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Canadian Intellectual Property Office

CA 2937365 C 2018/09/18

(11)(21) 2 937 365

(12) BREVET CANADIEN
CANADIAN PATENT

(13) C

(22) Date de dépôt/Filing Date: 2016/07/28

(41) Mise à la disp. pub./Open to Public Insp.: 2016/12/22

(45) Date de délivrance/Issue Date: 2018/09/18

(30) Priorité/Priority: 2016/03/29 (US62/314,933)

(51) Cl.Int./Int.Cl. *A61K 9/16* (2006.01),
A61K 31/4418 (2006.01), *A61K 9/20* (2006.01)

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(54) Titre : FORMULATION EN GRANULES DE 5-METHYL-1-PHENYL-2-(1H)-PYRIDONE ET METHODE DE FABRICATION ASSOCIEE

(54) Title: GRANULATE FORMULATION OF 5-METHYL-1-PHENYL-2-(1H)-PYRIDONE AND METHOD OF MAKING THE SAME

(57) Abrégé/Abstract:
The disclosure relates to granulate formulations of pirfenidone and methods of making such formulations.

ABSTRACT

The disclosure relates to granulate formulations of pirfenidone and methods of making such formulations.

GRANULATE FORMULATION OF 5-METHYL-1-PHENYL-2-(1H)-PYRIDONE AND METHOD OF MAKING THE SAME

BACKGROUND

FIELD OF THE DISCLOSURE

[0001] The disclosure relates to granulate formulations of pirfenidone and methods of making granulate formulations of pirfenidone.

BRIEF DESCRIPTION OF RELATED TECHNOLOGY

[0002] 5-methyl-1-phenyl-2-(1H)-pyridone (also referred to as pirfenidone) is a non-peptide synthetic molecule with a molecular weight of 185.23 daltons. Its chemical elements are expressed as $C_{12}H_{11}NO$, and its structure is known. Pirfenidone has anti-fibrotic properties via: decreased TNF-α expression, decreased PDGF expression, and decreased collagen expression.

[0003] One important use of pirfenidone is known to be providing therapeutic benefits to patients suffering from fibrosis conditions such as Hermansky-Pudlak Syndrome (HPS) associated pulmonary fibrosis and idiopathic pulmonary fibrosis (IPF). Pirfenidone demonstrates a pharmacologic ability to prevent or remove excessive scar tissue found in fibrosis associated with injured tissues including that of lungs, skin, joints, kidneys, prostate glands, and livers. Published and unpublished basic and clinical research suggests that pirfenidone may safely slow or inhibit the progressive enlargement of fibrotic lesions, remove pre-existing fibrotic lesions, and prevent formation of new fibrotic lesions following tissue injuries.

[0004] It is understood that one mechanism by which pirfenidone exerts its therapeutic effects is modulating cytokine actions. Pirfenidone is a potent inhibitor of fibrogenic cytokines and TNF-α. It is well documented that pirfenidone inhibits excessive biosynthesis or release of various fibrogenic cytokines such as TGF-β1, bFGF, PDGF, and EGF. Zhang S et al., Australian and New England Journal Ophthalmology, 26; S74-S76, 1998. Experimental reports also show that pirfenidone blocks the synthesis and release of excessive amounts of TNF-α from macrophages and other cells. Cain et al., International Journal Immunopharmacology, 20:685-695 (1998).

SUMMARY OF THE DISCLOSURE

[0005] In accordance with an embodiment of the disclosure, a granulate formulation of pirfenidone can include granules of pirfenidone and glidant and optionally one or more additional pharmaceutically acceptable excipients admixed with the granules.

[0006] In accordance with an embodiment of the disclosure, a method of making a granulate formulation of 5-methyl-1-phenyl-2-(1H)-pyridone can include mixing the 5-methyl-1-phenyl-2-(1H)-pyridone and intragranular excipients in a fluid bed granulator to form granules, wherein the granules comprise a glidant; and optionally adding one or more extragranular excipients to the granules to form the granulate formulation.

[0007] In any of the foregoing embodiments, the glidant can be included intragranularly in an amount of at least 1% by weight based on the total weight of the formulation.

[0008] In any of the foregoing embodiments, the formulation can include an intragranular glidant and an extragranular disintegrant.

[0009] In any of the foregoing embodiments, the formulation can include granules with pirfenidone, filler, binder, and glidant. The formulation can further include in some embodiments, disintegrant, lubricant, and further glidant as extragranular components added to granules.

[0010] In accordance with an embodiment of the disclosure, a tablet can comprise the formulation of any of the foregoing embodiments or embodiments disclosed herein. In accordance with other embodiments of the disclosure, the tablet can consist of the formulation of any of the foregoing embodiments or embodiments disclosed herein. In accordance with other embodiments of the disclosure, the tablet can consist essentially of the formulation of any of the foregoing embodiments or embodiments disclosed herein.

[0010a] In one aspect, the present invention provides a granulate formulation of 5-methyl-1-phenyl-2-(1H)-pyridone, comprising: granules comprising 5-methyl-1-phenyl-2-(1H)-pyridone and a glidant; and one or more extragranular excipients comprising an extragranular glidant.

[0010b] In another aspect, the present invention provides a granulate formulation of 5-methyl-1-phenyl-2-(1H)-pyridone, comprising: granules comprising 5-methyl-1-phenyl-2-(1H)-pyridone in an amount of about 84.23 wt% based on the total weight of the formulation, a filler in an amount of about 6.21 wt% based on the total weight of the formulation, wherein the filler is microcrystalline cellulose, a glidant in an amount of about 2.05 wt% based on the total weight of the formulation, wherein the glidant is silica, and a binder in an amount of about 4.64 wt% based on the total weight of the formulation, wherein the binder is polyvinylpyrrolidone; and the formulation comprises as extragranular components: a disintegrant in an amount of about 1.89 wt% based on the total weight of the formulation, wherein the disintegrant is croscarmellose sodium, a lubricant in an amount of about 0.5 wt% based on the total weight of the formulation, wherein the lubricant is magnesium stearate, and an extragranular glidant in an amount of about 0.47 wt% based on the total weight of the formulation, wherein the extragranular glidant is silica.

[0010c] In another aspect, the present invention provides a granulate formulation of 5-methyl-1-phenyl-2-(1H)-pyridone, comprising: granules comprising 5-methyl-1-phenyl-2-(1H)-pyridone in an amount of about 80 wt% to about 95 wt% based on the total weight of the formulation, a filler in an amount of about 2 wt% to about 10 wt% based on the total weight of the formulation, herein the filler is microcrystalline cellulose, a glidant in an amount of about 2 wt% to about 5 wt% based on the total weight of the formulation, wherein the glidant is silica, and a binder in an amount of about 3 wt% to about 5 wt% based on the total weight of the formulation, wherein the binder is polyvinylpyrrolidone; and the formulation comprises as extragranular components: a disintegrant in an amount of about 1 wt% to about 2 wt% based on the total weight of the formulation, wherein the disintegrant is croscarmellose sodium, a lubricant in an amount of about 0.1 wt% to about 0.8 wt% based on the total weight of the formulation, wherein the lubricant is magnesium stearate, and an extragranular glidant in an amount of about 0.03 wt% to about 0.8 wt% based on the total weight of the formulation, wherein the extragranular glidant is silica.

[0010d] In another aspect, the present invention provides a unit dose comprising the formulation of the invention.

[0010e] In another aspect, the present invention provides a tablet comprising the formulation of the invention.

[0010f]In another aspect, the present invention provides a method of making a granulate formulation of 5-methyl-1-phenyl-2-(1H)-pyridone, comprising: mixing the 5-methyl-1-phenyl-2-(1H)-pyridone and intragranular excipients in a fluid bed granulator to form granules, wherein the intragranular excipients comprise a glidant and a wet-granulation fluid; adding an extragranular glidant to the granules; and optionally adding one or more extragranular excipients to the granules,wherein the granules comprise the glidant in an amount of about 2 wt% to about 5 wt% by weight based on the total weight of the formulation.

[0010g] In another aspect, the present invention provides a method of making a granulate formulation of 5-methyl-1-phenyl-2-(1H)-pyridone, comprising: mixing the 5-methyl-1-phenyl-2-(1H)-pyridone and intragranular excipients in a fluid bed granulator to form granules, wherein the intragranular excipients comprise a glidant and a wet-granulation fluid; and adding one or more extragranular excipients to the granules, wherein the one or more extragranular excipients comprise an extragranular glidant.

[0010h] In another aspect, the present invention provides a method of making a tablet, comprising: compressing the granulate formulation of the invention to a predetermined tablet thickness.

[0010i] In another aspect, the present invention provides a use of the granulate formulation of the invention for treatment of idiopathic pulmonary fibrosis.

[0010j] In another aspect, the present invention provides a use of the granulate formulation of the invention, for treatment of a disease selected from the group consisting of: idiopathic pulmonary fibrosis; pulmonary fibrosis; bronchiolitis obliterans; chronic lung transplant rejection; scleroderma; primary focal segmental glomerulosclerosis (FSGC); membranoproliferative glomerulonephritis (MPGN); idiopathic interstitial pneumonia; interstitial lung disease in systemic sclerosis; a fibrosis condition of the lung; autoimmune lung diseases; benign prostate hypertrophy; coronary infarction; myocardial infarction; atrial fibrillation; cerebral infarction; myocardiac fibrosis; musculoskeletal fibrosis; post-surgical adhesions; liver

cirrhosis; renal fibrotic disease; fibrotic vascular disease; Hermansky-Pudlak syndrome; neurofibromatosis; Alzheimer's disease; diabetic retinopathy; diabetic skin lesions; lymph node fibrosis associated with HIV; chronic obstructive pulmonary disease (COPD); inflammatory pulmonary fibrosis; rheumatoid arthritis; rheumatoid arthritis-associated interstitial lung disease; rheumatoid spondylitis; osteoarthritis; gout; arthritic conditions; sepsis; septic shock; endotoxic shock; gram-negative sepsis; toxic shock syndrome; myofacial pain syndrome (MPS); Shigellosis; asthma; adult respiratory distress syndrome; inflammatory bowel disease; Crohn's disease; psoriasis; eczema; ulcerative colitis; glomerular nephritis; chronic thyroiditis; Grave's disease; Ormond's disease; autoimmune gastritis; myasthenia gravis; autoimmune hemolytic anemia; autoimmune neutropenia; thrombocytopenia; pancreatic fibrosis; chronic active hepatitis including hepatic fibrosis; acute renal disease; chronic renal disease; renal fibrosis; diabetic nephropathy; irritable bowel syndrome; pyresis; restenosis; cerebral malaria; stroke; ischemic injury; neural trauma; Huntington's disease; Parkinson's disease; acute pain; chronic pain; allergies; allergic rhinitis; allergic conjunctivitis; cardiac hypertrophy, chronic heart failure; acute coronary syndrome; cachexia; malaria; leprosy; leishmaniasis; Lyme disease; Reiter's syndrome; acute synoviitis; muscle degeneration, bursitis; tendonitis; tenosynoviitis; herniated, ruptured, or prolapsed intervertebral disk syndrome; osteopetrosis; thrombosis; silicosis; pulmonary sarcosis; bone resorption diseases; osteoporosis; multiple myeloma-related bone disorders; cancer; metastatic breast carcinoma; colorectal carcinoma; malignant melanoma; gastric cancer; non-small cell lung cancer; graft-versus-host reaction; auto-immune diseases; multiple sclerosis; lupus; fibromyalgia; AIDS; viral diseases; Herpes Zoster; Herpes Simplex I or II; influenza virus; Severe Acute Respiratory Syndrome (SARS); cytomegalovirus; diabetes mellitus; proliferative disorders; benign hyperplasia; malignant hyperplasia; acute myelogenous leukemia; chronic myelogenous leukemia; Kaposi's sarcoma; metastatic melanoma; multiple myeloma; breast cancer; bone metastases; pain disorders; neuromuscular pain; headache; cancer pain; dental pain; arthritis pain; angiogenic disorders; solid tumor angiogenesis; ocular neovascularization; infantile hemangioma; edema, fever, analgesia, and pain associated with the cyclooxygenase or lipoxygenase signaling pathways or prostaglandin endoperoxide synthase-2; organ hypoxia; thrombin-induced platelet aggregation; and protozoal diseases.

[0010k] In another aspect, present invention provides a use of the granulate formulation of the invention for treatment of a fibrotic condition.

[0010l] In another aspect, the present invention provides a use of the granulate formulation of the invention for treatment of a disorder mediated by cytokines.

[0010m] In other aspects, the present invention provides use of the granulate formulation of the invention in the preparation of a medicament for any of the above-mentioned treatments; and the granulate formulation of the invention for use in any of the above-mentioned treatments.

RIEF DESCRIPTION OF THE DRAWINGS

[0011] Figure 1 is a schematic illustration of a process of forming a granulate formulation and film coated tablets in accordance with an embodiment of the disclosure;

[0012] Figure 2A is a photograph of a granulator bowl after processing a formulation without intragranular glidant;

[0013] Figure 2B is a photograph of a granulator bowl after processing a formulation with intragranular glidant in accordance with an embodiment of the disclosure;

[0014] Figure 3 is a graph illustrating the differences in particle size distribution of pirfenidone supplied from two different sources, Source 1 and Source 2;

[0015] Figure 4A is scanning electron microscope images of pirfenidone supplied from Source 2;

[0016] Figure 4B is scanning electron microscope images of pirfenidone supplied from Source 1;

[0017] Figure 5 is a graph illustrating the correlation between disintegration time and tablet core solid fraction for a formulation in accordance with embodiments of the disclosure;

[0018] Figure 6 is a graph illustrating the correlation between disintegration time and tablet core thickness for three dosage strengths of a formulation in accordance with embodiments of the disclosure;

[0019] Figure 7 is a graph illustrating the effect of compression pressure on tensile strength of a compressed dosage form in accordance with an embodiment of the disclosure;

[0020] Figure 8 is a graph illustrating the effect of solid fraction percentage on tensile strength of a compressed dosage form in accordance with an embodiment of the disclosure;

[0021] Figure 9 is a graph of percent drug substance dissolved as a function of time for dissolution of 267 mg commercial pirfenidone capsules in 900 mL HCl 0.1 N, acetate pH 4.5, or phosphate pH 6.8;

[0022] Figure 10 is a graph of percent drug substance dissolved as a function of time for dissolution of pirfenidone tablets in accordance with embodiments of the disclosure, having dosage strengths of 267 mg, 534 mg, and 801 mg in 900 mL HCl 0.1N;

[0023] Figure 11 is a graph of percent drug substance dissolved as a function of time for dissolution of pirfenidone tablets in accordance with embodiments of the disclosure, having dosage strengths of 267 mg, 534 mg, and 801 mg in 900 mL acetate at pH 4.5;

[0024] Figure 12 is a graph of percent drug substance dissolved as a function of time for dissolution of pirfenidone tablets in accordance with embodiments of the disclosure, having dosage strengths of 267 mg, 534 mg, and 801 mg in 900 mL phosphate at pH 6.8;

[0025] Figure 13 is a graph of percent drug substance dissolved as a function of time for dissolution of pirfenidone tablets in accordance with embodiments of the disclosure, having dosage strengths of 267 mg, 534 mg, and 801 mg in 900 mL distilled water;

[0026] Figure 14 is a graph of percent drug substance dissolved as a function of time for dissolution of 267 mg pirfenidone tablets in accordance with an embodiment of the disclosure, in 1000 mL distilled water;

[0027] Figure 15 is a graph of percent drug substance dissolved as a function of time for dissolution of 534 mg pirfenidone tablets in accordance with an embodiment of the disclosure, in 1000 mL distilled water;

[0028] Figure 16 is a graph of percent drug substance dissolved as a function of time for dissolution of 801 mg pirfenidone tablets in accordance with an embodiment of the disclosure, in 1000 mL distilled water;

[0029] Figure 17 is a graph of percent drug substance dissolved as a function of time for dissolution of 267 mg pirfenidone tablets in accordance with an embodiment of the disclosure, in 900 mL HCl 0.1 N, acetate pH 4.5, or phosphate pH 6.8;

[0030] Figure 18 is a graph of percent drug substance dissolved as a function of time for dissolution of 534 mg pirfenidone tablets in accordance with an embodiment of the disclosure, in 900 mL HCl 0.1 N, acetate pH 4.5, or phosphate pH 6.8;

[0031] Figure 19 is a graph of percent drug substance dissolved as a function of time for dissolution of 801 mg pirfenidone tablets in accordance with an embodiment of the disclosure, in 900 mL HCl 0.1 N, acetate pH 4.5, or phosphate pH 6.8;

[0032] Figure 20 is a graph of percent drug substance dissolved as a function of time for dissolution of 801 mg pirfenidone tablets in accordance with an embodiment of the disclosure, illustrating the effect of compression pressure and drug substance particle size on dissolution;

[0033] Figure 21 is a graph of percent drug substance dissolved as a function of time for dissolution of 534 mg pirfenidone tablets in accordance with an embodiment of the disclosure, illustrating the effect of compression force on early stage dissolution; and

[0034] Figure 22 is a graph of percent drug substance dissolved as a function of time for dissolution of 267 mg pirfenidone tablets in accordance with an embodiment of the disclosure, illustrating the effect of compression force on early stage dissolution.

DETAILED DESCRIPTION

[0035] Pirfenidone capsules are commercially available under the tradename Esbriet®, and are provided as a size #1 267 mg capsule. For many treatment regimens, including, for example, treatment of idiopathic pulmonary fibrosis, dosage amounts of 801 mg three times per day are often prescribed, requiring a patient to take 9 capsules per day. For some patients, tablet formulations can represent a more patient friendly and compliant regimen. For example, in accordance with embodiments of the disclosure, tablets can include 801 mg of pirfenidone, allowing for administration of one tablet, three times a day, or a total of three tablets. Tablets in accordance with embodiments of the disclosure can include from 100 mg to 1200 mg of pirfenidone. For example, a dosage strength can be 200 mg, 267 mg, 534 mg, 600 mg, or 801 mg pirfenidone for a unit dose in accordance with an embodiment of the disclosure. Variations of the dosage strength can ease patient administration, for example, when dose titrating. Tablets in accordance with embodiments of the disclosure can be film coated. The film coating can be colored, for example, to distinguish between different dosage strengths.

[0036] In view of the dosage requirements, oral dosage forms of pirfenidone, and particularly tablets, generally require high concentrations of pirfenidone in order to provide a tablet size that is of a manageable size for oral administration. Pirfenidone as an active ingredient, however, has poor powder flowability characteristics, e.g. for formulation processing. In view of the high concentrations of the active ingredient needed in the dosage form, there remains little room for excipients to aid in improving the flowability and processability of pirfenidone powder. Typically, formulation processes would utilize higher concentrations of excipients, particularly with difficult to process active ingredients. Such conventional formulation techniques, however, cannot be utilized where a high concentration of active is needed. It has been discovered that the

formulations disclosed herein provide a formulation that exhibits good flow properties during the granulation process, are capable of being compressed into tablets under standard compression conditions and result in stable tablets that resist cracking, yet maintain the desired dissolution properties.

[0037] Pirfenidone is a highly crystalline, non-hygroscopic solid with a melting point range between 106 °C to 112 °C. It has been found that the particle size of pirfenidone can vary by suppliers. Referring to Figure 3, for example, it was found that pirfenidone from two different suppliers, Source 1 and Source 2, had distinct particle size distributions. In particular, pirfenidone from Source 1 was found to have a d_{90} particle size between 50 μm to 64 μm, while pirfenidone supplied from Source 2 was found to have a d_{90} particle size between 114 μm to 151 μm. Figures 4A and 4B are scanning electron microscopy images that further illustrate the differences in particle sizes observed with the differently sourced pirfenidone. As shown in Figures 4A and 4B, pirfenidone consists of irregular shaped primary particles. The shape of the primary particles is comparable between the two sources. The smaller primary particles were found to have a tendency to form agglomerates. Higher levels of agglomerates were found in Source 1 as compared to Source 2 and in some batches of Source 1 drug substance, larger-sized agglomerates were found.

[0038] Particle size variations of the drug substance were found to affect the hardness (tensile strength) of a tablet formed from the granulate formulation. It was, however, surprisingly discovered that the solid fraction of the tablets in accordance with the disclosure, and not the tensile strength, influenced the drug release characteristics. Thus, it was determined that tablet thickness, which controls the solid fraction, can be used as a parameter in the tablet compression step instead of tablet hardness to ensure desired drug release characteristics. Figures 5 and 6 illustrate the correlation between disintegration time and solid fraction and tablet thickness respectively, for a tablet in accordance with an embodiment of the disclosure.

[0039] It has been further discovered that methods of forming pirfenidone granulations and compressing such formulations into tablets can render the properties of the resulting tablets sensitive to particle size variations in the active ingredient and the water content of the formulation produced through various wet granulation methods, such as high shear mixing methods. Surprisingly, processing pirfenidone formulations in accordance with embodiments of

the disclosure using a fluid bed granulation process can allow for a formulation process that is significantly less sensitive to moisture content of the granulate and which can accommodate variations in particle size of the active ingredient. As discussed in detail below, methods of forming the granulate formulation in accordance with embodiments of the disclosure can also allow for subsequent formation of tablets that are free of micro-cracks and have sufficient hardness, despite variations in the particle size of the drug substance that may occur, e.g. from supplier to supplier. This can advantageously provide a more robust commercial scale process that can accommodate variations in the particle size without a need to change the tablet manufacturing process or tablet compression conditions.

[0040] In accordance with embodiments of the disclosure, a granulate formulation can include granules which include pirfenidone and one or more pharmaceutically acceptable excipients. As used herein, "intragranular components" refers to the ingredients included in the granule. In addition to the granules, the granulate formulation can include one or more excipients added to the granules as extragranular components. As used herein, "extragranular components" refers to ingredients added to the as-formed granules. In various embodiments, the formulation can include pirfenidone and a glidant as intragranular components. It has been found that inclusion of glidant within the granule in an amount of at least about 1% by weight of the formulation advantageously improves the flowability and processability of the granules and the granulate formulations. In various embodiments, the formulations include an effective amount of intragranular glidant to improve powder and/or granule flow characteristics, for example, as measured by a flow function coefficient of about 4 to about 20, about 5 to about 15, or about 10 to about 14. In various embodiments, the pre-granulation powders, granules, and/or granule formulation can have a flow function coefficient of about 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20.

[0041] Typically, glidants are utilized only extragranularly to improve the flow of the as-formed granules in the tableting machine, but are not conventionally used or expected to improve flow of a drug substance during granulation. However, it has been advantageously and surprisingly discovered that use of an intragranular glidant in the present formulation with pirfenidone can improve flow of the intragranular components in powder form, improve processing and flow of the granules, and improve flow of the granules with or without the addition of extragranular components during compression, such as in a tableting process. In

some embodiments, the formulations of the disclosure can be compressed, for example tableted, without the need for the addition of glidant as an extragranular component.

[0042] Referring to Figures 2A and 2B, formulations with and without glidant were tested. A powder mixture of pirfenidone, filler and glidant was granulated in a granulator bowl using a wet granulation process in which binder was sprayed onto the mixture. It was observed that a reduced amount of granules and residual powder that stuck to the sides of the granulator bowl when the granules contained the intragranular glidant (Figure 2B). As illustrated in Figure 2A, without an intragranular glidant, the granules were observed as sticking to the sides of the bowl and a significant amount of residual powder remained stuck to the granulator bowl, which is indicative of the cohesive nature of the formulation.

[0043] Additional excipients can be included in some embodiments. Examples of excipients include binders, fillers, disintegrants, lubricants, and further glidants, which can be provided as intragranular and/or extragranular components. For example, in an embodiment, a formulation includes pirfenidone, filler, binder, and a glidant as intragranular components, and a disintegrant, lubricant, and further glidant as extragranular components.

[0044] For dosage forms that include coatings, such as film coated tablets, unless specified otherwise, weight by weight percentages (w/w%) of pirfenidone or excipients in the formulation as used herein refer to the weight based on the total weight of the core (e.g., tablet core) and exclude any weight of the exterior coatings.

[0045] A formulation can include about 60 wt% to 95 wt% pirfenidone based on the total weight of the formulation. Other suitable amounts include about 70 wt% to about 95 wt%, about 65 wt% to about 90 wt%, about 80 wt% to about 95 wt%. For example, the formulations can include pirfenidone in an amount of about 60, 62, 64, 66, 68, 70, 72, 74, 76, 78, 80, 82, 84, 86, 88, 90, 92 94 and 95 wt% based on the total weight of the formulation. In accordance with embodiments of the disclosure, the unit doses can be provided with a dosage amount of pirfenidone in a range of about 100 mg to about 1100 mg. For example, dosage strengths can include 200 mg, 267 mg, 534 mg, 600 mg, and 801 mg pirfenidone. In alternative embodiments, dosage strengths can include 266 mg, 268 mg, 533 mg, 535 mg, and 800 mg pirfenidone. In an embodiment, the unit dose is a compressed dosage form, for example, tablets.

[0046] In accordance with embodiments of the disclosure, formulations of pirfenidone can include one or more excipients selected from the group consisting of binders, disintegrants, glidants, lubricants, and fillers. Excipients conventionally used as binders, fillers, glidants, lubricants, and fillers can be used in the formulations of the disclosure. Example listings of suitable excipients are provided below.

[0047] The binder can be selected from the group consisting of hydroxymethyl cellulose, hydroxypropylcellulose, polyvinylpyrrolidone, calcium carbonate, dicalcium phosphate, carbomers, cellulose acetate phthalates, copovidone, hydroxypropyl methyl cellulose, ethylene glycol and vinyl glycol grafted copolymer, isomalt, poloxamer, polyethylene oxide, polymethacrylates, and combinations thereof.

[0048] The binder can be included in an amount in a range of about 1 wt% to about 10 wt%, about 2 wt% to about 10 wt%, about 2 wt% to about 5 wt%, about 4 wt% to about 8 wt%, about 3 wt% to about 7 wt, and about 3 wt% to about 5 wt%, based on the total weight of the formulation. Other suitable amounts of binder include about 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7, 7.5, 8, 8.5, 9, 9.5, and 10 wt% based on the total weight of the formulation. It has been advantageously found that binder amounts greater than 4 wt% can improve granule flowability and compaction behavior during tableting. Binder amounts ranging from about 3.9 wt% to about 4.8 wt% were found to improve compaction behavior of the granules without significant effect on the dissolution and disintegration characteristics of the formulation. The binder amounts are contemplated for any suitable binder, including polyvinylpyrrolidone.

[0049] The disintegrant can be selected from the group consisting of agar-agar, algins, calcium carbonate, carboxmethylcellulose and salts thereof, cellulose, clays, corn starch, croscarmellose sodium, crospovidone, gums, methyl cellulose, polacrilin potassium, sodium alginate, cross-linked polyvinylpyrrolidone, sodium starch glycolate, starch, and combinations thereof. In various embodiments, the disintegrant can be provided both within the granules (intragranularly) and extragranularly in a granulate formulation. Alternatively, the disintegrant can be included only intragranularly or only extragranularly.

[0050] The disintegrant can be included in an amount in a range of about 0 wt% to about 10 wt%, 0 wt% to about 10 wt%, about 1 wt% to about 10 wt%, about 2 wt% to about 10 wt%, about 2 wt% to about 5 wt%, about 4 wt% to about 8 wt%, about 3 wt% to about 7 wt, and about

3 wt% to about 5 wt%, based on the total weight of the formulation. Other suitable amounts of disintegrant include about 0, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7, 7.5, 8, 8.5, 9, 9.5, and 10 wt%.

[0051] The lubricant can be selected from the group consisting of agar, calcium stearate, ethyl oleate, ethyl laureate, glycerin, glyceryl behenate, glyceryl palmitostearate, hydrogenated vegetable oil, magnesium oxide, magnesium stearate, mannitol, poloxamer, glycols, sodium benzoate, sodium lauryl sulfate, sodium stearylstearate, sorbitol, stearic acid, talc, zinc stearate, and combinations thereof.

[0052] The lubricant can be included in an amount in a range of about 0.05 wt% to about 2 wt%, about 0.1 wt% to about 1.8 wt%, about 0.5 wt% to about 1.5 wt%, about 1 wt% to about 2 wt%, about 0.05 wt% to about 0.5 wt%, about 0.1 wt% to about 0.8 wt%, or about 0.2 wt% to about 0.6 wt%, based on the total weight of the formulation. Other suitable amounts of lubricant include about 0.05, 0.06, 0.07, 0.08, 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1, 1.2, 1.4, 1.6, 1.8, and 2 wt%, based on the total weight of the formulation.

[0053] The filler can be selected from the group consisting of calcium carbonate, calcium phosphate, dibasic calcium phosphate, calcium silicate, tribasic calcium sulfate, calcium carboxymethylcellulose and salts thereof, cellulose, dextrin derivatives, dextrin, dextrose, fructose, isomalt, kaolin, lactitol, lactose, magnesium carbonate, magnesium oxide, maltitol, maltodextrins, maltose, mannitol, microcrystalline cellulose, sodium bicarbonate, sodium carbonate, sorbitol, starch, sucrose, sugar, xylitol, and combinations thereof.

[0054] The filler can be included in an amount in a range of about 2 wt% to about 30 wt%, about 4 wt% to about 20 wt%, about 10 wt% to about 30 wt%, about 2 wt% to about 10 wt%, and about 6 wt% to about 15 wt% based on the total weight of the formulation. Other suitable amounts include, about 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, and 30 wt% based on the total weight of the formulation. The filler amounts are contemplated for any suitable filler, including microcrystalline cellulose.

[0055] The glidant can be selected from the group consisting of silica, fumed silica, silicified cellulose, sodium stearate, magnesium aluminum silicate, pyrogenic silica, hydrated sodium silioaluminate, cellulose, calcium phosphate, sodium lauryl sulfate, pregelatinized starch, talc, and physical or coprocessed combinations thereof. The glidant can be silica, and can be a

hydrophilic fumed silica (a.k.a. colloidal silicon dioxide) . The glidant can be provided intragranularly and optionally extragranularly. In embodiments in which the glidant is provided both intragranularly and extragranularly, the glidant can be the same or different materials.

[0056] The glidant can be included intragranularly in an amount, based on the total weight of the formulation, of at least about 1 wt%, at least about 1.5 wt%, at least about 2 wt%, at least about 2.5 wt%, at least about 3 wt%, at least about 3.5 wt% or at least about 4 wt%. For example, when included intragranularly, the glidant can be in an amount of about 1 wt% to about 5 wt%, about 1.5 wt% to about 4.5 wt%, about 1.5 wt% to about 3.5 wt%, about 2 wt% to about 5 wt%, or about 1 wt% to about 4 wt%. Other suitable amounts of intragranular glidant includes about 1, 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, 1.9, 2, 2.1, 2.2, 2.3, 2.4, 2.5, 2.6, 2.7, 2.8, 2.9, 3, 3.1, 3.2, 3.3, 3.4, 3.5, 3.6, 3.7, 3.8, 3.9, 4, 4.1, 4.2, 4.3, 4.4, 4.5, 4.6, 4.7, 4.8, 4.9, and 5 wt%, based on the total weight of the formulation.

[0057] The glidant can be included extragranularly in an amount of about 0 wt% to about 5 wt%, 0 wt% to about 5 wt%, about 0.01wt% to about 1wt%, about 0.03wt% to about 0.8 wt%, about 1 wt% to about 5 wt%, about 0.01 wt% to about 0.05 wt%, about 0.5 wt% to about 3 wt%, about 0.01 wt % to about 0.2 wt%, and about 0.05 wt% to about 1 wt%. Other suitable amounts of extragranular glidant include about 0, 0.01, 0.02, 0.04, 0.06, 0.08, 0.1, 0.2, 0.4, 0.6, 0.8, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, and 5 wt%, based on the total weight of the formulation. The glidant amounts are contemplated for any suitable glidant, including silica.

[0058] In one type of embodiment, the extragranular components make up 10 wt% or less of a compressed formulation. The extragranular components can be 10 wt% or less, 10 wt% or less, 8 wt% or less, 7 wt% or less, 6 wt% or less, 5 wt% or less, 4 wt% or less, 3 wt% or less, 2 wt% or less, or in a range of 0.01 wt% to 10 wt%, or 0.01 to 8 wt%, or 0.01 to 6 wt%, or 0.01 to 5 wt%, or 0.01 to 4 wt%, or 0.01 to 3 wt%, or 0.01 to 2 wt%, or 0.01 to 1 wt%, for example.

[0059] In various embodiments, the granulate formulation can be compressed into a tablet formulation. It has advantageously been discovered that tablets in accordance with the disclosure have drug release characteristics that correlate to the solid fraction. Solid fraction is a normalized process parameter calculated using the dimension of the tablet core (size of the compression tooling and thickness of the tablet), tablet weight, and true density (in contrast to bulk density) of the final blend. During a standard tablet compression operation, for a given

dosage strength, all the other factors that define the solid fraction remain unchanged, with the exception of tablet thickness. Therefore, it has been determined that controlling the thickness of the tablet in a standard tablet compression operation can be used to target a predefined solid fraction during tablet compression, which in turn can be used to target a predefined pirfenidone release characteristic.

[0060] In various embodiments, the formulations are immediate release formulations. In such embodiments, it can be desirable to have release of at least 80% of the drug substance in approximately 15 minutes. To achieve such release parameters, the compressed unit doses, for example tablets, can have a solid fraction of at least 80%. In some embodiments, the solid fraction is greater than 80%. For example, the unit dose can have a solid fraction of about 80% to about 95%, about 85% to about 90%, about 90% to about 95%, greater than about 80% to 90%, about 81% to about 95%, and about 82% to about 94%. Other suitable solid fractions include 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, and 95%.

[0061] In general, a tablet in accordance with embodiments of the disclosure can have a thickness of about 2 mm to about 10 mm, about 2 mm to about 8 mm, about 3 mm to about 8 mm, and about 5 mm to about 10 mm. While the relationship between disintegration time and solid fraction generally has not varied depending on dosage amount in the embodiments tested, there has been some variation when utilizing tablet thickness as a parameter as shown in Figure 6. It has been found that drug release of at least about 80% in 15 minutes can be achieved in a compressed dosage form having 801 mg of pirfenidone with a tablet thickness of about 5 mm to about 10 mm; in a compressed dosage form having 534 mg of pirfenidone with a tablet thickness of about 3 mm to about 8 mm; and in a compressed dosage form having 267 mg of pirfenidone with a tablet thickness of about 2 mm to about 8 mm.

[0062] Referring to Figure 1, in an embodiment, a process for forming a granulation in accordance with an embodiment of the disclosure can include mixing pirfenidone with one or more excipients using fluid bed granulation. In various embodiments, the pirfenidone is mixed with a glidant using fluid bed granulation to form an granules. One or more excipients can be added to the granules (extragranularly). It has been advantageously found that use of a fluid bed granulation process can not only improve the processability of the formulation and toleration of

pirfenidone particle size variation, but also provide improved tolerance of moisture content in the granulation. For example, when utilizing high shear wet-granulation methods, it was observed that the compressibility of the granules were dependent on a moisture content, requiring a moisture content as measured by loss on drying of 1.5% to 2.0% in order to be processed into tablet cores having suitable physical characteristics (tablet compression to suitable hardness values). However, methods in accordance with the disclosure utilizing fluid bed granulation processing are less sensitive to moisture content, allowing for moisture contents of less than 3 %, for example, 0% to 2.9%, thereby accommodating variations (both over- and under- drying) of the granules while allowing for tablets with suitable physical characteristics to be achieved.

[0063] Formulations processed with conventional high-shear wet-granulation techniques were also found to be sensitive to changes in pirfenidone particle size distribution from different sources of pirfenidone, resulting in tablets with poor hardness values and oftentimes with microcracks forming in the tablets. By comparison, formulations and methods in accordance with the disclosure were significantly less sensitive to pirfenidone particle size changes and moisture contents, as discussed in detail below. For example, fluid bed granulation can be used. Fluid bed granulation can allow for a multiple-step wet granulation process performed in the same vessel, for example, to do one or more of pre-heat, granulate, and dry the powders.

[0064] In an example embodiment, a method of making a formulation in accordance with the disclosure can include mixing pirfenidone and the intragranular excipients to form granules. In various embodiments, the pirfenidone can be mixed with a glidant and a binder or binder solution or suspension to form granules. The granules can further include a filler mixed with the pirfenidone and glidant. In various embodiments, the binder can be added as a solution or suspension. For example, the binder can be sprayed onto the pirfenidone and intragranular excipients. The binder can be provided, for example, as an aqueous solution, aqueous suspension, alcoholic solution, alcoholic suspension, or in an aqueous-alcoholic mixture, which can be a solution or suspension. In some embodiments, the pirfenidone and intragranular excipients can be premixed prior to adding the binder.

[0065] The granules can be dried to a target moisture content. For example, drying can be used to remove excess moisture that may have been introduced for example from a binder solution or suspension. Mixing and drying can be completed, for example, using a fluid bed

granulator. The granules can then be screened in some embodiments. For example, a 2 mm screen can be used to aid in delumping of the granules. The dried and optionally screened granules can then be mixed with extragranular components. In an embodiment, this can include mixing the granules with a disintegrant and/or a further amount of glidant and/or a lubricant. In an embodiment, the granules are mixed with a disintegrant and further amount of glidant and then the resulting mixture is mixed with a lubricant. In another embodiment, the extragranular components are premixed and added to the granules in a single step.

[0066] The method can optionally include heating the pirfenidone and excipients (intragranular) prior to and/or during addition of the solution or suspension of binder. The preheating can aid in ensuring the mixture is in a fluidized, mixed state at the time of initiation of the spraying of the binder.

[0067] Where multiple extragranular components are added to the granules, the additions can be made simultaneously or serially. For example, in an embodiment, disintegrant, lubricant, and additional glidant are added extragranularly in a single step. In another embodiment, disintegrant and glidant are added extragranularly in a first step and blended and then lubricant is added in a second step with further blending. Any suitable number of addition steps can be utilized.

[0068] Optionally, any or all of the drug substance and excipients of the formulation can be premixed and/or screened prior to granulation, for example, prior to charging the components into a granulator bowl. Premixing excipients at the given stages (for example) prior to loading the intragranular components into a mixer or granulator or adding the extragranular excipients to the granules can aid in ensuring good distribution of the components. Screening the excipients and/or premixtures prior to addition can further aid in delump the formulation components prior to loading into the granulator.

[0069] In various embodiments, the granulate formulation can be compressed into a compressed dosage form, e.g. a tablet. For example, the formulation can be compressed using a compression pressure of about 50 MPa to about 500 MPa, about 100 MPa to about 400 MPa, about 200 MPa to about 300 MPa, about 100 MPa to about 170 MPa, and about 75 MPa to about 200 MPa. Other suitable compression pressures include about 50, 55, 60, 65, 70 75, 80, 85, 90, 95, 00, 110, 120, 130, 140, 150, 160, 170, 180, 190, 200, 210, 220, 230, 240, 250, 260, 270, 280,

290, 300, 310, 320, 330, 340, 350, 360, 370, 380, 390, 400, 410, 420, 430, 440, 450, 460, 470, 480, 490, and 500 MPa.

[0070] In some embodiments, a pre-compression force can be applied during the compression process (e.g. tablet making) for a time prior to application of the full main compression force. For example, a pre-compression force of 20-30% of the main compression force can be applied.

[0071] Compression force can affect the dissolution profile in the early stages of dissolution, generally within the initial 15 minutes. Figures 21 and 22 illustrate the changes in the early stage dissolution profile for two dosage strengths (534 mg tablet and 267 mg tablet, respectively) that can result from changing the compression force.

[0072] In various embodiments, the compressed dosage form is further coated with a film coating. For example, tablets can be coated with a film coating. In some embodiments, the coating is an immediate release coating. Exemplary coatings including, for example, Opadry II Yellow, Opadry II Pink, and Opadry II Purple. Coatings can be used, for example, to color the dosage form to identify by color, different dosage amounts. Coatings can also include light shielding agents in some embodiments, which can aid in maintaining the photostability of the dosage form. Any coatings and methods of coating compressed dosage forms can be used. Coatings can include one or more of titanium dioxide, iron oxide, talc, polyethylene glycol, and polyvinyl alcohol. The coatings can be applied as a solution using any suitable coating techniques. The coatings can be colored, for example, to differentiate dosage strengths. In various embodiments, the coloring can be provided by a color iron oxide, for example, iron oxide black, iron oxide red, iron oxide yellow, and combinations thereof. In various embodiments, the coatings add 1% to 5% weight to the formulation, for example, a tablet core. Any suitable coating amounts, coat weights, and added weight percentages can be used.

[0073] Advantageously, formulations in accordance with embodiments of the disclosure can be compressed into a compressed dosage form without formation of microcracks and with suitable tablet physical properties including tensile strength. The methods and formulations in accordance with the disclosure are capable of tolerating differences in particle size of the drug substance. Figures 3 and 4 illustrate the differences in the particle size distribution of drug substance pirfenidone provided by two different suppliers. As shown in detail in the examples, tabletability and compactability of the formulation can be affected by the differences in particle

size. Formulations and methods of making such formulations, disclosed herein, for example, using fluid bed granulation, can allow for the formation of compressed dosage forms having suitable physical characteristics despite the variability in particle size of the drug substance. This can allow for a commercial scale process and formulation that can accommodate drug substance regardless of the supplier and any variations in particle size. Further, while it was observed that the particle size variation could result in differences in the tensile strength, it was determined that such differences did not affect the dissolution behavior of the dosage form, which instead was controlled by the solid fraction.

[0074] Formulations in accordance with embodiments of the disclosure can comprise any combination of excipients disclosed herein. Formulations in accordance with embodiments of the disclosure can consist of any combination of excipients disclosed herein. Formulations in accordance with embodiments of the disclosure can consist essentially of any combination of excipients disclosed herein. For example, a formulation in accordance with an embodiment of the disclosure can consist of pirfenidone, intragranular glidant, binder, and optionally one or more of a filler, disintegrant, further glidant, and lubricant.

[0075] Any of the foregoing embodiments of the granulate formulation can be provided in an oral dosage form. For example, any of the granulate formulations disclosed herein can be provided as a compressed dosage form, e.g. a tablet. Tablets can comprise any combination of excipients disclosed herein. Tablets can consist of any combination of excipients disclosed herein. Tablets can consist essentially of any combination of excipients disclosed herein. For example, tablets in accordance with embodiments of the disclosure can consist of pirfenidone, intragranular glidant, binder, and optionally one or more of a filler, disintegrant, further glidant, and lubricant.

Therapeutic Indications

[0076] One embodiment of this disclosure provides methods for treating fibrotic conditions and other cytokine-mediated disorders. These methods comprise administering the formulation of this disclosure to a patient in need thereof. As used herein, a patient "in need of pirfenidone therapy" is a patient who would benefit from administration of pirfenidone. The patient may be suffering from any disease or condition for which pirfenidone therapy may be useful in ameliorating symptoms. Pirfenidone is a known anti-fibrotic agent, so such disorders include

fibrotic disorders, such as fibrotic disorders of the lung, kidney, liver, heart, or other organs. Other disorders that would benefit from therapy with pirfenidone include inflammatory disorders or autoimmune disorders. Yet other disorders that would benefit from therapy with pirfenidone include diseases that result in fibrosis, or where accompanying fibrosis is responsible in part for symptoms or complications of the disease, such as infarctions (tissue death), infection, cancer, cirrhosis, and the like. For example, such diseases or conditions include pulmonary fibrosis, idiopathic pulmonary fibrosis, bronchiolitis obliterans, chronic lung transplant rejection, scleroderma, primary focal segmental glomerulosclerosis (FSGC) or membranoproliferative glomerulonephritis (MPGN), idiopathic interstitial pneumonia, interstitial lung disease in systemic sclerosis, a fibrosis condition of the lung, autoimmune lung diseases, benign prostate hypertrophy, coronary or myocardial infarction, atrial fibrillation, cerebral infarction, myocardiac fibrosis, musculoskeletal fibrosis, post-surgical adhesions, liver cirrhosis, renal fibrotic disease, fibrotic vascular disease, scleroderma, Hermansky-Pudlak syndrome, neurofibromatosis, Alzheimer's disease, diabetic retinopathy, and/or skin lesions, lymph node fibrosis associated with HIV, chronic obstructive pulmonary disease (COPD), inflammatory pulmonary fibrosis, rheumatoid arthritis; rheumatoid spondylitis; osteoarthritis; gout, other arthritic conditions; sepsis; septic shock; endotoxic shock; gram-negative sepsis; toxic shock syndrome; myofacial pain syndrome (MPS); Shigellosis; asthma; adult respiratory distress syndrome; inflammatory bowel disease; Crohn's disease; psoriasis; eczema; ulcerative colitis; glomerular nephritis; scleroderma; chronic thyroiditis; Grave's disease; Ormond's disease; autoimmune gastritis; myasthenia gravis; autoimmune hemolytic anemia; autoimmune neutropenia; thrombocytopenia; pancreatic fibrosis; chronic active hepatitis including hepatic fibrosis; acute and chronic renal disease; renal fibrosis; diabetic nephropathy; irritable bowel syndrome; pyresis; restenosis; cerebral malaria; stroke and ischemic injury; neural trauma; Alzheimer's disease; Huntington's disease; Parkinson's disease; acute and chronic pain; allergies, including allergic rhinitis and allergic conjunctivitis; cardiac hypertrophy, chronic heart failure; acute coronary syndrome; cachexia; malaria; leprosy; leishmaniasis; Lyme disease; Reiter's syndrome; acute synoviitis; muscle degeneration, bursitis; tendonitis; tenosynoviitis; herniated, ruptured, or prolapsed intervertebral disk syndrome; osteopetrosis; thrombosis; silicosis; pulmonary sarcosis; bone resorption diseases, such as osteoporosis or multiple myeloma-related bone disorders; cancer, including but not limited to metastatic breast carcinoma, colorectal

carcinoma, malignant melanoma, gastric cancer, and non-small cell lung cancer; graft-versus-host reaction; and auto-immune diseases, such as multiple sclerosis, lupus and fibromyalgia; AIDS and other viral diseases such as Herpes Zoster, Herpes Simplex I or II, influenza virus, Severe Acute Respiratory Syndrome (SARS) and cytomegalovirus; and diabetes mellitus. In addition, the methods of the embodiments can be used to treat proliferative disorders (including both benign and malignant hyperplasias), including acute myelogenous leukemia, chronic myelogenous leukemia, Kaposi's sarcoma, metastatic melanoma, multiple myeloma, breast cancer, including metastatic breast carcinoma; colorectal. carcinoma; malignant melanoma; gastric cancer; non-small cell lung cancer (NSCLC); bone metastases, and the like; pain disorders including neuromuscular pain, headache, cancer pain, dental pain, and arthritis pain; angiogenic disorders including solid tumor angiogenesis, ocular neovascularization, and infantile hemangioma; conditions associated with the cyclooxygenase and lipoxygenase signaling pathways, including conditions associated with prostaglandin endoperoxide synthase-2 (including edema, fever, analgesia, and pain); organ hypoxia; thrombin-induced platelet aggregation; protozoal diseases. For example, IPF and scleroderma (or systemic sclerosis) associated interstitial lung disease (SSc-ILD) share overlapping pathologic pathways, most notably the activation and proliferation of fibroblasts, expression of fibrogenic cytokines and growth factors, and progressive interstitial fibrosis (Tzouvelekis et al. 2005; Castro and Jimenez 2010; Collard et al. 2010; Hummers 2010; van den Blink et al. 2010; Richards et al. 2012; Vij and Noth 2012). IPF and SSc-ILD also have biomarkers in common, including CCL 18, SP-A, SP D, KL 6, ICAM-1, VCAM 1, CCL 2, YKL-40, and vWF

[0077] In any of the methods or uses described herein, the patient may suffer from a disease selected from the group consisting of lung transplantation/chronic rejection, bronchiolitis obliterans, scleroderma, Primary focal segmental glomerulosclerosis (FSGS), membranoproliferative glomerulonephritis (MPGN), Pneumotosis intestinalis, Susac's syndrome, microvascular impairment during chronic catheterization, Hamartomatous disease, blood spinal cord barrier dysfunction following spinal cord injury, corneal perforation, paraneoplastic disease, rhabdomyolysis, pulmonary capillaritis, chronic hyperhomocysteinemia, frontal-subcortical syndrome, Wegener's granulomatosis, acute intestinal microvascular dysfunction, atherosclerotic disease, keratitis, episcleritis/scleritis, cystic fibrosis, polycystic kidney disease, sickle cell disease, dementia, diabetic ulcer, microangiopathy or small vessel disease, hypothyroidism,

thrombotic thrombocytopenic purpura, ischemia-reperfusion injury and haemolytic uraemic syndrome.

[0078] In any of the methods or uses described herein, the patient may suffer from a disease or disorder selected from one or more of "autoimmune" disorders of the central nervous system (CNS); a dementia that is not Alzheimer's Disease; a patient in need of pirfenidone therapy; a person who would benefit from pirfenidone administration optionally with the proviso that the patient is not suffering from idiopathic pulmonary fibrosis; Absence seizure; acquired immunodeficiency syndrome (AIDS) encephalitis; acute adult respiratory distress syndrome; acute coronary syndrome; acute intestinal microvascular dysfunction; acute myelogenous leukemia; acute or chronic pain; acute or chronic renal disease; acute synoviitis; acute tissue injury; adenovirus infection; adult respiratory distress syndrome; advanced benign prostate hypertrophy (BPH non-cancerous fibrous enlargement of the male prostate gland); AIDS; airway basement membrane collagen deposition; airway hyperresponsiveness; airway inflammation; airway remodeling; akinetic seizure; allergen-induced chronic airway inflammation; allergic and traumatic disorders; allergic conjunctivitis; allergic rhinitis; allergies; allograft vasculopathy; Alzheimer's disease; amylotrophic lateral sclerosis; an acute ischemic event; an atherosclerotic disease; an autoimmune disease; an inflammatory disease; analgesia; angiogenic disorders; arresting the proliferation of and then killing abnormal cells of neoplastic tissue without serious or fatal injury to healthy normal cells and tissues; arteriosclerosis; arthritic conditions; arthritis caused by a microbial infection; arthritis caused by a parasite; arthritis induced by medical products or drugs (including small synthetic molecules as well as purified natural or synthesized peptides or proteins); arthritis pain; ascites; asthma; atherosclerosis; atherosclerosis of the brain vasculature; atherosclerosis of the cardiac vasculature; atherosclerosis of the peripheral vasculature; atherosclerosis of the renal vasculature; atherosclerotic disease; atonic seizure; atrial fibrillation; auto-immune diseases; autoimmune gastritis; autoimmune hemolytic anemia; autoimmune lung diseases; autoimmune neutropenia; bacterial infection; bacterial meningitis; benign and malignant hyperplasias; benign and malignant tumors lymphomas; benign or malignant hyperplasias; benign prostate hypertrophy; bleomycin-induced pulmonary fibrosis; Blood spinal cord barrier dysfunction following spinal cord injury; bone metastases; bone resorption diseases; brain concussion or contusion; brain edema; breast cancer; Bronchial asthma; bronchiolitis obliterans; bursitis; cachexia; cancer; cancer pain; cardiac fibrosis; cardiac

hypertrophy; cardiovascular damage; carotid initimal hyperplasia after balloon angioplasty; cerebral infarction; cerebral malaria; Chagas disease; chronic active hepatitis; chronic bronchitis; chronic glomerulonephritis; chronic heart failure; chronic hyperhomocysteinemia; chronic lung transplant rejection; chronic myelogenous leukemia; chronic obstructive pulmonary disease; chronic thyroiditis; classical allergic response; CNS stroke and infarction; colorectal carcinoma; conditions associated with cytokine activity; conditions associated with p38 activity; conditions associated with prostaglandin endoperoxide synthase-2; conditions associated with the cyclooxygenase or lipoxygenase signaling pathways; Congestive heart failure; corneal perforation; coronary or myocardial infarction; coronary restenosis; Crohn's disease; cystic fibrosis; cytomegalovirus; dementia; dental pain; dermal blisters; dermal burns; dermal damage; dermal fibrosis; dermal scars; diabetes mellitus; diabetic mellitus (type II); diabetic nephropathy; diabetic retinopathy; diabetic ulcer; eczema; edema; endotoxemia shock syndrome; endotoxic shock; eosinophilic granuloma; epileptic condition; episcleritis/scleritis; excessive cellular proliferation; excluding acute myocardial infarction; excluding lung transplantation; excluding wound healing; extravasation from blood vessels or blood vessel rupture with hemorrhage into adjacent tissues occlusions (clots or stenosis) of blood vessels; fever; fibromyalgia; fibrosis; fibrosis accompanying tissue injury from cancer; fibrosis accompanying tissue injury from cirrhosis; fibrosis accompanying tissue injury from infarction; fibrosis accompanying tissue injury from infection; fibrosis associated with injured tissues including that of joints; fibrosis associated with injured tissues including that of kidneys; fibrosis associated with injured tissues including that of livers; fibrosis associated with injured tissues including that of lungs; fibrosis associated with injured tissues including that of prostate glands; fibrosis associated with injured tissues including that of skin; fibrosis secondary to asthma; fibrosis secondary to graft-versus-host reaction; fibrosis secondary to lung cancer; fibrosis secondary to viral diseases; fibrotic conditions and other disorders mediated by cytokines; fibrotic disorder; fibrotic disorder of the heart; fibrotic disorder of the kidney; fibrotic disorder of the liver; fibrotic disorder of the lung; fibrotic vascular disease; formation of new fibrotic lesions following tissue injuries; frontal-subcortical syndrome; fungal infections; gastric cancer; general or dermal traumatic or contusion injuries; glomerular nephritis; goblet cell hyperplasia; gout; graft rejection; graft-host disease; graft-host disease following bone marrow transplantation; graft-versus-host reaction; gram-negative sepsis; Grand mal seizure; Grave's disease; haemolytic uraemic syndrome;

Hamartomatous disease; headache; heart failure; hemorrhagic shock; Hermansky-Pudlak syndrome; Hermansky-Pudlak Syndrome (HPS) associated pulmonary fibrosis; herniated, ruptured, or prolapsed intervertebral disk syndrome; Herpes Simplex I or II; Herpes simplex infection; Herpes viral infections; Herpes Zoster; HIV viral infection; Huntington's disease; hyperplasia of mucus glands; hypertrophic (post burn injury) scars; hypertrophic scarring (keloids); hypothyroidism; idiopathic interstitial pneumonia; idiopathic or usual interstitial pneumonia; idiopathic pulmonary fibrosis; immunologic phenomena; infantile hemangioma; infantile spasm; inflammatory bowel disease; inflammatory conditions; inflammatory pulmonary fibrosis; influenza virus; influenza virus infection; inhibit post-operative surgical adhesions; inhibit the TGF-β1 induced rise in collagen output in lung and dermal fibroblast cultures; inhibiting effect to the synthesis and release of TNF-α; insect bite; Insulin resistance; insulin resistance in type 2 diabetes; interstitial lung disease in systemic sclerosis; irritable bowel syndrome; ischemia-reperfusion injury; ischemic injury; Kaposi's sarcoma; keratitis; leiomyomas; leishmaniasis; leprosy; Leukemias; liver cirrhosis; liver damage; liver inflammatory disorders; localized edema; lung sarcoidosis; lung transplantation/chronic rejection; lupus; Lyme disease; lymph node fibrosis associated with HIV; Lymphomas; malaria; malignant melanoma; membranoproliferative glomerulonephritis; metastatic breast carcinoma; metastatic melanoma; microangiopathy or small vessel disease; microangiopathy or small vessel disease that is not related to diabetes; microvascular disorder; microvascular impairment during chronic catheterization; microvascular integrity; mucus hypersecretion; multiple myeloma; multiple myeloma-related bone disorders; multiple sclerosis; muscle degeneration; musculoskeletal fibrosis; myasthenia gravis; myocardial fibrosis; myoclonic seizure; myofacial pain syndrome; myofibroblast hypertrophy; neoplastic disease; neural trauma; neurofibromatosis; neurologic injury; neuromuscular pain; non-small cell lung cancer; NULL; ocular neovascularization; organ hypoxia; Ormond's disease; osteoarthritis; osteopetrosis; osteoporosis; other arthritic conditions; other fibrotic disorders; other viral diseases; pain; pain disorders; pancreatic damage; pancreatic fibrosis; paraneoplastic disease; Parkinson's syndrome; Parkinson's disease; Petit mal seizure; Pneumotosis intestinalis; polycystic kidney disease; post-renal dialysis syndrome; post-surgical adhesions; Pre-eclampsia; pressure bruises; prevent formation of new fibrotic lesions following tissue injuries; primary and secondary multiple sclerosis; primary focal segmental glomerulosclerosis; proliferative disorders; protozoal diseases;

psoriasis; pulmonary asbestosis; pulmonary capillaritis; Pulmonary fibrosis caused by collagen vascular disease; Pulmonary fibrosis caused by hypersensitivity pneumonitis; Pulmonary fibrosis caused by inhalant exposure; Pulmonary fibrosis caused by sarcoidosis; pulmonary sarcosis pyresis; radiation and drug-induced lung fibrosis; radiation exposure; radiation injury; Reiter's syndrome; relapsing-remitting multiple sclerosis; remodel or remove scar tissue or fibrosis; remove pre-existing fibrotic lesions; renal glomerulosclerosis; reperfusion injury of the brain or myocardium; restenosis; rhabdomyolysis; rheumatoid arthritis; rheumatoid arthritis-associated interstitial lung disease; rheumatoid spondylitis; scleroderma; scleroderma with pulmonary fibrosis; Scrapie; selective autoimmune disorders; selectively arrest scar enlargement; sepsis; septic shock; Severe Acute Respiratory Syndrome; severe pulmonary fibrosis; Shigellosis; sickle cell disease; silicosis; skin disorders including atopic dermatitis urticarial; skin lesions; slow or inhibit the progressive enlargement of fibrotic lesions; solid tumor angiogenesis; spinal multiple sclerosis; stroke; subepithelial fibrosis; sunburn; surgery; surgical sites immediately after keloid resection; Susac's syndrome; systemic lupus erythromatosus; tendonitis; tenosynovitis; thermal burns; thrombin-induced platelet aggregation; thrombocytopenia; thrombosis; thrombotic thrombocytopenic purpura; tissue fibrosis; tissue injuries caused by bacterial or fungal infections; tissue injuries caused by trauma; toxic shock; toxic shock syndrome; trauma-induced arthritis; treating inflammation in respiratory organs or cutis; ulcerative colitis; vascular restenosis; vernal conjunctivitis; vesicant responses (blisters); viral infection; viral or bacterial infections of the CNS; and Wegener's granulomatosis.

[0079] According to embodiments, the patient may suffer from an atherosclerotic disease, including but not limited to atherosclerosis of the renal vasculature, cardiac vasculature, brain vasculature and/or peripheral vasculature. As another example, according to any of the embodiments, the patient may suffer from thrombosis, an acute ischemic event, surgery, or an acute tissue injury.

[0080] The dosing may be twice or three times daily, with one or more unit doses per intake. According to a particular embodiment, the total daily intake is at least 1200 mg pirfenidone. The total daily intake amount may vary, depending on the patient profile, including among other things the patient's demographic characteristics, physiological and genetic conditions, and disease prognosis. For example, a child or a senior person may be given a lower amount daily than that given to an ordinary adult.

[0081] The anti-fibrotic activity of pirfenidone is demonstrated in *in vivo* animal fibrosis models, as well as *in vitro* cell culture studies with human or animal lung fibroblasts, dermal fibroblasts, and fibroblast-like cells. Those data indicate that pirfenidone may be an effective agent for preventing and treating post-surgical adhesions, myocardial fibrosis, renal fibrosis, liver cirrhosis, atherosclerosis, and other fibrotic disorders. *In vitro* cell cultures with human mesenchymal-like cells (including lung fibroblasts, skin fibroblasts, prostate stromal cells, and renal mesangial cells, etc.) have shown pharmacologic inhibition by pirfenidone of excessive cell proliferation induced by cytokine growth factors (TGF-β1, bFGF, PDGF, and EGF). In cell culture media, graded concentrations of pirfenidone were effective at levels which were ten to twenty times lower than those exerting any pharmacologically toxic effects on the cells.

[0082] At the site of injury, otherwise normal resident cells (e.g., fibroblasts, pericytes, mesangial cells, astrocytes, microglia, and oligodendrocytes) manufacture and discharge high concentrations of growth factors into adjacent tissue spaces. These resident sources of pathologically high levels of growth factors are directly responsible for the persistently excessive levels of growth factors. They cause excessive and harmful formation of collagen or amyloid matrix as well as damage to adjacent cells, the associated organ dysfunction, and frequently, organ malformation.

[0083] TGF-β1 is a potent growth-related peptide whose effects may be observed at femtomolar concentrations. It appears to be ubiquitous, and is a bifunctional regulator of cell proliferation *in vitro*. It acts either as a mitogen or a growth inhibitor depending on tissue concentration and the state of cell confluence (L.J. Striker et al., Lab. Invest. 64:446-456, 1991). In skin incisions, after attracting macrophages and fibroblasts, TGF-β1 enhances extracellular matrix formation by increasing transcription of genes for collagen and fibronectin, decreasing secretion of proteases, increasing secretion of protease inhibitors, and increasing transcription of cellular receptors for matrix proteins.

[0084] The anti-fibrotic activities of pirfenidone have been demonstrated *in vivo* in laboratory animals with fibrotic lesions, *in vitro* with human lung fibroblast (WI38) cell cultures, and observed through pilot open trials in patients with severe pulmonary fibrosis, benign prostate hypertrophy, or keloids. Pirfenidone may selectively arrest scar enlargement, and remodels or removes scar tissue or fibrosis. The dysfunction caused by fibrotic lesions may be ameliorated

by the reduction or removal of the fibrotic lesion following pirfenidone treatment. Apparently organ and tissue function can be restored, even after the presence of fibrosis for several years. When given immediately after an insult, such as trauma, infection, or allergy, to a tissue, pirfenidone also may prevent formation of excessive scar tissue, or fibrotic lesions, and thus help retain normal function and appearance of the tissue.

[0085] Pirfenidone may cause removal of excessive collagenous fibrotic tissue by a phagocytic action of local fibroblasts. This has been observed by examination of histological sections of lung tissue under the light microscope from dogs, mice, rats, and hamsters with pulmonary fibrosis treated with pirfenidone, and also through the electron micrographs of histological sections of lung tissue taken from hamsters with experimentally-induced asbestosis that were treated with pirfenidone. No infiltration of inflammation-inducing neutrophils, PMN cells, monocytes, lymphocytes occurred.

[0086] The enhanced proliferation of WI38 fibroblasts upon *in vitro* exposure to PDGF or bFGF may be blocked by pirfenidone added to cell growth media. Pirfenidone may also inhibit the TGF-β1 induced rise in collagen output in lung and dermal fibroblast cultures.

[0087] The human clinical findings after treatment with pirfenidone have been consistent with the anti-fibrotic effects observed in the laboratory animals. Pilot open clinical trials with oral pirfenidone have been undertaken with patients afflicted with pulmonary asbestosis, bleomycin-induced pulmonary fibrosis, idiopathic pulmonary fibrosis, scleroderma with pulmonary fibrosis, and Hermansky-Pudlak Syndrome characterized by pulmonary fibrosis.

[0088] The clinical criteria for beneficial response during the first months on pirfenidone included reduction in incidence of coughs, reduction in supplemental oxygen requirements, increased exercise tolerance, reduced dyspnea during exercise, amelioration of cor pulmonale, resumption of normal daily tasks, body weight gain, and survival. During the early months, pulmonary function as gauged by chest x-ray, spirometry, or CO diffusion (DLCO) showed little, if any, change. However, after 4 to 6 months on pirfenidone, inhibition or blocking of further deterioration in lung function was evidenced by pulmonary function tests, vital capacity (VC), in the diffusing capacity of the lung for carbon monoxide (DLCO). These overall observations compare favorably with those described by Van Barneveld et al. (Amer. Rev. Respr. Dis., vol.

135, 48-51, 1987), during the spontaneous recovery by patients from bleomycin-induced pulmonary pneumonitis (early stage fibrosis).

[0089] Martinet et al. (NE Jour. Med., vol 317, 202-209, 1987) have described an exaggerated release of PDGF by alveolar macrophages in patients with idiopathic pulmonary fibrosis. The *in vitro* demonstration of inhibition by pirfenidone of the mitogenesis and enhanced formation of collagen caused by growth factors (bFGF, PDGF, and TGF- β1) may partly explain the beneficial *in vivo* anti-fibrotic action of pirfenidone.

[0090] In an open pilot trial of pirfenidone in older men with clinically advanced benign prostate hypertrophy (BPH, non-cancerous fibrous enlargement of the male prostate gland), the patients experienced functional improvement based on objective criteria. After taking oral pirfenidone the frequent urinary bladder urgency was ameliorated, and nocturia rarely recurred. In another pilot open trial, topical applications of pirfenidone ointment to surgical sites immediately after keloid resection has prevented recurrence of the keloids as observed in two-year follow-ups in the patients. Each of those patients had a prior history of repeated early keloid re-growths after such surgery. Pirfenidone may induce a remodeling of skin fibrotic lesions to reduce or remove keloids, reduce or remove dermal scars, and remove or lessen the contractures of hypertrophic (post burn injury) scars. In a similar condition, pirfenidone also acts to inhibit post-operative surgical adhesions.

[0091] Thus, clinical investigations under both controlled protocol designs and open label trials have demonstrated that pirfenidone exerts anti-fibrotic and cytoprotective actions. The observed side effects after oral administration were relatively mild (drowsiness, gastric nausea or photosensitivity rash). No serious adverse reactions have been reported.

[0092] Based on the TNF-α inhibitor (cytoprotective) activity of pirfenidone, the formulation of the present disclosure may be administered according to certain embodiments of this disclosure to treat patients suffering from the following disorders:

[0093] 1) Central Nervous System syndromes: relapsing-remitting multiple sclerosis, primary and secondary multiple sclerosis, spinal multiple sclerosis, cerebral malaria, viral or bacterial infections of the CNS, bacterial meningitis, "autoimmune" disorders of the central nervous system (CNS), CNS stroke and infarction, brain edema, Parkinson's syndrome, Alzheimer's disease, amylotrophic lateral sclerosis (ALS), and brain concussion or contusion;

[0094] 2) Musculo-skeletal syndromes: rheumatoid arthritis, trauma-induced arthritis, arthritis caused by a microbial infection, or by a parasite, tendonitis, and, arthritis induced by medical products or drugs (including small synthetic molecules as well as purified natural or synthesized peptides or proteins);

[0095] 3) Pulmonary syndromes: acute adult respiratory distress syndrome, asthma, allergic rhinitis, allergic conjunctivitis, chronic obstructive pulmonary disease (COPD), and lung sarcoidosis;

[0096] 4) Systemic immunologic, inflammatory or toxic syndromes: endotoxemia shock syndrome, septic shock, graft-host disease, allograft vasculopathy, hemorrhagic shock, reperfusion injury of the brain or myocardium, thermal burns, radiation injury, general or dermal traumatic or contusion injuries, eosinophilic granuloma, diabetic mellitus (type II), or systemic lupus erythromatosus;

[0097] 5) Gastro-intestinal syndromes: Crohn's disease, ulcerative colitis, and liver inflammatory disorders; and

[0098] 6) Congestive heart failure. Further, based on the anti-fibrotic activity of pirfenidone, the formulation of the present disclosure may be administered according to other embodiments to treat patients suffering from the following disorders: pulmonary fibrosis, radiation and drug-induced lung fibrosis, hepatic fibrosis, cardiac fibrosis, keloid, post-surgical adhesions, benign prostate hypertrophy in humans, arteriosclerosis, dermal fibrosis, and coronary restenosis.

EXAMPLES

EXAMPLES 1 AND 2: FORMULATION

[0099] Tablet formulations having good manufacturability were produced having the following components:

Table 1: Granulate Formulation

Component	Function	Example 1 Amount (% w/w)	Example 2 Amount (% w/w)
INTRAGRANULAR COMPONENTS			
Pirfenidone	Active	84.23%	85.3%
Microcrystalline Cellulose PH101	Filler	6.21%	6.2%
Silica	Glidant	2.05%	2.08%
Polyvinylpyrrolidone K30	Binder	4.64%	3.83%
EXTRAGRANULAR COMPONENTS			
Croscarmellose sodium	Disintegrant	1.89%	1.92%
Mg Stearate	Lubricant	0.50%	0.19%
Silica	Glidant	0.47%	0.48%
Total (tablet core)		100%	100%

EXAMPLE 3: COMPARISON TO FORMULATION WITHOUT GLIDANT

[00100] A comparison was made between a pirfenidone formulation with (the formulation of Example 1) and without (comparative example) intragranular glidant. The comparative formulation had the following components:

Table 2: Comparative Example

Component	Function	Amount (% w/w)
INTRAGRANULAR COMPONENTS		
Pirfenidone	Active	87.11%
Microcrystalline Cellulose PH101	Filler	6.33%
Silica (Aerosil® 200)	Glidant	0%
Polyvinylpyrrolidone K30	Binder	3.92%
EXTRAGRANULAR COMPONENTS		
Croscarmellose sodium	Disintegrant	1.96%
Mg Stearate	Lubricant	0.20%
Silica (Aerosil® 200)	Glidant	0.49%
Total (tablet core)		**100%**

[00101] Both the formulation of Example 1 and the formulation of the comparative example (Table 2) were processed using fluid bed granulation. As illustrated in Figure 2A, the comparative example resulted in residual powder remaining stuck to the side walls of the fluid bed granulator. Such sticking of the powder is indicative of the cohesive nature of the intragranular formulation and was found to be an impediment to commercial scale processing of the formulation of the comparative example. By comparison, as shown in Figure 2B, the formulation of Example 1 did not have a significant amount of residual powder stuck to the side-walls of the fluid bed granulator, resulting in a granulate formulation that was capable of being processed on a commercial scale.

EXAMPLE 4: FLOWABILITY ANALYSIS

[00102] Flow function coefficient (FFC) is a measure of powder flow. Values less than about 4 are considered poor and sub-optimal for powder processing. Values between 4-10 are considered acceptable flow values for powder processing. Flow behavior was analyzed for pure pirfenidone (without excipients) and a binary powder mixture of pirfenidone and microcrystalline cellulose mixed with either about 1% by weight silica or about 2% by weight silica, as shown in Table 3 below. The components were mixed in a turbula mixer and the different flow properties of the blends were measured.

Table 3: Comparative Test Formulations with and without Silica

	Pure API	Binary Mixture with ~1 wt.% silica	Binary Mixture with ~2 wt% silica
Pirfenidone	100%	92.31%	91.40%
Microcrystalline cellulose PH101		6.70%	6.64%
Silica		0.99%	1.96%
Total	**100%**	**100%**	**100%**

[00103] The testing confirmed that pure pirfenidone has poor flow behavior, having a FFC value of 2.3. Adding 1% silica improved the flow behavior slightly, resulting in a mixture with flow properties that were border-line suitable for commercial processing. The 1% silica mixture had an FFC of 3.9. Adding 2% silica resulted in a significant improvement in the flow behavior, resulting in an FCC of 5, which is indicative of good flow.

Table 4: Flow Function Coefficient

	Pure API (pirfenidone only)	Binary Mixture with ~1wt% silica	Binary Mixture with ~2% wt% silica
Flow Function Coefficient (Avg.)	2.3 (poor flow)	3.0 (borderline flow)	5.0 (good flow)

EXAMPLE 5: TABLETING

[00104] Tablets were formed from the formulation of Example 1 by applying a compression force of approximately 100 to 170 MPA and utilizing a pre-compression force that was 20-30% of the main compression force. Such compression forces produced tablet cores of solid fraction values between 87% and 93% and tensile strength values greater than 1.6 MPa. The tablets showed good abrasion characteristics (abrasion less 0.5%).

[00105] Figures 7 and 8 illustrate the tabletability and compactability profiles for tablets having dosage amounts of pirfenidone of 801 mg (triangle symbol), 267 mg (diamond symbol), and 534 mg (square symbol).

EXAMPLE 6: DISINTEGRATION CONTROL

[00106] It has been surprisingly discovered that the disintegration of pirfenidone tablets in accordance with embodiments of the disclosure can be controlled by the solid fraction percentage (normalized tablet thickness), independent of the tablet dosage strength. While the particle size of the pirfenidone was found to affect the tablet core hardness, it is the solid fraction and not the tensile strength that was found to influence the drug release characteristics of the tablet cores. This relationship was confirmed over a wide range of pirfenidone particle sizes, from d_{90} of 50-150 μm. Identification of this relationship allowed the tablet core thickness, which controls the solid fraction, to be used as a target parameter in the tablet compression step instead of tablet core hardness.

[00107] Solid fraction is a normalized process parameter calculated using the dimensions of the tablet core (size of the compression tooling and thickness of the tablet), tablet weight and true density of the final blend. During a standard tablet compression operation, all the other factors that define the solid fraction remain unchanged, with the exception of tablet thickness. Therefore, controlling the thickness of the tablet can be used to target a predefined solid fraction during tablet compression. Literature studies have shown that tablet solid fraction may have a strong

influence on the mechanical strength (or hardness) of a resulting tablet core as well as its disintegration characteristics (Hancock et al., "The relative densities of pharmaceutical powders, blends, dry granulations, and immediate-release tablets," Pharm. Technol. 2003;27(4):64–80). However, it has been surprisingly discovered that for pirfenidone formulations in accordance with the disclosure, the relationship between the solid fraction (normalized tablet thickness) and the disintegration characteristics of the tablet are independent of the tablet mechanical strength.

[00108] For calculation of the solid fraction (Pitt et al., "Compression prediction accuracy from small scale compaction studies to production presses," Powder Tech. 2015;270(Part B):490–493), the true density of the final blend was estimated by use of the true density of the pure pirfenidone. The drug load in the pirfenidone film coated tablet composition is very high and the true density of the final blends was expected to be close to that of the pure pirfenidone.

$$SF = \frac{Wt}{\rho\text{true} \cdot \text{v}}$$

[00109] Figure 5 illustrates the correlation of the disintegration time to the solid fraction percentage, and Figure 6 illustrates the correlation of disintegration time to tablet core thickness. Identification of this relationship between tablet core thickness and drug release characteristics advantageously provides for control of a drug release properties by readily measureable and controllable parameter – tablet thickness.

EXAMPLE 7: BIOEQUIVALENCE

[00110] A bioequivalence study was conducted, demonstrating bioequivalence between a film-coated tablet having a formulation in accordance with the disclosure and the commercially available capsule formulation (sold as the ESBRIET® capsule), which is a pirfenidone formulation having no intragranular glidant.

Table 5: Formulations Used in Bioequivalence Study

	ESBRIET® Capsule	Tablet
Description	267 mg white hard capsule size #1	801 mg greyish brown film-coated tablet
Drug Loading	82.15% w/w	84.23% w/w[a]
	Ingredient	Ingredient
Active pharmaceutical ingredient	Pirfenidone	Pirfenidone
Filler	Microcrystalline cellulose	Microcrystalline cellulose
Glidant (intragranular)	—	Colloidal silicon dioxide
Binder	Povidone	Povidone
Disintegrant	Croscarmellose sodium	Croscarmellose sodium
Lubricant	Magnesium stearate	Magnesium stearate
Glidant (extragranular)	—	Colloidal silicon dioxide
Film coat	—	Film-coating mixture purple

[00111] The film-coated tablets met the bioequivalence criteria of 90% confidence interval (80.00% to 125.00%) when compared to the capsules in the fasted state, based on $AUC_{0-\infty}$, AUC_{0-24} and C_{max}. The film coated tablets met the bioequivalence criteria when compared to the capsules in the fed state with regard to $AUC_{0-\infty}$ and AUC_{0-24}, but for C_{max} the upper bound of 90% confidence interval was slightly outside the limit of 125.00%.

[00112] Overall, the bioequivalence results indicate that pirfenidone oral exposure is expected to be unaltered by change in formulation from capsule to film-coated tablets.

Table 6: Bioequivalence Results Summary in Fasted State

State of Subjects	Variable	Unit	Ratio Tablets/Capsules	CI 90% Lower	CI 90% Upper
Fasted	$AUC_{0-\infty}$	h*ng/mL	99.61%	96.64	102.68
Fasted	AUC_{0-24}	h*ng/mL	99.63%	96.66	102.69
Fasted	C_{max}	ng/mL	101.26%	94.41	108.60

Abbreviations: $AUC_{0-\infty}$ = area under the curve from zero to infinity; AUC_{0-24} = area under the curve from zero to 24 hours; CI = confidence interval; C_{max} = maximal concentration.

Table 7: Bioequivalence Results Summary in Fed State

State of Subjects	Variable	Unit	Ratio Tablets/Capsules	CI 90% Lower	CI 90% Upper
Fed	$AUC_{0-\infty}$	h*ng/mL	103.05%	99.54	106.69
Fed	AUC_{0-24}	h*ng/mL	103.06%	99.55	106.69
Fed	C_{max}	ng/mL	116.16%	108.26	125.60

Abbreviations: $AUC_{0-\infty}$ = area under the curve from zero to infinity; AUC_{0-24} = area under the curve from zero to 24 hours; CI = confidence interval; C_{max} = maximal concentration.

[00113] The bioequivalence of two lower-dose tablets (267 mg and 534 mg) was confirmed by means of a comparative dissolution to the 801 mg tablet tested in the bioequivalence study.

[00114] Comparative dissolution profiles of all three strengths are provided in three different media without surfactant, i.e., 0.1N HCl, acetate buffer pH 4.5, phosphate buffer pH 6.8, as well as in the proposed commercial dissolution medium (water). Profiles were recorded with the paddle apparatus (apparatus II) operated at 50 rpm. Twelve samples were measured in 900 mL of the dissolution media described above at 37°C.

[00115] Figure 9 illustrates the dissolution profile of the hard capsule (267 mg) used in the bioequivalence study.

[00116] Figures 10-13 illustrate the comparative dissolution profiles for the different tablet strengths tested in four different media: HCl 0.1 N; acetate buffer pH 4.5; phosphate buffer pH 6.8; and water, respectively.

[00117] For all strengths tested (801 mg, 534 mg, and 267 mg) in all tested media, the film-coated tablets were found to have an average dissolution of at least 85% at 15 minutes. From this, it was concluded that the lower-dose tablets were also bioequivalent to the capsules.

EXAMPLE 8: DISSOLUTION TESTING

[00118] In vitro performance of the film coated tablets in accordance with the disclosure, having a formulation as disclosed in Example 6, was assessed according to the matrix of conditions shown below using Ph. Eur./USP apparatus II, rotating paddles, or Ph. Eur./USP apparatus I, rotating baskets, and 1000 mL of the stated medium at 37°C.

Table 8: Dissolution Conditions

Agitation	Dist. Water	HCl 0.1 N	Acetate pH 4.5	Phosphate pH 6.8
Paddles, 50 rpm	X	X	X	X
Paddles, 75 rpm	X	—	—	—
Baskets, 75 rpm	X	—	—	—

Abbreviation: Dist. = distilled.

[00119] Aliquots were sampled at 5 minute intervals to ensure generation of data reflecting the ascending part and plateau phase of the profile. Plots of [% mean dissolution] against time were generated for each of the dosage amounts and medium tested. The min/max values are reflected with the error bars. Figures 14-16 illustrate the % mean dissolution over time in distilled water for the 267 mg, 534 mg, and 801 mg dosage amounts, respectively. Figures 17-19 illustrate the % mean dissolution over time in HCl, acetate, and phosphate for the 267 mg, 534 mg, and 801 mg dosage amounts, respectively.

[00120] Dissolution in distilled water with an agitation of 75 rpm using rotating basket (Ph. Eur./USP apparatus I) or 50/75 rpm using paddles (Ph. Eur./USP apparatus II) results in a rapidly dissolving profile (>85% after 15 minutes) and shows an ascending profile between the start of the test up to 15 minutes by reaching a plateau by up to 15−20 minutes for the 801 mg and faster for the other strengths. Under all working conditions a standard deviation around 1% to 3% can be observed after 15 minutes. Dissolution in conventional USP buffers, (HCl 0.1N; 50 mM acetate pH 4.5 and 50 mM phosphate pH 6.8) exhibits similar rapidly dissolving profiles as observed using water with rotating paddles at 50 rpm.

EXAMPLE 9: EFFECT OF DRUG SUBSTANCE PARTICLE SIZE ON TABLET PROPERTIES

[00121] Drug substance particle size in the formulations of the disclosure was not found to affect the dissolution of tablets formed form the formulations, where the tablets had the same solid fraction. Formulations with drug substance from two different sources were evaluated. The following tablet provides the particle size distribution information of the sources tested.

Table 9: Particle Size Distribution of Two Sources of Pirfenidone

DS PSD (μm) / Batch ID[a]	(D [v, 0.1])	(D [v, 0.5])	(D [v, 0.9])
D - 801mg (Source 2)	16	53	133
F - 801mg (Source 1)	11	27	58

Abbreviations: DS = Drug Substance; PSD = particle size distribution.

[a] Drug Substance source and batch number is given in bracket.

[00122] During dissolution testing, after 10 minutes a plateau was reached and both batches reflected a rapid dissolution over a tested range of process parameters. All tested tablets were 801 mg strength. A main compression force of 10 KN, 20 KN, and 21 KN were tested. Particle size distribution differences resulted in differences in the hardness of the resulting tablets, as illustrated in the table below.

Table 10: Tablet Hardness as a Function of Compression Force for Tablets Having Pirfenidone with Different Particle Size Distributions

Batch ID	Main Compression Force (equiv. Compaction Pressure)	Tablet Hardness (equiv Tensile Strength)	Tablet Thickness (equiv Solid Fraction)
F - 801 mg	10 KN (56 MPa)	176 N (1.3 MPa)	7.7 mm (81.4%)
D - 801 mg	10 KN (59 MPa)	114 N (0.9 MPa)	7.5 mm (84.0%)
F - 801 mg	21 KN (119 MPa)	265 N (2.3 MPa)	7.1 mm (89.1%)
D - 801 mg	20 KN (112 MPa)	177 N (1.6 MPa)	7.0 mm (90.2%)

[00123] As shown in Figure 20, despite these differences in hardness, the data demonstrate that the dissolution is insensitive to changes in drug substance particle size distribution. Also, tablets compressed to similar thickness values (7.5-7.7 mm versus 7.0-7.1 mm) result in tablets with significant difference in hardness, but that exhibit more comparable dissolution drug release profiles.

EXAMPLE 10: EFFECT OF COMPRESSION FORCE ON DISSOLUTION

[00124] Compression force can affect the dissolution profile in the early stages of dissolution, generally after less than 15 minutes. The impact of compression force on the dissolution of three dosage strengths (801 mg, 534 mg, and 267 mg) were studied over a range of 5 KN to 25 KN. The dissolution profile can be affected by the compression force and generally manifested in a change in the shape of the profile during early dissolution stages (between approximately 0-15 minutes). Figures 21 and 22 illustrate the changes in the early stage dissolution profile of 534 mg tablets and 267 mg tablets, respectively, that can result from changing the compression force.

EXAMPLE 11: FLUID-BED GRANULATION PROCESS PARAMETERS

[00125] Eight batches, each at one of the eight fluid-bed granulation and drying settings of interest, were produced and processed into a final blend. Each final blend was split into two batches, each compressed into tablets to a different hardness setting (120N and 200N).

Table 11: Fluid-Bed Granulation Conditions

Process	Factor Name	Label	Unit	Low	Target	High
Granulation	Inlet air temperature[a]	Inlet air temp	°C	50	58	66
	Spray rate[a,b,c]	Spray rate	g/min	375	450	525
	Drying time	Drying time	min	1	8	15
Tableting	Tablet hardness	Hardness	N	120	170	200

[a] Same settings of inlet air temperature and inlet air volumes were used in both granulation and drying phases.

[b] The spray rate and inlet air flow volume were combined together into a nominal factor, and varied concurrently. Corresponding air flow volumes: 1600 (low)/1850 (target)/2100 m^3/h (high).

[c] Normalized spray rate range equivalent 3.3 – 4.6 g/min/kg.

[00126] Different material attributes of granules, final blend, and tablet cores were measured as responses, with acceptable ranges specified, wherever applicable. Product temperature at the end of drying and loss on drying of the granules were measured as responses to identify if there was a correlation between the two responses. Sieve analysis (to determine the amount of fines), bulk density and flow function coefficients of the final blend were measured as responses which are indicative of the flow behavior of the granules. Where tablets of predefined hardness values were produced, main compression force and tablet thickness were measured as responses. Tablet core attributes of UDU (by mass variation), dissolution at 15 minutes and disintegration time were also studied as responses for the 120N and 200N resulting tablet cores.

[00127] All batches were produced using a single drug substance source and compressed into 801 mg strength tablets using the same tooling (20.0 x 9.3 mm).

[00128] Table 12 shows a summary of the effect on the material attributes of the resulting granules.

Table 12: Results for Granule Material Attributes

	Factors			**Batch # (801 mg Mxxx)**	**Responses**				
Pattern	Inlet air temperature (°C)	Spray rate-Inlet air volume (g/min-m^3/h)	Drying time (min)		Product temperature at end of drying (°C)	LOD at end of drying (%)	Final blend (% fines)	Bulk density (g/cm^3)	FFC
- + -	50	525-2100	1	K	24.0	2.5	10.0	0.44	12.3
+ - +	66	375-1600	15	L	53.1	0.6	9.4	0.40	11.6
+ + -	66	525-2100	1	M	32.8	1.0	27.7	0.46	9.7
+ + +	66	525-2100	15	N	50.4	0.7	33.4	0.50	12.4
- + +	50	525-2100	15	O	30.9	1.1	19.1	0.45	16.4
- - +	50	375-1600	15	P	32.4	1.1	16.9	0.47	13.1
- - -	50	375-1600	1	Q	23.7	2.9	13.2	0.45	14.1
+ - -	66	375-1600	1	R	35.8	0.9	18.0	0.46	10.1
0[a]	58	450-1850	8	I	37.0	0.8	22.7	0.45	13.4
0[a]	58	450-1850	8	J	36.7	0.8	25.2	0.45	10.6

Abbreviations: DOE = Design of Experiment; FFC = flow function coefficient; LOD = loss on drying.
[a] Pseudo-center points.

[00129] Table 13 shows a summary of the effect on material attributes of the tablet cores.

Table 13: Results for Tablet Core Material Attributes

	Factors				Batch # (801 mg)	Responses					
Pattern	Inlet air temp. (°C)	Spray rate-inlet air flow volume (g/min-m^3/h)	Drying time (min)	Hard. (N)		Main compression force (KN) (compaction pressure [MPa])	Mass variation (% RSD)	Thickness (mm) (solid fraction [%])	Disintegration time (s)	Dissolution at 15 min AVG (%)	Appearance
- + -	50	525-2100	1	200[a]	L	16.4 (104.8)	0.64	6.66 (97.5)	337	96	Acceptable
				120[b]		7.1 (45.4)	0.56	7.07 (90.4)	81	97	Acceptable
+ - +	66	375-1600	15	200[a]	L	20.3 (129.8)	0.38	6.96 (91.5)	678	94	Acceptable
				120[b]		10.4 (66.5)	0.36	7.31 (86.3)	268	99	Acceptable
+ + -	66	525-2100	1	120[b]	M	8.5 (54.3)	0.74	7.38 (85.0)	69	97	Acceptable
				200[a]		15.8 (101.0)	0.67	6.99 (91.0)	230	96	Acceptable
+ + +	66	525-2100	15	200[a]	N	19.2 (122.7)	0.56	6.94 (92.0)	463	97	Acceptable
				120[b]		9.7 (62.0)	0.65	7.44 (84.7)	140	98	Acceptable

Table 13 Cont.

	Factors				Batch # (801 mg)	Responses					
Pattern	Inlet air temp. (°C)	Spray rate-inlet air flow volume (g/min-m^3/h)	Drying time (min)	Hard. (N)		Main compression force (KN) (compaction pressure [MPa])	Mass variation (% RSD)	Thickness (mm) (solid fraction [%])	Disintegration time (s)	Dissolution at 15 min AVG (%)	Appearance
- + +	50	525-2100	15	120[b]	O	10.3 (65.8)	0.45	7.32 (86.7)	87	97	Acceptable
				200[a]		19.7 (125.9)	0.51	6.94 (92.5)	362	98	Acceptable
- - +	50	375-1600	15	120[b]	P	9.4 (60.1)	0.66	7.36 (85.7)	88	97	Acceptable
				200[a]		19.3 (123.4)	0.75	6.93 (92.7)	446	98	Acceptable
- - -	50	375-1600	1	200[a]	Q	13.8 (88.2)	0.56	6.88 (93.7)	308	95	Acceptable
				120[b]		6.6 (42.2)	0.57	7.19 (87.8)	84	96	Acceptable

Table 13 Cont.

	Factors				Batch # (801 mg)	Responses					
Pattern	Inlet air temp. (°C)	Spray rate-inlet air flow volume (g/min-m^3/h)	Drying time (min)	Hard. (N)		Main compression force (KN) (compaction pressure [MPa])	Mass variation (% RSD)	Thickness (mm) (solid fraction [%])	Disintegration time (s)	Dissolution at 15 min AVG (%)	Appearance
+ - -	66	375-1600	1	200[a]	R	17.9 (114.4)	0.69	6.93 (92.3)	364	98	Acceptable
				120[b]		9.5 (60.7)	0.80	7.37 (85.0)	108	98	Acceptable
0[c]	58	450-1850	8	200[a]	I	20.2 (129.1)	0.60	6.92 (92.4)	282	98	Acceptable
0[c]	58	450-1850	8	120[b]	J	10.6 (67.8)	0.75	7.32 (85.9)	59	97	Acceptable

Abbreviations: AVG = average; DOE = Design of Experiment; Hard. = tablet core hardness; RSD = relative standard deviation; temp. = temperature.

[a] Approximate tensile strength = 1.7 – 1.8 MPa.

[b] Approximate tensile strength = 0.9 – 1.0 MPa.

[c] Pseudo-center points.

[00130] The foregoing describes and exemplifies the invention but is not intended to limit the invention defined by the claims which follow. All of the formulations and methods disclosed and claimed herein can be made and executed without undue experimentation in light of the present disclosure. While the materials and methods of this invention have been described in terms of specific embodiments, it will be apparent to those of skill in the art that variations may be applied to the materials and/or methods and in the steps or in the sequence of steps of the methods described herein without departing from the concept, spirit and scope of the invention.

[00131] In case of conflict between the present disclosure and patents, publications and references cited herein, the present disclosure should control.

[00132] Throughout this application, the term "about" is used to indicate that a value includes the standard deviation of error for the device or method being employed to determine the value.

Claims

1. A granulate formulation of 5-methyl-1-phenyl-2-(1H)-pyridone, comprising: granules comprising 5-methyl-1-phenyl-2-(1H)-pyridone and a glidant; and one or more extragranular excipients comprising an extragranular glidant.

2. The formulation of claim 1, wherein the extragranular glidant is selected from the group consisting of silica, silicified cellulose, sodium stearate, magnesium aluminum silicate, pyrogenic silica, hydrated sodium silioaluminate, calcium phosphate, sodium lauryl sulfate, pregelatinized starch, talc, and physical or coprocessed combinations thereof.

3. The formulation of claim 1 or 2, wherein the formulation is prepared by wet granulation.

4. The formulation of any one of claims 1 to 3, wherein the granules comprise the glidant in an amount of at least 1% by weight based on total weight of the formulation.

5. The formulation of any one of claims 1 to 3, wherein the granules comprise the glidant in an amount of at least 2% by weight based on total weight of the formulation.

6. The formulation of any one of claims 1 to 3, wherein the granules comprise the glidant in an amount of about 1% to about 5% by weight based on the total weight of the formulation.

7. The formulation of any one of claims 1 to 3, wherein the granules comprise the glidant in an amount of about 2% to about 5% by weight based on the total weight of the formulation.

8. The formulation of any one of claims 1 to 7, wherein the granulate formulation

comprises the extragranular glidant in an amount of about 0.1% to about 5% by weight based on the total weight of the formulation.

9. The formulation of any one of claims 1 to 8, wherein the glidant is selected from the group consisting of silica, silicified cellulose, sodium stearate, magnesium aluminum silicate, pyrogenic silica, hydrated sodium silioaluminate, cellulose, calcium phosphate, sodium lauryl sulfate, pregelatinized starch, talc, and physical or coprocessed combinations thereof.

10. The formulation of any one of claims 1 to 9, wherein the formulation is an immediate release formulation.

11. The formulation of any one of claims 1 to 10, wherein the 5-methyl-1-phenyl-2-(1H)-pyridone is present in an amount of about 60% to about 95% by weight, based on the total weight of the formulation.

12. The formulation of any one of claims 1 to 11, wherein the 5-methyl-1-phenyl-2-(1H)-pyridone is present in an amount of about 100 mg to about 1100 mg.

13. The formulation of any one of claims 1 to 12, wherein the granulate formulation comprises one or more pharmaceutically acceptable excipients selected from a disintegrant, a binder, a filler, and a lubricant.

14. The formulation of any one of claims 1 to 13, comprising a disintegrant as an extragranular component.

15. The formulation of any one of claims 1 to 14, comprising a lubricant as an extragranular component.

16. The formulation of any one of claims 13 to 15, wherein the granules comprise one

or more of a disintegrant, a binder, and a filler.

17. The formulation of claim 16, wherein the granules comprise a filler and a binder.

18. The formulation of claim 17, wherein the granules further comprise a disintegrant.

19. The formulation of any one of claims 13 to 18, wherein the disintegrant is present in an amount of about 0.5% to about 10% by weight based on the total weight of the formulation.

20. The formulation of any one of claims 13 to 19, wherein the disintegrant is selected from the group consisting of agar-agar, algins, calcium carbonate, carboxmethylcellulose, salts of carboxymethylcellulose, cellulose, clays, corn starch, croscarmellose sodium, crospovidone, gums, methyl cellulose, polacrilin potassium, sodium alginate, cross-linked polyvinylpyrrolidone, sodium starch glycolate, starch, and combinations thereof.

21. The formulation of any one of claims 13 to 20, wherein the binder is present in an amount of about 1% to about 10% by weight based on the total weight of the formulation.

22. The formulation of any one of claims 13 to 21, wherein the binder is present in an amount of about 2% to about 5% by weight based on the total weight of the formulation.

23. The formulation of any one of claims 13 to 22, wherein the binder is selected from the group consisting of hydroxymethylcellulose, hydroxypropylcellulose, polyvinylpyrrolidone, calcium carbonate, dicalcium phosphate, carbomers, cellulose acetate phthalates, copovidone, hydroxypropyl methyl cellulose, ethylene glycol and vinyl glycol grafted copolymer, isomalt, poloxamer, polyethylene oxide, polymethacrylates, and combinations thereof.

24. The formulation of any one of claims 13 to 23, wherein the filler is present in an amount of about 2% to about 30% by weight based on the total weight of the formulation.

25. The formulation of any one of claims 13 to 24, wherein the filler is selected from the group consisting of calcium carbonate, calcium phosphate, dibasic calcium phosphate, calcium silicate, tribasic calcium sulfate, calcium carboxymethylcellulose, cellulose, dextrin derivatives, dextrin, dextrose, fructose, isomalt, kaolin, lactitol, lactose, magnesium carbonate, magnesium oxide, maltitol, maltodextrins, maltose, mannitol, microcrystalline cellulose, sodium bicarbonate, sodium carbonate, sorbitol, starch, sucrose, sugar, xylitol, and combinations thereof.

26. The formulation of any one of claims 13 to 25, wherein the lubricant is present in an amount of about 0.05% to about 2% by weight based on the total weight of the formulation.

27. The formulation of any one of claims 13 to 26, wherein the lubricant is selected from the group consisting of agar, calcium stearate, ethyl oleate, ethyl laureate, glycerin, glyceryl behenate, glyceryl palmitostearate, hydrogenated vegetable oil, magnesium oxide, magnesium stearate, mannitol, poloxamer, glycols, sodium benzoate, sodium lauryl sulfate, sodium stearate, sorbitol, stearic acid, talc, zinc stearate, and combinations thereof.

28. The formulation of claim 13, wherein the filler is microcrystalline cellulose, the glidant is silica, the binder is polyvinylpyrrolidone, the disintegrant is croscarmellose sodium, and the lubricant is magnesium stearate.

29. The formulation of claim 13, wherein the filler is lactose, the glidant is magnesium aluiminum silicate, the binder is hydroxypropylcellulose, the disintegrant is croscarmellose sodium, and the lubricant is magnesium stearate.

30. The formulation of claim 13, wherein the filler is lactose, the glidant is pyrogenic silica, the binder is polyvinylpyrrolidone, and the lubricant is sodium stearate.

31. The formulation of claim 1, wherein:

the granules comprise:

the glidant in an amount of about 1 wt% to about 3 wt% based on the total weight of the formulation,

a binder in an amount of about 1 wt% to about 10 wt% based on the total weight of the formulation, and

a filler in an amount of about 2 wt% to about 30 wt% based on the total weight of the formulation;

the extragranular glidant is in an amount of about 0.1 wt% to about 5 wt% based on the total weight of the formulation; and

the formulation further comprises as extragranular components one or both of:

a disintegrant in an amount of about 1 wt% to about 10 wt% based on the total weight of the formulation, and

a lubricant in an amount of about 0.05 wt% to about 2 wt% based on the total weight of the formulation.

32. The formulation of claim 1, wherein:

the granules comprise:

the glidant in an amount of about 1 wt% to about 2.5 wt% based on the total weight of the formulation,

a binder in an amount of about 3 wt% to about 5 wt% based on the total weight of the formulation, and

a filler in an amount of about 3 wt% to about 10 wt% based on the total weight of the formulation;

the extragranular glidant is in an amount of about 0.2 wt% to about 0.6 wt% based on the total weight of the formulation; and

the formulation further comprises as extragranular components one or both of:

a disintegrant in an amount of about 1 wt% to about 3 wt% based on the total weight of

the formulation, and

a lubricant in an amount of about 0.1 wt% to about 0.8 wt% based on the total weight of the formulation.

33. A granulate formulation of 5-methyl-1-phenyl-2-(1H)-pyridone, comprising:

granules comprising:

5-methyl-1-phenyl-2-(1H)-pyridone in an amount of about 84.23 wt% based on the total weight of the formulation,

a filler in an amount of about 6.21 wt% based on the total weight of the formulation, wherein the filler is microcrystalline cellulose,

a glidant in an amount of about 2.05 wt% based on the total weight of the formulation, wherein the glidant is silica, and

a binder in an amount of about 4.64 wt% based on the total weight of the formulation, wherein the binder is polyvinylpyrrolidone; and

the formulation comprises as extragranular components:

a disintegrant in an amount of about 1.89 wt% based on the total weight of the formulation, wherein the disintegrant is croscarmellose sodium,

a lubricant in an amount of about 0.5 wt% based on the total weight of the formulation, wherein the lubricant is magnesium stearate, and

an extragranular glidant in an amount of about 0.47 wt% based on the total weight of the formulation, wherein the extragranular glidant is silica.

34. A granulate formulation of 5-methyl-1-phenyl-2-(1H)-pyridone, comprising:

granules comprising:

5-methyl-1-phenyl-2-(1H)-pyridone in an amount of about 80 wt% to about 95 wt% based on the total weight of the formulation,

a filler in an amount of about 2 wt% to about 10 wt% based on the total weight of the formulation, wherein the filler is microcrystalline cellulose,

a glidant in an amount of about 2 wt% to about 5 wt% based on the total weight of the formulation, wherein the glidant is silica, and

a binder in an amount of about 3 wt% to about 5 wt% based on the total weight of the formulation, wherein the binder is polyvinylpyrrolidone; and

the formulation comprises as extragranular components:

a disintegrant in an amount of about 1 wt% to about 2 wt% based on the total weight of the formulation, wherein the disintegrant is croscarmellose sodium,

a lubricant in an amount of about 0.1 wt% to about 0.8 wt% based on the total weight of the formulation, wherein the lubricant is magnesium stearate, and

an extragranular glidant in an amount of about 0.03 wt% to about 0.8 wt% based on the total weight of the formulation, wherein the extragranular glidant is silica.

35. The formulation of claim 33 or 34, wherein the formulation is prepared by wet granulation.

36. The formulation of any one of claims 33 to 35, wherein the formulation is an immediate release formulation.

37. The formulation of any one of claims 1 to 36, wherein the granules comprise an effective amount of the glidant to provide a flow function coefficient of the formulation of at least 4.

38. The formulation of any one of claims 1 to 37, wherein the formulation has a flow function coefficient of 5 to 20.

39. The formulation of any one of claims 1 to 38, wherein the formulation has a moisture content of less than 3% as measured by loss on drying.

40. The formulation of any one of claims 1 to 39, wherein the formulation has a moisture content of 0% to about 2.9% as measured by loss on drying.

41. A unit dose comprising the formulation of any one of claims 1 to 40.

42. A tablet comprising the formulation of any one of claims 1 to 40.

43. The tablet of claim 42, wherein the tablet has a solid fraction of about 80% to about 95%.

44. The tablet of claim 42 or 43, wherein the tablet has a thickness of about 2 mm to about 10 mm.

45. The tablet of any one of claims 42 to 44, comprising the 5-methyl-1-phenyl-2-(1H)-pyridone in an amount of about 200 mg to about 1100 mg.

46. The tablet of claim 45, comprising the 5-methyl-1-phenyl-2-(1H)-pyridone in an amount of 200 mg, 267 mg, 534 mg, 600 mg, or 801 mg.

47. The tablet of any one of claims 42 to 46, wherein the tablet comprises about 801 mg of the 5-methyl-1-phenyl-2-(1H)-pyridone and the tablet has a thickness of about 5 mm to about 10 mm.

48. The tablet of any one of claims 42 to 46, wherein the tablet comprises about 534 mg of the 5-methyl-1-phenyl-2-(1H)-pyridone and the tablet has a thickness of about 3 mm to about 8 mm.

49. The tablet of any one of claims 42 to 46, wherein the tablet comprises about 267 mg of the 5-methyl-1-phenyl-2-(1H)-pyridone and the tablet has a thickness of about 2 mm to about 8 mm.

50. The tablet of any one of claims 42 to 49, further comprising a film coating.

51. A method of making a granulate formulation of 5-methyl-1-phenyl-2-(1H)-pyridone, comprising:

mixing the 5-methyl-1-phenyl-2-(1H)-pyridone and intragranular excipients in a fluid bed granulator to form granules, wherein the intragranular excipients comprise a glidant and a wet-granulation fluid;

adding an extragranular glidant to the granules; and

optionally adding one or more extragranular excipients to the granules,

wherein the granules comprise the glidant in an amount of about 2 wt% to about 5 wt% by weight based on the total weight of the formulation.

52. The method of claim 51, wherein the extragranular glidant is present in an amount of about 0.1% to about 5% by weight based on the total weight of the formulation.

53. A method of making a granulate formulation of 5-methyl-1-phenyl-2-(1H)-pyridone, comprising:

mixing the 5-methyl-1-phenyl-2-(1H)-pyridone and intragranular excipients in a fluid bed granulator to form granules, wherein the intragranular excipients comprise a glidant and a wet-granulation fluid; and

adding one or more extragranular excipients to the granules, wherein the one or more extragranular excipients comprise an extragranular glidant.

54. The method of claim 53, wherein the granules comprise the glidant in an amount of at least 1% by weight based on total weight of the formulation.

55. The method of claim 53, wherein the granules comprise the glidant in an amount of at least 2% by weight based on total weight of the formulation.

56. The method of claim 53, wherein the granules comprise the glidant in an amount of about 1% to about 5% by weight based on the total weight of the formulation.

57. The method of any one of claims 51 to 56, further comprising drying the granules.

58. The method of claim 57, wherein the granules are dried on a fluid bed dryer.

59. The method of claim 57 or 58, wherein the granules are dried to a moisture content of less than 3% as measured by loss on drying.

60. The method of claim 57 or 58, wherein the granules are dried to a moisture content of 0% to about 2.9% as measured by loss on drying.

61. The method of any one of claims 51 to 60, wherein the intragranular excipients further comprise a filler.

62. The method of claim 61, wherein the filler is present in an amount of about 2% to about 30% by weight based on the total weight of the formulation.

63. The method of claim 61 or 62, wherein the filler is selected from the group consisting of calcium carbonate, calcium phosphate, dibasic calcium phosphate, calcium silicate, tribasic calcium sulfate, calcium carboxymethylcellulose, cellulose, dextrin derivatives, dextrin, dextrose, fructose, isomalt, kaolin, lactitol, lactose, magnesium carbonate, magnesium oxide, maltitol, maltodextrins, maltose, mannitol, microcrystalline cellulose, sodium bicarbonate, sodium carbonate, sorbitol, starch, sucrose, sugar, xylitol, and combinations thereof.

64. The method of any one of claims 51 to 63, wherein the intragranular excipients further comprise a binder.

65. The method of claim 64, wherein the binder is in an aqueous solution, an aqueous suspension, an alcoholic solution, an alcoholic suspension, or an aqueous-alcoholic mixture, and applied to form the granules by wet granulation.

66. The method of claim 64 or 65, wherein the binder is present in an amount of about 1% to about 10% by weight based on the total weight of the formulation.

67. The method of any one of claims 64 to 66 wherein the binder is selected from the group consisting hydroxymethylcellulose, hydroxypropylcellulose, polyvinylpyrrolidone, calcium carbonate, dicalcium phosphate, carbomers, cellulose acetate phthalates, copovidone, hydroxypropyl methyl cellulose, ethylene glycol and vinyl glycol grafted copolymer, isomalt, poloxamer, polyethylene oxide, polymethacrylates, and combinations thereof.

68. The method of any one of claims 52 to 67, wherein the extragranular excipients comprise one or more of a disintegrant, a lubricant, and the extragranular glidant.

69. The method of any one of claims 51 to 68, wherein the intragranular excipients comprise one or more of a binder, a filler, and disintegrant.

70. The method of claim 68 or 69, wherein the lubricant is present in an amount of about 0.05% to about 2% by weight based on the total weight of the formulation.

71. The method of any one of claims 68 to 70, wherein the lubricant is selected from the group consisting of agar, calcium stearate, ethyl oleate, ethyl laureate, glycerin, glyceryl behenate, glyceryl palmitostearate, hydrogenated vegetable oil, magnesium oxide, magnesium stearate, mannitol, poloxamer, glycols, sodium benzoate, sodium lauryl sulfate, sodium stearate, sorbitol, stearic acid, talc, zinc stearate, and combinations thereof.

72. The method of any one of claims 68 to 71, wherein the disintegrant is present in

an amount of about 0.1 % to about 10% by weight based on the total weight of the formulation.

73. The method of any one of claims 51 to 71, wherein the extragranular excipients comprise a disintegrant in an amount of 0% to about 10% by weight based on the total weight of the formulation.

74. The method of any one of claims 68 to 73, wherein the disintegrant is selected from the group consisting of agar-agar, algins, calcium carbonate, carboxmethylcellulose, salts of carboxmethylcellulose, cellulose, clays, corn starch, croscarmellose sodium, crospovidone, gums, methyl cellulose, polacrilin potassium, sodium alginate, cross-linked polyvinylpyrrolidone, sodium starch glycolate, starch, and combinations thereof.

75. The method of any one of claims 52 to 74, wherein the extragranular glidant is in an amount of about 0.1% to about 5% by weight based on the total weight of the formulation.

76. The method of any one of claims 51 to 75, wherein the glidant is selected from the group consisting of silica, silicified cellulose, sodium stearate, magnesium aluiminum silicate, pyrogenic silica, hydrated sodium silioaluminate, cellulose, calcium phosphate, sodium lauryl sulfate, pregelatinized starch, talc, and physical or coprocessed combinations thereof.

77. The method of any one of claims 51 to 76, further comprising applying a compression pressure to the granulate formulation to form a tablet.

78. The method of claim 77, wherein the compression pressure is in a range of about 50 MPa to about 500 MPa.

79. The method of claim 77 or 78, further comprising film coating the tablet.

80. The method of any one of claims 51 to 79, further comprising premixing the 5-

methyl-1-phenyl-2-(1H)-pyridone and intragranular excipients.

81. The method of any one of claims 51 to 80, further comprising heating the 5-methyl-1-phenyl-2-(1H)-pyridone and intragranular excipients prior to or during mixing.

82. The method of any one of claims 51 to 81, further comprising screening one or both of the 5-methyl-1-phenyl-2-(1H)-pyridone and intragranular excipients prior to mixing.

83. The method of any one of claims 51 to 82, further comprising screening the extragranular excipients prior to mixing with the granules.

84. The method of any one of claims 51 to 83, further comprising premixing the extragranular excipients prior to mixing with the granules.

85. The method of any one of claims 51 to 84, wherein the extragranular excipients comprise at least two excipients and the at least two excipients are added serially to the granules.

86. The method of any one of claims 51 to 85, wherein the extragranular excipients are added to the granules in a single step.

87. A method of making a tablet, comprising:

compressing the granulate formulation of any one of claims 1 to 40 to a predetermined tablet thickness.

88. The method of claim 87, wherein the predetermined tablet thickness is about 2 mm to about 10 mm.

89. The method of claim 87 or 88, wherein the granulate formulation comprises about 801 mg of the 5-methyl-1-phenyl-2-(1H)-pyridone and the predetermined tablet thickness is

about 5 mm to about 10 mm.

90. The method of clam 87 or 88, wherein the granulate formulation comprises about 534 mg of the 5-methyl-1-phenyl-2-(1H)-pyridone and the predetermined tablet thickness is about 3 mm to about 8 mm.

91. The method of clam 87 or 88, wherein the granulate formulation comprises about 267 mg of the 5-methyl-1-phenyl-2-(1H)-pyridone and the predetermined tablet thickness is about 2 mm to about 8 mm.

92. A use of the granulate formulation of any one of claims 1 to 40 for treatment of idiopathic pulmonary fibrosis.

93. A use of the granulate formulation of any one of claims 1 to 40, for treatment of a disease selected from the group consisting of: idiopathic pulmonary fibrosis; pulmonary fibrosis; bronchiolitis obliterans; chronic lung transplant rejection; scleroderma; primary focal segmental glomerulosclerosis (FSGC); membranoproliferative glomerulonephritis (MPGN); idiopathic interstitial pneumonia; interstitial lung disease in systemic sclerosis; a fibrosis condition of the lung; autoimmune lung diseases; benign prostate hypertrophy; coronary infarction; myocardial infarction; atrial fibrillation; cerebral infarction; myocardiac fibrosis; musculoskeletal fibrosis; post-surgical adhesions; liver cirrhosis; renal fibrotic disease; fibrotic vascular disease; Hermansky-Pudlak syndrome; neurofibromatosis; Alzheimer's disease; diabetic retinopathy; diabetic skin lesions; lymph node fibrosis associated with HIV; chronic obstructive pulmonary disease (COPD); inflammatory pulmonary fibrosis; rheumatoid arthritis; rheumatoid arthritis-associated interstitial lung disease; rheumatoid spondylitis; osteoarthritis; gout; arthritic conditions; sepsis; septic shock; endotoxic shock; gram-negative sepsis; toxic shock syndrome; myofacial pain syndrome (MPS); Shigellosis; asthma; adult respiratory distress syndrome; inflammatory bowel disease; Crohn's disease; psoriasis; eczema; ulcerative colitis; glomerular nephritis; chronic thyroiditis; Grave's disease; Ormond's disease; autoimmune gastritis;

myasthenia gravis; autoimmune hemolytic anemia; autoimmune neutropenia; thrombocytopenia; pancreatic fibrosis; chronic active hepatitis including hepatic fibrosis; acute renal disease; chronic renal disease; renal fibrosis; diabetic nephropathy; irritable bowel syndrome; pyresis; restenosis; cerebral malaria; stroke; ischemic injury; neural trauma; Huntington's disease; Parkinson's disease; acute pain; chronic pain; allergies; allergic rhinitis; allergic conjunctivitis; cardiac hypertrophy, chronic heart failure; acute coronary syndrome; cachexia; malaria; leprosy; leishmaniasis; Lyme disease; Reiter's syndrome; acute synoviitis; muscle degeneration, bursitis; tendonitis; tenosynoviitis; herniated, ruptured, or prolapsed intervertebral disk syndrome; osteopetrosis; thrombosis; silicosis; pulmonary sarcosis; bone resorption diseases; osteoporosis; multiple myeloma-related bone disorders; cancer; metastatic breast carcinoma; colorectal carcinoma; malignant melanoma; gastric cancer; non-small cell lung cancer; graft-versus-host reaction; auto-immune diseases; multiple sclerosis; lupus; fibromyalgia; AIDS; viral diseases; Herpes Zoster; Herpes Simplex I or II; influenza virus; Severe Acute Respiratory Syndrome (SARS); cytomegalovirus; diabetes mellitus; proliferative disorders; benign hyperplasia; malignant hyperplasia; acute myelogenous leukemia; chronic myelogenous leukemia; Kaposi's sarcoma; metastatic melanoma; multiple myeloma; breast cancer; bone metastases; pain disorders; neuromuscular pain; headache; cancer pain; dental pain; arthritis pain; angiogenic disorders; solid tumor angiogenesis; ocular neovascularization; infantile hemangioma; edema, fever, analgesia, and pain associated with the cyclooxygenase or lipoxygenase signaling pathways or prostaglandin endoperoxide synthase-2; organ hypoxia; thrombin-induced platelet aggregation; and protozoal diseases.

94. A use of the granulate formulation of any one of claims 1 to 40 for treatment of a fibrotic condition.

95. The use of claim 94, wherein the fibrotic condition is selected from the group consisting of pulmonary fibrosis, hepatic fibrosis, cardiac fibrosis, keloid, dermal fibrosis, coronary restenosis, post-surgical adhesions, and combinations thereof.

96. The use of claim 95, wherein said pulmonary fibrosis is selected from the group consisting of idiopathic pulmonary fibrosis and Hermansky-Pudlak Syndrome.

97. A use of the granulate formulation of any one of claims 1 to 40 for treatment of a disorder mediated by cytokines.

98. The use of claim 97, wherein the cytokines comprises one or more selected from the group consisting of TNF-α, TGF-β1, bFGF, PDGF, and EGF.

99. The use of claim 97 or 98, wherein said disorder is selected from the group consisting of multiple sclerosis, arthritis, asthma, chronic rhinitis, and edema.

100. The use of any one of claims 92 to 99, wherein the granulate formulation is a tablet.

101. The use of claim 100, wherein the tablet comprises 267 mg, 534 mg, or 801 mg of the 5-methyl-1-phenyl-2-(1H)-pyridone.

102. The use of any one of claims 92 to 101, in one or more unit doses, one or more times a day.

103. The use of claim 102, wherein the one or more unit doses, one or more times a day, delivers at least 1200 mg of the 5-methyl-1-phenyl-2-(1H)-pyridone per day.

104. The use of claim 102, wherein the one or more unit doses, one or more times a day, delivers about 800 mg per day to about 2405 mg of the 5-methyl-1-phenyl-2-(1H)-pyridone per day.

105. The use of any one of claims 92 to 100, wherein the granulate formulation

delivers 267 mg of the 5-methyl-1-phenyl-2-(1H)-pyridone three times per day.

106. The use of any one of claims 92 to 100, wherein the granulate formulation delivers 534 mg of the 5-methyl-1-phenyl-2-(1H)-pyridone three times per day.

107. The use of any one of claims 92 to 100, wherein the granulate formulation delivers 801 mg of the 5-methyl-1-phenyl-2-(1H)-pyridone three times per day.

108. A use of the granulate formulation of any one of claims 1 to 40 in the preparation of medicament for treatment of idiopathic pulmonary fibrosis.

109. A use of the granulate formulation of any one of claims 1 to 40, in the preparation of a medicament for treatment of a disease selected from the group consisting of: idiopathic pulmonary fibrosis; pulmonary fibrosis; bronchiolitis obliterans; chronic lung transplant rejection; scleroderma; primary focal segmental glomerulosclerosis (FSGC); membranoproliferative glomerulonephritis (MPGN); idiopathic interstitial pneumonia; interstitial lung disease in systemic sclerosis; a fibrosis condition of the lung; autoimmune lung diseases; benign prostate hypertrophy; coronary infarction; myocardial infarction; atrial fibrillation; cerebral infarction; myocardiac fibrosis; musculoskeletal fibrosis; post-surgical adhesions; liver cirrhosis; renal fibrotic disease; fibrotic vascular disease; Hermansky-Pudlak syndrome; neurofibromatosis; Alzheimer's disease; diabetic retinopathy; diabetic skin lesions; lymph node fibrosis associated with HIV; chronic obstructive pulmonary disease (COPD); inflammatory pulmonary fibrosis; rheumatoid arthritis; rheumatoid arthritis-associated interstitial lung disease; rheumatoid spondylitis; osteoarthritis; gout; arthritic conditions; sepsis; septic shock; endotoxic shock; gram-negative sepsis; toxic shock syndrome; myofacial pain syndrome (MPS); Shigellosis; asthma; adult respiratory distress syndrome; inflammatory bowel disease; Crohn's disease; psoriasis; eczema; ulcerative colitis; glomerular nephritis; chronic thyroiditis; Grave's disease; Ormond's disease; autoimmune gastritis; myasthenia gravis; autoimmune hemolytic anemia; autoimmune neutropenia; thrombocytopenia; pancreatic fibrosis; chronic active hepatitis

including hepatic fibrosis; acute renal disease; chronic renal disease; renal fibrosis; diabetic nephropathy; irritable bowel syndrome; pyresis; restenosis; cerebral malaria; stroke; ischemic injury; neural trauma; Huntington's disease; Parkinson's disease; acute pain; chronic pain; allergies; allergic rhinitis; allergic conjunctivitis; cardiac hypertrophy, chronic heart failure; acute coronary syndrome; cachexia; malaria; leprosy; leishmaniasis; Lyme disease; Reiter's syndrome; acute synoviitis; muscle degeneration, bursitis; tendonitis; tenosynoviitis; herniated, ruptured, or prolapsed intervertebral disk syndrome; osteopetrosis; thrombosis; silicosis; pulmonary sarcosis; bone resorption diseases; osteoporosis; multiple myeloma-related bone disorders; cancer; metastatic breast carcinoma; colorectal carcinoma; malignant melanoma; gastric cancer; non-small cell lung cancer; graft-versus-host reaction; auto-immune diseases; multiple sclerosis; lupus; fibromyalgia; AIDS; viral diseases; Herpes Zoster; Herpes Simplex I or II; influenza virus; Severe Acute Respiratory Syndrome (SARS); cytomegalovirus; diabetes mellitus; proliferative disorders; benign hyperplasia; malignant hyperplasia; acute myelogenous leukemia; chronic myelogenous leukemia; Kaposi's sarcoma; metastatic melanoma; multiple myeloma; breast cancer; bone metastases; pain disorders; neuromuscular pain; headache; cancer pain; dental pain; arthritis pain; angiogenic disorders; solid tumor angiogenesis; ocular neovascularization; infantile hemangioma; edema, fever, analgesia, and pain associated with the cyclooxygenase or lipoxygenase signaling pathways or prostaglandin endoperoxide synthase-2; organ hypoxia; thrombin-induced platelet aggregation; and protozoal diseases.

110. A use of the granulate formulation of any one of claims 1 to 40 in the preparation of a medicament for treatment of a fibrotic condition.

111. The use of claim 110, wherein the fibrotic condition is selected from the group consisting of pulmonary fibrosis, hepatic fibrosis, cardiac fibrosis, keloid, dermal fibrosis, coronary restenosis, post-surgical adhesions, and combinations thereof.

112. The use of claim 111, wherein said pulmonary fibrosis is selected from the group consisting of idiopathic pulmonary fibrosis and Hermansky-Pudlak Syndrome.

113. A use of the granulate formulation of any one of claims 1 to 40 in the preparation of a medicament for treatment of a disorder mediated by cytokines.

114. The use of claim 113, wherein the cytokines comprises one or more selected from the group consisting of TNF-α, TGF-β1, bFGF, PDGF, and EGF.

115. The use of claim 113 or 114, wherein said disorder is selected from the group consisting of multiple sclerosis, arthritis, asthma, chronic rhinitis, and edema.

116. The use of any one of claims 108 to 115, wherein the medicament is a tablet.

117. The use of claim 116, wherein the tablet comprises 267 mg, 534 mg, or 801 mg of the 5-methyl-1-phenyl-2-(1H)-pyridone.

118. The use of any one of claims 108 to 117, wherein the medicament is for delivery in one or more unit doses, one or more times a day.

119. The use of claim 118, wherein the one or more unit doses, one or more times a day, delivers at least 1200 mg of the 5-methyl-1-phenyl-2-(1H)-pyridone per day.

120. The use of claim 118, wherein the one or more unit doses, one or more times a day, delivers about 800 mg per day to about 2405 mg of the 5-methyl-1-phenyl-2-(1H)-pyridone per day.

121. The use of any one of claims 108 to 116, wherein the medicament delivers 267 mg of the 5-methyl-1-phenyl-2-(1H)-pyridone three times per day.

122. The use of any one of claims 108 to 116, wherein the medicament delivers 534

mg of the 5-methyl-1-phenyl-2-(1H)-pyridone three times per day.

123. The use of any one of claims 108 to 116, wherein the medicament delivers 801 mg of the 5-methyl-1-phenyl-2-(1H)-pyridone three times per day.

124. The granulate formulation of any one of claims 1 to 40 for use in the treatment of idiopathic pulmonary fibrosis.

125. The granulate formulation of any one of claims 1 to 40 for use in the treatment of a disease selected from the group consisting of: idiopathic pulmonary fibrosis; pulmonary fibrosis; bronchiolitis obliterans; chronic lung transplant rejection; scleroderma; primary focal segmental glomerulosclerosis (FSGC); membranoproliferative glomerulonephritis (MPGN); idiopathic interstitial pneumonia; interstitial lung disease in systemic sclerosis; a fibrosis condition of the lung; autoimmune lung diseases; benign prostate hypertrophy; coronary infarction; myocardial infarction; atrial fibrillation; cerebral infarction; myocardiac fibrosis; musculoskeletal fibrosis; post-surgical adhesions; liver cirrhosis; renal fibrotic disease; fibrotic vascular disease; Hermansky-Pudlak syndrome; neurofibromatosis; Alzheimer's disease; diabetic retinopathy; diabetic skin lesions; lymph node fibrosis associated with HIV; chronic obstructive pulmonary disease (COPD); inflammatory pulmonary fibrosis; rheumatoid arthritis; rheumatoid arthritis-associated interstitial lung disease; rheumatoid spondylitis; osteoarthritis; gout; arthritic conditions; sepsis; septic shock; endotoxic shock; gram-negative sepsis; toxic shock syndrome; myofacial pain syndrome (MPS); Shigellosis; asthma; adult respiratory distress syndrome; inflammatory bowel disease; Crohn's disease; psoriasis; eczema; ulcerative colitis; glomerular nephritis; chronic thyroiditis; Grave's disease; Ormond's disease; autoimmune gastritis; myasthenia gravis; autoimmune hemolytic anemia; autoimmune neutropenia; thrombocytopenia; pancreatic fibrosis; chronic active hepatitis including hepatic fibrosis; acute renal disease; chronic renal disease; renal fibrosis; diabetic nephropathy; irritable bowel syndrome; pyresis; restenosis; cerebral malaria; stroke; ischemic injury; neural trauma; Huntington's disease; Parkinson's disease; acute pain; chronic pain; allergies; allergic rhinitis; allergic conjunctivitis;

cardiac hypertrophy, chronic heart failure; acute coronary syndrome; cachexia; malaria; leprosy; leishmaniasis; Lyme disease; Reiter's syndrome; acute synoviitis; muscle degeneration, bursitis; tendonitis; tenosynoviitis; herniated, ruptured, or prolapsed intervertebral disk syndrome; osteopetrosis; thrombosis; silicosis; pulmonary sarcosis; bone resorption diseases; osteoporosis; multiple myeloma-related bone disorders; cancer; metastatic breast carcinoma; colorectal carcinoma; malignant melanoma; gastric cancer; non-small cell lung cancer; graft-versus-host reaction; auto-immune diseases; multiple sclerosis; lupus; fibromyalgia; AIDS; viral diseases; Herpes Zoster; Herpes Simplex I or II; influenza virus; Severe Acute Respiratory Syndrome (SARS); cytomegalovirus; diabetes mellitus; proliferative disorders; benign hyperplasia; malignant hyperplasia; acute myelogenous leukemia; chronic myelogenous leukemia; Kaposi's sarcoma; metastatic melanoma; multiple myeloma; breast cancer; bone metastases; pain disorders; neuromuscular pain; headache; cancer pain; dental pain; arthritis pain; angiogenic disorders; solid tumor angiogenesis; ocular neovascularization; infantile hemangioma; edema, fever, analgesia, and pain associated with the cyclooxygenase or lipoxygenase signaling pathways or prostaglandin endoperoxide synthase-2; organ hypoxia; thrombin-induced platelet aggregation; and protozoal diseases.

126. The granulate formulation of any one of claims 1 to 40 for use in the treatment of a fibrotic condition.

127. The granulate formulation for use of claim 126, wherein the fibrotic condition is selected from the group consisting of pulmonary fibrosis, hepatic fibrosis, cardiac fibrosis, keloid, dermal fibrosis, coronary restenosis, post-surgical adhesions, and combinations thereof.

128. The granulate formulation for use of claim 127, wherein said pulmonary fibrosis is selected from the group consisting of idiopathic pulmonary fibrosis and Hermansky-Pudlak Syndrome.

129. The granulate formulation of any one of claims 1 to 40 for use in the treatment of

a disorder mediated by cytokines.

130. The granulate formulation for use of claim 129, wherein the cytokines comprises one or more selected from the group consisting of TNF-α, TGF-β1, bFGF, PDGF, and EGF.

131. The granulate formulation for use of claim 129 or 130, wherein said disorder is selected from the group consisting of multiple sclerosis, arthritis, asthma, chronic rhinitis, and edema.

132. The granulate formulation for use of any one of claims 124 to 131, which is a tablet.

133. The granulate formulation for use of claim 132, wherein the tablet comprises 267 mg, 534 mg, or 801 mg of the 5-methyl-1-phenyl-2-(1H)-pyridone.

134. The granulate formulation for use of any one of claims 124 to 133, in one or more unit doses, one or more times a day.

135. The granulate formulation for use of claim 134, wherein the one or more unit doses, one or more times a day, delivers at least 1200 mg of the 5-methyl-1-phenyl-2-(1H)-pyridone per day.

136. The granulate formulation for use of claim 134, wherein the one or more unit doses, one or more times a day, delivers about 800 mg per day to about 2405 mg of the 5-methyl-1-phenyl-2-(1H)-pyridone per day.

137. The granulate formulation for use of any one of claims 124 to 132, wherein the granulate formulation delivers 267 mg of the 5-methyl-1-phenyl-2-(1H)-pyridone three times per day.

138. The granulate formulation for use of any one of claims 124 to 132, wherein the granulate formulation delivers 534 mg of the 5-methyl-1-phenyl-2-(1H)-pyridone three times per day.

139. The granulate formulation for use of any one of claims 124 to 132, wherein the granulate formulation delivers 801 mg of the 5-methyl-1-phenyl-2-(1H)-pyridone three times per day.

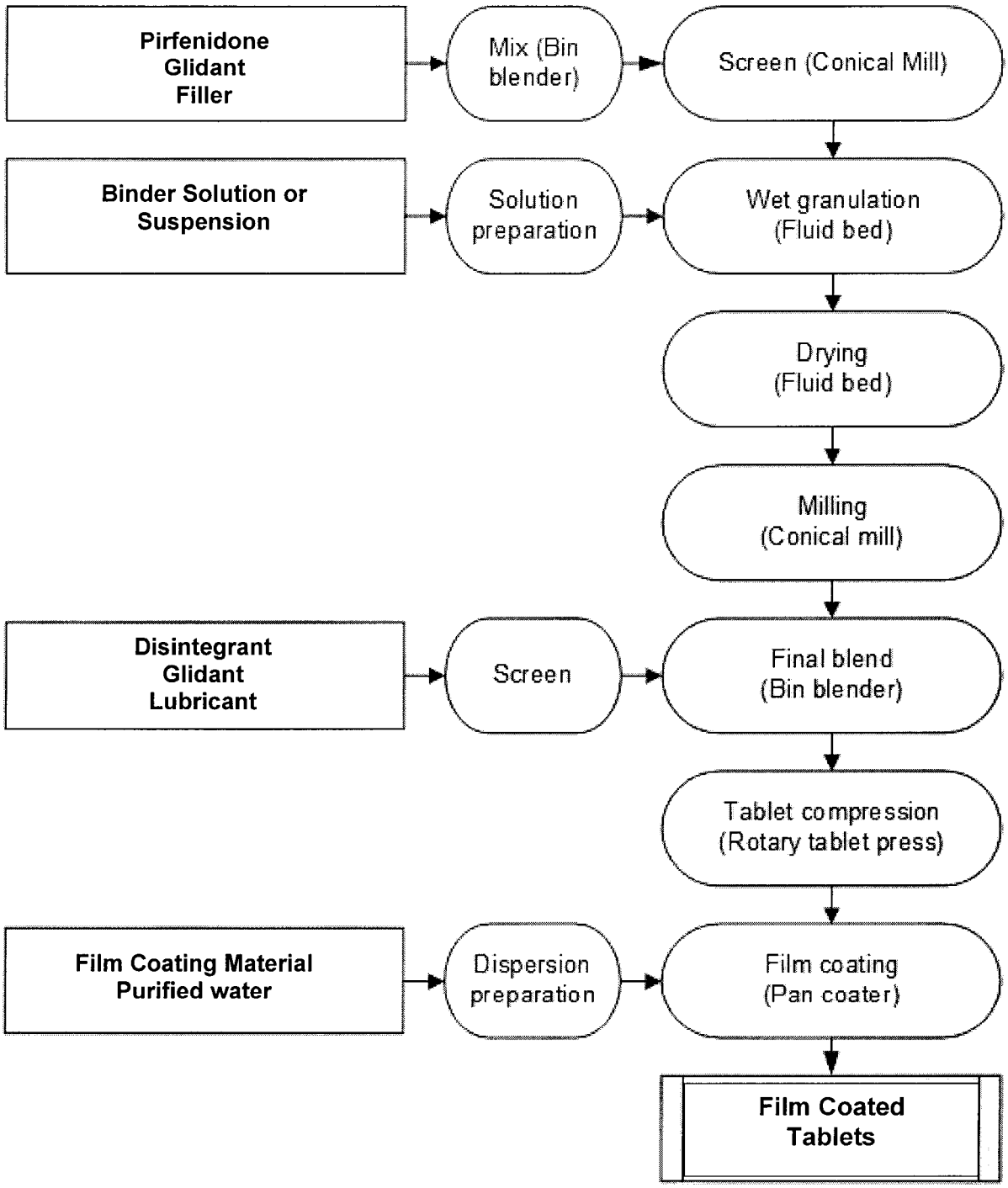
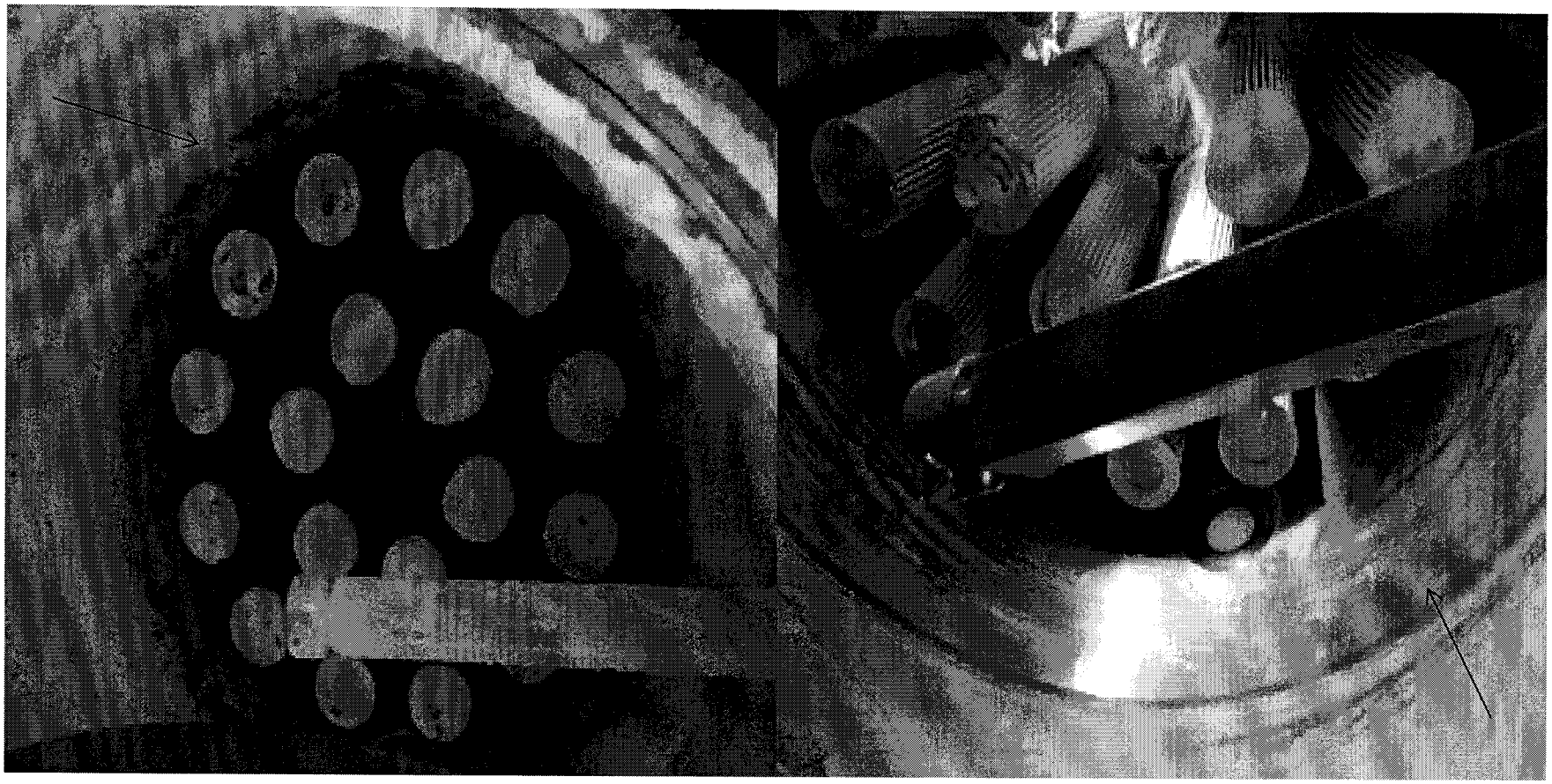

Pirfenidone
Glidant
Filler
Mix (Bin blender)
Screen (Conical Mill)
Binder Solution or Suspension
Solution preparation
Wet granulation (Fluid bed)
Drying (Fluid bed)
Milling (Conical mill)
Disintegrant
Glidant
Lubricant
Screen
Final blend (Bin blender)
Tablet compression (Rotary tablet press)
Film Coating Material
Purified water
Dispersion preparation
Film coating (Pan coater)
Film Coated Tablets

FIGURE 1



Comparative Example Formulation
(Without Intragranular Glidant)

FIGURE 2A

Example 1 Formulation
(With Intragranular Glidant)

FIGURE 2B

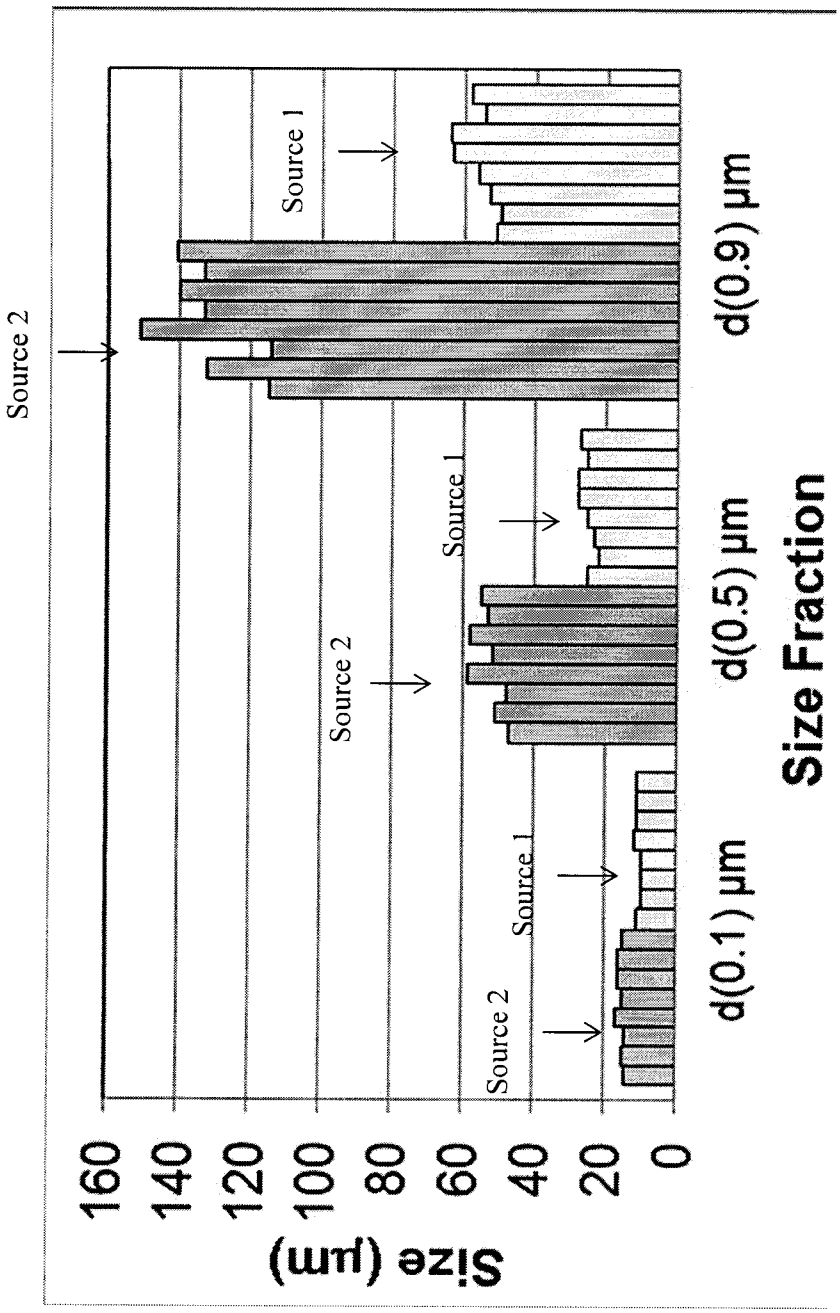

Source 2
Source 1
Source 2
Source 1
Source 2
Source 1
Size (µm)
160
140
120
100
80
60
40
20
0
d(0.1) µm
d(0.5) µm
d(0.9) µm
Size Fraction

FIGURE 3

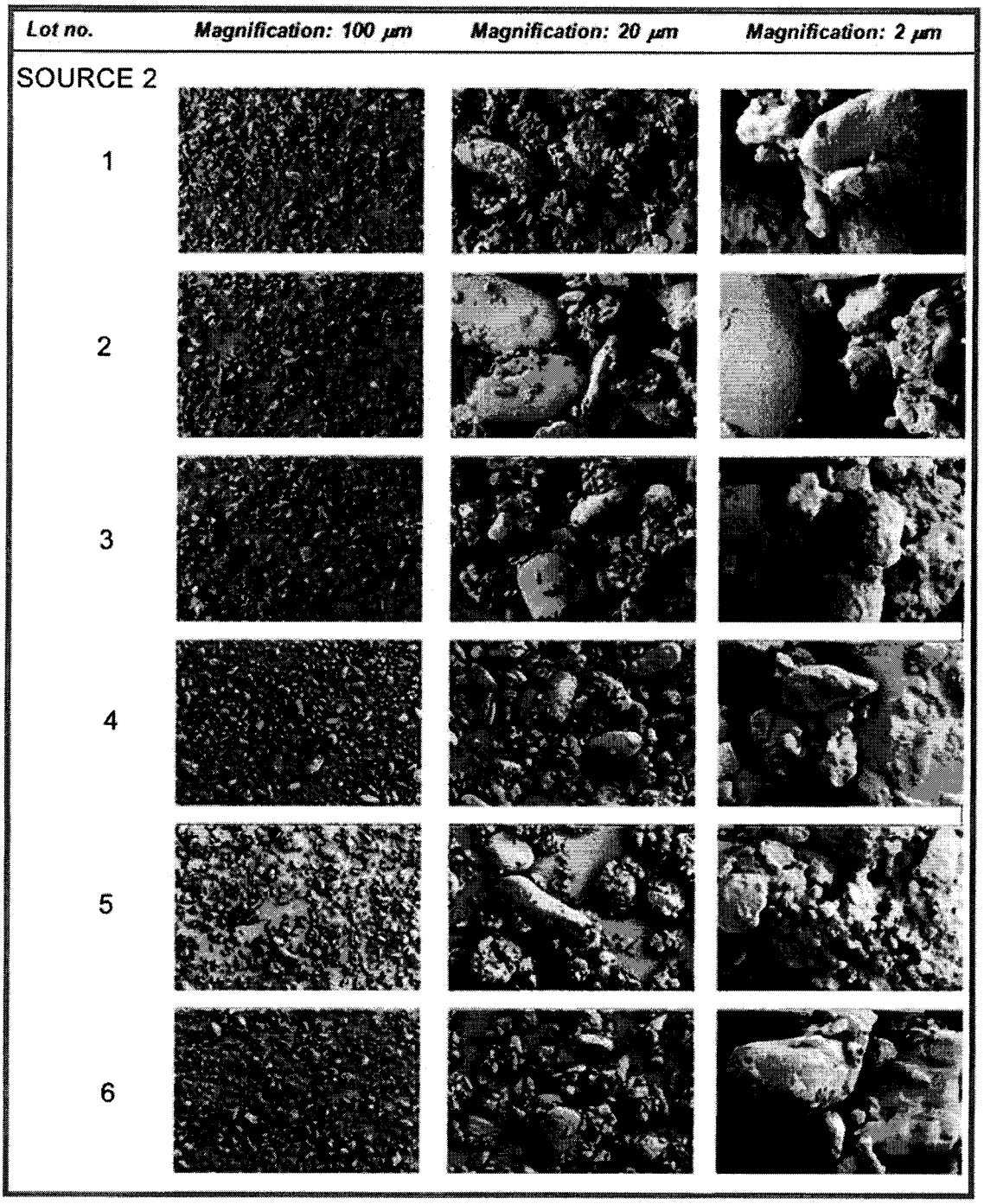

Lot no.
Magnification: 100 µm
Magnification: 20 µm
Magnification: 2 µm
SOURCE 2
1
2
3
4
5
6

FIGURE 4A

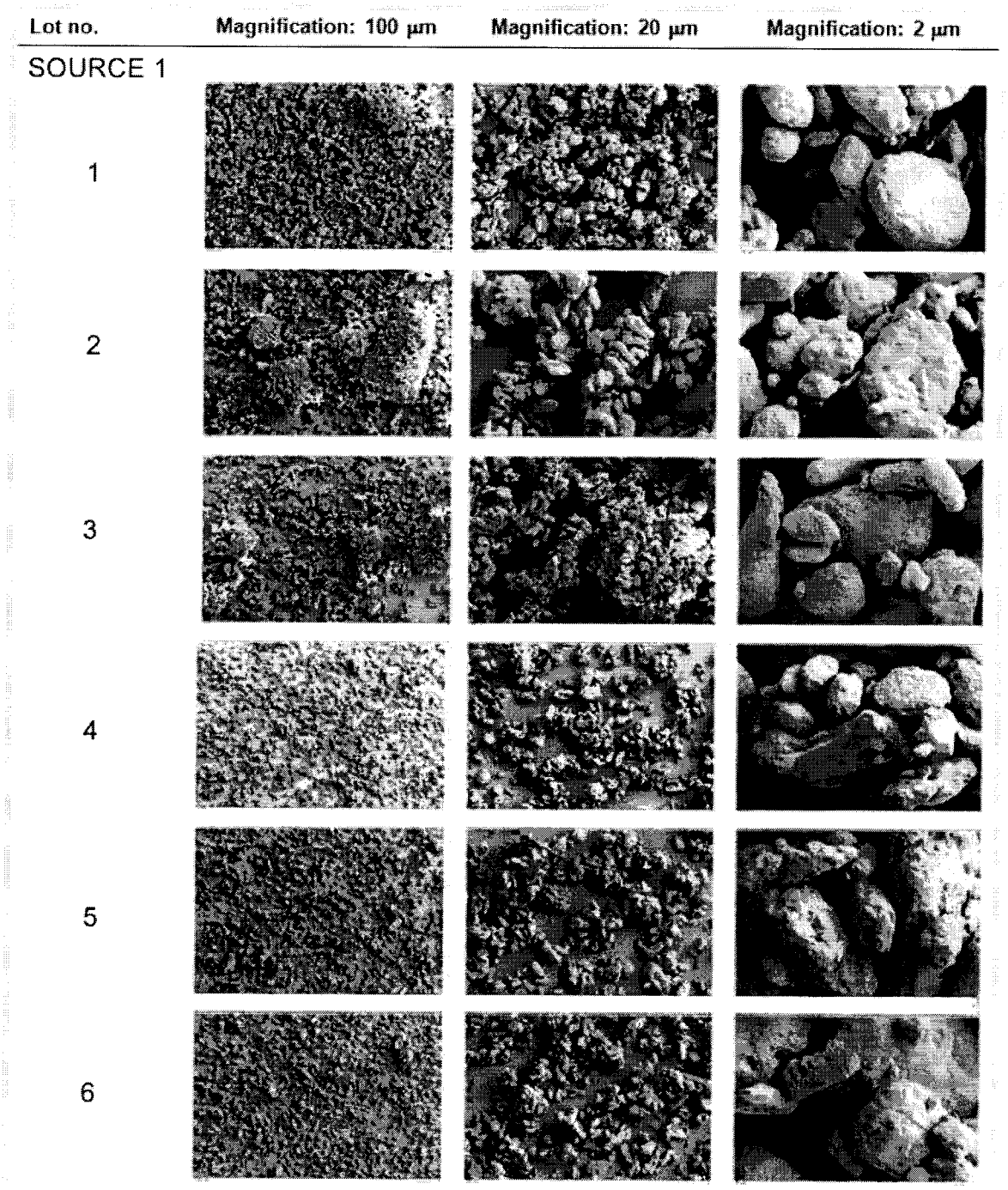

Lot no.
Magnification: 100 µm
Magnification: 20 µm
Magnification: 2 µm
SOURCE 1
1
2
3
4
5
6

FIGURE 4B

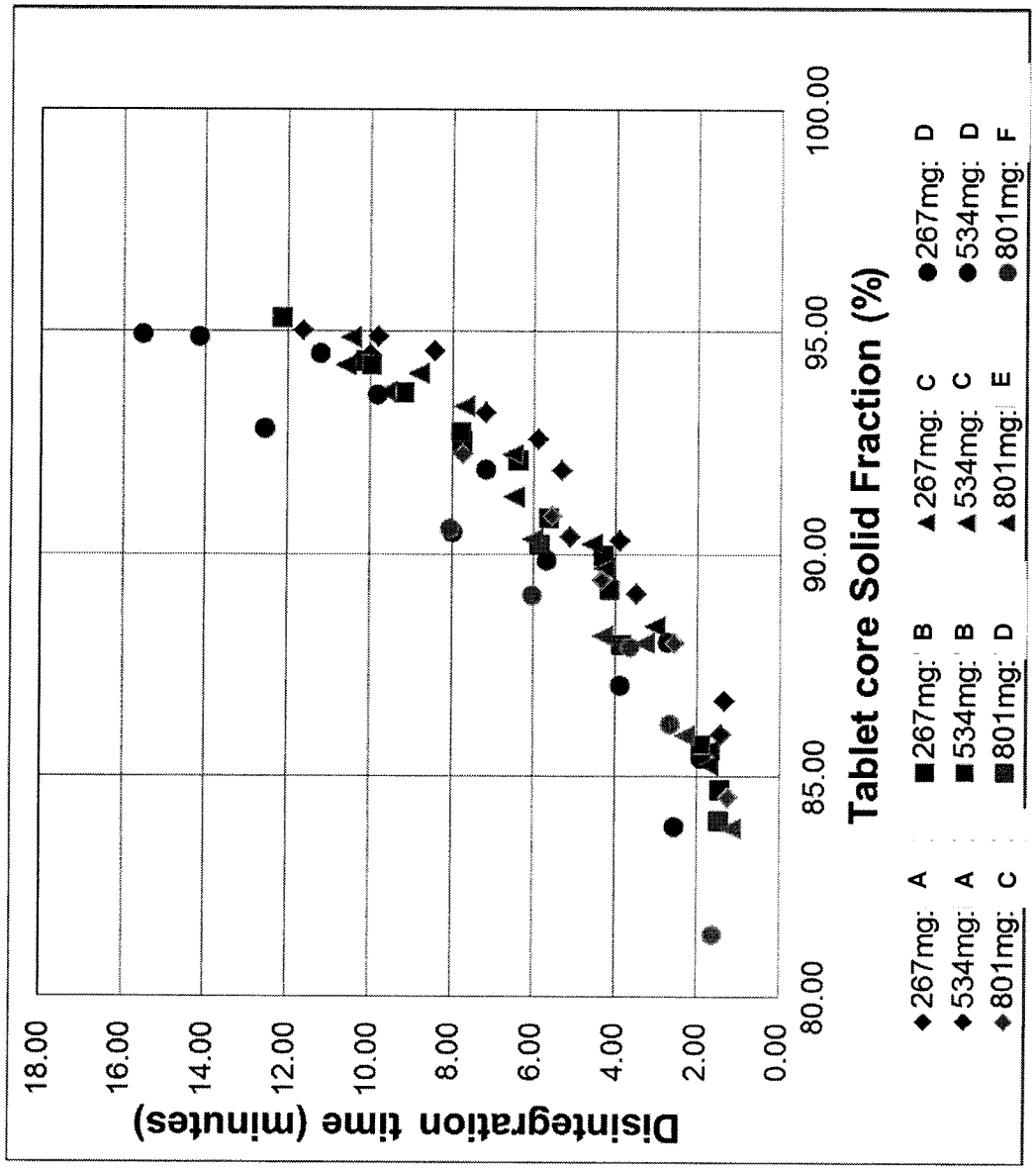

Disintegration time (minutes)
18.00
16.00
14.00
12.00
10.00
8.00
6.00
4.00
2.00
0.00
80.00
85.00
90.00
95.00
100.00
Tablet core Solid Fraction (%)
◆267mg: A
◆534mg: A
◆801mg: C
■267mg: B
■534mg: B
■801mg: D
▲267mg: C
▲534mg: C
▲801mg: E
●267mg: D
●534mg: D
●801mg: F

FIGURE 5

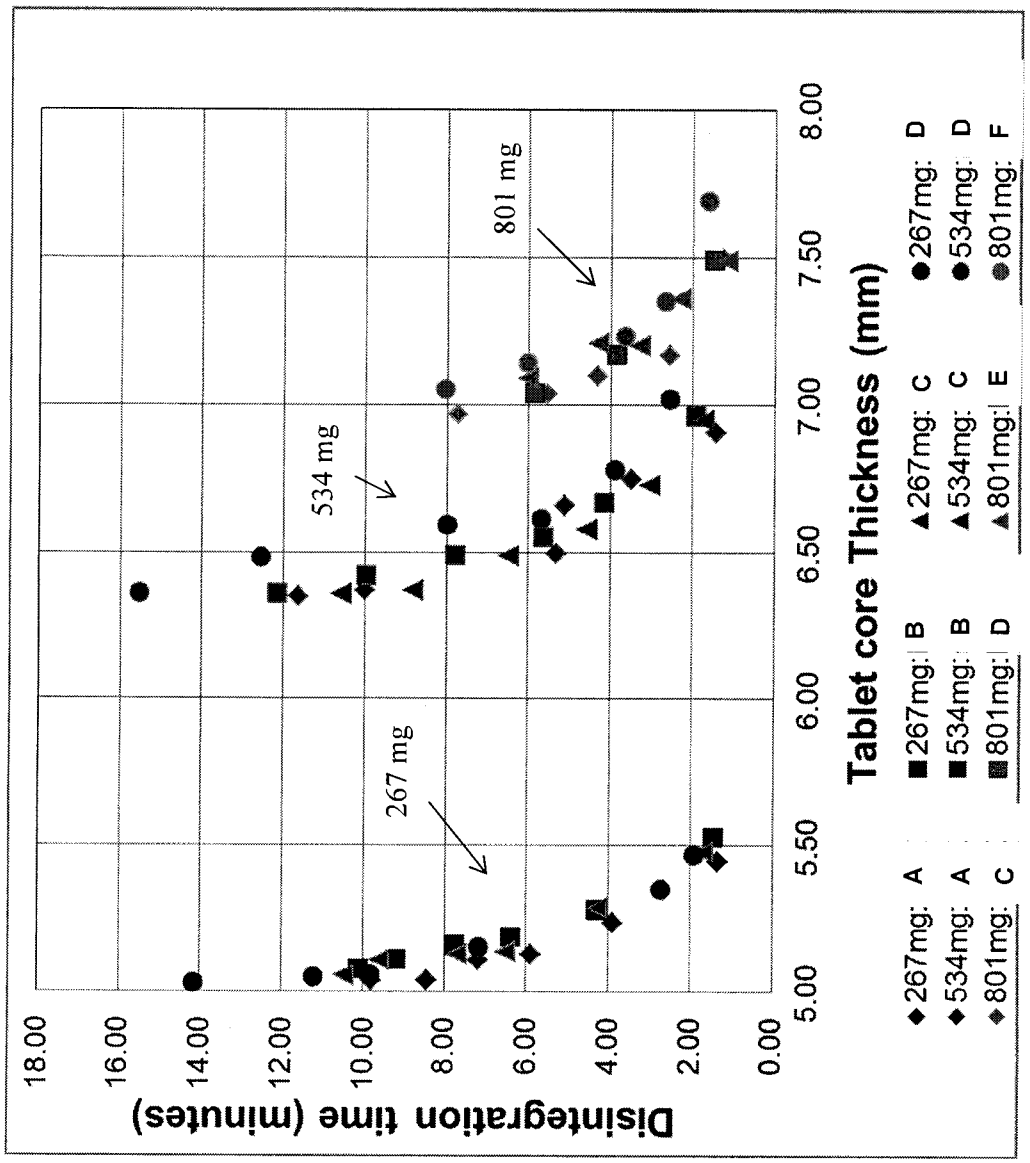

Disintegration time (minutes)
18.00
16.00
14.00
12.00
10.00
8.00
6.00
4.00
2.00
0.00
5.00
5.50
6.00
6.50
7.00
7.50
8.00
Tablet core Thickness (mm)
267 mg
534 mg
801 mg
◆267mg: A
◆534mg: A
◆801mg: C
■267mg: B
■534mg: B
■801mg: D
▲267mg: C
▲534mg: C
▲801mg: E
●267mg: D
●534mg: D
●801mg: F

FIGURE 6

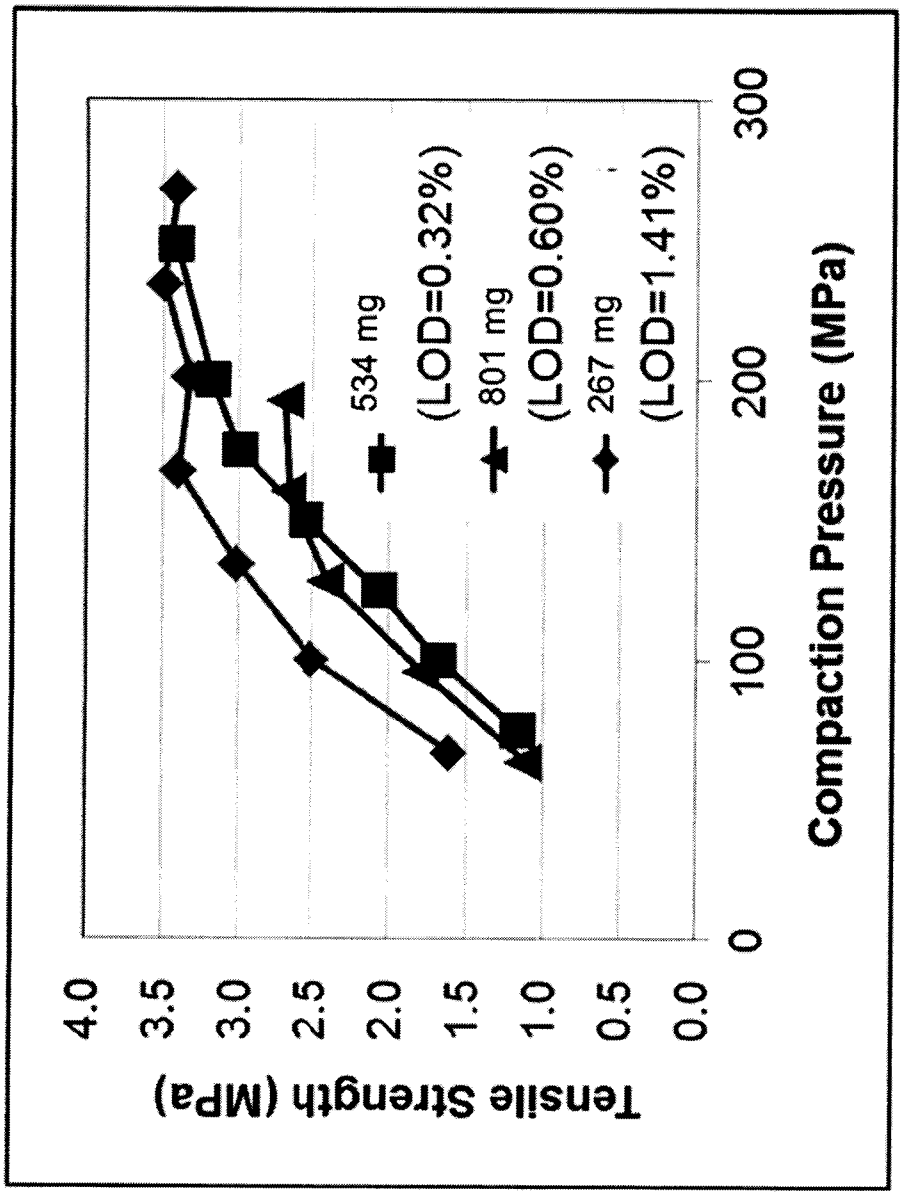

Tensile Strength (MPa)
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
0
100
200
300
Compaction Pressure (MPa)
534 mg
(LOD=0.32%)
801 mg
(LOD=0.60%)
267 mg
(LOD=1.41%)

FIGURE 7

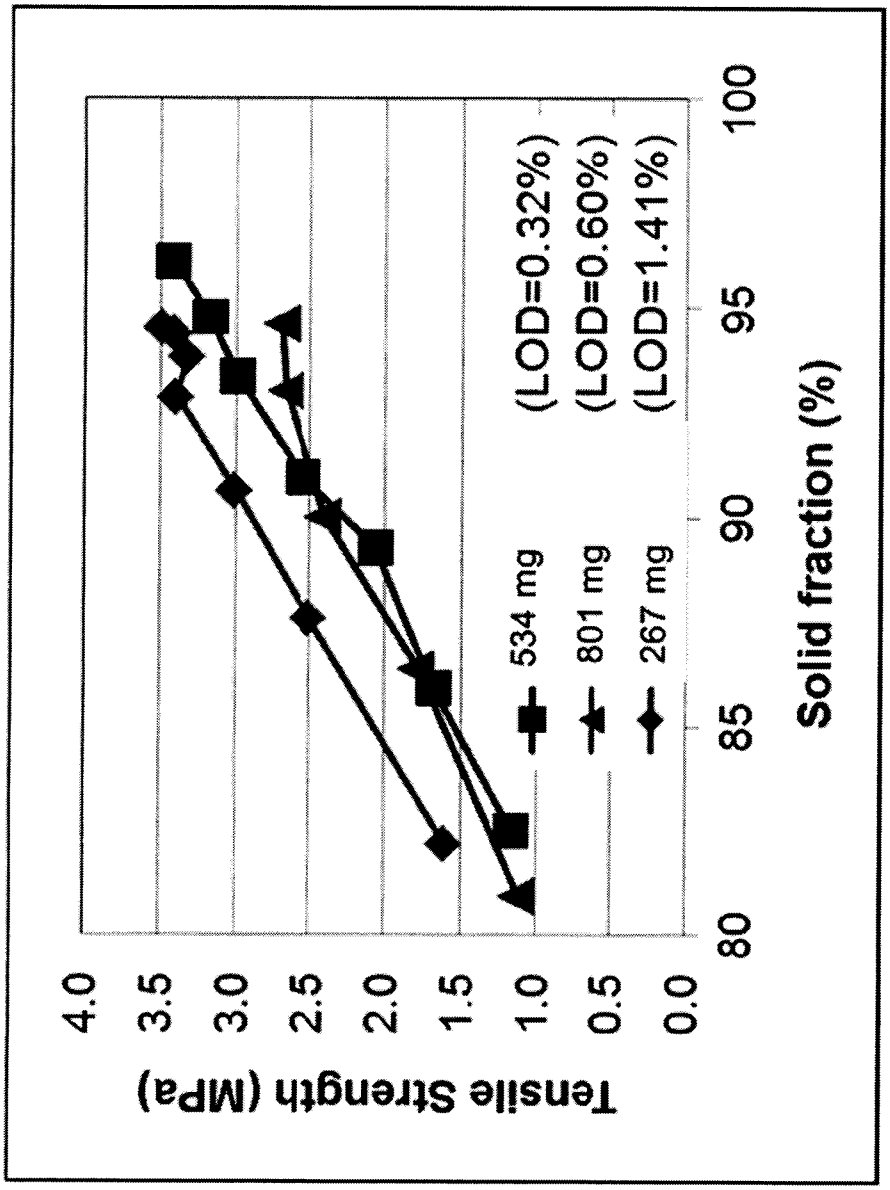

Tensile Strength (MPa)
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
80
85
90
95
100
Solid fraction (%)
534 mg (LOD=0.32%)
801 mg (LOD=0.60%)
267 mg (LOD=1.41%)

FIGURE 8

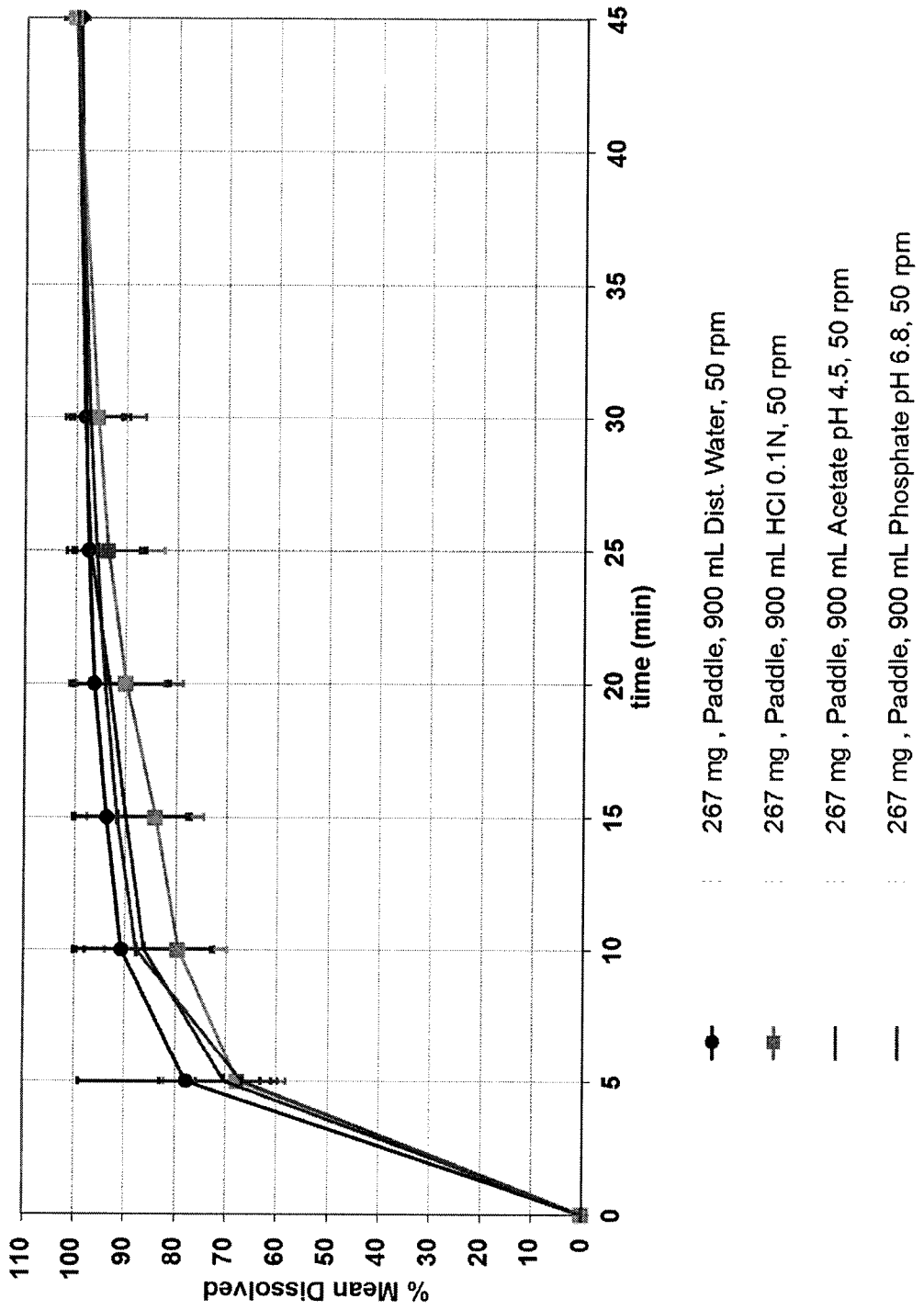

% Mean Dissolved
110
100
90
80
70
60
50
40
30
20
10
0
0
5
10
15
20
25
30
35
40
45
time (min)
267 mg , Paddle, 900 mL Dist. Water, 50 rpm
267 mg , Paddle, 900 mL HCl 0.1N, 50 rpm
267 mg , Paddle, 900 mL Acetate pH 4.5, 50 rpm
267 mg , Paddle, 900 mL Phosphate pH 6.8, 50 rpm

FIGURE 9

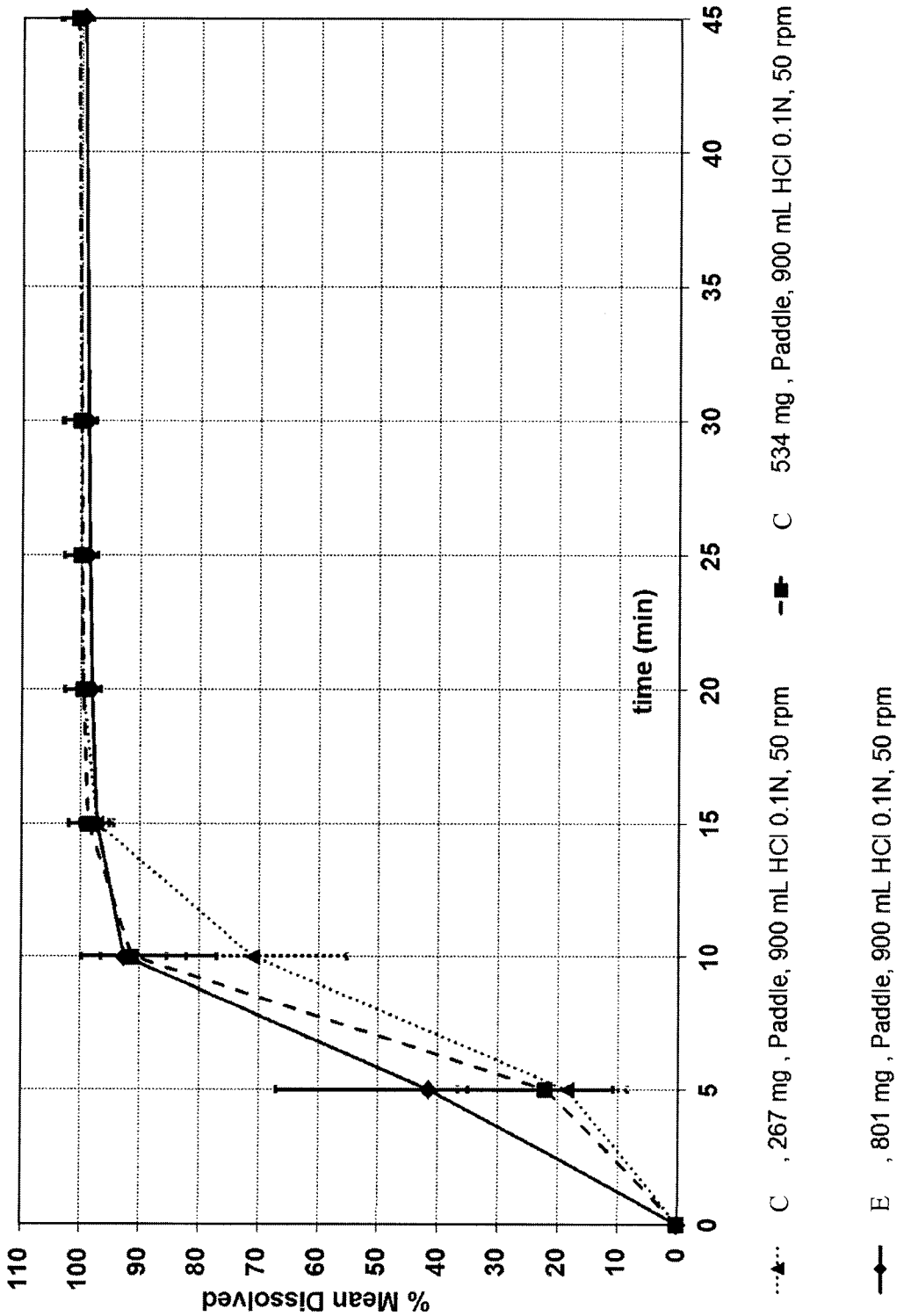

% Mean Dissolved
110
100
90
80
70
60
50
40
30
20
10
0
0
5
10
15
20
25
30
35
40
45
time (min)
C , 267 mg , Paddle, 900 mL HCl 0.1N, 50 rpm
C 534 mg , Paddle, 900 mL HCl 0.1N, 50 rpm
E , 801 mg , Paddle, 900 mL HCl 0.1N, 50 rpm

FIGURE 10

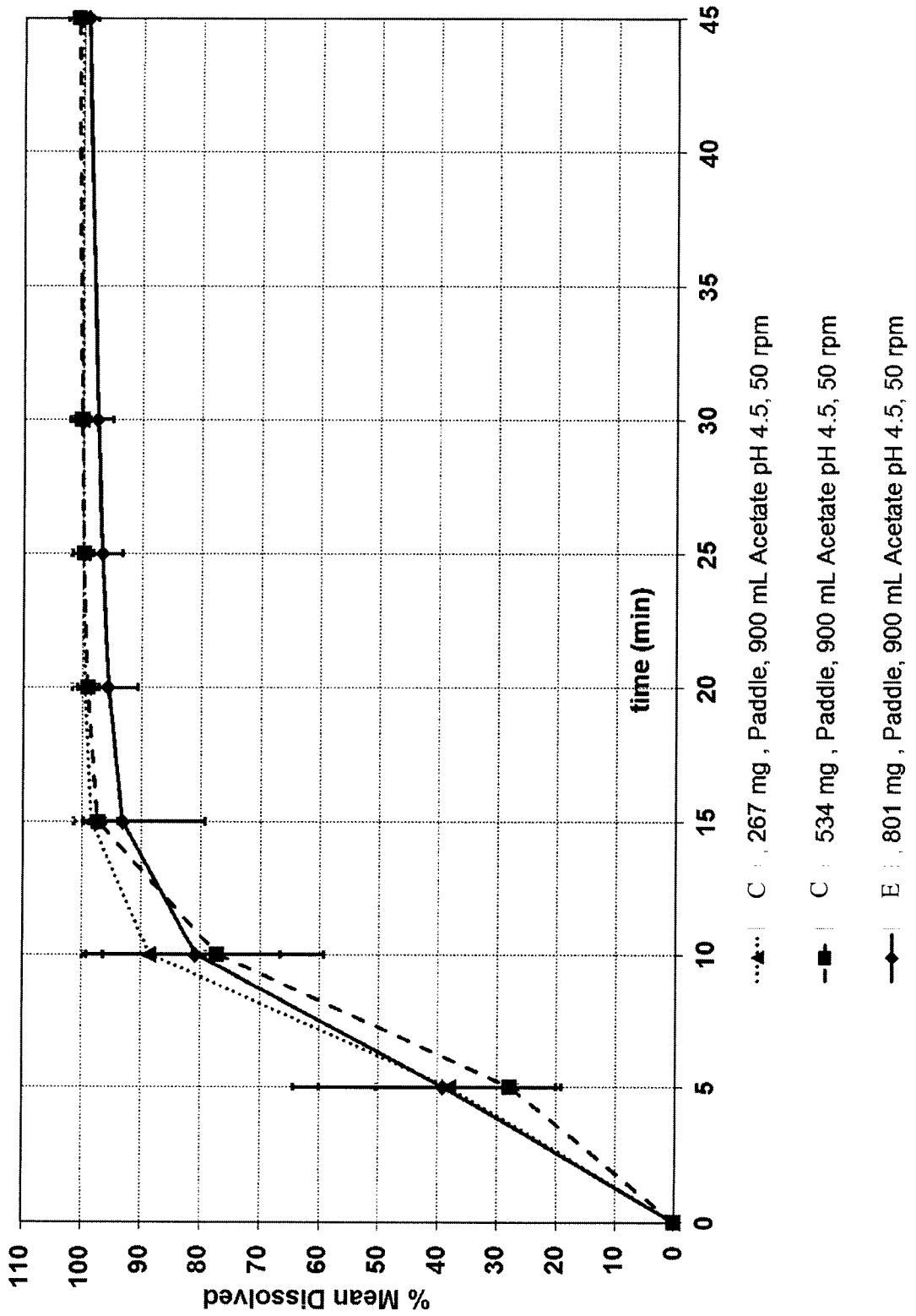

% Mean Dissolved
time (min)
0
10
20
30
40
50
60
70
80
90
100
110
0
5
10
15
20
25
30
35
40
45
C : 267 mg , Paddle, 900 mL Acetate pH 4.5, 50 rpm
C : 534 mg , Paddle, 900 mL Acetate pH 4.5, 50 rpm
E : 801 mg , Paddle, 900 mL Acetate pH 4.5, 50 rpm

FIGURE 11

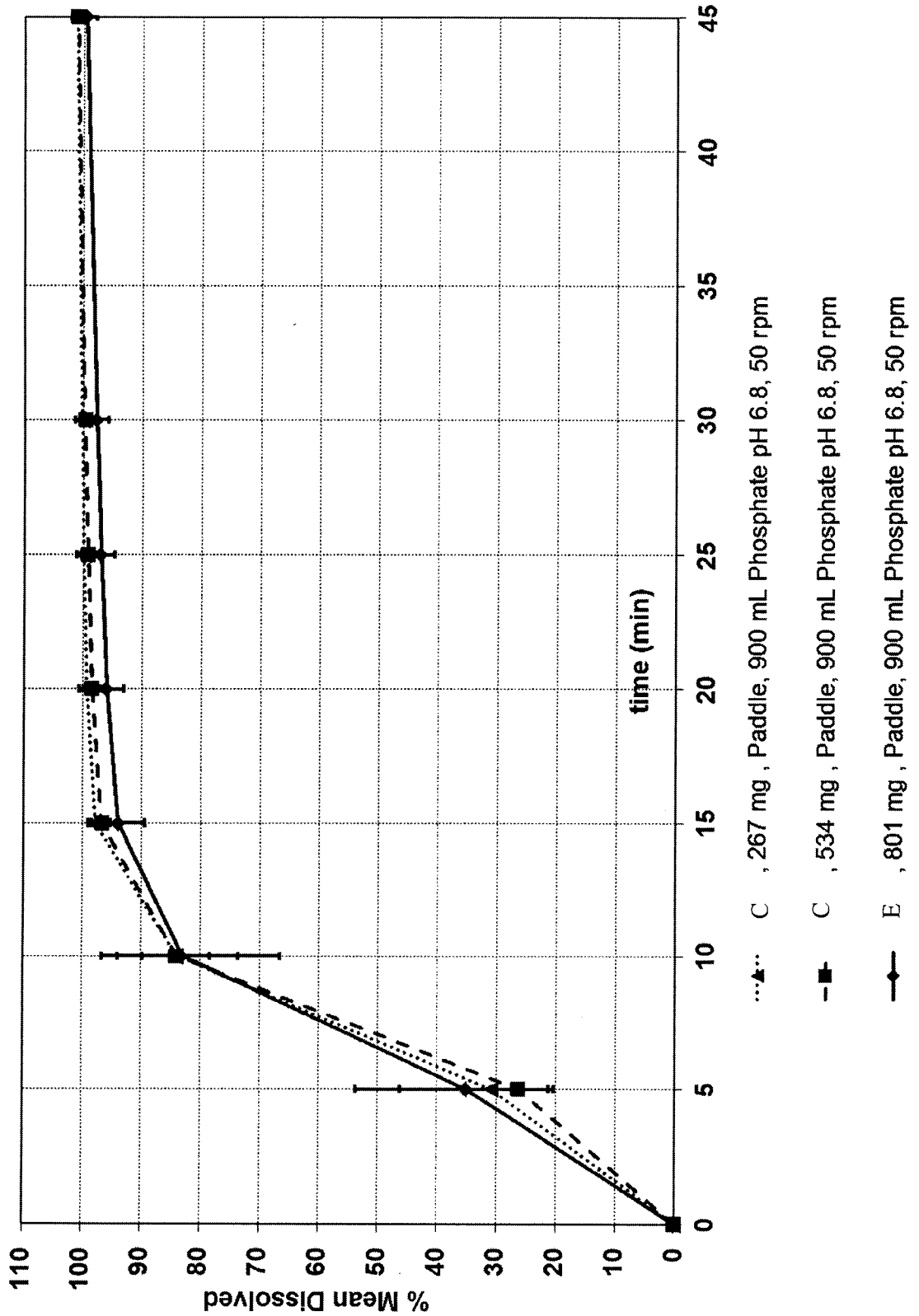

% Mean Dissolved
time (min)
0
10
20
30
40
50
60
70
80
90
100
110
0
5
10
15
20
25
30
35
40
45
C , 267 mg , Paddle, 900 mL Phosphate pH 6.8, 50 rpm
C , 534 mg , Paddle, 900 mL Phosphate pH 6.8, 50 rpm
E , 801 mg , Paddle, 900 mL Phosphate pH 6.8, 50 rpm

FIGURE 12

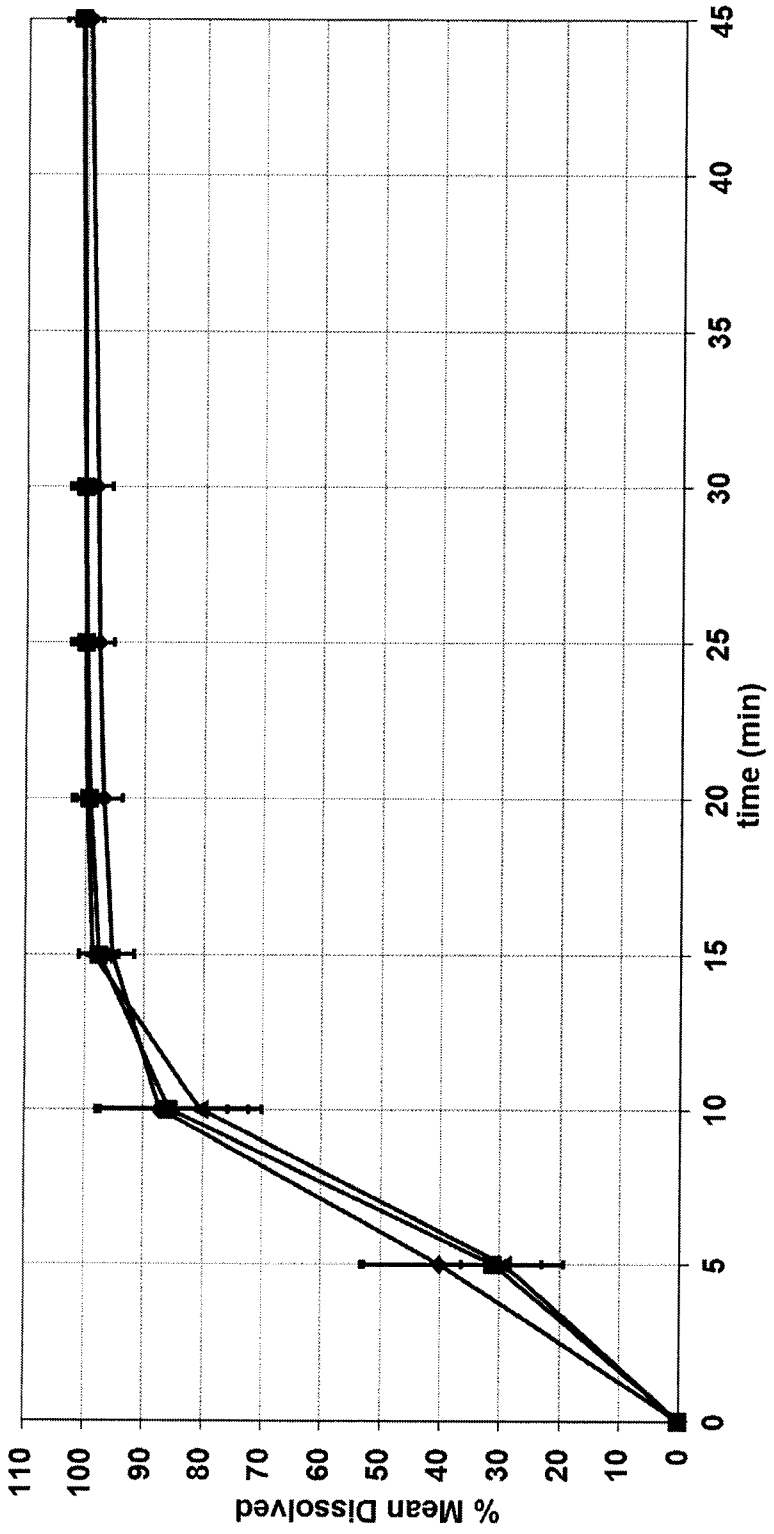

% Mean Dissolved
0
10
20
30
40
50
60
70
80
90
100
110
0
5
10
15
20
25
30
35
40
45
time (min)
C , 267 mg , Paddle, 900 mL Dist. Water, 50 rpm
C , 534 mg , Paddle, 900 mL Dist. Water, 50 rpm
E , 801 mg , Paddle, 900 mL Dist. Water, 50 rpm

FIGURE 13

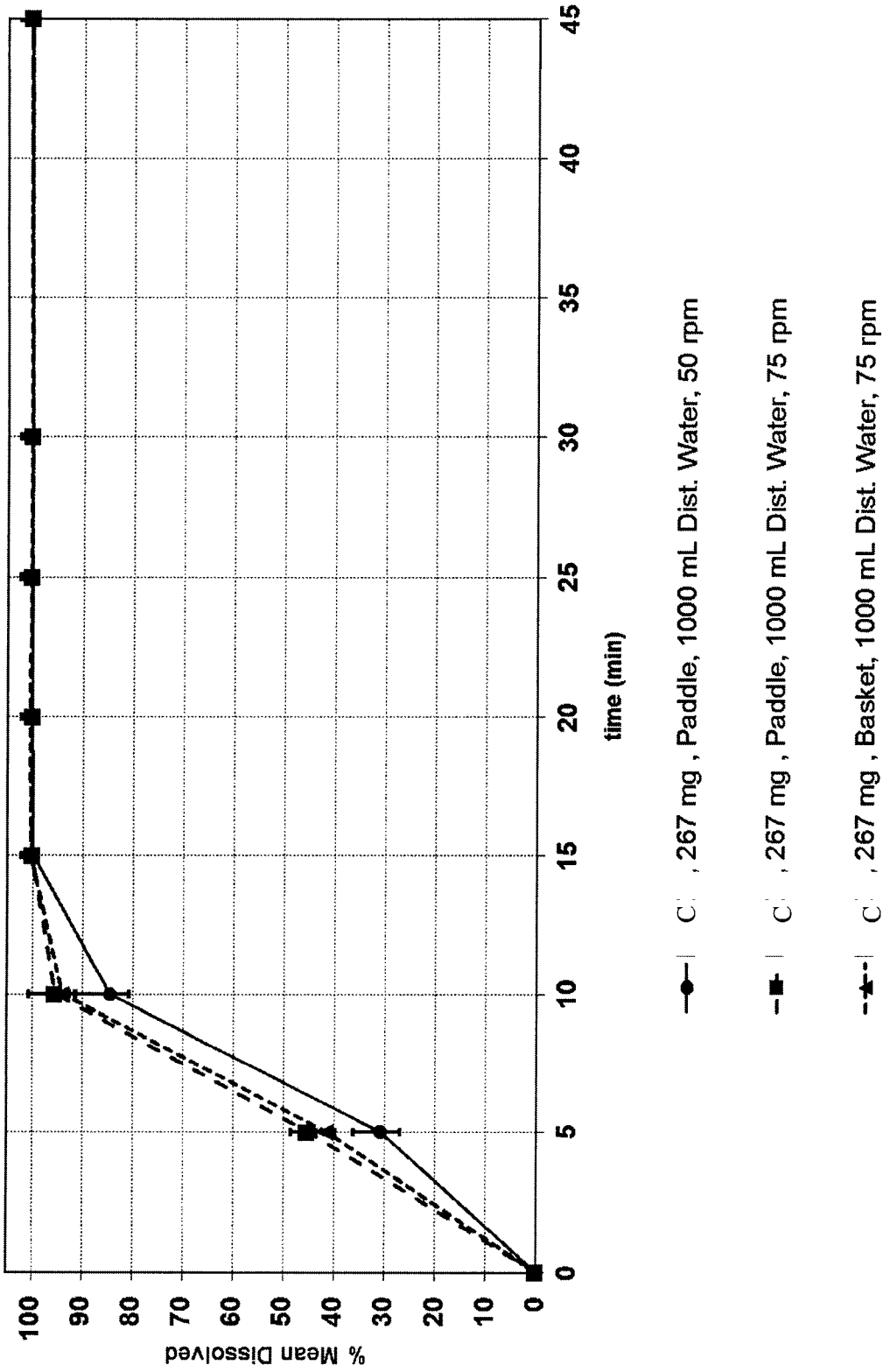

% Mean Dissolved
0
10
20
30
40
50
60
70
80
90
100
0
5
10
15
20
25
30
35
40
45
time (min)
C , 267 mg , Paddle, 1000 mL Dist. Water, 50 rpm
C , 267 mg , Paddle, 1000 mL Dist. Water, 75 rpm
C , 267 mg , Basket, 1000 mL Dist. Water, 75 rpm

FIGURE 14

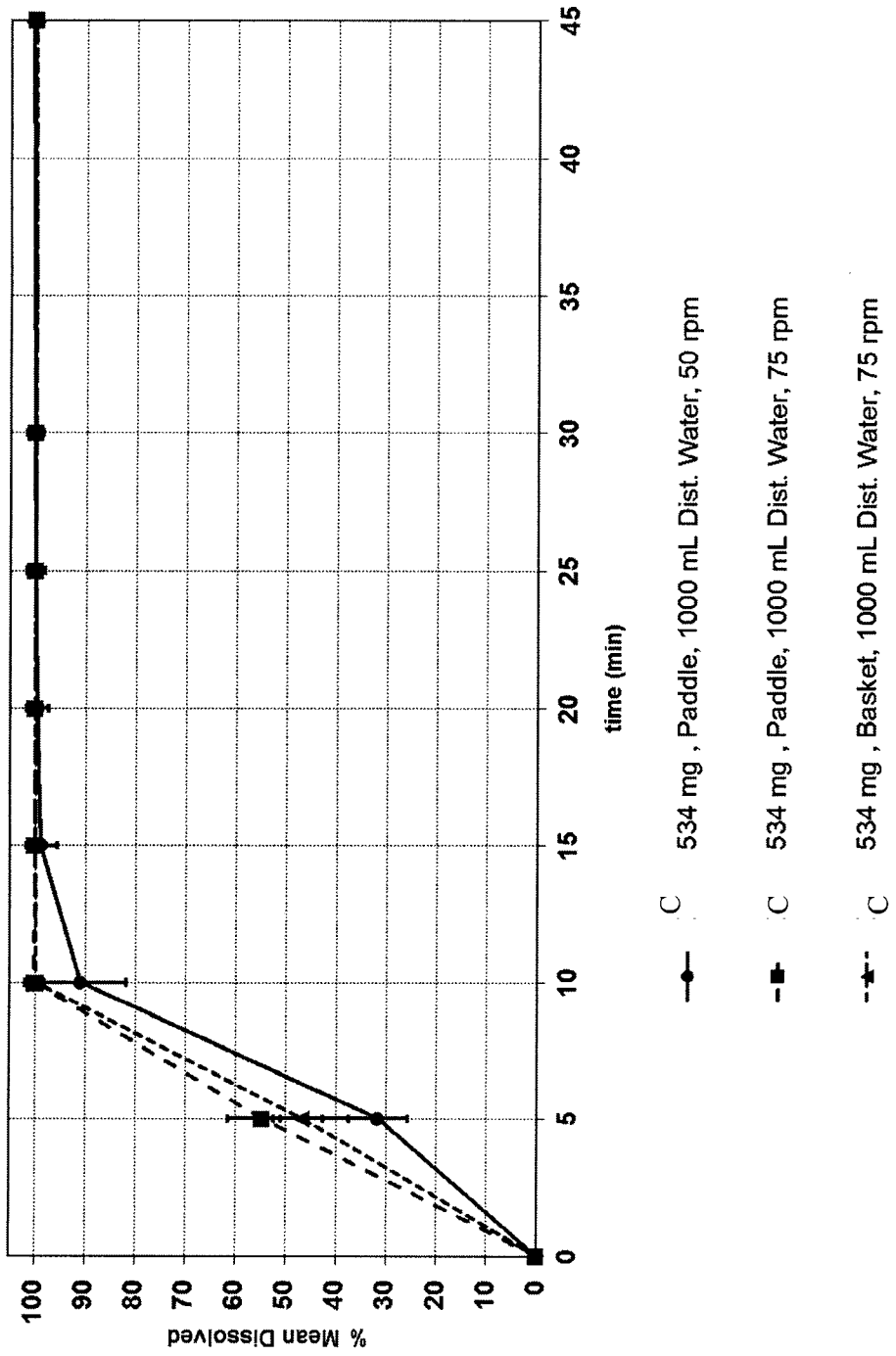

% Mean Dissolved
0
10
20
30
40
50
60
70
80
90
100
0
5
10
15
20
25
30
35
40
45
time (min)
C 534 mg , Paddle, 1000 mL Dist. Water, 50 rpm
C 534 mg , Paddle, 1000 mL Dist. Water, 75 rpm
C 534 mg , Basket, 1000 mL Dist. Water, 75 rpm

FIGURE 15

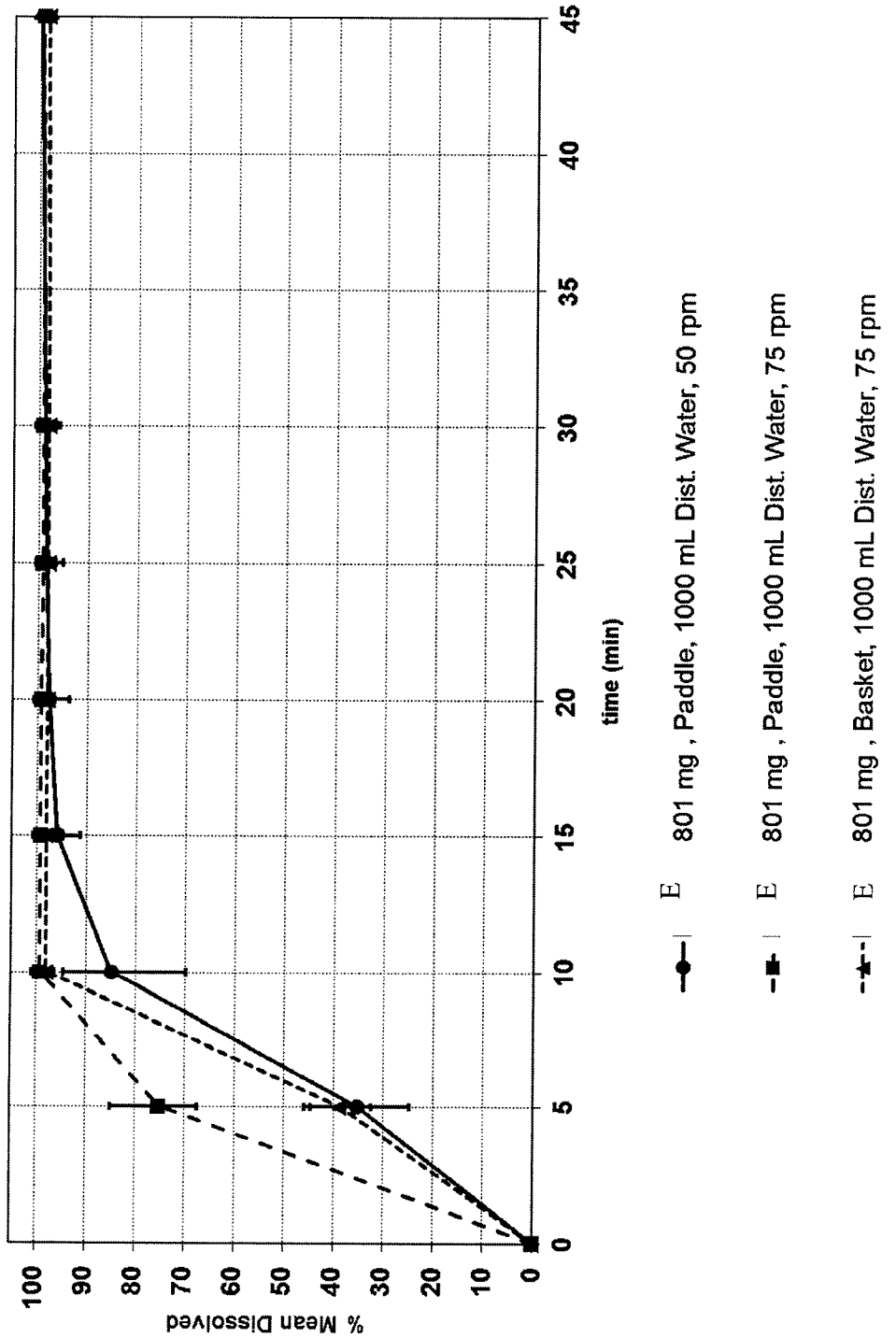

% Mean Dissolved
0
10
20
30
40
50
60
70
80
90
100
0
5
10
15
20
25
30
35
40
45
time (min)
E 801 mg , Paddle, 1000 mL Dist. Water, 50 rpm
E 801 mg , Paddle, 1000 mL Dist. Water, 75 rpm
E 801 mg , Basket, 1000 mL Dist. Water, 75 rpm

FIGURE 16

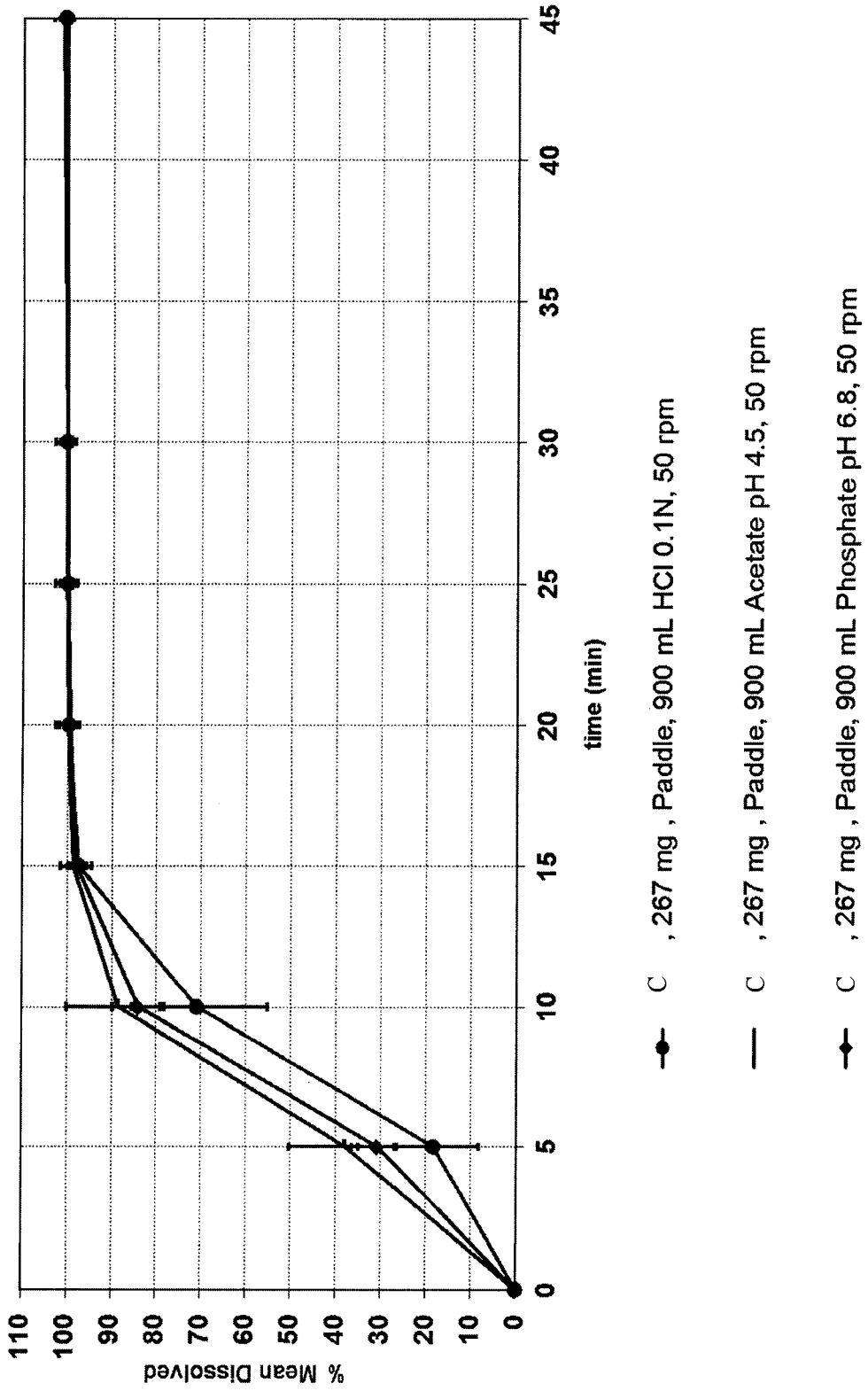

% Mean Dissolved
110
100
90
80
70
60
50
40
30
20
10
0
0
5
10
15
20
25
30
35
40
45
time (min)
C , 267 mg , Paddle, 900 mL HCl 0.1N, 50 rpm
C , 267 mg , Paddle, 900 mL Acetate pH 4.5, 50 rpm
C , 267 mg , Paddle, 900 mL Phosphate pH 6.8, 50 rpm

FIGURE 17

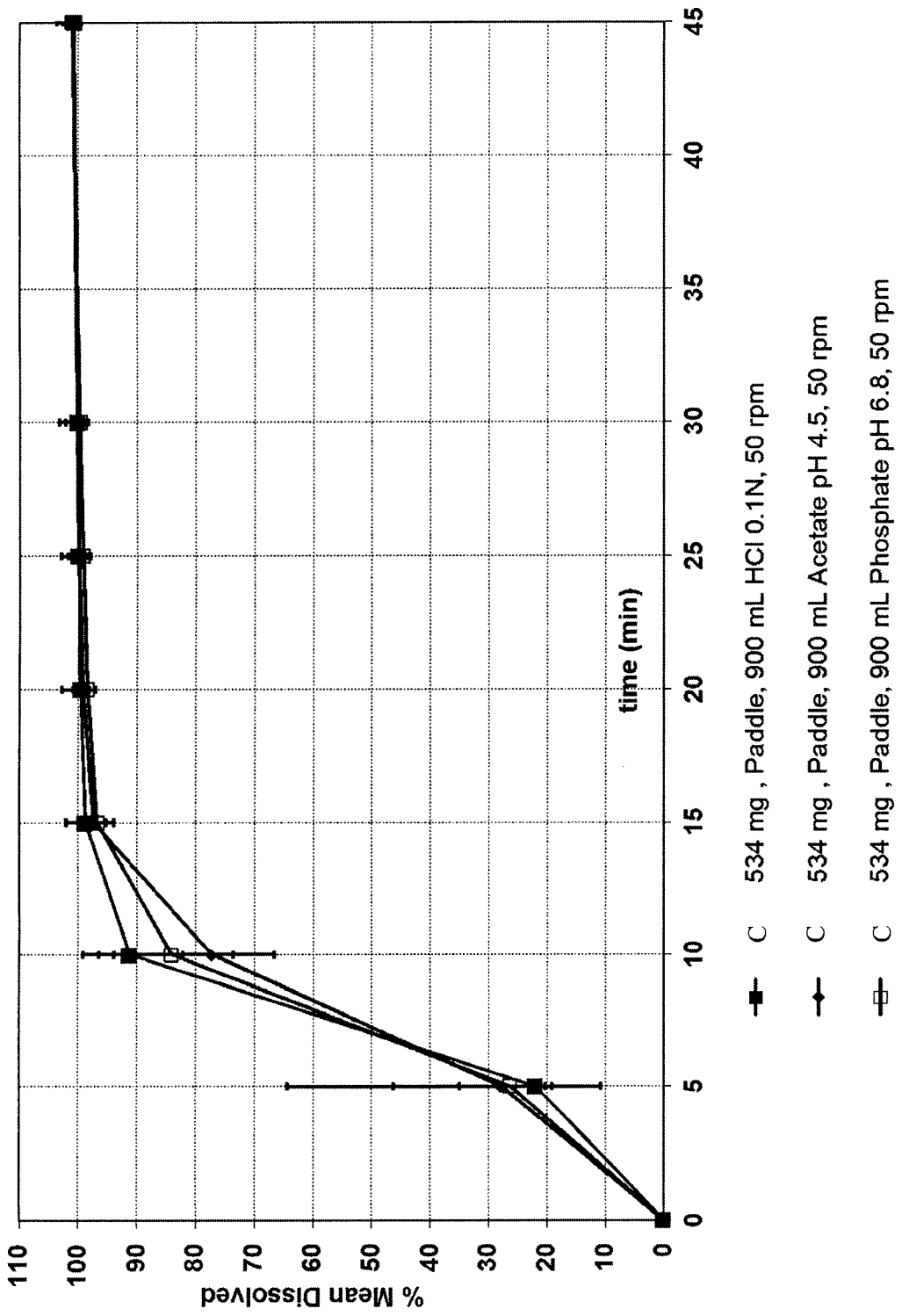

% Mean Dissolved
110
100
90
80
70
60
50
40
30
20
10
0
0
5
10
15
20
25
30
35
40
45
time (min)
C 534 mg , Paddle, 900 mL HCl 0.1N, 50 rpm
C 534 mg , Paddle, 900 mL Acetate pH 4.5, 50 rpm
C 534 mg , Paddle, 900 mL Phosphate pH 6.8, 50 rpm

FIGURE 18

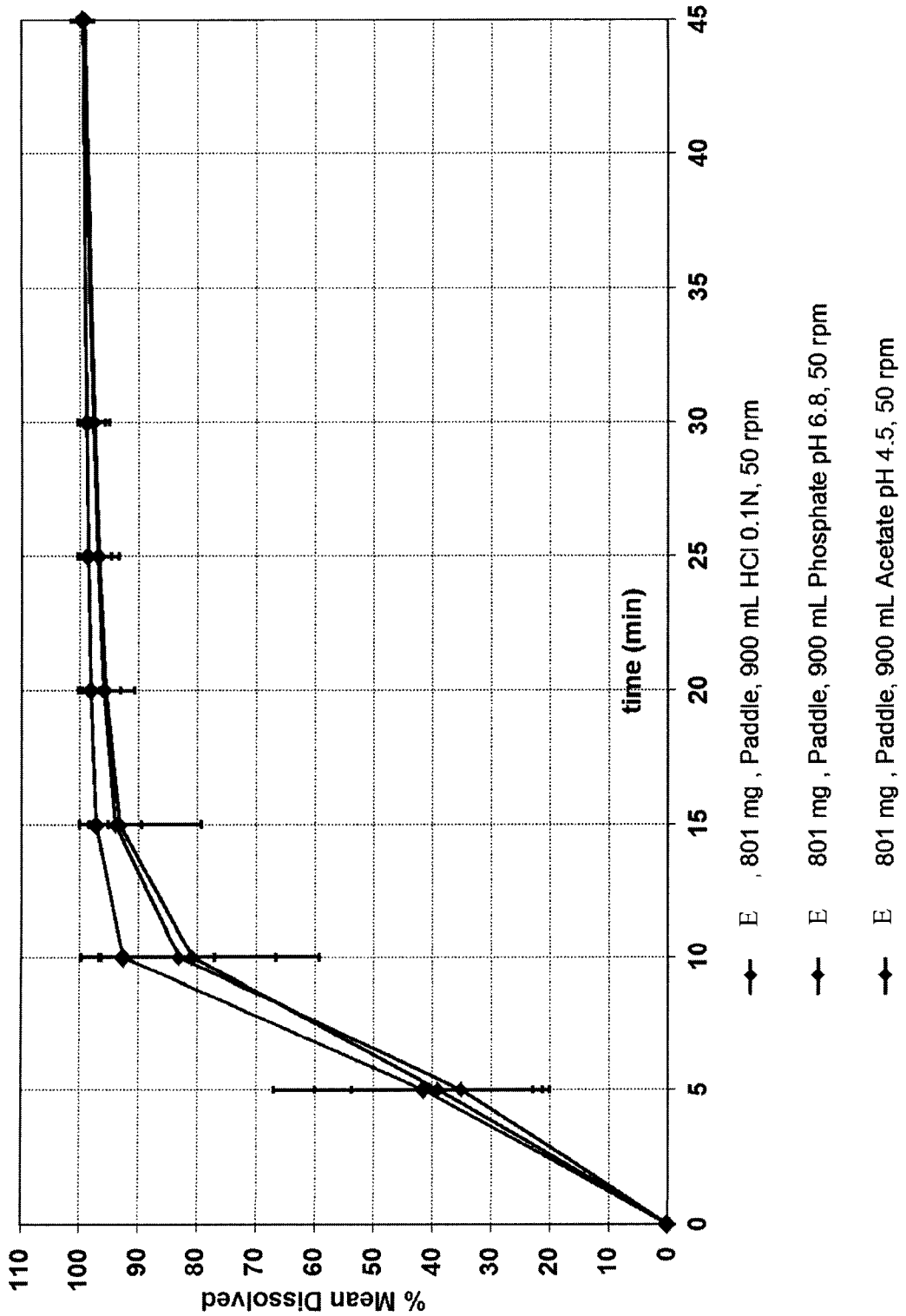
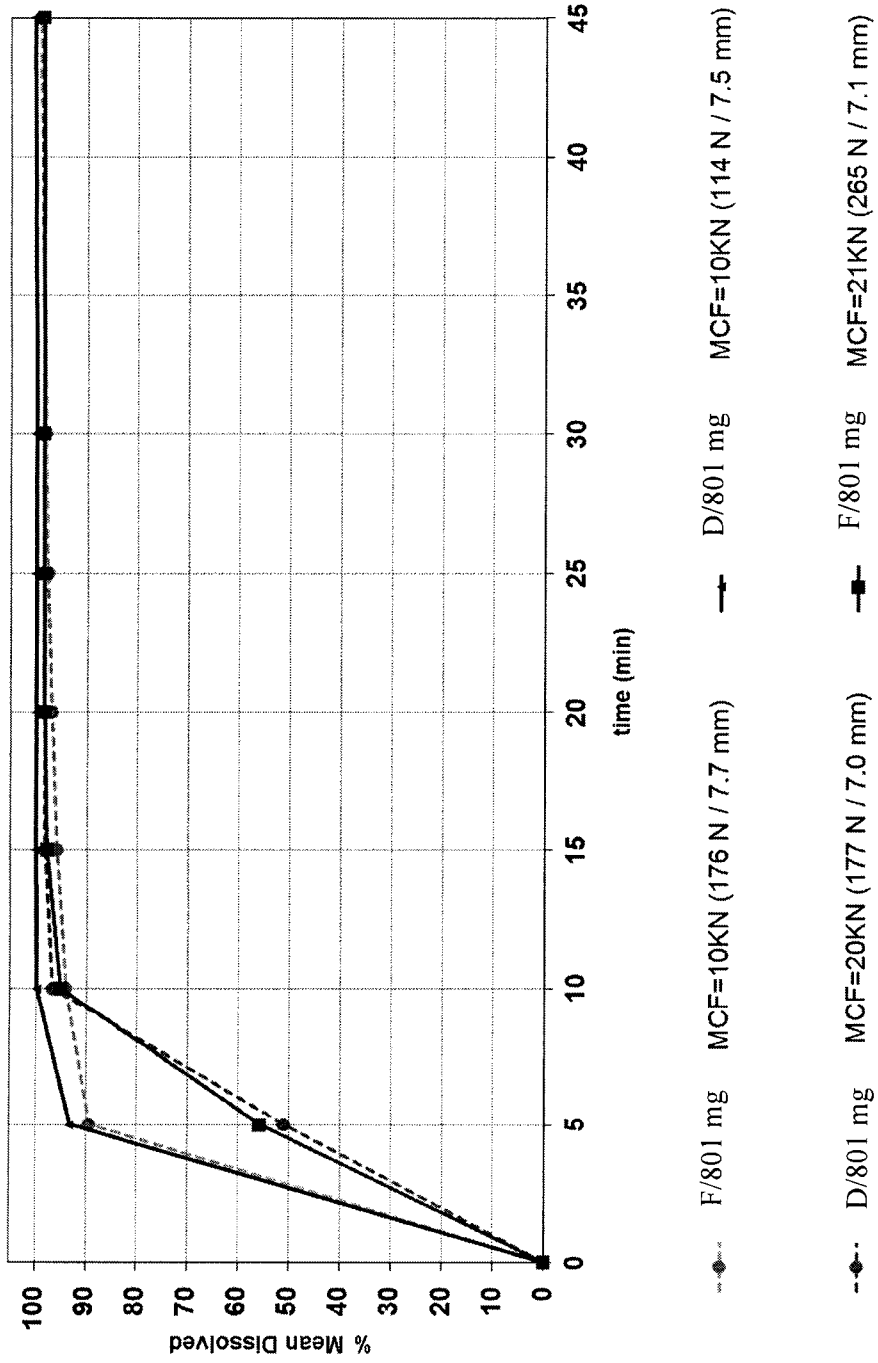
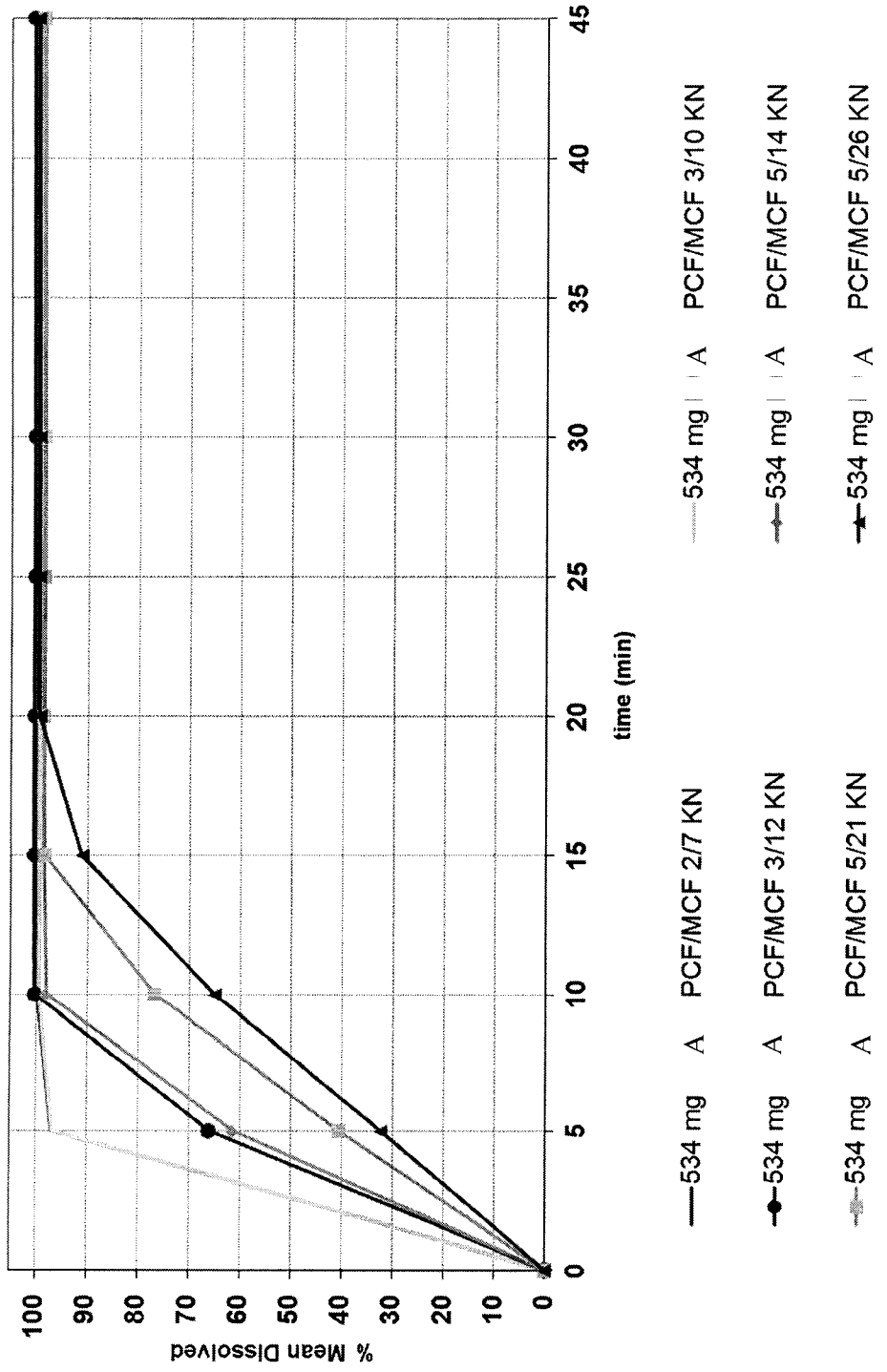

% Mean Dissolved
110
100
90
80
70
60
50
40
30
20
10
0
0
5
10
15
20
25
30
35
40
45
time (min)
E , 801 mg , Paddle, 900 mL HCl 0.1N, 50 rpm
E 801 mg , Paddle, 900 mL Phosphate pH 6.8, 50 rpm
E 801 mg , Paddle, 900 mL Acetate pH 4.5, 50 rpm

FIGURE 19



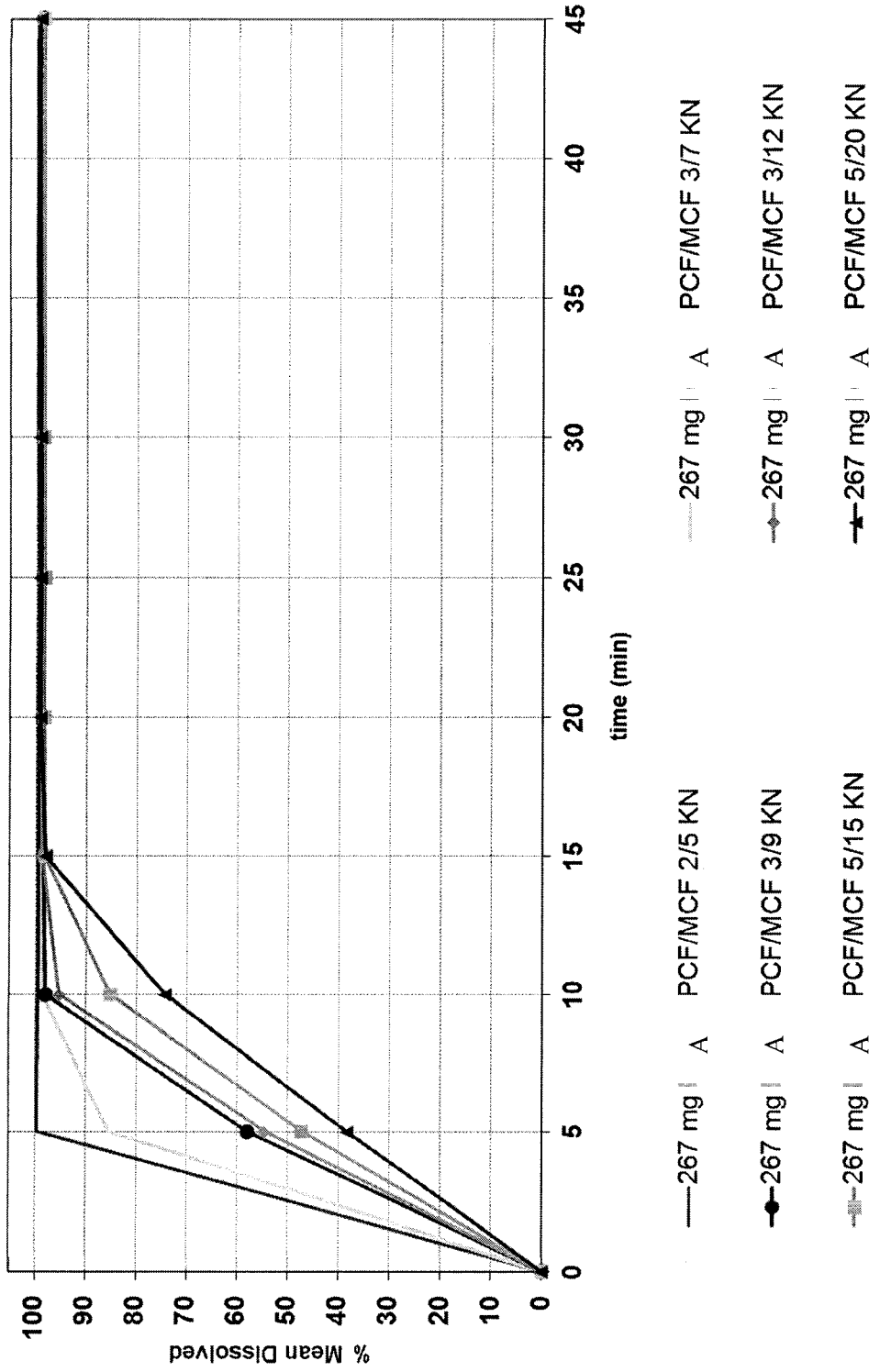
Hardness and thickness of resulting tablet cores are shown in parenthesis in Newton and millimeters, respectively.
Abbreviation: MCF = main compression force in kilo-Newton.

FIGURE 20



Abbreviations: MCF = main compression force; PCF = pre-compression force.

FIGURE 21



Abbreviations: MCF = main compression force; PCF = pre-compression force.

FIGURE 22