For many of the materials subject to the methods of this invention the particle size can be easily measured. Where the active material has poor water solubility and the matrix it is milled in has good water solubility the powder can simply be dispersed in an aqueous solvent. In this scenario the matrix dissolves leaving the active material dispersed in the solvent. This suspension can then be measured by techniques such as PCS or laser diffraction.

Suitable methods to measure an accurate particle size where the active material has substantive aqueous solubility or the matrix has low solubility in a water based dispersant are outlined below.

1. In the circumstance where insoluble matrix such as microcrystalline cellulose prevents the measurement of the active material separation techniques such as filtration or centrifugation could be used to separate the insoluble matrix from the active material particles. Other ancillary techniques would also be required to determine if any active material was removed by the separation technique so that this could be taken into account.
2. In the case where the active material is too soluble in water other solvents could be evaluated for the measurement of particle size. Where a solvent could be found that active material is poorly soluble in but is a good solvent for the matrix a measurement would be relatively straight forward. If such a solvent is difficult to find another approach would be to measure the ensemble of matrix and active material in a solvent (such as iso-octane) which both are insoluble in. Then the powder would be measured in another solvent where the active material is soluble but the matrix is not. Thus with a measurement of the matrix particle size and a measurement of the size of the matrix and active material together an understanding of the active material particle size can be obtained.
3. In some circumstances image analysis could be used to obtain information about the particle size distribution of the active material. Suitable image measurement techniques might include transmission electron microscopy (TEM), scanning electron microscopy (SEM), optical microscopy and confocal microscopy. In addition to these standard techniques some additional technique would be required to be used in parallel to differentiate the active material and matrix particles. Depending on the chemical makeup of the materials involved possible techniques could be elemental analysis, raman spectroscopy, FTIR spectroscopy or fluorescence spectroscopy.

Other Definitions

Throughout this specification, unless the context requires otherwise, the phrase "dry mill" or variations, such as "dry milling", should be understood to refer to milling in at least the substantial absence of liquids. If liquids are present, they are present in such amounts that the contents of the mill retain the characteristics of a dry powder.

"Flowable" means a powder having physical characteristics rendering it suitable for further processing using typical equipment used for the manufacture of pharmaceutical compositions and formulations.

Other definitions for selected terms used herein may be found within the detailed description of the invention and apply throughout. Unless otherwise defined, all other scientific and technical terms used herein have the same meaning as commonly understood to one of ordinary skill in the art to which the invention belongs.

The term "millable" means that the grinding matrix is capable of being physically degraded under the dry milling conditions of the method of the invention. In one embodiment of the invention, the milled grinding matrix is of a comparable particle size to the biologically active material. In another embodiment of the invention the particle size of the matrix is substantially reduced but not as small as the biologically active material

Other definitions for selected terms used herein may be found within the detailed description of the invention and apply throughout. Unless otherwise defined, all other scientific and technical terms used herein have the same meaning as commonly understood to one of ordinary skill in the art to which the invention belongs.

Specific

In one embodiment, the present invention is directed to a method for producing a composition, comprising the steps of: dry milling a solid biologically active material and a millable grinding matrix in a mill comprising a plurality of milling bodies, for a time period sufficient to produce particles of the biologically active material dispersed in an at least partially milled grinding material.

The mixture of active material and matrix may then be separated from the milling bodies and removed from the mill.

In one aspect the mixture of active material and matrix is then further processed. In another aspect, the grinding matrix is separated from the particles of biologically active material. In a further aspect, at least a portion of the milled grinding matrix is separated from the particulate biologically active material.

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The milling bodies are essentially resistant to fracture and erosion in the dry milling process. The quantity of the grinding matrix relative to the quantity of biologically active material in particulate form, and the extent of milling of the grinding matrix, is sufficient to inhibit re-agglomeration of the particles of the active material.

The present invention also relates to biologically active materials produced by said methods, to medicaments produced using said biologically active materials and to methods of treatment of an animal, including man, using a therapeutically effective amount of said biologically active materials administered by way of said medicaments.

Commercial Scale

The present invention is directed to the unexpected finding that particles of a biologically active material can be produced by dry milling processes as described herein at commercial scale. In one surprising aspect the particle size produced by the process is equal to or less than 2000nm. In another surprising aspect the particle size produced by the process is equal to or less than 1000nm. This can result in a more efficient and cost effective process.

One of the key goals of reducing manufacturing costs is the encapsulation of the nanoparticles into materials that do not have to be removed. This enables a simple manufacturing process where conventional formulation technologies can be used to progress the matrix encapsulated nanoparticles directly to a final product. In order to do this the materials used within the matrix must be acceptable to industry regulators. In some cases materials may be acceptable for use but only in limited quantities. Another aspect of matrix choice is functionality. Some matrices that produce good encapsulated nanoparticles may be acceptable from a safety perspective but these materials may make manufacture of a dosage form such as tablet limited.

Improving the dissolution profile

The process results in the biologically active material having an improved dissolution profile. An improved dissolution profile has significant advantages including the improvement of bioavailability of the biologically active material *in vivo*. Preferably, the improved dissolution profile is observed *in vitro*. Alternatively, the improved dissolution profile is observed *in vivo* by the observation of an improved bioavailability profile. Standard methods for determining the dissolution profile of a material *in vitro* are available in the art. A suitable method to determine an improved dissolution profile *in vitro* may include determining the concentration of the sample material in a solution over a period of time and comparing the results from the sample material to a control sample. An observation that peak solution concentration for the sample material was achieved in less time than the control sample would indicate (assuming

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it is statistically significant), that the sample material has an improved dissolution profile. The measurement sample is herein defined as the mixture of biologically active material with grinding matrix and/or other additives that has been subject to the processes of the invention described here. Herein a control sample is defined as a physical mixture (not subject to the processes described in this invention) of the components in the measurement sample with the same relative proportions of active, matrix and/or additive as the measurement sample. For the purposes of the dissolution testing a prototype formulation of the measurement sample could also be used. In this case the control sample would be formulated in the same way. Standard methods for determining the improved dissolution profile of a material *in vivo* are available in the art. A suitable method to determine an improved dissolution profile in a human may be after delivering the dose to measure the rate of active material absorption by measuring the plasma concentration of the sample compound over a period of time and comparing the results from the sample compound to a control. An observation that peak plasma concentration for the sample compound was achieved in less time than the control would indicate (assuming it is statistically significant) that the sample compound has improved bioavailability and an improved dissolution profile. Preferably, the improved dissolution profile is observed at a relevant gastrointestinal pH, when it is observed *in vitro*. Preferably, the improved dissolution profile is observed at a pH which is favourable at indicating improvements in dissolution when comparing the measurement sample to the control compound. Suitable methods for quantifying the concentration of a compound in an *in vitro* sample or an *in vivo* sample are widely available in the art. Suitable methods could include the use of spectroscopy or radioisotope labeling. In one preferred embodiment the method of quantification of dissolution is determined in a solution with a pH selected from the group consisting of: pH 1, pH 2, pH 3, pH 4, pH 5, pH 6, pH 7, pH 7.3, pH 7.4, pH 8, pH 9, pH 10, pH 11, pH 12, pH 13, pH 14 or a pH with 0.5 of a pH unit of any of this group.

Crystallization Profile

Methods for determining the crystallinity profile of the biologically active material are widely available in the art. Suitable methods may include X-ray diffraction, differential scanning calorimetry, raman or IR spectrocopy.

Amorphicity Profile

Methods for determining the amorphous content of the biologically active material are widely available in the art. Suitable methods may include X-ray diffraction, differential scanning calorimetry, raman or IR spectroscopy.

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Grinding Matrix

As will be described subsequently, selection of an appropriate grinding matrix affords particular advantageous applications of the method of the present invention.

A highly advantageous application of the method of the invention is the use of a water-soluble grinding matrix in conjunction with a poorly water-soluble biologically active material. This affords at least two advantages. The first being when the powder containing the biologically active material is placed into water – such as the ingestion of the powder as part of an oral medication - the matrix dissolves, releasing the particulate active material such that there is maximum surface area exposed to solution, thereby allowing a rapid dissolution of the active compound. The second key advantage is the ability, if required, to remove or partially remove the matrix prior to further processing or formulation.

Another advantageous application of the method of the invention is the use of a water-insoluble grinding matrix, particularly in the area of agricultural use, when a biologically active material such as a fungicide is commonly delivered as part of a dry powder or a suspension. The presence of a water insoluble matrix will afford benefits such as increased rain fastness.

Without wishing to be bound by theory, it is believed that the physical degradation (including but not limited to particle size reduction) of the millable grinding matrix affords the advantage of the invention, by acting as a more effective diluent than grinding matrix of a larger particle size.

Again, as will be described subsequently, a highly advantageous aspect of the present invention is that certain grinding matrixes appropriate for use in the method of the invention are also appropriate for use in a medicament. The present invention encompasses methods for the production of a medicament incorporating both the biologically active material and the grinding matrix or in some cases the biologically active material and a portion of the grinding matrix, medicaments so produced, and methods of treatment of an animal, including man, using a therapeutically effective amount of said biologically active materials by way of said medicaments.

Analogously, as will be described subsequently, a highly advantageous aspect of the present invention is that certain grinding matrixes appropriate for use in the method of the invention are also appropriate for use in a carrier for an agricultural chemical, such as a pesticide, fungicide, or herbicide. The present invention encompasses methods for the production of an agricultural chemical composition incorporating both the biologically active material in particulate form and the grinding matrix, or in some cases the biologically active material, and a portion of the grinding matrix, and agricultural chemical compositions so produced. The medicament may include only the biologically active material together with

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the milled grinding matrix or, more preferably, the biologically active material and milled grinding matrix may be combined with one or more pharmaceutically acceptable carriers, as well as any desired excipients or other like agents commonly used in the preparation of medicaments.

Analogously, the agricultural chemical composition may include only the biologically active material together with the milled grinding matrix or, more preferably, the biologically active materials and milled grinding matrix may be combined with one or more carriers, as well as any desired excipients or other like agents commonly used in the preparation of agricultural chemical compositions.

In one particular form of the invention, the grinding matrix is both appropriate for use in a medicament and readily separable from the biologically active material by methods not dependent on particle size. Such grinding matrixes are described in the following detailed description of the invention. Such grinding matrixes are highly advantageous in that they afford significant flexibility in the extent to which the grinding matrix may be incorporated with the biologically active material into a medicament.

In a highly preferred form, the grinding matrix is harder than the biologically active material, and is thus capable of reducing the particle size of the active material under the dry milling conditions of the invention. Again without wishing to be bound by theory, under these circumstances it is believed that the millable grinding matrix affords the advantage of the present invention through a second route, with the smaller particles of grinding matrix produced under the dry milling conditions enabling greater interaction with the biologically active material.

The quantity of the grinding matrix relative to the quantity of biologically active material, and the extent of physical degradation of the grinding matrix, is sufficient to inhibit re-agglomeration of the particles of the active material Preferably, the quantity of the grinding matrix relative to the quantity of biologically active material, and the extent of physical degradation of the grinding matrix, is sufficient to inhibit re-agglomeration of the particles of the active material in nanoparticulate form.The grinding matrix is not generally selected to be chemically reactive with the biologically active material under the milling conditions of the invention, excepting for example, where the matrix is deliberately chosen to undergo a mechanico-chemical reaction. Such a reaction might be the conversion of a free base or acid to a salt or vice versa.

As stated above, the method of the present invention requires the grinding matrix to be milled with the biologically active material; that is, the grinding matrix will physically degrade under the dry milling conditions of the invention to facilitate the formation and retention of particulates of the biologically active material with reduced particle size. The precise extent of degradation required will depend on certain properties of the grinding matrix and the

biologically active material, the ratio of biologically active material to grinding matrix, and the particle size distribution of the particles comprising the biologically active material.

The physical properties of the grinding matrix necessary to achieve the requisite degradation are dependent on the precise milling conditions. For example, a harder grinding matrix may degrade to a sufficient extent provided it is subjected to more vigorous dry milling conditions. Physical properties of the grinding matrix relevant to the extent that the agent will degrade under dry milling conditions include hardness, friability, as measured by indicia such as hardness, fracture toughness and brittleness index.

A low hardness (typically a Mohs Hardness less than 7) of the biologically active material is desirable to ensure fracture of the particles during processing, so that composite microstructures develop during milling. Preferably, the hardness is less than 3 as determined using the Mohs Hardness scale.

Preferably, the grinding matrix is of low abrasivity. Low abrasivity is desirable to minimise contamination of the mixture of the biologically active material in the grinding matrix by the milling bodies and/or the milling chamber of the media mill. An indirect indication of the abrasivity can be obtained by measuring the level of milling-based contaminants.

Preferably, the grinding matrix has a low tendency to agglomerate during dry milling. While it is difficult to objectively quantify the tendency to agglomerate during milling, it is possible to obtain a subjective measure by observing the level of "caking" of the grinding matrix on the milling bodies and the milling chamber of the media mill as dry milling progresses.

The grinding matrix may be an inorganic or organic substance.

In one embodiment, the grinding matrix is selected from the following, either as a single substance or a combination of two or more substances: Polyols (sugar alcohols) for example (but not limited to) mannitol, sorbitol, isomalt, xylitol, maltitol, lactitol, erythritol, arabitol, ribitol, monosaccharides for example (but not limited to) glucose, fructose, mannose, galactose, disaccharides and trisaccharides for example (but not limited to) anhydrous lactose, lactose monohydrate, sucrose, maltose, trehalose, polysaccharides for example (but not limited to) maltodextrins, dextrin, Inulin, dextrates, polydextrose, other carbohyrates for example (but not limited to) starch, wheat flour, corn flour, rice flour, rice starch, tapioca flour, tapioca starch, potato flour, potato starch, other flours and starches, , soy flour, soy meal or other soy products, cellulose, microcrystalline cellulose, microcrystalline cellulose based co blended excipients, chemically modified excipients such as pregelatinized (or partially) starch, modified celluloses such as HPMC, CMC, HPC, enteric polymer coatings such as hypromellose phthalate, cellulose acetate phthalate (Aquacoat®), polyvinyl acetate phthalate (Sureteric®), hypromellose acetate succinate (AQOAT®), and polmethacrylates (Eudragit® and Acryl-EZE®), Milk products for example (but not limited to) milk powder, skim milk powders, other milk solids and dreviatives, other functional Excipients, organic

acids for example (but not limited to) citric acid, tartaric acid, malic acid, maleic acid fumaric acid , ascorbic acid, succinic acid, the conjugate salt of organic acids for example (but not limited to) sodium citrate, sodium tartrate, sodium malate, sodium ascorbate, potassium citrate, potassium tartrate, potassium malate, potassium ascorbate, inorganics such as sodium carbonate, potassium carbonate, magnesium carbonate, sodium bicarbonate, potassium bicarbonate and calcium carbonate. dibasic calcium phosphate, tribasic calcium phosphate, sodium sulfate, sodium chloride, sodium metabisulphite, sodium thiosulfate, ammonium chloride, Glauber's salt, ammonium carbonate, sodium bisulfate, magnesium sulfate, potash alum, potassium chloride, sodium hydrogen sulfate, sodium hydroxide, crystalline hydroxides, hydrogen carbonates, hydrogen carbonates of pharmaceutical acceptable alkali metals, such as but not limited by, sodium, potassium, lithium, calcium, and barium, ammonium salts (or salts of volatile amines), for example (but not limited to) ammonium chloride, methylamine hydrochloride, ammonium bromide, other inorganics for example (but not limited to), thermal silica, chalk, mica, silica, alumina, titanium dioxide, talc, kaolin, bentonite, hectorite, magnesium trisilicate, other clay or clay derivatives or aluminium silicates, a surfactant for example (but not limited to) sodium lauryl sulfate, sodium stearyl sulfate, sodium cetyl sulfate, sodium cetostearyl sulfate, sodium docusate, sodium deoxycholate, N-lauroylsarcosine sodium salt, glyceryl monostearate , glycerol distearate glyceryl palmitostearate, glyceryl behenate, glyceryl caprylate, glyceryl oleate, benzalkonium chloride, CTAB, CTAC, Cetrimide, cetylpyridinium chloride, cetylpyridinium bromide, benzethonium chloride, PEG 40 stearate, PEG 100 stearate, poloxamer 188, , poloxamer 338, poloxamer 407 polyoxyl 2 stearyl ether, polyoxyl 100 stearyl ether, polyoxyl 20 stearyl ether, polyoxyl 10 stearyl ether, polyoxyl 20 cetyl ether, polysorbate 20, polysorbate 40, polysorbate 60, polysorbate 61, polysorbate 65, polysorbate 80, polyoxyl 35 castor oil, polyoxyl 40 castor oil, polyoxyl 60 castor oil, polyoxyl 100 castor oil, polyoxyl 200 castor oil, polyoxyl 40 hydrogenated castor oil, polyoxyl 60 hydrogenated castor oil, polyoxyl 100 hydrogenated castor oil, polyoxyl 200 hydrogenated castor oil, cetostearyl alcohol, macrogel 15 hydroxystearate, sorbitan monopalmitate, sorbitan monostearate, sorbitan trioleate, Sucrose Palmitate, Sucrose Stearate, Sucrose Distearate, Sucrose laurate, Glycocholic acid, sodium Glycholate, Cholic Acid, Soidum Cholate, Sodium Deoxycholate, Deoxycholic acid, Sodium taurocholate, taurocholic acid, Sodium taurodeoxycholate, taurodeoxycholic acid, soy lecithin, phosphatidylcholine, phosphatidylethanolamine, phosphatidylserine, phosphatidylinositol, PEG4000, PEG6000, PEG8000, PEG10000, PEG20000, alkyl naphthalene sulfonate condensate/Lignosulfonate blend,Calcium Dodecylbenzene Sulfonate, Sodium Dodecylbenzene Sulfonate,Diisopropyl naphthaenesulphonate, erythritol distearate, Naphthalene Sulfonate Formaldehyde Condensate, nonylphenol ethoxylate (poe-30), Tristyrylphenol Ethoxylate, Polyoxyethylene (15) tallowalkylamines, sodium alkyl

naphthalene sulfonate, sodium alkyl naphthalene sulfonate condensate, sodium alkylbenzene sulfonate, sodium isopropyl naphthalene sulfonate, Sodium Methyl Naphthalene Formaldehyde Sulfonate, sodium n-butyl naphthalene sulfonate, tridecyl alcohol ethoxylate (poe-18), Triethanolamine isodecanol phosphate ester, Triethanolamine tristyrylphosphate ester, Tristyrylphenol Ethoxylate Sulfate, Bis(2-hydroxyethyl)tallowalkylamines.

In a preferred embodiment, the grinding matrix is a matrix that is considered GRAS (generally regarded as safe) by persons skilled in the pharmaceutical arts.

In another preferred aspect a combination of two or more suitable matrices, such as those listed above, can be used as the grinding matrix to provide improved properties such as the reduction of caking, and greater improvement of the dissolution profile. Combination matrices may also be advantageous when the matrices have different solubility's allowing the removal or partial removal of one matrix, while leaving the other or part of the other to provide encapsulation or partial encapsulation of the biologically active material.

Another highly preferred aspect of the method is the inclusion of a suitable milling aid in the matrix to improve milling performance. Improvements to milling performance would be things such as, but not limited to, a reduction in caking or higher recovery of powder from the mill. Examples of suitable milling aids include surfactants, polymers and inorganics such as silica (including colloidal silica), aluminium silicates and clays.

There are a wide range of surfactants that will make suitable milling aids. The highly preferred form is where the surfactant is a solid, or can be manufactured into a solid. Preferably, the surfactant is selected from the group consisting of: polyoxyethylene alkyl ethers, polyoxyethylene stearates, polyethylene glycols (PEG), poloxamers, poloxamines, sarcosine based surfactants, polysorbates, aliphatic alcohols, alkyl and aryl sulfates, alkyl and aryl polyether sulfonates and other sulfate surfactants, trimethyl ammonium based surfactants, lecithin and other phospholipids, bile salts, polyoxyethylene castor oil derivatives, polyoxyethylene sorbitan fatty acid esters, Sorbitan fatty acid esters, Sucrose fatty acid esters, alkyl glucopyranosides, alkyl maltopyranosides, glycerol fatty acid esters, Alkyl Benzene Sulphonic Acids, Alkyl Ether Carboxylic Acids, Alkyl and aryl Phosphate esters, Alkyl and aryl Sulphate esters, Alkyl and aryl Sulphonic acids, Alkyl Phenol Phosphates esters, Alkyl Phenol Sulphates esters, Alkyl and Aryl Phosphates, Alkyl Polysaccharides, Alkylamine Ethoxylates, Alkyl-Naphthalene Sulphonates formaldehyde condensates, Sulfosuccinates, lignosulfonates, Ceto-Oleyl Alcohol Ethoxylates, Condensed Naphthalene Sulphonates, Dialkyl and Alkyl Naphthalene Sulphonates,Di-alkyl Sulphosuccinates, Ethoxylated nonylphenols, Ethylene Glycol Esters,Fatty Alcohol Alkoxylates, Hydrogenated tallowalkylamines, Mono-alkyl Sulphosuccinamates, Nonyl

Phenol Ethoxylates, Sodium Oleyl N-methyl Taurate, Tallowalkylamines, linear and branched dodecylbenzene sulfonic acids

Preferably, the surfactant is selected from the group consisting of: sodium lauryl sulfate, sodium stearyl sulfate, sodium cetyl sulfate, sodium cetostearyl sulfate, sodium docusate, sodium deoxycholate, N-lauroylsarcosine sodium salt, glyceryl monostearate , glycerol distearate glyceryl palmitostearate, glyceryl behenate, glyceryl caprylate, glyceryl oleate, benzalkonium chloride, CTAB, CTAC, Cetrimide, cetylpyridinium chloride, cetylpyridinium bromide, benzethonium chloride, PEG 40 stearate, PEG 100 stearate, poloxamer 188, , poloxamer 338, poloxamer 407 polyoxyl 2 stearyl ether, polyoxyl 100 stearyl ether, polyoxyl 20 stearyl ether, polyoxyl 10 stearyl ether, polyoxyl 20 cetyl ether, polysorbate 20, polysorbate 40, polysorbate 60, polysorbate 61, polysorbate 65, polysorbate 80, polyoxyl 35 castor oil, polyoxyl 40 castor oil, polyoxyl 60 castor oil, polyoxyl 100 castor oil, polyoxyl 200 castor oil, polyoxyl 40 hydrogenated castor oil, polyoxyl 60 hydrogenated castor oil, polyoxyl 100 hydrogenated castor oil, polyoxyl 200 hydrogenated castor oil, cetostearyl alcohol, macrogel 15 hydroxystearate, sorbitan monopalmitate, sorbitan monostearate, sorbitan trioleate, Sucrose Palmitate, Sucrose Stearate, Sucrose Distearate, Sucrose laurate, Glycocholic acid, sodium Glycholate, Cholic Acid, Soidum Cholate, Sodium Deoxycholate, Deoxycholic acid, Sodium taurocholate, taurocholic acid, Sodium taurodeoxycholate, taurodeoxycholic acid, soy lecithin, phosphatidylcholine, phosphatidylethanolamine, phosphatidylserine, phosphatidylinositol, PEG4000, PEG6000, PEG8000, PEG10000, PEG20000, alkyl naphthalene sulfonate condensate/Lignosulfonate blend,Calcium Dodecylbenzene Sulfonate, Sodium Dodecylbenzene Sulfonate,Diisopropyl naphthaenesulphonate, erythritol distearate, Naphthalene Sulfonate Formaldehyde Condensate, nonylphenol ethoxylate (poe-30), Tristyrylphenol Ethoxylate, Polyoxyethylene (15) tallowalkylamines, sodium alkyl naphthalene sulfonate, sodium alkyl naphthalene sulfonate condensate, sodium alkylbenzene sulfonate, sodium isopropyl naphthalene sulfonate, Sodium Methyl Naphthalene Formaldehyde Sulfonate, sodium n-butyl naphthalene sulfonate, tridecyl alcohol ethoxylate (poe-18), Triethanolamine isodecanol phosphate ester, Triethanolamine tristyrylphosphate ester, Tristyrylphenol Ethoxylate Sulfate, Bis(2-hydroxyethyl)tallowalkylamines.

Preferably the polymer is selected from the list of: polyvinylpyrrolidones (PVP), polyvinylalcohol, Acrylic acid based polymers and copolymers of acrylic acid

Preferably, the milling aid has a concentration selected from the group consisting of: 0.1 -10 % w/w, 0.1 -5 % w/w, 0.1 -2.5 % w/w, of 0.1 – 2% w/w, 0.1 -1 %, 0.5 -5% w/w, 0.5 -3% w/w, 0.5 -2% w/w, 0.5 – 1.5%, 0.5 -1 % w/w, of 0.75 – 1.25 % w/w, 0.75 -1% and 1% w/w.

Milling bodies

In the method of the present invention, the milling bodies are preferably chemically inert and rigid. The term "chemically-inert", as used herein, means that the milling bodies do not react chemically with the biologically active material or the grinding matrix.

As described above, the milling bodies are essentially resistant to fracture and erosion in the milling process.

The milling bodies are desirably provided in the form of bodies which may have any of a variety of smooth, regular shapes, flat or curved surfaces, and lacking sharp or raised edges. For example, suitable milling bodies can be in the form of bodies having ellipsoidal, ovoid, spherical or right cylindrical shapes. Preferably, the milling bodies are provided in the form of one or more of beads, balls, spheres, rods, right cylinders, drums or radius-end right cylinders (i.e., right cylinders having hemispherical bases with the same radius as the cylinder).

Depending on the nature of the biologically active material and the grinding matrix, the milling media bodies desirably have an effective mean particle diameter (i.e. "particle size") between about 0.1 and 30 mm, more preferably between about 1 and about 15 mm, still more preferably between about 3 and 10 mm.

The milling bodies may comprise various substances such as ceramic, glass, metal or polymeric compositions, in a particulate form. Suitable metal milling bodies are typically spherical and generally have good hardness (i.e. RHC 60-70), roundness, high wear resistance, and narrow size distribution and can include, for example, balls fabricated from type 52100 chrome steel, type 316 or 440C stainless steel or type 1065 high carbon steel.

Preferred ceramics, for example, can be selected from a wide array of ceramics desirably having sufficient hardness and resistance to fracture to enable them to avoid being chipped or crushed during milling and also having sufficiently high density. Suitable densities for milling media can range from about 1 to 15 g/cm^3, preferably from about 1 to 8 g/cm^3. Preferred ceramics can be selected from steatite, aluminum oxide, zirconium oxide, zirconia-silica, yttria-stabilized zirconium oxide, magnesia-stabilized zirconium oxide, silicon nitride, silicon carbide, cobalt-stabilized tungsten carbide, and the like, as well as mixtures thereof.

Preferred glass milling media are spherical (e.g. beads), have a narrow size distribution, are durable, and include, for example, lead-free soda lime glass and borosilicate glass. Polymeric milling media are preferably substantially spherical and can be selected from a wide array of polymeric resins having sufficient hardness and friability to enable them to avoid being chipped or crushed during milling, abrasion-resistance to minimize attrition resulting in contamination of the product, and freedom from impurities such as metals, solvents, and residual monomers.

Preferred polymeric resins, for example, can be selected from crosslinked polystyrenes, such as polystyrene crosslinked with divinylbenzene, styrene copolymers, polyacrylates such as polymethylmethacrylate, polycarbonates, polyacetals, vinyl chloride polymers and copolymers, polyurethanes, polyamides, high density polyethylenes, polypropylenes, and the like. The use of polymeric milling media to grind materials down to a very small particle size (as opposed to mechanochemical synthesis) is disclosed, for example, in U.S. patents 5,478,705 and 5,500,331. Polymeric resins typically can have densities ranging from about 0.8 to 3.0 g/cm^3. Higher density polymeric resins are preferred. Alternatively, the milling media can be composite particles comprising dense core particles having a polymeric resin adhered thereon. Core particles can be selected from substances known to be useful as milling media, for example, glass, alumina, zirconia silica, zirconium oxide, stainless steel, and the like. Preferred core substances have densities greater than about 2.5 g/cm^3.

In one embodiment of the invention, the milling media are formed from a ferromagnetic substance, thereby facilitating removal of contaminants arising from wear of the milling media by the use of magnetic separation techniques.

Each type of milling body has its own advantages. For example, metals have the highest specific gravities, which increase grinding efficiency due to increased impact energy. Metal costs range from low to high, but metal contamination of final product can be an issue. Glasses are advantageous from the standpoint of low cost and the availability of small bead sizes as low as 0.004 mm. However, the specific gravity of glasses is lower than other media and significantly more milling time is required. Finally, ceramics are advantageous from the standpoint of low wear and contamination, ease of cleaning, and high hardness.

Dry Milling

In the dry milling process of the present invention, the biologically active material and grinding matrix, in the form of crystals, powders, or the like, are combined in suitable proportions with the plurality of milling bodies in a milling chamber that is mechanically agitated (i.e. with or without stirring) for a predetermined period of time at a predetermined intensity of agitation. Typically, a milling apparatus is used to impart motion to the milling bodies by the external application of agitation, whereby various translational, rotational or inversion motions or combinations thereof are applied to the milling chamber and its contents, or by the internal application of agitation through a rotating shaft terminating in a blade, propeller, impeller or paddle or by a combination of both actions.

During milling, motion imparted to the milling bodies can result in application of shearing forces as well as multiple impacts or collisions having significant intensity between milling bodies and particles of the biologically active material and grinding matrix. The nature and

intensity of the forces applied by the milling bodies to the biologically active material and the grinding matrix is influenced by a wide variety of processing parameters including: the type of milling apparatus; the intensity of the forces generated, the kinematic aspects of the process; the size, density, shape, and composition of the milling bodies; the weight ratio of the biologically active material and grinding matrix mixture to the milling bodies; the duration of milling; the physical properties of both the biologically active material and the grinding matrix; the atmosphere present during activation; and others.

Advantageously, the media mill is capable of repeatedly or continuously applying mechanical compressive forces and shear stress to the biologically active material and the grinding matrix. Suitable media mills include but are not limited to the following: high-energy ball, sand, bead or pearl mills, basket mill, planetary mill, vibratory action ball mill, multi-axial shaker/mixer, stirred ball mill, horizontal small media mill, multi-ring pulverizing mill, and the like, including small milling media. The milling apparatus also can contain one or more rotating shafts.

In a preferred form of the invention, the dry milling is performed in a ball mill. Throughout the remainder of the specification reference will be made to dry milling being carried out by way of a ball mill. Examples of this type of mill are attritor mills, nutating mills, tower mills, planetary mills, vibratory mills and gravity-dependent-type ball mills. It will be appreciated that dry milling in accordance with the method of the invention may also be achieved by any suitable means other than ball milling. For example, dry milling may also be achieved using jet mills, rod mills, roller mills or crusher mills.

Biologically active material

The biologically active material includes active compounds, including compounds for veterinary and human use such as but not limited to, pharmaceutical actives and the like.

The biologically active material is ordinarily a material for which one of skill in the art desires improved dissolution properties. The biologically active material may be a conventional active agent or drug, although the process of the invention may be employed on formulations or agents that already have reduced particle size compared to their conventional form.

Biologically active materials suitable for use in the invention include diclofenac.

As discussed in the context of the background to the invention, biologically active materials that are poorly water soluble at gastrointestinal pH will particularly benefit from being prepared, and the method of the present invention is particularly advantageously applied to materials that are poorly water soluble at gastrointestinal pH.

Conveniently, the biologically active material is capable of withstanding temperatures that are typical in uncooled dry milling, which may exceed 80 °C. Therefore, materials with a

melting point about 80 °C or greater are highly suitable. For biologically active materials with lower melting points, the media mill may be cooled, thereby allowing materials with significantly lower melting temperatures to be processed according to the method of the invention. For instance, a simple water-cooled mill will keep temperatures below 50 °C, or chilled water could be used to further lower the milling temperature. Those skilled in the art will understand that a high energy ball mill could be designed to run at any temperature between say -30 to 200 °C. For some biologically active materials it may be advantageous to control the milling temperature to temperatures significantly below the melting points of the biologically active materials.

The biologically active material is obtained in a conventional form commercially and/or prepared by techniques known in the art.

It is preferred, but not essential, that the particle size of the biologically active material be less than about 1000 µm, as determined by sieve analysis. If the coarse particle size of the biologically active material is greater than about 1000 µm, then it is preferred that the particles of the biologically active material substrate be reduced in size to less than 1000 µm using another standard milling method.

Processed biologically active material

Preferably, the biologically active materials, which have been subject to the methods of the invention, comprises particles of biologically active material of an average particle size, determined on a particle number basis, is equal to or less than a size selected from the group 2000 nm, 1900 nm, 1800nm, 1700nm, 1600nm, 1500nm, 1400nm, 1300nm, 1200 nm, 1100nm, 1000nm, 900nm, 800nm, 700nm, 600nm, 500nm, 400 nm, 300nm, 200nm and 100 nm.

Preferably, the biologically active materials, which have been subject to the methods of the invention, comprises particles of biologically active material of a median particle size, determined on a particle volume basis, equal or less than a size selected from the group 2000 nm, 1900 nm, 1800nm, 1700nm, 1600nm, 1500nm, 1400nm, 1300nm, 1200 nm, 1100nm, 1000nm, 900nm, 800nm, 700nm, 600nm, 500nm, 400 nm, 300nm, 200nm and 100 nm.

These sizes refer to particles either fully dispersed or partially agglomerated.

Agglomerates of biologically active material after processing

Agglomerates comprising particles of biologically active material, said particles having a particle size within the ranges specified above, should be understood to fall within the scope

of the present invention, regardless of whether the agglomerates exceed the ranges specified above.

Agglomerates comprising particles of biologically active material, said agglomerates having a total agglomerate size within the ranges specified above, should be understood to fall within the scope of the present invention.

Agglomerates comprising particles of biologically active material should be understood to fall within the scope of the present invention if at the time of use, or further processing, the particle size of the agglomerate is within the ranges specified above.

Agglomerates comprising particles of biologically active material, said particles having a particle size within the ranges specified above, at the time of use, or further processing, should be understood to fall within the scope of the present invention, regardless of whether the agglomerates exceed the ranges specified above.

Processing Time

Preferably, the biologically active material and the grinding matrix are dry milled for the shortest time necessary to form the mixture of the biologically active material in the grinding matrix such that the active material has improved dissolution to minimise any possible contamination from the media mill and/or the plurality of milling bodies. This time varies greatly, depending on the biologically active material and the grinding matrix, and may range from as short as 1 minute to several hours. Dry milling times in excess of 2 hours may lead to degradation of the biologically active material and an increased level of undesirable contaminants.

Suitable rates of agitation and total milling times are adjusted for the type and size of milling apparatus as well as the milling media, the weight ratio of the biologically active material and grinding matrix mixture to the plurality of milling bodies, the chemical and physical properties of the biologically active material and grinding matrix, and other parameters that may be optimized empirically.

Inclusion of the grinding matrix with the biologically active material and separation of the grinding matrix from the biologically active material

In a preferred aspect, the grinding matrix is not separated from the biologically active material but is maintained with the biologically active material in the final product. Preferably the grinding matrix is considered to be Generally Regarded as Safe (GRAS) for pharmaceutical products.

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In an alternative aspect, the grinding matrix is separated from the biologically active material. In one aspect, where the grinding matrix is not fully milled, the unmilled grinding matrix is separated from the biologically active material. In a further aspect, at least a portion of the milled grinding matrix is separated from the biologically active material.

Any portion of the grinding matrix may be removed, including but not limited to 10%, 25%, 50%, 75%, or substantially all of the grinding matrix.

In some embodiments of the invention, a significant portion of the milled grinding matrix may comprise particles of a size similar to and/or smaller than the particles comprising the biologically active material. Where the portion of the milled grinding matrix to be separated from the particles comprising the biologically active material comprises particles of a size similar to and/or smaller than the particles comprising the biologically active material, separation techniques based on size distribution are inapplicable.

In these circumstances, the method of the present invention may involve separation of at least a portion of the milled grinding matrix from the biologically active material by techniques including but not limited to electrostatic separation, magnetic separation, centrifugation (density separation), hydrodynamic separation, froth flotation.

Advantageously, the step of removing at least a portion of the milled grinding matrix from the biologically active material may be performed through means such as selective dissolution, washing, or sublimation.

An advantageous aspect of the invention would be the use of grinding matrix that has two or more components where at least one component is water soluble and at least one component has low solubility in water. In this case washing can be used to remove the matrix component soluble in water leaving the biologically active material encapsulated in the remaining matrix components. In a highly advantageous aspect of the invention the matrix with low solubility is a functional excipient.

A highly advantageous aspect of the present invention is that certain grinding matrixes appropriate for use in the method of the invention (in that they physically degrade to the desired extent under dry milling conditions) are also pharmaceutically acceptable and thus appropriate for use in a medicament. Where the method of the present invention does not involve complete separation of the grinding matrix from the biologically active material, the present invention encompasses methods for the production of a medicament incorporating both the biologically active material and at least a portion of the milled grinding matrix, medicaments so produced and methods of treatment of an animal, including man, using a therapeutically effective amount of said biologically active materials by way of said medicaments.

The medicament may include only the biologically active material and the grinding matrix or, more preferably, the biologically active materials and grinding matrix may be combined with

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one or more pharmaceutically acceptable carriers, as well as any desired excipients or other like agents commonly used in the preparation of medicaments.

Analogously, a highly advantageous aspect of the present invention is that certain grinding matrixes appropriate for use in the method of the invention (in that they physically degrade to a desirable extent under dry milling conditions) are also appropriate for use in an agricultural chemical composition. Where the method of the present invention does not involve complete separation of the grinding matrix from the biologically active material, the present invention encompasses methods for the production of a agricultural chemical composition incorporating both the biologically active material and at least a portion of the milled grinding matrix, agricultural chemical composition so produced and methods of use of such compositions.

The agricultural chemical composition may include only the biologically active material and the grinding matrix or, more preferably, the biologically active materials and grinding matrix may be combined with one or more acceptable carriers, as well as any desired excipients or other like agents commonly used in the preparation of agricultural chemical compositions.

In one particular form of the invention, the grinding matrix is both appropriate for use in a medicament and readily separable from the biologically active material by methods not dependent on particle size. Such grinding matrixes are described in the following detailed description of the invention. Such grinding matrixes are highly advantageous in that they afford significant flexibility in the extent to which the grinding matrix may be incorporated with the biologically active material into a medicament.

The mixture of biologically active material and grinding matrix may then be separated from the milling bodies and removed from the mill.

In one embodiment, the grinding matrix is separated from the mixture of biologically active material and grinding matrix. Where the grinding matrix is not fully milled, the unmilled grinding matrix is separated from the biologically active material. In a further aspect, at least a portion of the milled grinding matrix is separated from the biologically active material.

The milling bodies are essentially resistant to fracture and erosion in the dry milling process.

The quantity of the grinding matrix relative to the quantity of biologically active material, and the extent of milling of the grinding matrix, is sufficient to provide reduced particle size of the biologically active material.

The grinding matrix is neither chemically nor mechanically reactive with the pharmaceutical material under the dry milling conditions of the method of the invention except, for example, where the matrix is deliberately chosen to undergo a mechanico-chemical reaction. Such a reaction might be the conversion of a free base or acid to a salt or vice versa.

Preferably, the medicament is a solid dosage form, however, other dosage forms may be prepared by those of ordinary skill in the art.

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In one form, after the step of separating said mixture of biologically active material and grinding matrix from the plurality of milling bodies, and before the step of using said mixture of biologically active material and grinding matrix in the manufacture of a medicament, the method may comprise the step of:

removing a portion of the grinding matrix from said mixture of biologically active material and grinding matrix to provide a mixture enriched in the biologically active material;

and the step of using said mixture of biologically active material and grinding matrix in the manufacture of a medicament, more particularly comprises the step of using the mixture of biologically active material and grinding matrix enriched in the biologically active material form in the manufacture of a medicament.

The present invention includes medicaments manufactured by said methods, and methods for the treatment of an animal, including man, by the administration of a therapeutically effective amount of the biologically active materials by way of said medicaments.

In another embodiment of the invention, a facilitating agent or a combination of facilitating agents is also comprised in the mixture to be milled. Such facilitating agents appropriate for use in the invention include diluents, surfactants, polymers, binding agents, filling agents, lubricating agents, sweeteners, flavouring agents, preservatives, buffers, wetting agents, disintegrants, effervescent agents and agents that may form part of a medicament, including a solid dosage form, or other excipients required for other specific drug delivery, such as the agents and media listed below under the heading *Medicinal and Pharmaceutical Compositions*, or any combination thereof.

Biologically active materials and compositions

The present invention encompasses pharmaceutically acceptable materials produced according to the methods of the present invention, compositions including such materials, including compositions comprising such materials together with the grinding matrix with or without milling aids, facilitating agents, with at least a portion of the grinding matrix or separated from the grinding matrix.

The pharmaceutically acceptable materials within the compositions of the invention are present at a concentration of between about 0.1% and about 99.0% by weight. Preferably, the concentration of pharmaceutically acceptable materials within the compositions will be about 5% to about 80% by weight, while concentrations of 10% to about 50% by weight are highly preferred. Desirably, the concentration will be in the range of about 10 to 15% by weight, 15 to 20% by weight, 20 to 25% by weight, 25 to 30% by weight, 30 to 35% by weight, 35 to 40% by weight, 40 to 45% by weight, 45 to 50% by weight, 50 to 55% by weight, 55 to 60% by weight, 60 to 65% by weight, 65 to 70% by weight, 70 to 75% by

weight or 75 to 80% by weight for the composition prior to any later removal (if desired) of any portion of the grinding matrix. Where part or all of the grinding matrix has been removed, the relative concentration of pharmaceutically acceptable materials in the composition may be considerably higher depending on the amount of the grinding matrix that is removed. For example, if all of the grinding matrix is removed the concentration of particles in the preparation may approach 100% by weight (subject to the presence of facilitating agents).

Compositions produced according to the present invention are not limited to the inclusion of a single species of pharmaceutically acceptable materials. More than one species of pharmaceutically acceptable materials may therefore be present in the composition. Where more than one species of pharmaceutically acceptable materials is present, the composition so formed may either be prepared in a dry milling step, or the pharmaceutically acceptable materials may be prepared separately and then combined to form a single composition.

Medicaments

The medicaments of the present invention may include the pharmaceutically acceptable material, optionally together with the grinding matrix or at least a portion of the grinding matrix, with or without milling aids, facilitating agents, combined with one or more pharmaceutically acceptable carriers, as well as other agents commonly used in the preparation of pharmaceutically acceptable compositions.

As used herein "pharmaceutically acceptable carrier" includes any and all solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents, and the like that are physiologically compatible. Preferably, the carrier is suitable for parenteral administration, intravenous, intraperitoneal, intramuscular, sublingual, pulmonary, transdermal or oral administration. Pharmaceutically acceptable carriers include sterile aqueous solutions or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersion. The use of such media and agents for the manufacture of medicaments is well known in the art. Except insofar as any conventional media or agent is incompatible with the pharmaceutically acceptable material, use thereof in the manufacture of a pharmaceutical composition according to the invention is contemplated.

Pharmaceutical acceptable carriers according to the invention may include one or more of the following examples:

(1) surfactants and polymers including, but not limited to polyethylene glycol (PEG), polyvinylpyrrolidone (PVP), polyvinylalcohol, crospovidone, polyvinylpyrrolidone-polyvinylacrylate copolymer, cellulose derivatives, hydroxypropylmethyl cellulose,

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hydroxypropyl cellulose, carboxymethylethyl cellulose, hydroxypropylmethyl cellulose phthalate, polyacrylates and polymethacrylates, urea, sugars, polyols, and their polymers, emulsifiers, sugar gum, starch, organic acids and their salts, vinyl pyrrolidone and vinyl acetate

(2) binding agents such as various celluloses and cross-linked polyvinylpyrrolidone, microcrystalline cellulose; and or

(3) filling agents such as lactose monohydrate, lactose anhydrous, microcrystalline cellulose and various starches; and or

(4) lubricating agents such as agents that act on the flowability of the powder to be compressed, including colloidal silicon dioxide, talc, stearic acid, magnesium stearate, calcium stearate, silica gel; and or

(5) sweeteners such as any natural or artificial sweetener including sucrose, xylitol, sodium saccharin, cyclamate, aspartame, and accsulfame K; and or

(6) flavouring agents; and or

(7) preservatives such as 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 chemicals such as phenol, or quarternary compounds such as benzalkonium chloride; and or

(8) buffers; and or

(9) Diluents such as pharmaceutically acceptable inert fillers, such as microcrystalline cellulose, lactose, dibasic calcium phosphate, saccharides, and/or mixtures of any of the foregoing; and or

(10) wetting agents such as corn starch, potato starch, maize starch, and modified starches, croscarmellose sodium, crosspovidone, sodium starch glycolate, and mixtures thereof; and or

(11) disintegrants; and or

(12) effervescent agents such as effervescent couples such as an organic acid (e.g., citric, tartaric, malic, fumaric, adipic, succinic, and alginic acids and anhydrides and acid salts), or a carbonate (e.g. sodium carbonate, potassium carbonate, magnesium carbonate, sodium glycine carbonate, L-lysine carbonate, and arginine carbonate) or bicarbonate (e.g. sodium bicarbonate or potassium bicarbonate); and or

(13) other pharmaceutically acceptable excipients.

Medicaments of the invention suitable for use in animals and in particular in man typically must be stable under the conditions of manufacture and storage. The medicaments of the invention comprising the biologically active material can be formulated as a solid, a solution,

a microemulsion, a liposome, or other ordered structures suitable to high drug concentration. Actual dosage levels of the biologically active material in the medicament of the invention may be varied in accordance with the nature of the biologically active material, as well as the potential increased efficacy due to the advantages of providing and administering the biologically active material (e.g., increased solubility, more rapid dissolution, increased surface area of the biologically active material, etc.). Thus as used herein "therapeutically effective amount" will refer to an amount of biologically active material required to effect a therapeutic response in an animal. Amounts effective for such a use will depend on: the desired therapeutic effect; the route of administration; the potency of the biologically active material; the desired duration of treatment; the stage and severity of the disease being treated; the weight and general state of health of the patient; and the judgment of the prescribing physician.

In another embodiment, the biologically active material, optionally together with the grinding matrix or at least a portion of the grinding matrix, of the invention may be combined into a medicament with another biologically active material, or even the same biologically active material. In the latter embodiment, a medicament may be achieved which provides for different release characteristics – early release from the biologically active material, and later release from a larger average size biologically active material.

Pharmacokinetic Properties of Diclofenac Compositions

Suitable animal models to determine pharmacokinetic parameters are described in the prior art, such as the beagle dog model described in United States Patent No. 7,101,576.

Fast Onset of Activity

The diclofenac compositions of the invention exhibit faster therapeutic effects.

In one example, following administration the diclofenac compositions of the invention comprising diclofenac have a T_{max} of less than about 5 hours, less than about 4.5 hours, less than about 4 hours, less than about 3.5 hours, less than about 3 hours, less than about 2.75 hours, less than about 2.5 hours, less than about 2.25 hours, less than about 2 hours, less than about 1.75 hours, less than about 1.5 hours, less than about 1.25 hours, less than about 1.0 hours, less than about 50 minutes, less than about 40 minutes, less than about 30 minutes, less than about 25 minutes, less than about 20 minutes, less than about 15 minutes, less than about 10 minutes, less than about 5 minutes, or less than about 1 minute.

Increased Bioavailability

The diclofenac compositions of the invention preferably exhibit increased bioavailability (AUC) and require smaller doses as compared to prior conventional compositions administered at the same dose. Any drug composition can have adverse side effects. Thus, lower doses of drugs which can achieve the same or better therapeutic effects as those observed with larger doses of conventional compositions are desired. Such lower doses can be realized with the compositions of the invention because the greater bioavailability observed with the compositions as compared to conventional drug formulations means that smaller doses of drug are required to obtain the desired therapeutic effect.

The Pharmacokinetic Profiles of the Compositions of the Invention are not Substantially Affected by the Fed or Fasted State of the Subject Ingesting the Compositions

The invention encompasses diclofenac compositions wherein the pharmacokinetic profile of the composition is not substantially affected by the fed or fasted state of a subject ingesting the composition. This means that there is no substantial difference in the quantity of composition or the rate of composition absorption when the compositions are administered in the fed versus the fasted state. Thus, the compositions of the invention substantially eliminate the effect of food on the pharmacokinetics of the composition.

The difference in absorption of the diclofenac composition of the invention, when administered in the fed versus the fasted state, is less than about 35%, less than about 30%, less than about 25%, less than about 20%, less than about 15%, less than about 10%, less than about 5%, or less than about 3%. This is an especially important feature in treating patients with difficulty in maintaining a fed state.

In addition, preferably the difference in the rate of absorption (i.e., T_{max}) of the diclofenac compositions of the invention, when administered in the fed versus the fasted state, is less than about 100%, less than about 90%, less than about 80%, less than about 70%, less than about 60%, less than about 50%, less than about 40%, less than about 30%, less than about 20%, less than about 15%, less than about 10%, less than about 5%, less than about 3%, or essentially no difference. Benefits of a dosage form which substantially eliminates the effect of food include an increase in subject convenience, thereby increasing subject compliance, as the subject does not need to ensure that they are taking a dose either with or without food.

Preferably, the T_{max} of an administered dose of a diclofenac composition of the invention is less than that of a conventional drug active composition, administered at the same dosage.

A preferred diclofenac composition of the invention exhibits in comparative pharmacokinetic testing with a standard conventional drug active composition, in oral suspension, capsule or tablet form, a T_{max} which is less than about 100%, less than about 90%, less than about 80%, less than about 70%, less than about 60%, less than about 50%, less than about 40%, less than about 30%, less than about 25%, less than about 20%, less than about 15%, or less than about 10% of the T_{max} exhibited by the standard conventional drug active composition.

In addition, preferably the C_{max} of a diclofenac composition of the invention is greater than the C_{max} of a conventional drug active composition, administered at the same dosage. A preferred diclofenac composition of the invention exhibits in comparative pharmacokinetic testing with a standard conventional drug active composition, in oral suspension, capsule or tablet form, a C_{max} which is greater than about 5%, greater than about 10%, greater than about 15%, greater than about 20%, greater than about 30%, greater than about 40%, greater than about 50%, greater than about 60%, greater than about 70%, greater than about 80%, greater than about 90%, greater than about 100%, greater than about 110%, greater than about 120%, greater than about 130%, greater than about 140%, or greater than about 150% than the C_{max} exhibited by the standard conventional drug active composition.

In addition, preferably the diclofenac composition has an AUC greater than that of the equivalent conventional composition administered at the same dosage. A preferred diclofenac composition of the invention exhibits in comparative pharmacokinetic testing with a standard conventional drug active composition, in oral suspension, capsule or tablet form, a AUC which is greater than about 5%, greater than about 10%, greater than about 15%, greater than about 20%, greater than about 30%, greater than about 40%, greater than about 50%, greater than about 60%, greater than about 70%, greater than about 80%, greater than about 90%, greater than about 100%, greater than about 110%, greater than about 120%, greater than about 130%, greater than about 140%, or greater than about 150% than the AUC exhibited by the standard conventional drug active composition.

Any standard pharmacokinetic protocol can be used to determine blood plasma concentration profile in humans following administration of a composition, and thereby establish whether that composition meets the pharmacokinetic criteria set out herein. For example, a randomized single-dose crossover study can be performed using a group of healthy adult human subjects. The number of subjects should be sufficient to provide adequate control of variation in a statistical analysis, and is typically about 10 or greater, although for certain purposes a smaller group can suffice. Each subject receives by oral administration at time zero a single dose (e.g., 300 mg) of a test formulation of composition, normally at around 8 am following an overnight fast. The subjects continue to fast and

remain in an upright position for about 4 hours after administration of the composition. Blood samples are collected from each subject prior to administration (e.g., 15 minutes) and at several intervals after administration. For the present purpose it is preferred to take several samples within the first hour, and to sample less frequently thereafter. Illustratively, blood samples could be collected at 15, 30, 45, 60, and 90 minutes after administration, then every hour from 2 to 10 hours after administration. Additional blood samples may also be taken later, for example at 12 and 24 hours after administration. If the same subjects are to be used for study of a second test formulation, a period of at least 7 days should elapse before administration of the second formulation. Plasma is separated from the blood samples by centrifugation and the separated plasma is analyzed for composition by a validated high performance liquid chromatography (HPLC)or liquid chromatography mass spectrometry (LCMS) procedure. . Plasma concentrations of composition referenced herein are intended to mean total concentrations including both free and bound composition.

Any formulation giving the desired pharmacokinetic profile is suitable for administration according to the present methods. Exemplary types of formulations giving such profiles are liquid dispersions and solid dose forms of composition. If the liquid dispersion medium is one in which the composition has very low solubility, the particles are present as suspended particles. The smaller the particles the higher the probability that the formulation will exhibit the desired pharmacokinetic profile.

Modes of administration of medicaments comprising biologically active materials

Medicaments of the invention can be administered to animals, including man, in any pharmaceutically acceptable manner, such as orally, rectally, pulmonary, intravaginally, locally (powders, ointments or drops), transdermal, parenteral administration, intravenous, intraperitoneal, intramuscular, sublingual or as a buccal or nasal spray

Solid dosage forms for oral administration include capsules, tablets, pills, powders, pellets, and granules. Further, incorporating any of the normally employed excipients, such as those previously listed, and generally 5-95% of the biologically active agent, and more preferably at a concentration of 10%-75% will form a pharmaceutically acceptable non-toxic oral composition.

Medicaments of the invention may be parenterally administered as a solution of the biologically active agent suspended in an acceptable carrier, preferably an aqueous carrier. A variety of aqueous carriers may be used, e.g. water, buffered water, 0.4% saline, 0.3% glycine, hyaluronic acid and the like. These compositions may be sterilized by conventional, well known sterilization techniques, or may be sterile filtered. The resulting aqueous

solutions may be packaged for use as is, or lyophilized, the lyophilized preparation being combined with a sterile solution prior to administration.

For aerosol administration, medicaments of the invention are preferably supplied along with a surfactant or polymer and propellant. The surfactant or polymer must, of course, be non-toxic, and preferably soluble in the propellant. Representative of such agents are the esters or partial esters of fatty acids containing from 6 to 22 carbon atoms, such as caproic, octanoic, lauric, palmitic, stearic, linoleic, linolenic, olesteric and oleic acids with an aliphatic polyhydric alcohol or its cyclic anhydride. Mixed esters, such as mixed or natural glycerides may be employed. The surfactant or polymer may constitute 0.1%-20% by weight of the composition, preferably 0.25-5%. The balance of the composition is ordinarily propellant. A carrier can also be included, as desired, as with, e.g., lecithin for intranasal delivery.

Medicaments of the invention may also be administered via liposomes, which serve to target the active agent to a particular tissue, such as lymphoid tissue, or targeted selectively to cells. Liposomes include emulsions, foams, micelles, insoluble monolayers, liquid crystals, phospholipid dispersions, lamellar layers and the like. In these preparations the composite microstructure composition is incorporated as part of a liposome, alone or in conjunction with a molecule that binds to or with other therapeutic or immunogenic compositions.

As described above, the biologically active material can be formulated into a solid dosage form (e.g., for oral or suppository administration), together with the grinding matrix or at least a portion of it. In this case there may be little or no need to add stabilizing agents since the grinding matrix may effectively act as a solid-state stabilizer.

However, if the biologically active material is to be utilized in a liquid suspension, the particles comprising the biologically active material may require further stabilization once the solid carrier has been substantially removed to ensure the elimination, or at least minimisation of particle agglomeration.

Therapeutic uses

Therapeutic uses of the medicaments of the invention include pain relief, anti-inflammatory, migraine, asthma, and other disorders that require the active agent to be administered with a high bioavailability.

One of the main areas when rapid bioavailability of a biologically active material is required is in the relief of pain. The minor analgesics, such as cyclooxgenase inhibitors (aspirin related drugs) may be prepared as medicaments according to the present invention.

Medicaments of the invention may also be used for treatment of eye disorders. That is, the biologically active material may be formulated for administration on the eye as an aqueous suspension in physiological saline, or a gel. In addition, the biologically active material may

be prepared in a powder form for administration via the nose for rapid central nervous system penetration.

Treatment of cardiovascular disease may also benefit from biologically active materials according to the invention, such as treatment of angina pectoris and, in particular, molsidomine may benefit from better bioavailability.

Other therapeutic uses of the medicaments of the present invention include treatment of hair loss, sexual dysfunction, or dermal treatment of psoriasis.

The present invention will now be described with reference to the following non-limiting Examples. The description of the Examples is in no way limiting on the preceding paragraphs of this specification, but is provided for exemplification of the methods and compositions of the invention.

Examples

It will be apparent to persons skilled in the milling and pharmaceutical arts that numerous enhancements and modifications can be made to the above described processes without departing from the basic inventive concepts. For example, in some applications the biologically active material may be pretreated and supplied to the process in the pretreated form. All such modifications and enhancements are considered to be within the scope of the present invention, the nature of which is to be determined from the foregoing description and the appended claims. Furthermore, the following Examples are provided for illustrative purposes only, and are not intended to limit the scope of the processes or compositions of the invention.

The following materials were used in the examples

The following materials were used in the examples: Anhydrous Lactose (DMV-Fonterra)Indomethacin (Esteve, Spain), Diclofenac (Unique, India), Naproxen acid (Dayang, China), Meloxicam (Dayang, China), Halosulfuron-Methyl (Dayang, China), Metsulfuron-Methyl (Dayang, China), Tribenuron-Methyl (Dayang, China), Sulfur (UWA laboratory), Mancozeb (Dayang, China), Calcium Carbonate (APS Chemicals, Australia), Lactose monohydrate ((Capsulac 60), Meggle, Germany), D,L-Malic acid (Sigma-Aldrich, US), Mannitol (Roquette, France), Polyvinyl pyrrolidone (Kolloidon 30, BASF, Germany), Sodium Lauryl Sulfate (SLS) (Sigma-Aldrich, US), sodium octadecyl sulfate (Sigma-Aldrich, US), sodium pentane sulfate (Sigma-Aldrich, US), lecithin (Broadway Fair Health Foods), docusate sodium (Sigma-Aldrich, US), Tartaric Acid (BDH, UK), Trisodium Citrate Dihydrate (Univar, Ajax Finechem, Australia), Polyoxyl-40-stearate(Sigma-Aldrich, US), Xylitol (Sweetlife, Australia), Polyoxyl 10 stearyl ether (Brij76) (Sigma-Aldrich, US), Polyoxyl 100

stearyl ether (Brij700) (Sigma-Aldrich, US), Aerosil R972 (Degussa), Sulfur (UWA laboratory).

The following mills were used for the grinding experiments

Spex-type Mill:

Small scale milling experiments were conducted using a vibratory Spex 8000D mixer/mill. Twelve 9.5 mm stainless steel balls were used as the grinding media. The powder charge and grinding media was loaded into a hardened steel vial with an internal volume of approximately 75 mL. Following milling, the milled material was discharged from the vial and sieved to remove grinding media.

Attritor-type Mill:

Small scale attritor milling experiments were performed using a 1HD Union Process attritor mill with a 110 mL grinding chamber. The grinding media consisted of 330g of 5/16" stainless steel balls. The mill was loaded through the loading port, with dry materials added initially, followed by the grinding media. The milling process was conducted with the jacket cooled at 10-20°C with the shaft rotating at 500 rpm. Upon completion of milling, the milled material was discharged from the mill and sieved to remove the grinding media.

Medium scale attritor milling experiments were performed using a 1HD Union Process attritor mill with a 1 L grinding chamber or a 1S Union Process attritor mill with a 750 mL grinding chamber. The grinding media consisted of 3 kg of 5/16" stainless steel balls or 1.5 kg of 3/8" stainless steel balls for the 1S attritor. The mill was loaded through the loading port, with dry materials added initially, followed by the grinding media in the 1HD attritor mill, while the ginding media was added initially, followed by the dry materials in the 1S attritor mill. The milling process was conducted with the jacket cooled at 10-20°C with the shaft rotating at 300 rpm in the 1HD attritor or 550 rpm in the 1S attritor. Upon completion of milling, the milled material was discharged from the mill and sieved to remove the grinding media.

Medium to large scale attritor milling experiments were performed using a 1S Union Process attritor mill with a ½ gallon grinding chamber. The grinding media consisted of 7 kg of 3/8" stainless steel balls. The mill was loaded through the loading port, with the grinding media added initially, followed by the dry powders. The milling process was conducted with the jacket cooled at 18°C and the shaft rotating at 400 rpm. Upon completion of milling, the milled powder was discharged from the mill through the bottom discharge port.

Large scale attritor milling experiments were performed using a 1S Union Process attritor mill with a 1½ gallon grinding chamber. The grinding media consisted of 20 kg of 3/8" stainless steel balls. The mill was loaded through the loading port, with the grinding media added initially, and followed by the dry powders. The milling process was conducted with the jacket cooled with ambient temperature water and the shaft rotating at 300 rpm. Upon completion of milling, the milled powder was discharged from the mill through the bottom discharge port.

Sietechnik Mill

Medium scale milling experiments were also performed in a Sietechnik GSM06 (Sietechnik ,GmbH, Germany) with two 1 L milling chambers. Each chamber was filled with 2.7 kg stainless steel media with a diameter of 3/8". The media and powder were loaded with the lid off. The mill was operated at ambient temperature. The vibration speed was the standard mill settings. Upon completion of the milling the media was separated from the powder by sieving.

Simoloyer Mill

Medium to large scale milling experiments were also performed in a Simoloyer CM01 (ZOZ GmbH, Germany) with a 2 L milling chamber. The grinding media consisted of 2.5 kg stainless steel media with a diameter of 5 mm. the media was loaded though the loading port followed by the dry materials. The milling vessel was cooled using water at a temperature of about 18°C. The mill speed was operated in cycle mode: at 1300 rpm for two minutes and at 500 rpm for 0.5 min and so forth. Upon completion of the milling the media was discharged from the mill using a grated valve to retain the grinding media.

Particles size measurement:

The particle size distribution (PSD) was determined using a Malvern Mastersizer 2000 fitted with a Malvern Hydro 2000S pump unit. The dispersant in the measurement cell was for all samples other then Metaxalone 0.01M HCl (RI: 1.33), while deionized water (RI: 1.33) was used for Metaxalone. Measurement settings used: Measurement Time: 12 seconds, Measurement cycles: 3. Result generated by averaging the 3 measurements. Indomethacin specific conditions: Refractive index (RI): 1.73, absorption: 0.01. Diclofenac specific conditions: RI: 1.69, absorption: 0.01. Naproxen specific condition: 1.59, absorption: 0.01.

Metaxalone specific conditions: Refractive index (RI): 1.62, absorption: 0.01. Samples were prepared by adding 200mg of milled material to 5.0mL of 1% PVP in 0.01M hydrochloric acid (HCl), vortexing for 1 min and then sonicating. Samples of Metaxalone were prepared differently by adding 200mg of milled material to 8.0mL of a 0.2% Pluronic L81 solution in deionized water, vortexing for 1 min and then sonicating for 1 min. Sampes of Metaxalone containing sodiumbicarbonate were acidified using 1 M HCl. From this suspension enough was added into the dispersant to attain a desired obscuration level. If necessary an extra 1-2 minutes of sonication was applied using the internal sonication probe in the measurement cell.

Dissolution Method

Dissolution behaviour of milled Metaxalone, unmilled Metaxalone and commercial Skelaxin® (King Pharmaceuticals®, Inc, US) tablets were determined using an automated Varian 7025 dissolution unit fitted with a Cary 50 Tablet UV visible spectrometer. Dissolution settings used were according to USP 2 with stirrer speed at 100 rpm. Metaxalone specific conditions: wavelength λ=271nm, 750 mL Dissolution Media, Media: pH 2 (10mM HCL), with inline 1 µm filters. Each dissolution result was obtained by averaging results from 3 tablets. Tablets contained 60 mg Metaxalone, for example, a tablet required 150 mg of following composition: 99% granules (41% Metaxalone) and 1 % lubricant (magnesium stearate).

Granules were prepared using a dry granulation process. A typical granulation mixture consisted of 0.85 g of milling mixture (eg. containing 50% Metaxalone), 10% filler (tartaric acid), 5% superdisintegrant (Primojel) and 3% binder (Collidon 30). Compression was done at a pressure of 1.5 bar applied for 30 seconds using a KBr press, following the compression the obtained disk was ground using a grinder, and the obtained granules were sieved with a 1 mm mesh.

Tablets were prepared using such a mixture and in a 3/16" stainless steel die set by applying a pressure of about 1.5 bar in KBR press for 40 seconds.

Un-milled control samples were prepared using identical mixtures and procedures as detailed above, only replacing the milling step with a mixing step. The commercial tablets of Skelaxin® were cut into peaces to obtain single fragments with a mass corresponding to about 60 mg Metaxalone.

Abbreviations:

HCl: Hydrochloric acid

Nap: Naproxen acid
PSD: Particles size distribution
PVP: Polyvinyl pyrrolidone
RI: Refractive index
Rpm: Revolutions per minute
SLS: Sodium lauryl sulphate
SSB: Stainless Steel Balls
XRD: X-Ray Diffraction

Example 1: Milling of Indomethacin in lactose monohydrate with various length alkyl sulphate surfactants

Example 1a: Spex Milling

Powders were prepared by Spex milling for 30 minutes. The compositions used were (A) 1.20g (12 w/w %) of indomethacin and 8.80g of lactose monohydrate; (B) 1.20g (12 w/w %) of indomethacin, 8.70g of lactose monohydrate, and 0.10g (1.0 w/w %) of sodium pentane sulfate; (C) 1.20g (12 w/w %) of indomethacin, 8.70g of lactose monohydrate, and 0.10g (1.0 w/w %) of sodium lauryl sulfate; and (D) 1.20g (12 w/w %) of indomethacin, 8.70g of lactose monohydrate, and 0.10g (1.0 w/w %) of sodium octadecyl sulfate. Particle size distributions for each composition are shown in Figure 1 and summarised in Table 1. The data shows that the particle size is smaller when 1% of surfactant is used in the milling..

Example	D(0.5) µm	% < 0.20 µm	% < 0.30 µm	% < 0.5 µm	% < 1.0 µm	% < 2.0 µm
A	0.223	45	61	71	77	89
B	0.215	47	64	84	83	93
C	0.189	53	73	88	95	99
D	0.203	49	69	84	92	97

Table 1

Example 1b:Small scale attritor milling

Powders were prepared by attritor milling for 30 minutes using a 110 mL tank. The compositions used were (A) 1.20g (12 w/w %) of indomethacin and 8.80g of lactose

monohydrate; and (B) 1.20g (12 w/w %) of indomethacin, 0.10g (1.0 w/w %) of sodium lauryl sulfate, and 8.70g of lactose monohydrate. Particle size distributions for each composition are shown in Figure 2 and summarised in Table 2. The data shows that the particle size is smaller when 1% of SLS is used in the milling.

Example	D(0.5) µm	% < 0.20 µm	% < 0.30 µm	% < 0.5 µm	% < 1.0 µm	% < 2.0 µm
A	0.753	25	34	44	55	70
B	0.677	14	26	41	65	91

Table 2

Example 2: Milling of Indomethacin in lactose monohydrate with polyoxyethylene alkyl ether surfactants.

Example 2a: Spex Milling

Powders were prepared by Spex milling for 30 minutes. The compositions used were (A) 1.20g (12 w/w %) of indomethacin and 8.80g of lactose monohydrate; (B) 1.20g (12 w/w %) of indomethacin, 8.70g of lactose monohydrate, and 0.10g (1.0 w/w %) of Brij700; and (C) 1.20g (12 w/w %) of indomethacin, 8.70g of lactose monohydrate, and 0.10g (1.0 w/w %) of Brij76. Particle size distributions for each composition are shown in Figure 3 and summarised in Table 3. The data shows that the particle size is smaller when 1% of Brij 700 or Brij 76 is used in the milling.

Example	D(0.5) µm	% < 0.20 µm	% < 0.30 µm	% < 0.5 µm	% < 1.0 µm	% < 2.0 µm
A	0.223	45	61	71	77	89
B	0.167	60	80	93	97	99
C	0.192	52	72	89	96	99

Table 3

Example 2b: Small scale attritor milling

Powder mixtures consisting of (A) 1.20g (12 w/w %) of indomethacin and 8.80g of lactose monohydrate; and (B) 1.20g (12 w/w %) of indomethacin, 0.10g (1.0 w/w %) of Brij700, and 8.70g of lactose monohydrate were attritor milled for 30 minutes in a 110 mL tank. Particle size distributions for each composition are shown in Figure 4 and summarised in Table 4. The data shows that the particle size is smaller when 1% of Brij 700 is used in the milling.

Example	D(0.5) µm	% < 0.20 µm	% < 0.30 µm	% < 0.5 µm	% < 1.0 µm	% < 2.0 µm
A	0.753	25	34	44	55	70
B	0.621	13	25	43	68	91

Table 4

Example 3: Milling of Indomethacin in lactose monohydrate with other surfactants

Example 3a: Spex milling at 12 w/w %

Powders were prepared by Spex milling for 30 minutes. The compositions used were (A) 1.20g (12 w/w %) of indomethacin and 8.80g of lactose monohydrate, (B) 1.20g (12 w/w %) of indomethacin, 8.70g of lactose monohydrate, and 0.10g (1 w/w %) of sodium deoxycholate, (C) 1.20g (12 w/w %) of indomethacin, 8.70g of lactose monohydrate, and 0.10g (1 w/w %) of sodium n-lauroyl sarcosine, and (D) 1.20g (12 w/w %) of indomethacin, 8.70g of lactose monohydrate, and 0.10g of lecithin. Particle size distributions for each composition are shown in Figure 5 and summarised in Table 5. The data shows that the particle size is smaller when 1% of these surfactants are used in the milling.

Example	D(0.5) µm	% < 0.20 µm	% < 0.30 µm	% < 0.5 µm	% < 1.0 µm	% < 2.0 µm
A	0.223	46	61	71	77	89
B	0.191	52	67	77	83	93
C	0.225	44	63	79	88	96
D	0.23	44	61	75	85	95

Table 5

Example 3b: Spex milling at 10 w/w %

Powders were prepared by Spex milling for 20 minutes. The compositions used were (A) 0.5g (10 w/w %) of indomethacin and 4.5g of lactose monohydrate, (B) 0.5g (10 w/w %) of indomethacin, 4.45g of lactose monohydrate, and 0.05g (1 w/w %) of polyoxyl-40-stearate, (C)) 0.5g (10 w/w %) of indomethacin, 4.45g of lactose monohydrate, and 0.05g (1 w/w %) of docusate sodium, and (D)) 0.5g (10 w/w %) of indomethacin, 4.45g of lactose monohydrate, and 0.05g (1 w/w %) of Aerosil R972 fumed silica. Particle size distributions for each composition are shown in Figure 6 and summarised in Table 6. The data shows that the particle size is smaller when 1% of these surfactants or additives are used in the milling.

Example	D(0.5) µm	% < 0.20 µm	% < 0.30 µm	% < 0.5 µm	% < 1.0 µm	% < 2.0 µm
A	0.237	44	57	65	73	85
B	0.169	58	72	80	89	97
C	0.249	42	56	68	84	98
D	0.190	52	67	76	84	92

Table 6

Example 4: Milling of Indomethacin in lactose monohydrate with SLS compared with milling in the individual components

Powders were prepared by Spex milling for 30 minutes. The compositions used were (A) 1.00g (20 w/w %) of indomethacin, 3.95g (79 w/w %) of lactose monohydrate, and 0.05g (1 w/w %) of sodium lauryl sulfate; (B) 1.00g (20 w/w %) of indomethacin and 4.00g (80 w/w %) of sodium lauryl sulfate; (C) 4.95g (99 w/w %) of indomethacin and 0.05g (1 w/w %) of sodium lauryl sulfate; and (D) 1.00g (20 w/w %) of indomethacin and 4.00g (80 w/w %) of lactose monohydrate. Particle size distributions for each composition are shown in Figure 7 and summarised in Table 7. The data shows that the combination of lactose monohydrate grinding matrix together with 1% SLS (A) has produced nanoparticles.

Example	D(0.5) µm	% < 0.20 µm	% < 0.30 µm	% < 0.5 µm	% < 1.0 µm	% < 2.0 µm
A	0.435	24	38	53	67	83
B	2.612	0	0	0	6	34

C	1094	0	0	0	0	2
D	5.128	0	0	0	0	8

Table 7

Example 5: Milling of Diclofenac in lactose monohydrate with SLS compared with milling in the individual components

Powders were prepared by Spex milling for 30 minutes. The compositions used were (A) 1.00g (20 w/w %) of diclofenac, 3.95g (79 w/w %) of lactose monohydrate, and 0.05g (1 w/w %) of sodium lauryl sulfate; (B) 1.00g (20 w/w %) of diclofenac and 4.00g (80 w/w %) of sodium lauryl sulfate; (C) 4.95g (99 w/w %) of diclofenac and 0.05g (1 w/w %) of sodium lauryl sulfate; and (D) 1.00g (20 w/w %) of diclofenac and 4.00g (80 w/w %) of lactose monohydrate. Particle size distributions for each composition are shown in Figure 8 and summarised in Table 8. The data shows that the combination of lactose monohydrate grinding matrix together with 1% SLS (A) has produced smaller particles that milling with only the monohydrate lactose (D). This is consistent with the data from previous examples that shows the presence of a small amount of surfactant produces smaller particles.

Example	D(0.5) µm	% < 0.20 µm	% < 0.30 µm	% < 0.5 µm	% < 1.0 µm	% < 2.0 µm
A	0.153	66	84	95	98	99
B	3.173	0	0	0	3	24
C	117	0	0	0	1	4
D	0.178	56	74	86	92	97

Table 8

Example 6: Milling of Diclofenac with Mannitol in the Spex mill scaled up to mill in the Siebtechnik mill

Example 6a: Spex milling

Powders were prepared by Spex milling for 30 minutes. The compositions used were (A) 2.00g (20 w/w %) diclofenac and 8.00g of mannitol, (B) 2.00g (20 w/w %) of diclofenac, 0.10g (1 w/w %) of sodium lauryl sulfate, and 7.90g of mannitol, and (C) 2.00g (20 w/w %) of diclofenac, 0.10g (1 w/w %) of sodium octadecyl sulfate, and 7.90g of mannitol. Particle size distributions for each composition are shown in Figure 9 and summarised in Table 9. The data shows that at this solids loading nanoparticles can be made using all three formulations. The data also shows that the size distributions are the same.

Example	D(0.5) µm	% < 0.20 µm	% < 0.30 µm	% < 0.5 µm	% < 1.0 µm	% < 2.0 µm
A	0.200	50	69	84	91	97
B	0.201	50	69	83	91	97
C	0.195	51	71	85	92	97

Table 9

Example 6b: Siebtechnik Milling

A compositions of 2.5 (10 w/w %) diclofenac and 22.5g of mannitol was milled in the Siebtechnik mill for 15 minutes. After this time the powder was completely caked onto the walls of the mill and the media. No powder could be removed to measure the particle size. At this point 0.25 g (1 w/w%) SLS was added to mill chamber and milling was then undertaken for a further 15 minutes. After the second period of milling in the presence of SLS powder was no longer caked onto the media and some free powder was also present. The particle size distribution of this powder was measured and is shown in Figure 10 and summarised in Table 10. The observations made before and after the addition of the SLS demonstrate that the addition of the surfactant lessens the problem of caking. With the addition of surfactant the caked material could be recovered to become free powder again with small particle size.

Example	D(0.5) µm	% < 0.20 µm	% < 0.30 µm	% < 0.5 µm	% < 1.0 µm	% < 2.0 µm
	0.237	40	63	83	93	97

Table 10

Example 7: Milling of Naproxen in lactose monohydrate with surfactants

Example 7a: Milling of 35 w/w% in the Spex mill

Powders were prepared by spex milling for 20 minutes. Mixture A was composed of 1.75g (35 w/w%) of naproxen acid in 3.2 g lactose monohydrate. Mixture B was composed of 1.75g (35 w/w%) of naproxen acid, 3.25 g lactose monohydrate and 0.05 g (1 w/w%) polyoxyl-40-stearate. Mixture C was composed of 1.75g (35 w/w%) of naproxen acid, 3.25g lactose monohydrate and 0.05g (1w/w%) sodium lauryl sulfate. Particle size distributions for each composition are shown in Figure 11 and summarised in Table 11. The data show that the particle size is smaller when the surfactant polyoxyl-40-stearate or sodium lauryl sulfate is used in the milling.

Example	D(0.5) µm	% < 0.20 µm	% < 0.30 µm	% < 0.5 µm	% < 1.0 µm	% < 2.0 µm
A	2.9	18	23	25	26	38
B	0.373	33	45	56	70	87
C	0.293	38	50	60	65	75

Table 11

Example 7b: Milling of 35 w/w% Naproxen in lactose monohydrate at larger scale

Composition A and B consisted of 70g (35 w/w %) of naproxen acid, 128 g lactose monohydrate and 2 g (1w/w %) SLS. Mixture A was milled for 60 minutes using a 1-S attritor (1/2 gallon scale). Mixture B was milled for 60 min using a simoloyer mill.

Particle size distributions for each composition are shown in Figure 12 and summarised in Table 12. This composition milled at larger scale gives approximately the same particle size distribution as that observed for the small scale milling of this composition in example 7a(C). The simoloyer mill gave a finer particle size compared to the attritor mill. This data shows that this mixture, having 1 % SLS presence can be successfully scaled up from small scale to larger scale.

Example	D(0.5) µm	% < 0.20 µm	% < 0.30 µm	% < 0.5 µm	% < 1.0 µm	% < 2.0 µm
A	0.345	35	47	56	61	73

B	0.224	72	81	92	81	92

Table 12

Example 7c: Milling of 40 w/w% Naproxen in lactose monohydrate

Two mixtures, both containing 40 w/w% naproxen acid in lactose monohydrate, with and without a surfactant, were milled in a Spex mill for 120 min. Mixture A was composed of 4g (40 w/w%) of naproxen acid in 5.9g lactose monohydrate and 0.1g (1 w/w%) polyoxyl-40-stearate. Mixture B was composed of 4g (40 w/w%) of naproxen acid and 6g lactose monohydrate. PSDs of the milled products were measured (Figure 13) and results summarised in Table 13. The data shows that at this high volume fraction nanoparticles can be produced with the addition of 1 w/w % surfactant to the mixture.

Example .	D(0.5) µm	% < 0.20 µm	% < 0.30 µm	% < 0.5 µm	% < 1.0 µm	% < 2.0 µm
A	0.285	37	52	66	75	82
B	6.1	0	0	0	0	8

Table 13

Example 8: Milling of Naproxen in mannitol with surfactants

Example 8a: Milling of 35 w/w% Naproxen acid in mannitol in the Spex mill.

Mixture A was composed of 1.40g (35 w/w%) of naproxen acid in 2.6 g mannitol. Mixture B was composed of 1.40g (35 w/w%) of naproxen acid, 2.52 g mannitol and 0.08g (2 w/w%) of the surfactant SLS. The samples were milled in a Spex mill for 20 minutes. PSDs of the milled products were measured (Figure 14) and results are summarised in Table 14. The data show that the addition of a surfactant led to lower particle size.

Example	D(0.5) µm	% < 0.20 µm	% < 0.30 µm	% < 0.5 µm	% < 1.0 µm	% < 2.0 µm
A	0.171	58	73	82	86	88
B	0.131	76	90	95	96	98

Table 14

Example 8b: Milling of 35 w/w% Naproxen acid in Mannitol at larger scale

Mixture A and B consisted of 70g (35 w/w %) naproxen acid, 128g (64 w/w %) mannitol, and 2g (1 w/w %) SLS. Mixture A was milled for 50 minutes using a 1-S attritor (1/2 gallon) using 4 kg of grinding media. Mixture B was milled for 60 min using a simoloyer mill. The PSD of the milled product was measured (Figure 15) and the results summarised in Table 15. This mixture containing surfactant has successfully produced small particles at this high volume fraction at larger scale. The material milled in the simoloyer mill had an especially fine particle size with 90 % of particles less than 1000 nm.

Example	D(0.5) µm	% < 0.20 µm	% < 0.30 µm	% < 0.5 µm	% < 1.0 µm	% < 2.0 µm
A	0.730	31	41	48	51	58
B	0.177	57	74	86	90	93

Table 15

Example 8c: Milling of 30 w/w% naproxen acid in Mannitol in the Spex mill

Powders of 30 w/w% naproxen acid with and without surfactant were Spex milled for 20 minutes. Mixture A consisted of 1.2 g (30 w/w %) naproxen acid and 2.8 g mannitol. Mixture B consisted of 1.2 g (30 w/w %) naproxen acid, 2.76 g mannitol, and 0.04 g (1w/w%) SLS. The PSD of the milled product (Figure 16) was measured and the results summarised in Table 16. The data show that the addition of a surfactant led to smaller particle size.

Example	D(0.5) µm	% < 0.20 µm	% < 0.30 µm	% < 0.5 µm	% < 1.0 µm	% < 2.0 µm
A	0.208	48	64	75	79	84
B	0.173	58	75	86	91	96

Table 16

Example 8d: Milling of 30 w/w % naproxen acid in Mannitol at larger scale

Mixture (A) consisted of 60 g (30 w/w %) naproxen acid, 138 g mannitol and 2 g SLS. Mixture (B) consisted of 60 g (30 w/w %) naproxen acid and 138 g mannitol. Each mixture was milled for 50 minutes using a 1-S Attritor (1/2 gallon) using 4 kg of grinding media. The PSD of the milled product (Figure 17) was measured and the results summarised in Table 17. The amount of material recovered (yield) form the mill is also recorded in Table 17. The material milled with the surfactant (A) still has a very fine particle size which is basically the same as that at small scale (example 8c (B)). The most significant effect of the presence of the surfactant in the mixture at large scale is the yield of powder from the mill. The addition of the surfactant gave a very good yield of 92% compared with only 27 % without the surfactant.

Example	D(0.5) µm	% < 0.20 µm	% < 0.30 µm	% < 0.5 µm	% < 1.0 µm	% < 2.0 µm
A	0.181	55	73	86	92	96
B	0.319	35	48	59	64	75

Table 17

Example 9: Milling of Meloxicam with Lactose

Powders were prepared by attritor milling using the 1 litre tank with a speed of 350 rpm. The compositions used were (A) 20.0g (20 w/w %) of meloxicam, 3.0g (3.0 w/w %) of sodium lauryl sulfate and 77.0g of lactose monohydrate, (B) 20.0g (20 w/w %) of meloxicam, and 80.0g of lactose monohydrate. Particle size distributions for each composition are shown in Figure 18 and summarised inTable18. The yield of powder recovered from the mill is also shown in Table 18.

Examples	D(0.5) µm	% < 0.20 µm	% < 0.30 µm	% < 0.5 µm	% < 1.0 µm	% < 2.0 µm	Yield (%)
A	0.240	39	64	87	97.	100	89.5
B	0.166	59	74	82	87	90	0.7

Table 18

Example 10: Milling of Meloxicam with Mannitol

Powders were prepared by attritor milling using the 110ml tank. The compositions used were (A) 1.2g (20 w/w %) of meloxicam, 0.18g (3.0 w/w %) of sodium laurylsulfate and 4.62 of mannitol, (B) 1.2g (20 w/w %) of meloxicam, and 4.8g of mannitol. Particle size distributions for each composition are shown in Figure 19 and summarised in Table 19. The yield of powder recovered from the mill is also shown in Table 19.

Examples	D(0.5) µm	% < 0.20 µm	% < 0.30 µm	% < 0.5 µm	% < 1.0 µm	% < 2.0 µm	Yield (%)
A	0.277	37	53	66	74	86	83.3
B	2.493	10	12	12	15	39	33.3

Table 19

Example 11: Milling of naproxen in lactose monohydrate with another matrix

Example 11a: Milling of 30 w/w % naproxen acid in a mixed grinding matrix of trisodium citrate dihydrate and lactose monohydrate.

Mixture A was composed of 1.2 g (30 w/w %) of naproxen acid, 2.8 g Lactose monohydrate. Mixture B was composed of 1.2 g (30 w/w %) naproxen acid, 0.8 g (20 w/w %) trisodium citrate dihydrate and 2 g lactose monohydrate. Mixture C was composed of 1.2 g (30 w/w %) of naproxen acid and 2.8 g trisodium citrate dihydrate. The samples were milled for 20 minutes in a spex mill. PSDs were measured (Figure 20) and results summarised in Table 20. The data show that a mixed co-grinding matrix of trisodium citrate dihydrate and lactose monohydrate gave a smaller particle size.

Example	D(0.5) µm	% < 0.20 µm	% < 0.30 µm	% < 0.5 µm	% < 1.0 µm	% < 2.0 µm
A	0.396	33	44	53	58	70
B	0.188	48	64	75	81	92
C	3.1	18	24	27	27	37

Table 20

Example 11b: Milling of 30 w/w % naproxen acid in a mixed grinding matrix of calcium carbonate and lactose monohydrate.

Mixture A was composed of 1.2 g (30 w/w%) naproxen acid, 0.8 g (20 w/w%) calcium carbonate and 2 g lactose monohydrate. Mixture B was composed of 1.2 g (30 w/w%) of naproxen acid, 2.8 g calcium carbonate. The samples were milled for 20 minutes in a Spex mill. PSDs of the milled products were measured (Figure 21) and results summarised in Table 21. The data for milling in lactose monohydrate is shown above in example 11a (A). The data shows that a mixed co-grinding matrix of calcium carbonate and lactose monohydrate gave a smaller particle size.

Example	D(0.5) µm	% < 0.20 µm	% < 0.30 µm	% < 0.5 µm	% < 1.0 µm	% < 2.0 µm
A	0.213	47	63	76	84	91
B	28	3	4	5	6	10

Table 21

Example 12: Milling of naproxen acid in lactose anhydrous with another matrix

Example 12a: Milling of naproxen in lactose anhydrous and xylitol

Mixture A was composed of 1g (25 w/w%) of naproxen acid in 3 g lactose anhydrous. Mixture B was composed of 1g (25 w/w%) of naproxen acid and 0.8 g (20 w/w %) xylitol in 2.2 g lactose anhydrous. Mixture C was composed of 1g (25 w/w%) of naproxen acid in 3 g xylitol. The samples were milled for 20 minutes in a Spex mill. The PSD was measured (Figure 22) and the numerical results summarised in Table 22. The data show that xylitol produces the smallest PSD while milling with just anhydrous lactose produces the coarsest particles. When only 20 w/w % xylitol was added to lactose anhydrous the PSD was significantly improved compared to only milling with lactose anhydrous. This indicates that the performance of lactose anhydrous as a grinding matrix can be improved with the addition of a small amount of another matrix.

Example	D(0.5) µm	% < 0.20 µm	% < 0.30 µm	% < 0.5 µm	% < 1.0 µm	% < 2.0 µm
A	1.07	31	41	46	49	67

B	0.20	50	65	75	79	89
C	0.18	57	75	87	92	95

Table 22

Example 12b: Milling of Naproxen in lactose anhydrous and malic acid

Mixture A was composed of 1g (25 w/w%) of naproxen acid and 0.8g (20 w/w %) malic acid in 2.2 g lactose anhydrous. Mixture B was composed of 1g (25 w/w %) of naproxen acid in 3g malic acid. The samples were milled for 20 minutes in a spex mill. PSD was measured (Figure 23) and numerical results summarised in Table 23.

The data show that malic acid produces small particles. When 20 w/w % malic acid was added to lactose anhydrous the PSD was significantly improved compared to only milling with lactose anhydrous (example 12a(A)). This indicates that the performance of lactose anhydrous as a grinding matrix can be improved with the addition of a small amount of another matrix.

Example	D(0.5) µm	% < 0.20 µm	% < 0.30 µm	% < 0.5 µm	% < 1.0 µm	% < 2.0 µm
A	0.223	46	60	70	76	87
B	0.153	66	85	96	98	99

Table 23

Example 12c: Milling of naproxen in lactose anhydrous and trisodium citrate dihydrate

Mixture A was composed of 1g (25 w/w%) of naproxen acid and 0.8g (20 w/w%) trisodium citrate dihydrate in 2.2g lactose anhydrous. Mixture B was composed of 1g (25 w/w%) of naproxen acid in 3g trisodium citrate dihydrate. The samples were milled for 20 minutes in a spex mill. PSDs of the milled products were measured (Figure 24) and numerical results summarised in Table 24. The data for milling in lactose anhydrous is shown above in example 12a (A). The data shows that a mixed co-grinding matrix of trisodium citrate dihydrate and lactose anhydrous gave a smaller particle size.

Example	D(0.5)	% <	% <	% <	% <	% <

	µm	0.20 µm	0.30 µm	0.5 µm	1.0 µm	2.0 µm
A	0.215	47	62	70	73	83
B	0.331	35	48	57	62	72

Table 24

Example 13: Milling of Indomethacin with SLS and tartaric acid in lactose monohydrate at larger scale.

Example 13a: Milling in the 1 litre Attritor

Powders were prepared by attritor milling using the 1 litre tank. The compositions used were (A) 13.0g (13 w/w %) of indomethacin and 87.0g of lactose monohydrate, (B) 13.0g (13 w/w %) of indomethacin, 65.5g of lactose monohydrate, and 21.5g (21.5 w/w %) of tartaric acid, (C) 13.0g (13 w/w %) of indomethacin, 1.0g (1.0 w/w %) of sodium lauryl sulfate, and 86.0g of lactose monohydrate, and (D) 13.0g (13 w/w %) of indomethacin, 1.0g (1.0 w/w %) of sodium lauryl sulfate, 64.5g of lactose monohydrate, and 21.5g (21.5 w/w %) of tartaric acid. Particle size distributions for each composition are shown in Figure 9 and summarised in Table 25. The yield of powder recovered from the mill is also shown in Table 25. In example 1 Indomethacin was successfully milled in lactose monohydrate with no additives at small scale (10 grams in the Spex mill). In example A indomethacin milled in lactose monohydrate at 100gram scale did not produce any material below 500 nm and caked severely. The low yield of 1.2 % is the free powder that could be recovered from the mill. The remaining material was caked hard onto the bottom of the mill such that it had to be chiseled out. The addition of tartaric acid (example B) to this base mixture has dramatically improved the particle size with 75% of material now less than 500 nm. However severe caking was still present with a yield of less than 1%. When 1% SLS was added to both mixtures and milled under the same conditions (example C and D) the yields were very high. Significant yields were obtained with the mixture with both SLS and tartaric Acid added. The mixtures milled in examples C and D both also produced nanoparticle material. Example D with tartaric acid gave smaller particle size.

Examples	D(0.5) µm	% < 0.20 µm	% < 0.30 µm	% < 0.5 µm	% < 1.0 µm	% < 2.0 µm	Yield (%)
A	3.255	0	0	0	4	27	1

B	0.272	34	55	76	87	93	0
C	0.836	22	31	39	56	83	76
D	0.629	15	28	43	67	91	85

Table 25

Example 13b: Milling in the 1.5 gallon attritor

Powder was prepared by attritor milling using the 1½ gallon tank. The composition used was 130g (13 w/w %) of indomethacin, 10g (1.0 w/w %) of sodium lauryl sulfate, 652.5 g of lactose monohydrate, and 217.5g (21.5 w/w %) of tartaric acid. The Particle size distribution is shown in Figure 26 and summarised in Table 26. The yield of powder recovered from the mill is also shown in Table 26. The yield of powder recovered from the mill is also shown in Table 26. For each example two yields are shown, the first (top) is the yield when the material is discharged from the mill at the lowest speed of 57 rpm within 5 minutes. This discharge removes all the loose powder from the mill. In addition a second discharge at the speed of milling was also undertaken. This discharge removes any powder loosely caked onto the mill. The second yield (the lower one in brackets) is the combination of both the first and second discharge. The PSD and yield data for this 1 kg scale milling demonstrate that this formulation approach delivers both small particles and beneficial yields at large scale.

Example	D(0.5) µm	% < 0.20 µm	% < 0.30 µm	% < 0.5 µm	% < 1.0 µm	% < 2.0 µm	Yield (%)
A	0.16	64	63	82	94	98	77.5 (82)

Table 26

Example 14: Milling of Diclofenac with SLS and tartaric acid in lactose monohydrate at larger scale.

Powders were prepared by attritor milling using the ½ gallon tank. The compositions used were (A) 52.5g (15 w/w %) of diclofenac, 3.5g (1 w/w %) of sodium lauryl sulfate, and 294.0g of lactose monohydrate and (B) 52.5g (13 w/w %) of diclofenac, 3.5g (1 w/w %) of sodium lauryl sulfate, 224.0g of lactose monohydrate, and 70.0g (20 w/w %) of tartaric acid. Particle

size distributions for each composition are shown in Figure 27 and summarised in Table 27. The yield of powder recovered from the mill is also shown in Table 27. For each example two yields are shown, the first (top) is the yield when the material is discharged from the mill at the lowest speed of 77 rpm. This discharge removes all the loose powder from the mill. In addition a second discharge at the speed of milling was also undertaken. This discharge removes any powder loosely caked onto the mill. The second yield (the lower one in brackets) is the combination of both the first and second discharge. Note that the median particle size of the second offload (shown in brackets under D(0.5) in Table 27) is marginally smaller than the first offload indicating the material from the second discharge is the same quality as the first. The particle size of both example A and B (with 20% tartaric acid) are essentially the same with both mixtures giving a good particle size distribution with over 95 % less than 500 nm. The difference between these two examples is the much higher yield for example B, the mixture containing tartaric acid. For the initial discharge example B has a yield over 87% compared with 64% for example A. For the overall yield (both discharges) example B practically gives full recovery with a 98% yield compared with 80% for example A.

	D(0.5) µm	% < 0.20 µm	% < 0.30 µm	% < 0.5 µm	% < 1.0 µm	% < 2.0 µm	Yield (%)
A	0.160 (0.151)	64	84	97	99	99	64 (80)
B	0.160 (0.156)	63	83	95	98	99	87 (98)

Table 27

Example 15 – Spex milling of Halosulfuron -Methyl

Powders were prepared by Spex milling for 40 minutes. The compositions used were (A) 1.00g (10 w/w %) of halosulfuron and 9.00g of lactose monohydrate; and (B) 1.00g (10 w/w %) of halosulfuron, 8.90g of lactose monohydrate, and 0.10g (1.0 w/w %) of lecithin. Particle size distributions for each composition are shown in Figure 28 and summarised in Table 28. The data shows that the particle size is smaller when 1% of surfactant is used in the milling.

Example	D(0.5) µm	% < 0.20 µm	% < 0.30 µm	% < 0.5 µm	% < 1.0 µm	% < 2.0 µm

A	2.123	0	0	0	0	5
B	0.135	74	90	97	98	99

Table 28

Example 16 – Spex milling of Metsulfuron-Methyl

Powders were prepared by Spex milling for 40 minutes. The compositions used were (A) 1.00g (10 w/w %) of metsulfuron and 9.00g of lactose monohydrate; and (B) 1.00g (10 w/w %) of metsulfuron, 8.90g of lactose monohydrate, and 0.10g (1.0 w/w %) of sodium lauryl sulfate. Particle size distributions for each composition are shown in Figure 29 and summarised in Table 29. The data shows that the particle size is smaller when 1% of surfactant is used in the milling.

Example	D(0.5) µm	% < 0.20 µm	% < 0.30 µm	% < 0.5 µm	% < 1.0 µm	% < 2.0 µm
A	4.727	0	0	0	0	4
B	0.129	80	93	96	97	98

Table 29

Example 17 – Spex milling of Tribenuran-Methyl

Powders were prepared by Spex milling for 40 minutes. The compositions used were (A) 1.00g (10 w/w %) of tribenuran and 9.00g of lactose monohydrate; and (B) 1.00g (10 w/w %) of tribenuran, 8.90g of lactose monohydrate, and 0.10g (1.0 w/w %) of Brij 700. Particle size distributions for each composition are shown in Figure 30 and summarised in Table 30. The data shows that the particle size is smaller when 1% of surfactant is used in the milling.

Example	D(0.5) µm	% < 0.20 µm	% < 0.30 µm	% < 0.5 µm	% < 1.0 µm	% < 2.0 µm
A	2.622	0	0	0	0	25
B	0.128	82	96	98	98	99

Table 30

Example 18: Milling of sulfur in lactose monohydrate

Powders were prepared by Spex milling for 40 minutes. The compositions used were (A) 1.00g (10 w/w %) of sulfur and 9.00g of lactose monohydrate and (B) 1.00g (10 w/w %) of sulfur and 8.90g of lactose monohydrate, and 0.10g (1.0 w/w %) of sodium lauryl sulfate. Particle size distributions for each composition are shown in Figure 31 and summarised in Table 31. It can be seen that milling with sodium lauryl sulfate gave a narrower particle size distribution with more material below 1 micron.

Example	D(0.5) µm	% < 0.20 µm	% < 0.30 µm	% < 0.5 µm	% < 1.0 µm	% < 2.0 µm
A	0.388	27	42	56	69	86
B	0.455	6	26	55	78	96

Table 31

Example 19: Milling of Mancozeb in lactose monohydrate.

Powders were prepared by Spex milling for 40 minutes. The compositions used were (A) 1.00g (10 w/w %) of Mancozeb and 9.00g of lactose monohydrate, (B) 1.00g (10 w/w %) of Mancozeb, 8.9g of lactose monohydrate and 0.10g (1.0 % w/w) Brij 700, (C) 1.00g (10 w/w %) of Mancozeb, 8.9g of lactose monohydrate and 0.10g (1.0 % w/w) SLS, (D) 1.00g (10 w/w %) of Mancozeb, 8.9g of lactose monohydrate and 0.10g (1.0 % w/w) lecithin, (E) 2.00g (20 w/w %) of Mancozeb, 7.9g of lactose monohydrate and 0.10g (1.0 % w/w) SLS, (F) 3.00g (30 w/w %) of Mancozeb, 6.9g of lactose monohydrate and 0.10g (1.0 % w/w) SLS. The particle size distribution of A is shown in Figure 32 and the particle size of all compositions is summarised in Table 32. Compositions B-D show that the particle size is smaller when 1% of surfactant is used in the milling. Composition E at 20% w/w with 1 % SLS gives almost as good a particle size distribution as composition A, 10% w/w with no surfactant. This demonstrates the benefit 1% surfactant can make to achieving a small particle size. Composition F, at 30 w/w % with 1% SLS is also very small with more than 80% less than 500 nm.

Example	D(0.5) µm	% < 0.20 µm	% < 0.30 µm	% < 0.5 µm	% < 1.0 µm	% < 2.0 µm
A	0.198	50	71	88	97	97

B	0.170	60	82	96	100	100
C	0.171	60	82	97	100	100
D	0.181	56	78	95	100	100
E	0.212	47	68	86	96	98
F	0.258	36	58	81	94	97

Table 32

Example 20. Milling of Metaxalone in Lactose monohydrate:

A mixture (A) of 1.5g (30w/w%) Metaxalone, 3.5g (69 w/w%) Lactose monohydrate and 0.05 g (1w/w%) Pluronic-F-127 was milled for 60 minutes in a Spex mill. A second mixture (B) of 1.5g Metaxalone (30w/w%), 3.5g Lactose monohydrate (70w/w%) without surfactant was milled for 60 minutes in a Spex mill. PSDs of the milled products and unmilled Metaxalone (C) are shown in Figure 33 and summarized in Table 33. The data shows that the particle size is smaller after milling and decreases further when 1% of Poloxamer 407 is used in the milling.

Example	D(0.5) µm	% < 0.20 µm	% < 0.30 µm	% < 0.5 µm	% < 1.0 µm	% < 2.0 µm
A	0.16	63	77	84	89	93
B	0.28	40	52	59	59	71
C	50	0	0	0	0	0

Table 33

Example 21. Milling of Metaxalone in Lactose monohydrate or Mannitol with surfactants and a combination of different surfactants and sodium bicarbonate.

Powders (A) and (B) were prepared by attritor milling using the 750 mL vessel with a stirring speed of 550 rpm. The compositions used were (A) 17.2g (43 w/w %) of metaxalone, 0.4g (1.0 w/w %) of sodium lauryl sulfate and 22g of lactose monohydrate, (B) 20.0g (50 w/w %) of metaxalone, 8.0g (20 w/w %) of sodium bicarbonate, 0.8g (2 w/w %) of sodium lauryl sulfate, 0.8g (2 w/w %) of Poloxamer 407 and 10.4g of lactose monohydrate.

Further compositions used were: (C) 2.5g (50 w/w %) of metaxalone, 2.35g (47 w/w %) of lactose monohydrate, and 0.076g (1.5 w/w %) of sodium lauryl sulfate, 0.076g (1.5 w/w %) of poloxamer 407 and was prepared by Spex milling for 60 minutes; (D) 17.2g (43 w/w %) of

metaxalone, 22.4g (56 w/w %) of mannitol, and 0.4g (1 w/w %) of sodium lauryl sulfate milled with a 750 mL Attritor for 60 minutes. Particle size distributions for composition A and B are shown in Figure 34 and summarised for each composition in Table 34.

The data shows that milling of Metaxalone with a variety of matrices and surfactants produces small particles at 43 to 50 w/w% in the Spex mill and in the larger 750 mL Attritor. A combination of SLS and Poloxamer 407 in Lactose monohydrate produces the smallest nanoparticles in the presence of sodium bicarbonate during milling at 50 w/w% Metaxalone. As can be seen in Figure 34 Metaxalone milled with a combination of SLS and Poloxamer 407 (B) produces smaller particles as Metaxalone milled with sodium lauryl sulfate (A).

The dissolution behaviour of the milled mix of (B) was tested after formulation into a tablet and compared with unmilled API of the same composition and a commercial Skelaxin® tablet, The composition and formulation are described in the method section. Using USP apparatus 2 the dissolution buffer is 750 mL 0.01 M HCL and the amount of API is about 60 mg for all samples, further details can be found in the method section.
Figure 35 shows that the tablet of milled powder (trace A) dissolves much more rapidly compared to the tablet of unmilled materials (trace B) and the commercial Skelaxin® tablet (trace C). The tablet containing milled material has a much improved dissolution compared with both the unmilled tablet of the same composition and an even greater improved dissolution compared with the commercial Skelaxin® tablets. The particles size reduction due to milling has improved the dissolution behaviour compared to the commercial Skelaxin® tablet.

Example	D(0.5) µm	% < 0.20 µm	% < 0.30 µm	% < 0.5 µm	% < 1.0 µm	% < 2.0 µm
A	0.142	70	83	88	91	94
B	0.137	73	89	95	100	100
C	0.148	67	83	92	98	99
D	0.254	42	55	64	67	72

Table 34

Example 22: Naproxen acid milling in mannitol using a combination of different surfactants

Powder mixtures consisting of (A) 17.5 g (35 w/w %) of Naproxen Acid, 0.5g (1.0 w/w %) of SLS and 32 g of Mannitol; and (B) 17.5 g (35 w/w %) of Naproxen Acid, 0.5g (1.0 w/w %) of SLS, 0.5g (1.0 w/w %) of POE 40 sterate,and 31.5 g of Mannitol and (C) 17.5 g (35 w/w %) of Naproxen Acid, 0.5g (1.0 w/w %) of SLS, 0.5g (1.0 w/w %) of PEG 3000,and 31.5 g of Mannitol were attritor milled for 80 minutes in a 750 mL tank. Particle size distributions for each composition are shown in Figure 36 and summarised in Table 35. The data shows that the particle size is smaller when PEG 3000 is used in combination with SLS in the milling.

Example	D(0.5) µm	% < 0.20 µm	% < 0.30 µm	% < 0.5 µm	% < 1.0 µm	% < 2.0 µm
A	0.249	42	56	64	67	74
B	0.261	39	55	67	77	88
C	0.188	53	70	81	88	95

Table 35

Example 23: Indomethacin milling in lactose monohydrate using a combination of different surfactants

Powder mixtures consisting of (A) 6.0 g (12 w/w %) of indomethacin, 0.5g (1.0 w/w %) of SLS and 43.5g of lactose monohydrate; (B) 6.0 g (12 w/w %) of indomethacin, 0.5g (1.0 w/w %) of SLS, 0.5g (1.0 w/w %) of Pluronic F127 and 43.0 g of lactose monohydrate and (C) 6.0 g (12 w/w %) of indomethacin, 0.5g (1.0 w/w %) of SLS, 0.5g (1.0 w/w %) of POE 40 sterate and 43.0 g of lactose monohydrate and were attritor milled for 40 minutes in a 750 mL tank. Particle size distributions for each composition are shown in Figure 37 and summarised in Table 36. The data shows that the particle size is smaller when Pluronic F127 or POE 40 sterate is used in combination with SLS in the milling.

Example	D(0.5) µm	% < 0.20 µm	% < 0.30 µm	% < 0.5 µm	% < 1.0 µm	% < 2.0 µm
A	0.231	43	61	78	91	97
B	0.152	66	85	95	97	98
C	0.155	65	85	96	98	98

Table 36

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The Claim Defining the Invention is as Follows:

1. A method for producing a composition, comprising the steps of:
   dry milling a solid biologically active material and a millable grinding matrix in a mill comprising a plurality of milling bodies, for a time period sufficient to produce particles of the biologically active material dispersed in an at least partially milled grinding material.

2. The method of claim 1, wherein the average particle size, determined on a particle number basis, is equal to or less than a size selected from the group 2000 nm, 1900 nm, 1800nm, 1700nm, 1600nm, 1500nm, 1400nm, 1300nm, 1200 nm, 1100nm, 1000nm, 900nm, 800nm, 700nm, 600nm, 500nm, 400 nm, 300nm, 200nm and 100 nm.

3. The method of claim 2, wherein the average particle size is equal to or greater than 25nm.

4. The method of claim 1, wherein the particles have a median particle size, determined on a particle volume basis, equal or less than a size selected from the group 2000 nm, 1900 nm, 1800nm, 1700nm, 1600nm, 1500nm, 1400nm, 1300nm, 1200 nm, 1100nm, 1000nm, 900nm, 800nm, 700nm, 600nm, 500nm, 400 nm, 300nm, 200nm and 100 nm.

5. The method of claim 4, wherein the median particle size is equal to or greater than 25nm.

6. The method of claim 4 wherein the percentage of particles, on a particle volume basis, is selected from the group consisting of: less than 2000nm (% < 2000 nm) is selected from the group 50 %, 60%, 70%, 80%, 90%, 95% and 100 %; less than 1000nm (% < 1000 nm) is selected from the group 50 %, 60%, 70%, 80%, 90%, 95% and 100 %; less than 500nm (% < 500 nm) is selected from the group 0%, 10%, 20%, 30%, 40%, 50 %, 60%, 70%, 80%, 90%, 95% and 100 %; less than 300nm (% < 300 nm) is selected from the group 0%, 10%, 20%, 30%, 40%, 50 %, 60%, 70%,

80%, 90%, 95% and 100 %; and less than 200nm (% < 200 nm) is selected from the group 0%, 10%, 20%, 30%, 40%, 50 %, 60%, 70%, 80%, 90%, 95% and 100 %.

7. The method of any preceding claim, wherein the milling time period is a range selected from the group consisting of: between 10 minutes and 2 hours, between 10 minutes and 90 minutes, between 10 minutes and 1 hour, between 10 minutes and 45 minutes, between 10 minutes and 30 minutes, between 5 minutes and 30 minutes, between 5 minutes and 20 minutes, between 2 minutes and 10 minutes, between 2 minutes and 5 minutes, between 1 minutes and 20 minutes, between 1 minute and 10 minutes, and between 1 minute and 5 minutes.

8. The method of any preceding claim, wherein the milling medium is selected from the group consisting of: ceramics, glasses, polymers, ferromagnetics and metals.

9. The method of claim 8, wherein the milling medium is steel balls having a diameter selected from the group consisting of: between 1 and 20 mm, between 2 and 15 mm and between 3 and 10 mm.

10. The method of any preceding claim, wherein the dry milling apparatus is a mill selected from the group consisting of: attritor mills (horizontal or vertical), nutating mills, tower mills, pearl mills, planetary mills, vibratory mills, eccentric vibratory mills, gravity-dependent-type ball mills, rod mills, roller mills and crusher mills.

11. The method of claim 10, wherein the milling medium within the milling apparatus is mechanically agitated by 1, 2 or 3 rotating shafts.

12. The method of any preceding claim, wherein the method is configured to produce the biologically active material in a continuous fashion.

13. The method of any preceding claim, wherein the total combined amount of biologically active material and grinding matrix in the mill at any given time is equal to or greater than a mass selected from the group consisting of: 200 grams, 500 grams, 1 kg, 2kg, 5 kg, 10 kg, 20 kg, 30 kg, 50 kg, 75 kg, 100kg, 150 kg, 200 kg.

14. The method of any preceding claim, wherein the biologically active material is diclofenac.

15. The method of any preceding claim, wherein the grinding matrix is a single material or is a mixture of two or more materials in any proportion.

16. The method of claim 15, wherein the single material or a mixture of two or more materials is selected from the group consisting of: mannitol, sorbitol, Isomalt, xylitol, maltitol, lactitol, erythritol, arabitol, ribitol, glucose, fructose, mannose, galactose, anhydrous lactose, lactose monohydrate, sucrose, maltose, trehalose, maltodextrins, dextrin, Inulin, dextrates, polydextrose, starch, wheat flour, corn flour, rice flour, rice starch, tapioca flour, tapioca starch, potato flour, potato starch, other flours and starches, milk powder, skim milk powders, other milk solids and dreviatives, soy flour, soy meal or other soy products, cellulose, microcystalline cellulose, microcystalline cellulose based co blended materials, pregelatinized (or partially) starch, HPMC, CMC, HPC, citric acid, tartaric acid, malic acid, maleic acid fumaric acid , ascorbic acid, succinic acid, sodium citrate, sodium tartrate, sodium malate, sodium ascorbate, potassium citrate, potassium tartrate, potassium malate, potassium ascorbate, sodium carbonate, potassium carbonate, magnesium carbonate, sodium bicarbonate, potassium bicarbonate and calcium carbonate., dibasic calcium phosphate, tribasic calcium phosphate, sodium sulfate, sodium chloride, sodium metabisulphite, sodium thiosulfate, ammonium chloride, Glauber's salt, ammonium carbonate, sodium bisulfate, magnesium sulfate, potash alum, potassium chloride, sodium hydrogen sulfate, sodium hydroxide, crystalline hydroxides, hydrogen carbonates, ammonium chloride, methylamine hydrochloride, ammonium bromide, silica, thermal silica, alumina, titanium dioxide, talc, chalk, mica, kaolin, bentonite, hectorite, magnesium trisilicate, clay based materials or aluminium silicates, sodium lauryl sulfate, sodium stearyl sulfate, sodium cetyl sulfate, sodium cetostearyl sulfate, sodium docusate, sodium deoxycholate, N-lauroylsarcosine sodium salt, glyceryl monostearate , glycerol distearate glyceryl palmitostearate, glyceryl behenate, glyceryl caprylate, glyceryl oleate, benzalkonium chloride, CTAB, CTAC, Cetrimide, cetylpyridinium chloride, cetylpyridinium bromide, benzethonium chloride, PEG 40 stearate, PEG 100 stearate, poloxamer 188, , poloxamer 338, poloxamer 407 polyoxyl 2 stearyl ether, polyoxyl 100 stearyl ether, polyoxyl 20 stearyl ether, polyoxyl 10 stearyl ether, polyoxyl 20 cetyl ether, polysorbate 20, polysorbate 40, polysorbate 60, polysorbate 61, polysorbate 65, polysorbate 80, polyoxyl 35 castor oil, polyoxyl

40 castor oil, polyoxyl 60 castor oil, polyoxyl 100 castor oil, polyoxyl 200 castor oil, polyoxyl 40 hydrogenated castor oil, polyoxyl 60 hydrogenated castor oil, polyoxyl 100 hydrogenated castor oil, polyoxyl 200 hydrogenated castor oil, cetostearyl alcohol, macrogel 15 hydroxystearate, sorbitan monopalmitate, sorbitan monostearate, sorbitan trioleate, Sucrose Palmitate, Sucrose Stearate, Sucrose Distearate, Sucrose laurate, Glycocholic acid, sodium Glycholate, Cholic Acid, Soidum Cholate, Sodium Deoxycholate, Deoxycholic acid, Sodium taurocholate, taurocholic acid, Sodium taurodeoxycholate, taurodeoxycholic acid, soy lecithin, phosphatidylcholine, phosphatidylethanolamine, phosphatidylserine, phosphatidylinositol, PEG4000, PEG6000, PEG8000, PEG10000, PEG20000, alkyl naphthalene sulfonate condensate/Lignosulfonate blend,Calcium Dodecylbenzene Sulfonate, Sodium Dodecylbenzene Sulfonate,Diisopropyl naphthaenesulphonate, erythritol distearate, Naphthalene Sulfonate Formaldehyde Condensate, nonylphenol ethoxylate (poe-30), Tristyrylphenol Ethoxylate, Polyoxyethylene (15) tallowalkylamines, sodium alkyl naphthalene sulfonate, sodium alkyl naphthalene sulfonate condensate, sodium alkylbenzene sulfonate, sodium isopropyl naphthalene sulfonate, Sodium Methyl Naphthalene Formaldehyde Sulfonate, sodium n-butyl naphthalene sulfonate, tridecyl alcohol ethoxylate (poe-18), Triethanolamine isodecanol phosphate ester, Triethanolamine tristyrylphosphate ester, Tristyrylphenol Ethoxylate Sulfate, Bis(2-hydroxyethyl)tallowalkylamines

17. The method of claim 15 or 16, wherein the concentration of the single material or a mixture of two or more materials is selected from the group consisting of: 5 - 99 % w/w, 10 - 95 % w/w, 15 - 85 % w/w, of 20 – 80% w/w, 25 - 75 % w/w, 30 - 60% w/w, 40 -50% w/w.

18. The method of claim 15 or 16, wherein the concentration of the second or subsequent material is selected from the group consisting of: 5 - 50 % w/w, 5 - 40 % w/w, 5 - 30 % w/w, of 5 – 20% w/w, 10 - 40 % w/w, 10 -30% w/w, 10 -20% w/w, 20 - 40% w/w, or 20 - 30% w/w or if the second or subsequent material is a surfactant or water soluble polymer the concentration is selected from 0.1 -10 % w/w, 0.1 -5 % w/w, 0.1 -2.5 % w/w, of 0.1 – 2% w/w, 0.1 -1 %, 0.5 -5% w/w, 0.5 -3% w/w, 0.5 -2% w/w, 0.5 – 1.5%, 0.5 -1 % w/w, of 0.75 – 1.25 % w/w, 0.75 -1% and 1% w/w.

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19. The method of any preceding claim, wherein the grinding matrix is selected from the group consisting of:

(i) lactose monohydrate or lactose monohydrate combined with a material selected from the group consisting of: sodium pentane sulfate; sodium octadecyl sulfate; Brij700; Brij76; sodium n-lauroyl sacrosine; lecithin; docusate sodium; polyoxyl-40-stearate; Aerosil R972 fumed silica; sodium lauryl sulfate or other alkyl sulfate surfactants with a chain length between C5 to C18; calcium carbonate; malic acid; tartaric acid; trisodium citrate dehydrate; D,L-Malic acid; Xylitol; Polyvinyl pyrrolidone; lactose anhydrous; mannitol; and microcrystalline cellulose;

(j) lactose anhydrous or lactose anhydrous combined with a material selected from the group consisting of: sodium pentane sulfate; sodium octadecyl sulfate; Brij700; Brij76; sodium n-lauroyl sacrosine; lecithin; docusate sodium; polyoxyl-40-stearate; Aerosil R972 fumed silica; sodium lauryl sulfate or other alkyl sulfate surfactants with a chain length between C5 to C18; calcium carbonate; malic acid; tartaric acid; trisodium citrate dehydrate; D,L-Malic acid; Xylitol; Polyvinyl pyrrolidone; lactose monohydrate; mannitol; and microcrystalline cellulose;

(k) mannitol or mannitol combined with a material selected from the group consisting of: sodium pentane sulfate; sodium octadecyl sulfate; Brij700; Brij76; sodium n-lauroyl sacrosine; lecithin; docusate sodium; polyoxyl-40-stearate; Aerosil R972 fumed silica; sodium lauryl sulfate or other alkyl sulfate surfactants with a chain length between C5 to C18; calcium carbonate; malic acid; tartaric acid; trisodium citrate dehydrate; D,L-Malic acid; Xylitol; Polyvinyl pyrrolidone; lactose monohydrate; microcrystalline cellulose; and lactose anhydrous;

(l) tartaric acid or tartaric acid combined with a material selected from the group consisting of: sodium pentane sulfate; sodium octadecyl sulfate; Brij700; Brij76; sodium n-lauroyl sacrosine; lecithin; docusate sodium; polyoxyl-40-stearate; Aerosil R972 fumed silica; sodium lauryl sulphate or other alkyl sulfate surfactants with a chain length between C5 to C18; calcium carbonate; malic acid; trisodium citrate dehydrate; D,L-Malic acid; Xylitol; Polyvinyl pyrrolidone; lactose monohydrate; microcrystalline cellulose; lactose anhydrous; and mannitol;

(m) xylitol or xylitol combined with a material selected from the group consisting of: sodium pentane sulfate; sodium octadecyl sulfate; Brij700; Brij76; sodium n-lauroyl sacrosine; lecithin; docusate sodium; polyoxyl-40-stearate; Aerosil R972 fumed silica; sodium lauryl sulphate or other alkyl sulfate surfactants with a chain length between C5 to C18; calcium carbonate; malic acid; tartaric acid; trisodium citrate dehydrate; D,L-Malic acid; Polyvinyl pyrrolidone; lactose monohydrate; microcrystalline cellulose; lactose anhydrous; and mannitol; and

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(n) microcrystalline cellulose or microcrystalline cellulose combined with a material selected from the group consisting of: sodium pentane sulfate; sodium octadecyl sulfate; Brij700; Brij76; sodium n-lauroyl sacrosine; lecithin; docusate sodium; polyoxyl-40-stearate; Aerosil R972 fumed silica; sodium lauryl sulphate or other alkyl sulfate surfactants with a chain length between C5 to C18; calcium carbonate; malic acid; tartaric acid; trisodium citrate dehydrate; D,L-Malic acid; polyvinyl pyrrolidone; lactose monohydrate; xylitol; lactose anhydrous and mannitol.

20. The method of any preceding claim, wherein the grinding matrix is selected from the group consisting of: a material considered to be Generally Regarded as Safe (GRAS) for pharmaceutical products; and a material considered acceptable for use in a veterinary formulation.

21. The method of any preceding claim, wherein a milling aid or combination of milling aids is used.

22. The method of any preceding claim, wherein the milling aid is selected from the group consisting of: colloidal silica, a surfactant, a polymer, a stearic acid and derivatives thereof.

23. The method of claim 22, wherein the surfactant is in a solid form or can be manufactured into a solid form.

24. The method of claims 22 or 23, wherein the surfactant is selected from the group consisting of: polyoxyethylene alkyl ethers, polyoxyethylene stearates, poloxamers, sarcosine based surfactants, polysorbates, alkyl sulfates and other sulfate surfactants, trimethyl ammonium based surfactants, lecithin and other phospholipids and bile salts.

25. The method of any one of claims 22 to 24, wherein the surfactant is selected from the group consisting of: sodium lauryl sulfate, sodium docusate, sodium deoxycholate, N-lauroylsarcosine sodium salt, benzalkonium chloride, cetylpyridinium chloride, cetylpyridinium bromide, benzethonium chloride, PEG 40 stearate, PEG 100 stearate, poloxamer 188, Brji 72, Brji 700, Brji 78, Brji 76 and polysorbate 61.

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26. The method of any one of claims 22 to 25, wherein the milling aid has a concentration selected from the group consisting of: 0.1 -10 % w/w, 0.1 -5 % w/w, 0.1 -2.5 % w/w, of 0.1 – 2% w/w, 0.1 -1 %, 0.5 -5% w/w, 0.5 -3% w/w, 0.5 -2% w/w, 0.5 – 1.5%, 0.5 -1 % w/w, of 0.75 – 1.25 % w/w, 0.75 -1% and 1% w/w.

27. The method of any preceding claim, wherein a facilitating agent is used or combination of facilitating agents is used.

28. The method of claim 27, wherein the facilitating agent is selected from the group consisting of: surfactants, polymers, binding agents, filling agents, lubricating agents, sweeteners, flavouring agents, preservatives, buffers, wetting agents, disintegrants, effervescent agents, agents that may form part of a medicament, including a solid dosage form.

29. The method of claims 27 or 28, wherein the facilitating agent is added during dry milling.

30. The method of claim 27, wherein the facilitating agent is added to the dry milling at a time selected from the group consisting of: with 1-5 % of the total milling time remaining, with 1-10 % of the total milling time remaining, with 1-20 % of the total milling time remaining, with 1-30 % of the total milling time remaining, with 2-5% of the total milling time remaining, with 2-10% of the total milling time remaining, with 5-20% of the total milling time remaining and with 5-20% of the total milling time remaining.

31. The method of any one of claims 28 to 30, wherein a disintegrant is selected from the group consisting of: crosslinked PVP, cross linked carmellose and sodium starch glycolate.

32. A composition comprising a biologically active material produced by the method of any one of claims 1-31.

33. A composition of claim 32, wherein the average particle size, determined on a particle number basis, is equal to or less than a size selected from the group 2000

nm, 1900 nm, 1800nm, 1700nm, 1600nm, 1500nm, 1400nm, 1300nm, 1200 nm, 1100nm, 1000nm, 900nm, 800nm, 700nm, 600nm, 500nm, 400 nm, 300nm, 200nm and 100 nm.

34. A composition of claim 33, wherein the average particle size is equal to or greater than 25nm.

35. A composition of claim 32 wherein the particles have a median particle size, determined on a particle volume basis, equal or less than a size selected from the group 2000 nm, 1900 nm, 1800nm, 1700nm, 1600nm, 1500nm, 1400nm, 1300nm, 1200 nm, 1100nm, 1000nm, 900nm, 800nm, 700nm, 600nm, 500nm, 400 nm, 300nm, 200nm and 100 nm.

36. A composition of claim 35, wherein the median particle size is equal to or greater than 25nm.

37. A composition of claim 35, wherein the percentage of particles, on a particle volume basis, is selected from the group consisting of: less than 2000nm (% < 2000 nm) is selected from the group 50 %, 60%, 70%, 80%, 90%, 95% and 100 %; less than 1000nm (% < 1000 nm) is selected from the group 50 %, 60%, 70%, 80%, 90%, 95% and 100 %; less than 500nm (% < 500 nm) is selected from the group 0%, 10%, 20%, 30%, 40%, 50 %, 60%, 70%, 80%, 90%, 95% and 100 %; less than 300nm (% < 300 nm) is selected from the group 0%, 10%, 20%, 30%, 40%, 50 %, 60%, 70%, 80%, 90%, 95% and 100 %; and less than 200nm (% < 200 nm) is selected from the group 0%, 10%, 20%, 30%, 40%, 50 %, 60%, 70%, 80%, 90%, 95% and 100 %.

38. A composition of claims 32 to 37, wherein the biologically active material is diclofenac.

39. A pharmaceutical composition comprising a biologically active material produced by the method of any one of claims 1-31.

40. A pharmaceutical composition of claim 39, wherein the average particle size, determined on a particle number basis, is equal to or less than a size selected from the group 2000 nm, 1900 nm, 1800nm, 1700nm, 1600nm, 1500nm, 1400nm, 1300nm, 1200 nm, 1100nm, 1000nm, 900nm, 800nm, 700nm, 600nm, 500nm, 400 nm, 300nm, 200nm and 100 nm.

41. A pharmaceutical composition of claim 40, wherein the average particle size is equal to or greater than 25nm.

42. A pharmaceutical composition of claim 41, wherein the particles have a median particle size, determined on a particle volume basis, size equal or less than a size selected from the group 2000 nm, 1900 nm, 1800nm, 1700nm, 1600nm, 1500nm, 1400nm, 1300nm, 1200 nm, 1100nm, 1000nm, 900nm, 800nm, 700nm, 600nm, 500nm, 400 nm, 300nm, 200nm and 100 nm.

43. A pharmaceutical composition of claim 42, wherein the median particle size is equal to or greater than 25nm.

44. A pharmaceutical composition of claim 43, wherein the percentage of particles, on a particle volume basis, is selected from the group consisting of: less than 2000nm (% < 2000 nm) is selected from the group 50 %, 60%, 70%, 80%, 90%, 95% and 100 %; less than 1000nm (% < 1000 nm) is selected from the group 50 %, 60%, 70%, 80%, 90%, 95% and 100 %; less than 500nm (% < 500 nm) is selected from the group 0%, 10%, 20%, 30%, 40%, 50 %, 60%, 70%, 80%, 90%, 95% and 100 %; less than 300nm (% < 300 nm) is selected from the group 0%, 10%, 20%, 30%, 40%, 50 %, 60%, 70%, 80%, 90%, 95% and 100 %; and less than 200nm (% < 200 nm) is selected from the group 0%, 10%, 20%, 30%, 40%, 50 %, 60%, 70%, 80%, 90%, 95% and 100 %.

45. A pharmaceutical composition of claims 39 to 44, wherein the biologically active material is diclofenac.

46. A pharmaceutical composition of claims 45, wherein the diclofenac composition has a T_{max} less than that of the equivalent conventional composition administered at the same dosage.

47. A pharmaceutical composition of claims 45 to 46, wherein the diclofenac composition of the invention exhibits in comparative pharmacokinetic testing with a standard conventional drug active composition, in oral suspension, capsule or tablet form, a T_{max} which is selected from the group consisting of: less than about 100%, less than about 90%, less than about 80%, less than about 70%, less than about 60%, less than about 50%, less than about 40%, less than about 30%, less than about 25%, less than about 20%, less than about 15%, or less than about 10%, of the T_{max} exhibited by the standard conventional drug active composition.

48. A pharmaceutical composition of claims 45 to 47, wherein the diclofenac composition has a C_{max} greater than that of the equivalent conventional composition administered at the same dosage.

49. A pharmaceutical composition of claims 45 to 48, wherein the diclofenac composition of the invention exhibits in comparative pharmacokinetic testing with a standard conventional drug active composition, in oral suspension, capsule or tablet form, a C_{max} which is selected from the groupd consisting of: greater than about 5%, greater than about 10%, greater than about 15%, greater than about 20%, greater than about 30%, greater than about 40%, greater than about 50%, greater than about 60%, greater than about 70%, greater than about 80%, greater than about 90%, greater than about 100%, greater than about 110%, greater than about 120%, greater than about 130%, greater than about 140%, or greater than about 150% ,than the C_{max} exhibited by the standard conventional drug active composition.

50. A pharmaceutical composition of claims 45 to 49, wherein the diclofenac composition has a AUC greater than that of the equivalent conventional composition administered at the same dosage.

51. A pharmaceutical composition of claims 45 to 50, wherein the diclofenac composition of the invention exhibits in comparative pharmacokinetic testing with a standard conventional drug active composition, in oral suspension, capsule or tablet form, a

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AUC which is selected from the group consisting of; greater than about 5%, greater than about 10%, greater than about 15%, greater than about 20%, greater than about 30%, greater than about 40%, greater than about 50%, greater than about 60%, greater than about 70%, greater than about 80%, greater than about 90%, greater than about 100%, greater than about 110%, greater than about 120%, greater than about 130%, greater than about 140%, or greater than about 150%, than the AUC exhibited by the standard conventional drug active composition.

52. A method of treating a human in need of such treatment comprising the step of administering to the human an effective amount of a pharmaceutical composition of any one of claims 39 to 51.

53. Use of a pharmaceutical composition of any one of claims 39 to 51 in the manufacture of a medicament for the treatment of a human in need of such treatment.

54. A method for manufacturing a pharmaceutical composition of any one of claims 39 to 51 comprising the step of combining a therapeutically effective amount of a biologically active material prepared by a method according to any one of the claims 1 to 31 together with a pharmaceutically acceptable carrier to produce a pharmaceutically acceptable dosage form.

55. A method for manufacturing a veterinary product comprising the step of combining a therapeutically effective amount of the biologically active material prepared by a method of any one of the claims of 1-31 together with an acceptable excipient to produce a dosage form acceptable for veterinary use.

56. A method for determining the particle size of a biologically active material as described with reference to the above description.

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Abstract

The present invention relates to methods for producing particles of diclofenac using dry milling processes as well as compositions comprising diclofenac, medicaments produced using diclofenac in particulate form and/or compositions, and to methods of treatment of an animal, including man, using a therapeutically effective amount of diclofenac administered by way of said medicaments.

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FIGURE 1

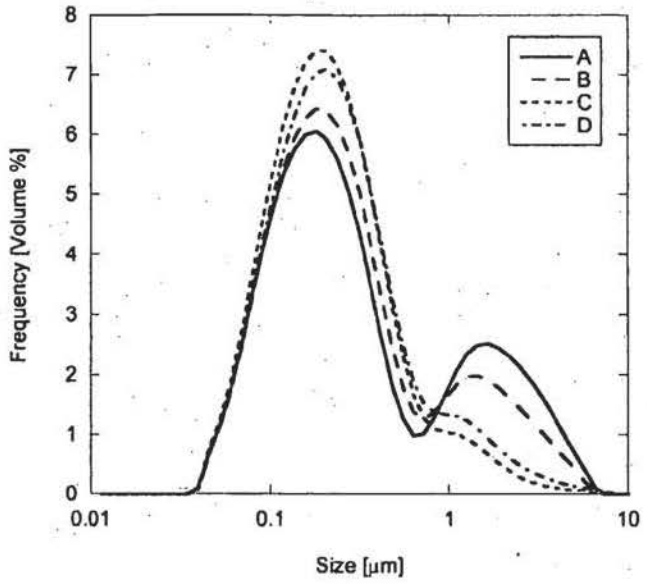

FIGURE 2

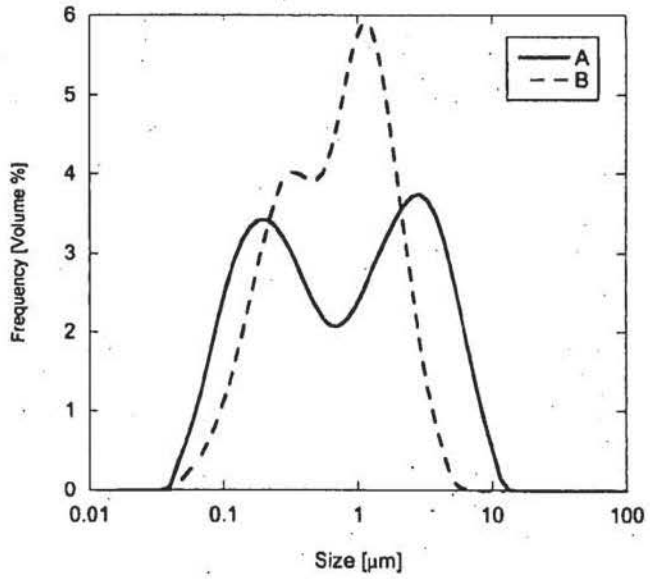

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FIGURE 3

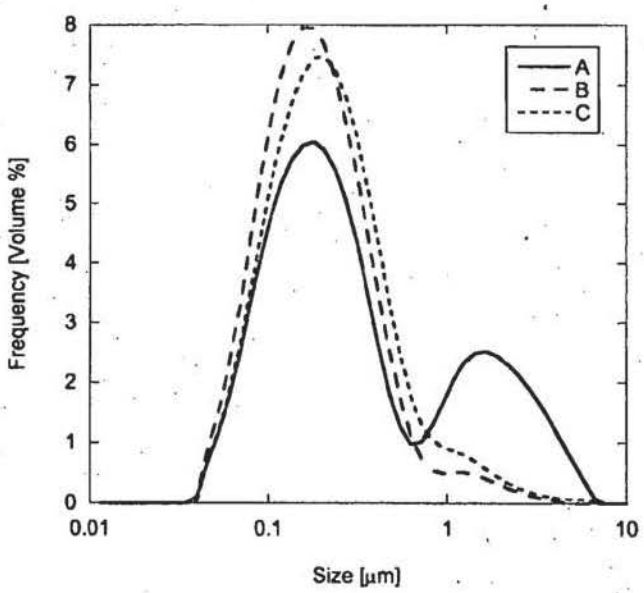

FIGURE 4

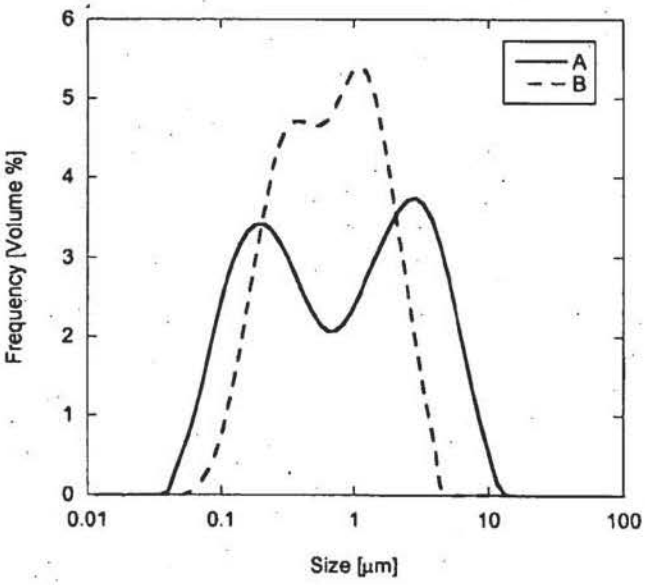

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FIGURE 5

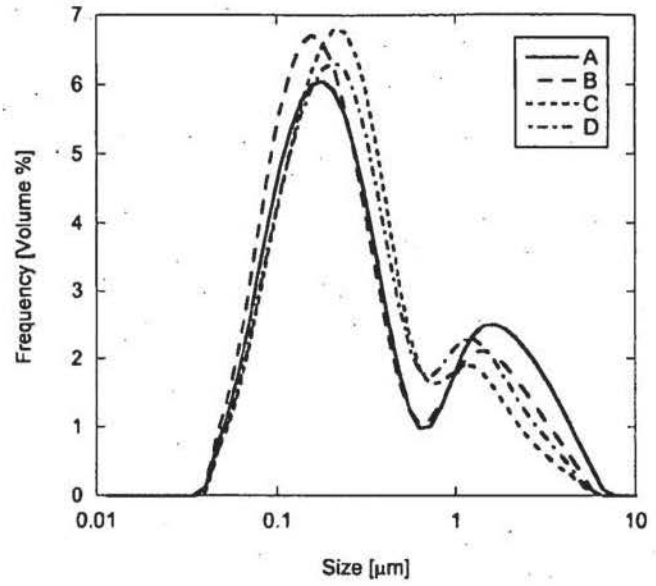

FIGURE 6

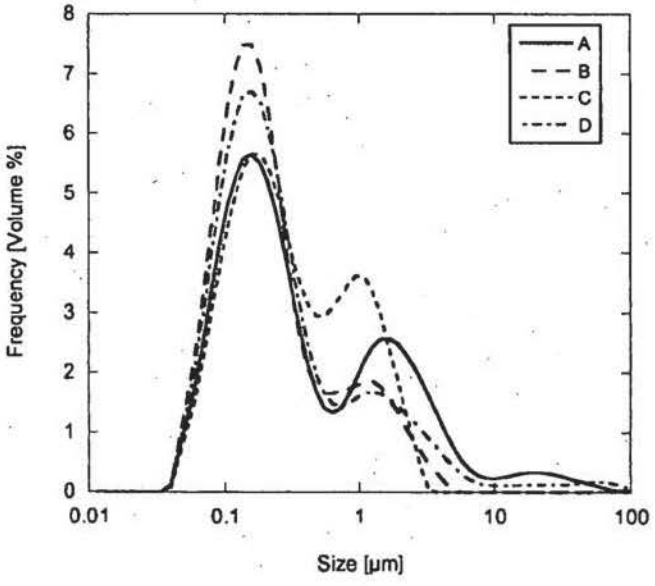

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FIGURE 7

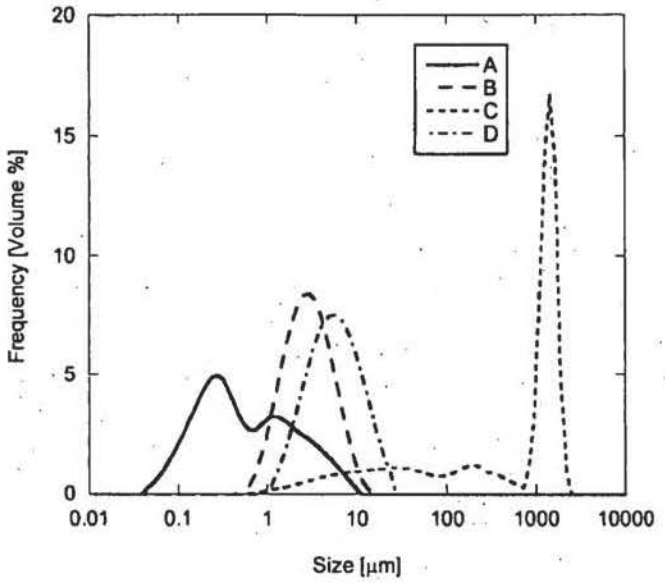

FIGURE 8

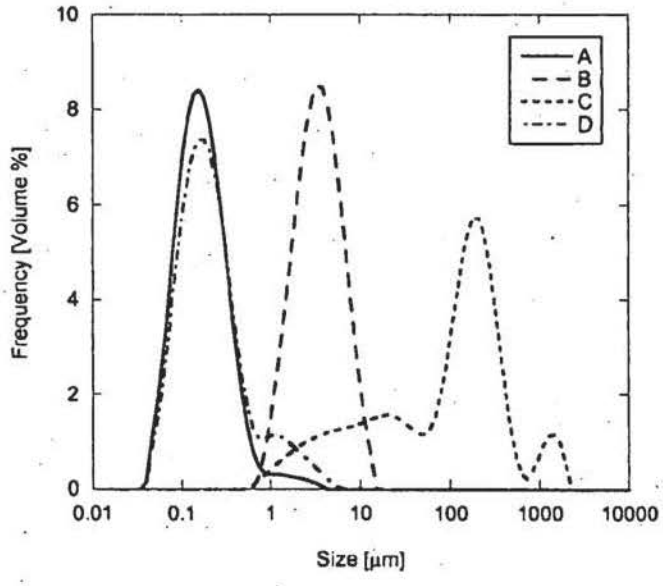

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FIGURE 9

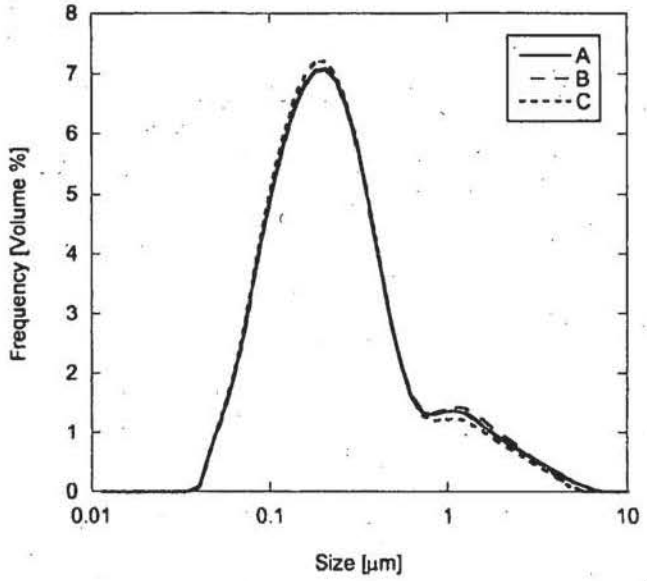

FIGURE 10

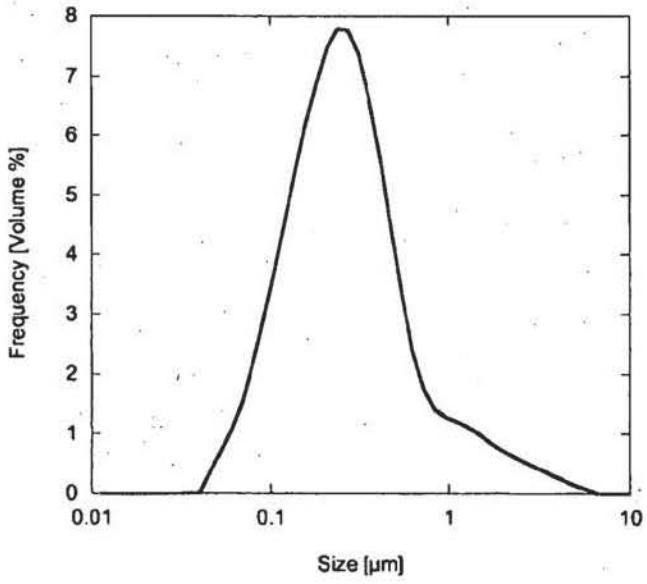

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FIGURE 11

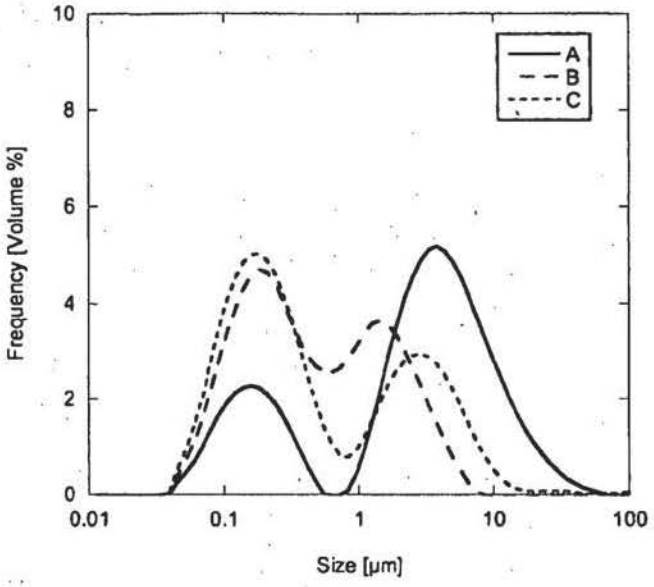

FIGURE 12

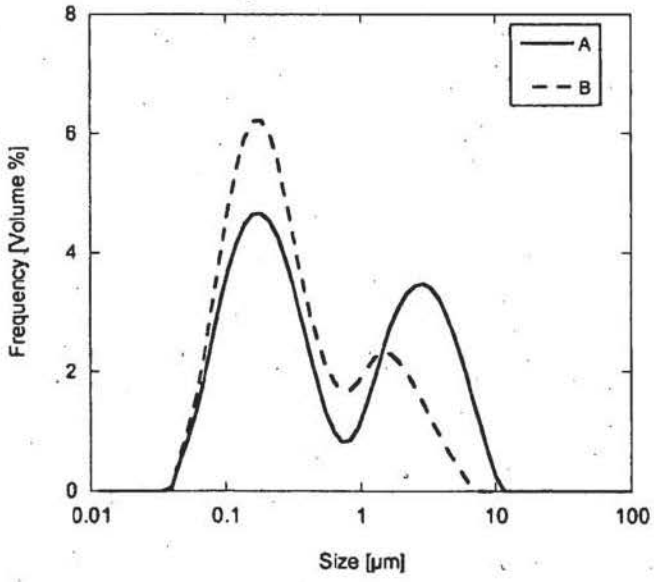

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FIGURE 13

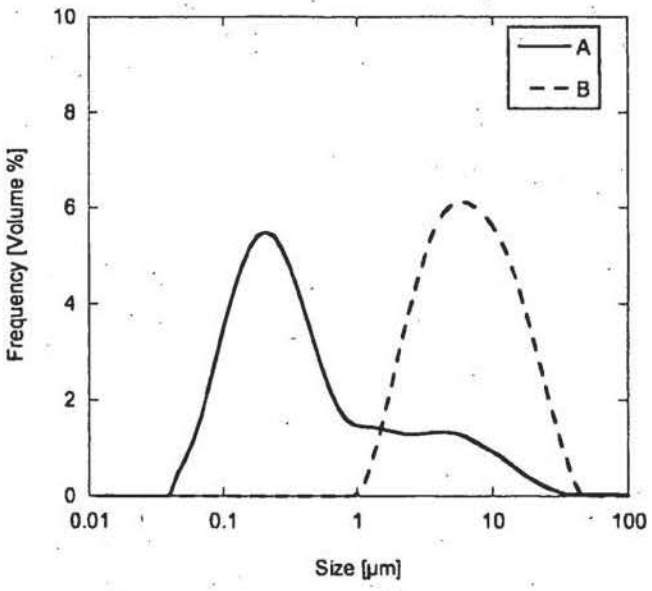

FIGURE 14

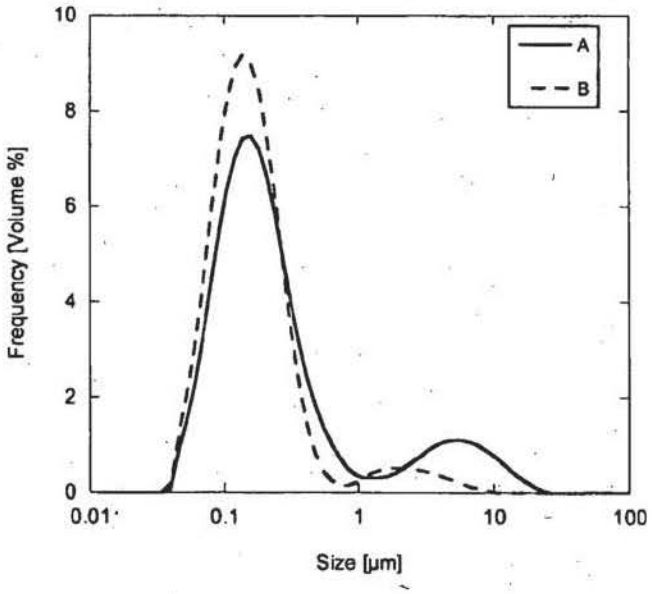

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FIGURE 15

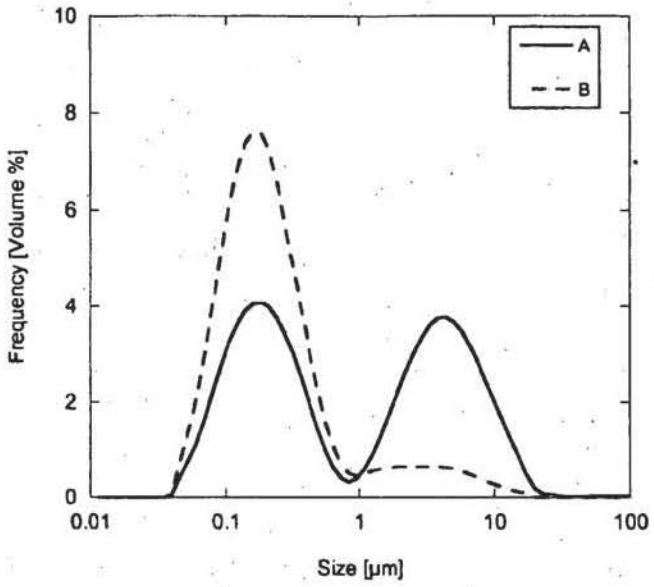

FIGURE 16

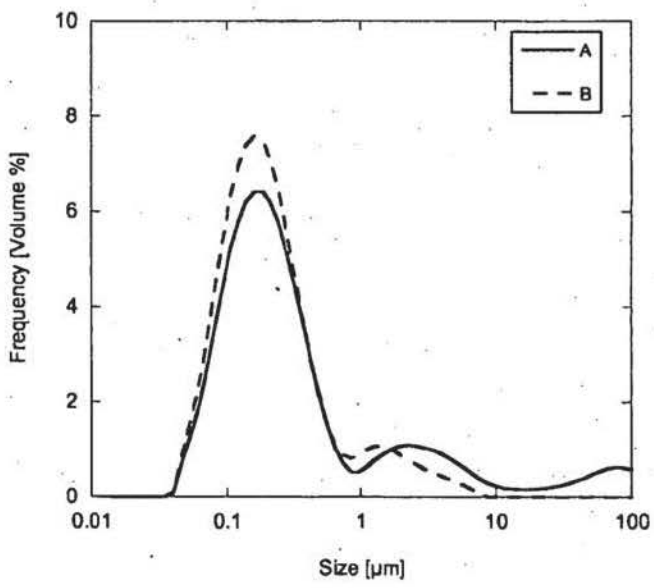

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FIGURE 17

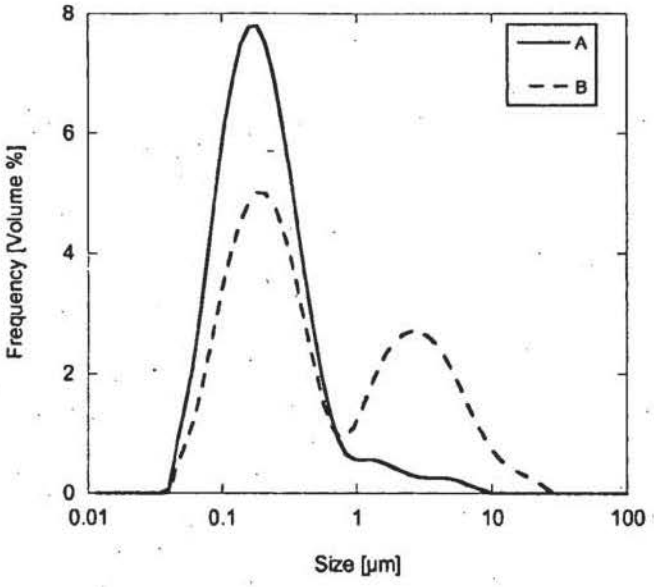

FIGURE 18

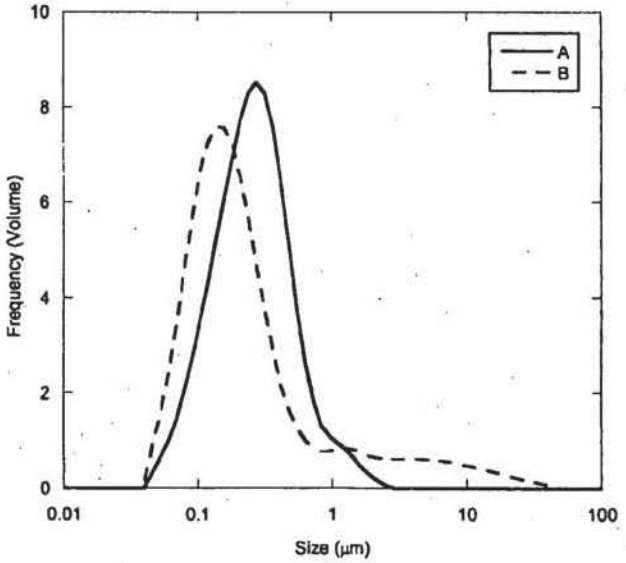

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FIGURE 19

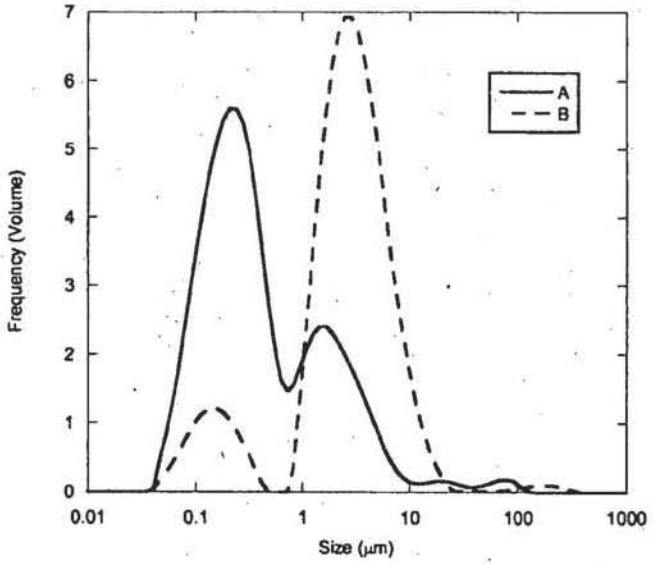

FIGURE 20

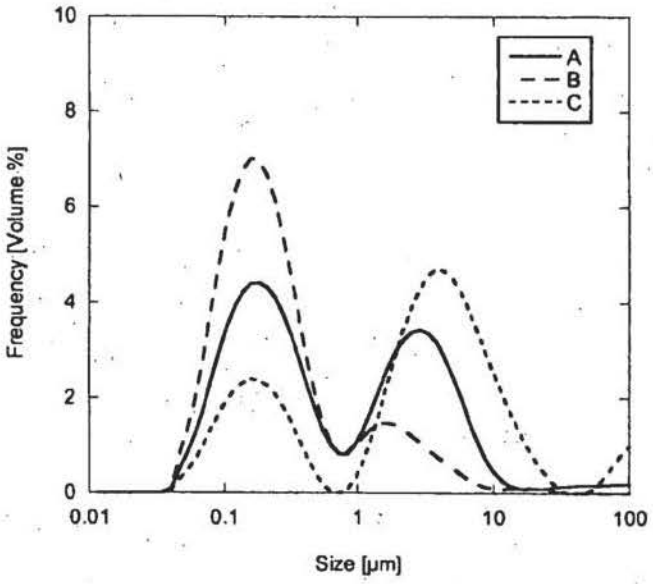

FIGURE 21

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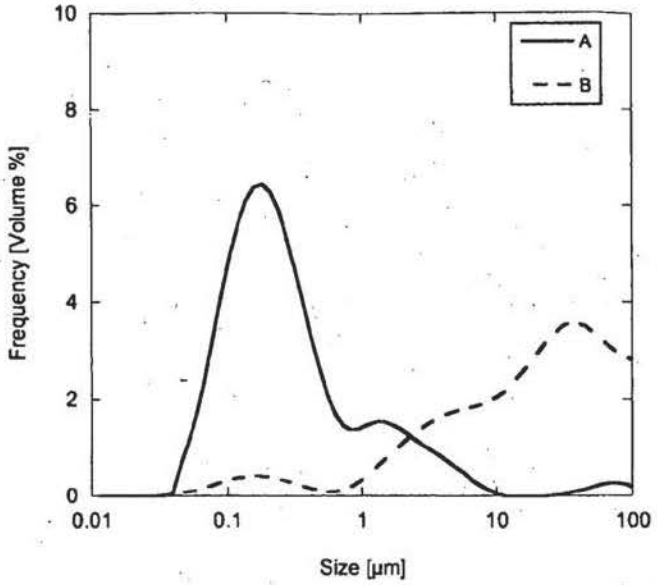

FIGURE 22

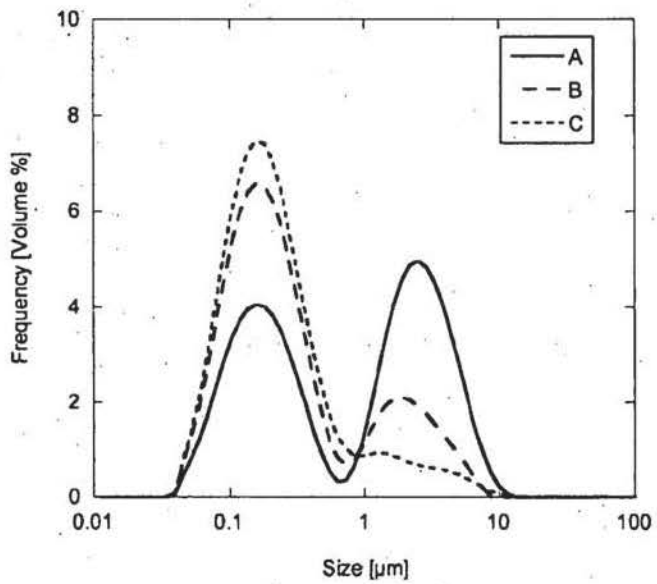

FIGURE 23

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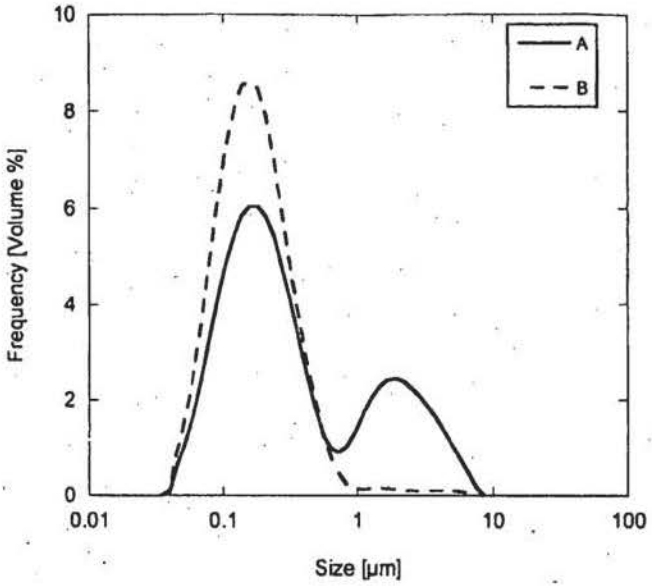

FIGURE 24

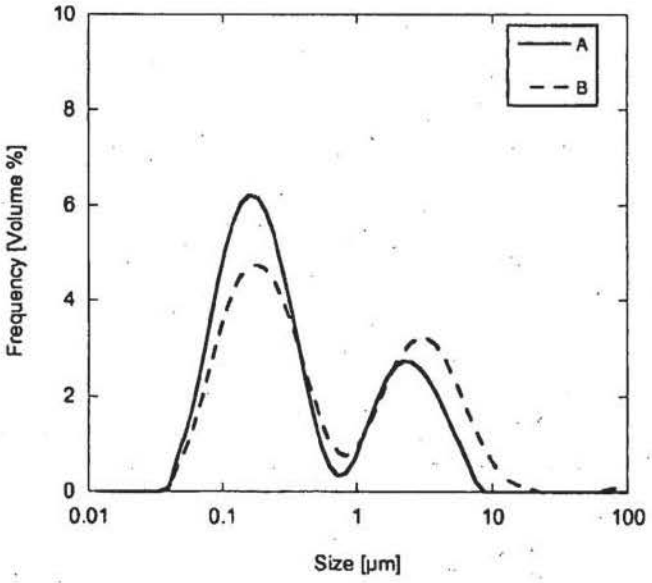

FIGURE 25

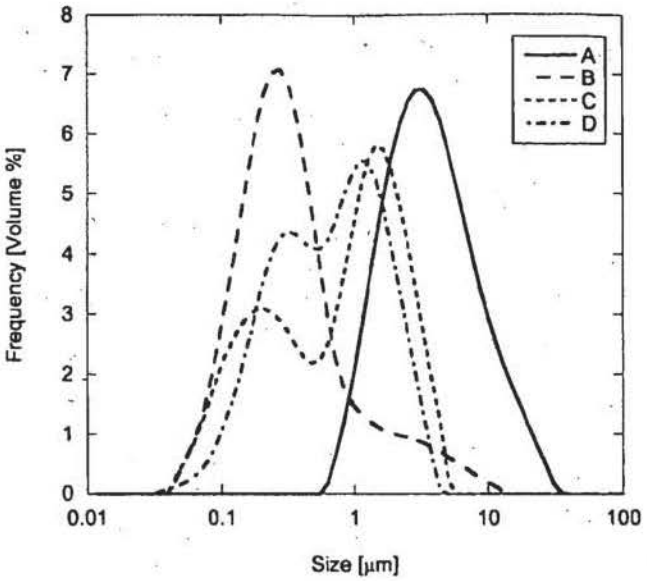

FIGURE 26

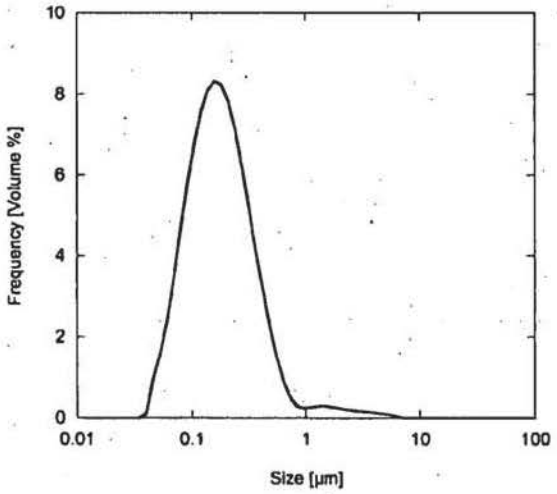

FIGURE 27

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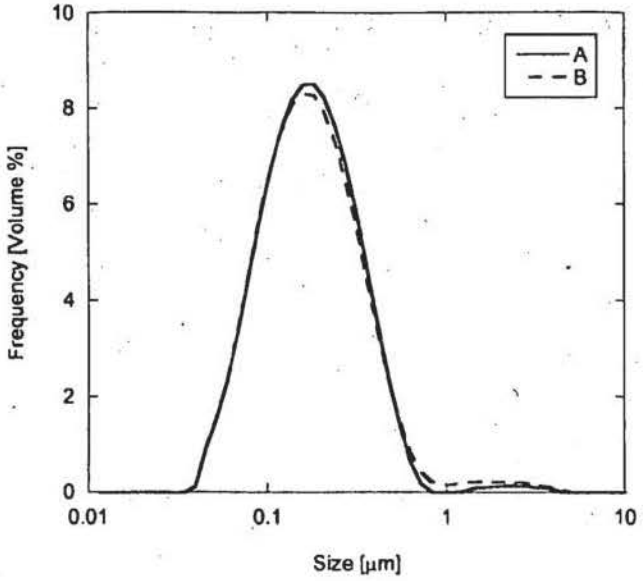

FIGURE 28

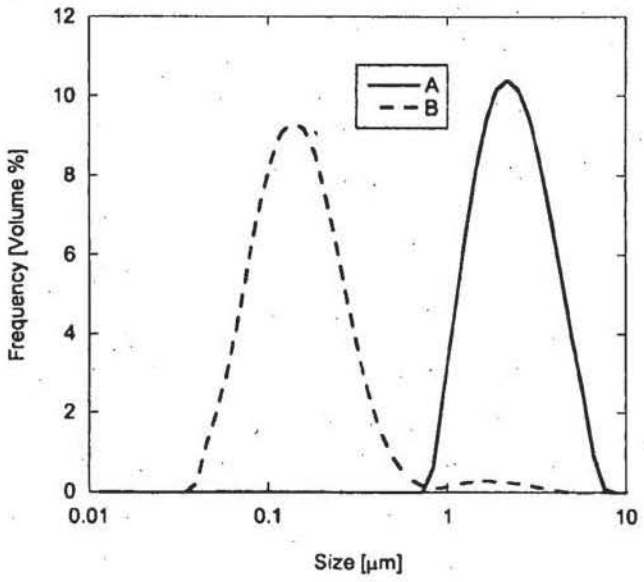

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FIGURE 29

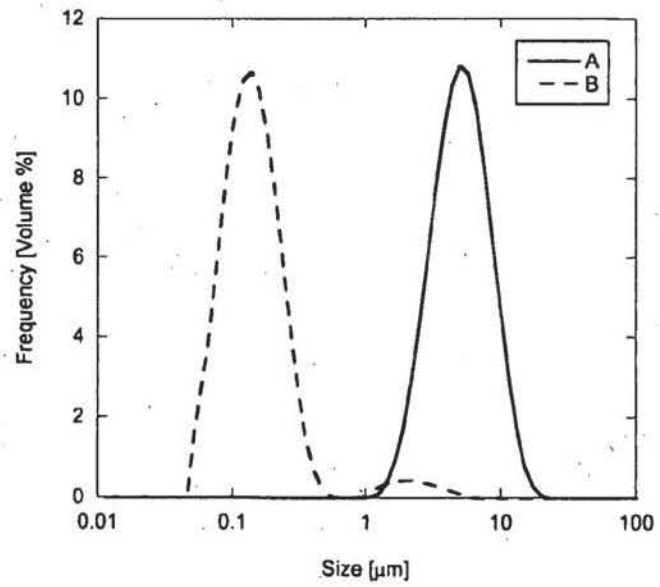

FIGURE 30

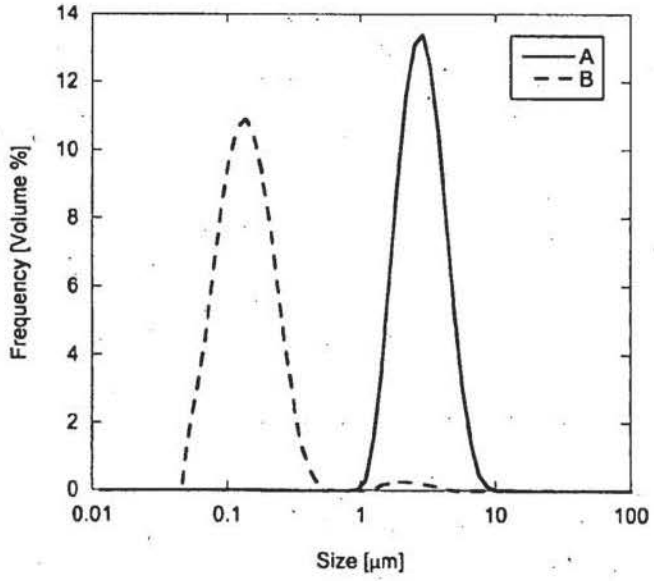

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FIGURE 31

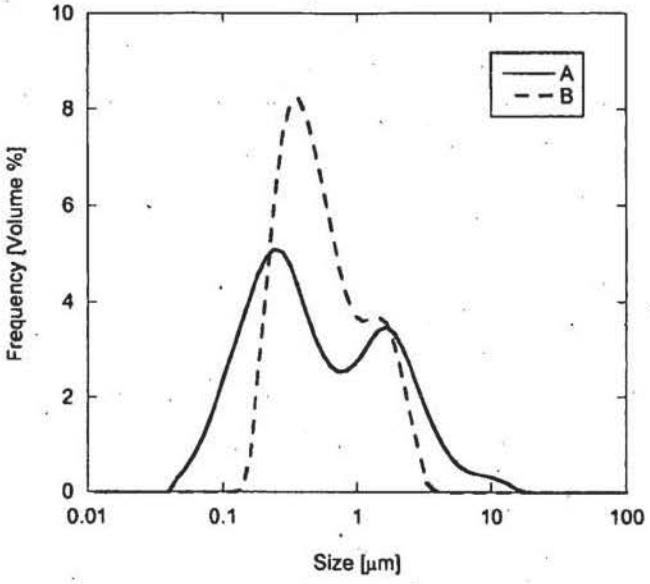

FIGURE 32

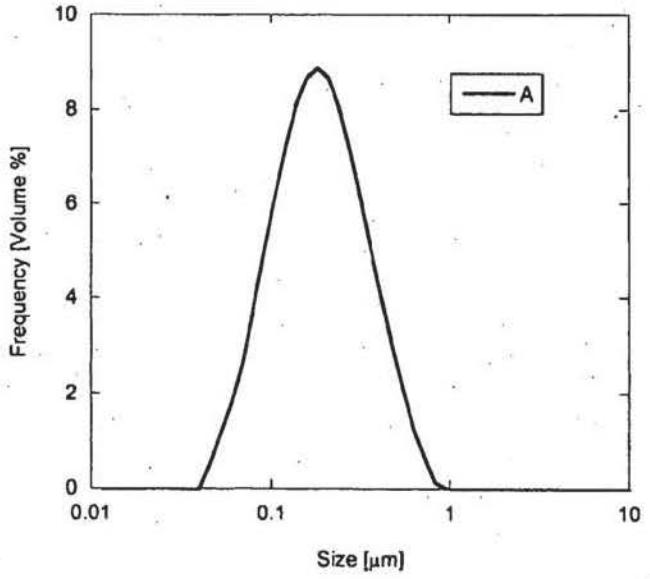

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FIGURE 33

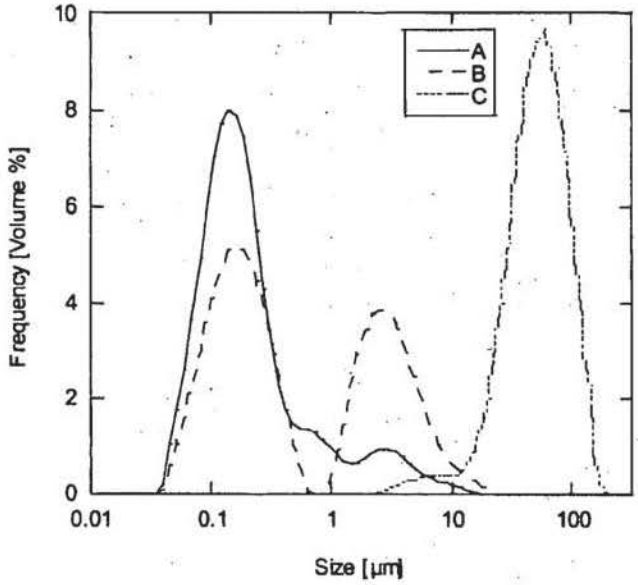

FIGURE 34

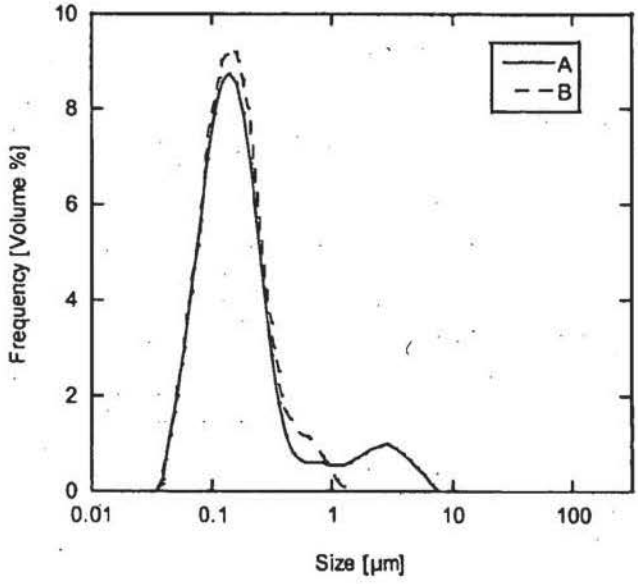

FIGURE 35

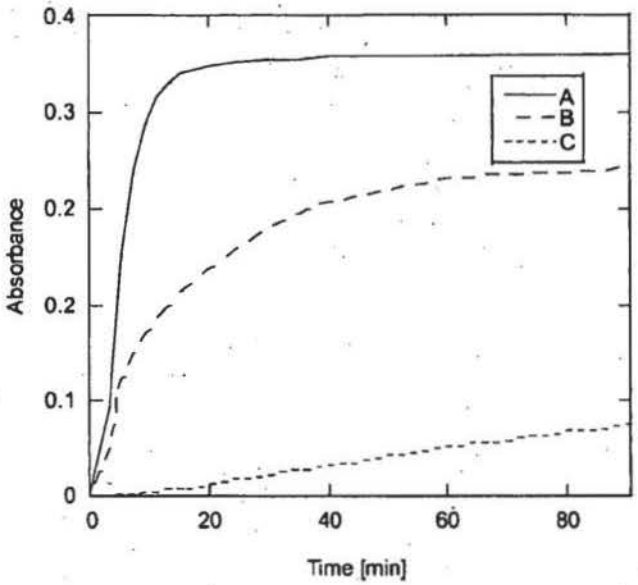

Figure 36

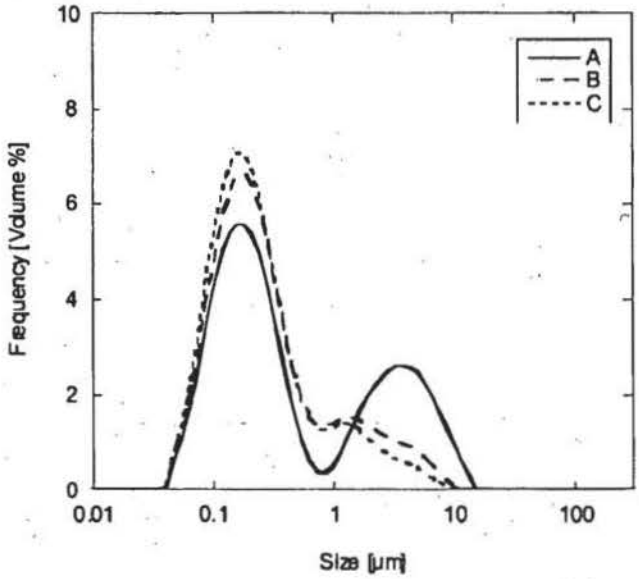

Figure 37