CLAIMS

1. A method of preparing solid particles of a compound, said method comprising controlling provision of a liquid phase, wherein said liquid phase comprises a solution of the compound, in a first flow direction to a membrane, said membrane defining a plurality of pores; and controlling the supersaturation of the liquid phase after it has passed through the membrane via the plurality of pores, to form solid particles of the compound.

2. The method according to claim 1 wherein the supersaturation of the liquid is controlled by cooling the liquid phase, antisolvent precipitation or reverse antisolvent precipitation.

3. The method according to claim 2 wherein the supersaturation of the liquid is controlled by cooling the liquid phase after it has passed through the membrane.

4. The method according to claim 2 wherein the supersaturation of the liquid is controlled by antisolvent precipitation after the liquid phase has passed through the membrane.

5. The method according to claim 2 wherein the supersaturation of the liquid is controlled by reverse antisolvent precipitation after the liquid phase has passed through the membrane.

6. The method according to any one of the preceding claims wherein the method comprises the preparation of solid particles of a compound in crystalline form or amorphous form, or a combination thereof.

~~7. The method according to claim 6 wherein the method comprises the preparation of solid crystalline particles of a compound.~~

~~8. The method according to claim 6 wherein the method comprises the preparation of solid amorphous particles of a compound.~~

~~9~~7. A method of preparing solid particles of a compound, said method comprising dispersing a first liquid phase in a second liquid phase;

wherein said first liquid phase comprises a solution of the compound and said second liquid phase comprises an antisolvent; or said first liquid phase comprises an antisolvent and said second liquid phase comprises a solution of the compound;

said method comprising controlling provision of the first liquid phase in a first flow direction to a membrane, said membrane defining a plurality of pores; and controlling provision of the second liquid phase to the membrane in a crossflow to the first flow direction, via the plurality of pores, to form solid particles of the compound.

~~10. The method according to claim 9 wherein the first liquid phase comprises a solution of the compound and the second liquid phase comprises an antisolvent.~~

~~11. The method according to claim 9 wherein the first liquid phase comprises an antisolvent and the second liquid phase comprises a solution of the compound.~~

~~12~~8. The method according to ~~any one of claims 9 to 11~~claim 7 wherein the method comprises the preparation of solid particles of a compound in crystalline form or amorphous form, or a combination thereof.

~~13. The method according to claim 12 wherein the method comprises the preparation of solid crystalline particles of a compound.~~

~~14. The method according to claim 12 wherein the method comprises the preparation of solid amorphous particles of a compound.~~

~~15~~9. A method of preparing solid particles of a compound, said method comprising dispersing a first liquid phase in a second liquid phase;

wherein said first liquid phase comprises a solution of the compound and said second liquid phase comprises an antisolvent phase; or said first liquid phase comprises an antisolvent and said second liquid phase comprises a solution of the compound;

wherein said method uses a crossflow emulsification apparatus; said crossflow emulsification apparatus (AXF) comprising:

an outer tubular sleeve provided with a first inlet at a first end; a particle outlet; and a second inlet, distal from and inclined relative to the first inlet;

a tubular membrane provided with a plurality of pores and adapted to be positioned inside the tubular sleeve; and

optionally an insert adapted to be located inside the tubular membrane, said insert comprising an inlet end and an outlet end, each of the inlet end and an outlet

end being provided with chamfered region; the chamfered region is provided with a plurality of orifices and a furcation plate; and

controlling provision of the first liquid phase to the tubular membrane; and controlling provision of a second liquid phase to the tubular membrane via the plurality of pores to form solid particles of the compound.

~~16. The method according to claim 15 wherein the first liquid phase comprises a solution of the compound and the second liquid phase comprises an antisolvent.~~

~~17. The method according to claim 15 wherein the first liquid phase comprises an antisolvent and the second liquid phase comprises a solution of the compound.~~

~~18~~10. The method according to ~~any one of claims 15 to 17~~ claim 9 wherein the method comprises the preparation of solid particles of a compound in crystalline form or amorphous form, or a combination thereof.

~~19. The method according to claim 18 wherein the method comprises the preparation of solid crystalline particles of a compound.~~

~~20~~11. The method according to claim ~~18~~10 wherein the method comprises the preparation of solid amorphous particles of a compound.

~~21. The method according to claim 15 wherein the solution comprises one or more dissolved organic compounds.~~

~~22~~12. The method according to claim ~~21~~9 wherein the solution comprises one or more dissolved organic compounds, the one or more organic compounds comprising pharmaceutically active compounds or drugs, bioactive agents, nutraceuticals, polymers and the like.

~~23. The method according to claim 22 wherein the solution comprises a pharmaceutically active compound.~~

~~24~~13. The method according to any one of the preceding claims wherein the compound is of low bioavailability.

~~25. The method according to claim 24 wherein the compound lies within Class II or IV of the Biopharmaceutics Classification System (BCS).~~

~~26. The method according to claim 25 wherein the compound lies within Class II of the BCS.~~

~~27. The method according to claim 25 wherein the compound lies within Class IV of the BCS.~~

~~28~~14. The method according to claim ~~23~~12 wherein the solution comprises a pharmaceutically active compound is selected from one or more of antifungal agents, such as, itraconazole fluoconazole, terconazole, ketoconazole and saperconazole; anti-infective agents, such as griseofulvin and griseoverdin; antibiotics, such as, amoxicillin, azithromycin, cephalexin, cefixime, cefoperazone, ceftriaxone,

ciprofloxacin, clarithromycin, clavulanic acid, clindamycin, doxycycline, erythromycin, gentamycin, levofloxacin, meropenem, metronidazole, neomycin, norfloxacin, ofloxacin, ornidazole, oxytctracycline, piperacillin, rifampicin, streptomycin, sulbactam, sulfadiazine, tazobactam, tetracycline and tinidazole; anti malaria drugs, such as, atovaquone and artesunate; protein kinase inhibitors, such as, afatinib, axitinib, bosutinib, cetuximab.crizotinib, dasatinib, erlotinib, fostamatinib, gefitinib, ibrutinib, imatinib, zemurasenib, lapatinib, lenvatinib, mubritinib and nilotinib; immune system modulators, such as, cyclosporine; cardiovascular drugs, such as, digoxin and spironolactone; sterols or steroids, such as, betamethasone; ACE inhibitors, such as, captopril, enalapril, ramipril, quinapril, perindopril, lisinopril, and fosinopril; adenohypophyseal hormones; adrenergic antagonists, such as, phentolamine, phenoxybenzamine, tamsulosin, propranolol, atenolol, metoprolol, timolol and acebutolol; adrenocortical steroids; inhibitors of the biosynthesis of adrenocortical steroids; alpha-adrenergic agonists, such as methoxamine, phenylephrine, methyldopa, norepinephrine; alpha-adrenergic antagonists, such as, phentolamine and phenoxybenzamine; analgesics, such as, aspirin and paracetamol; antipyretics and anti-inflammatory agents, such as, diclofenac, ibuprofen, naproxen and ketoprofen; androgens, local anaesthetics, such as, lidocaine; antiaddictive agents; antiandrogens; antiarrhythmic agents, such as, verapamil and diltiazem; antiasthmatic agents, such as, beclomethasone, budesonide, fluticasone, reproterol, salbutamol and salmeterol; anticholinergic agents, such as, ipratropium and oxybutynin; anticholinesterase agents, such as, donepezil; anticoagulants, such as, dabigatran, rivaroxaban, apixaban, edoxaban and betrixaban; antidiabetic agents, such as, metformin; antidiarrheal agents; antidiuretics; antiemetic and prokinetic agents; antiepileptic agents, such as carbamazepine, gabapentin oxcarbazepine;

antiestrogens; antifungal agents; antihypertensive agents, such as, losartan, olmesartan, telmisartan and valsartan; antimicrobial agents; antimigraine agents, such as, zolmitriptan; antimuscarinic agents; antineoplastic agents; antiparasitic agents; antiparkinsons agents, such as, carbidopa and levodopa; antiplatelet agents; antiprogestins; antithyroid agents; antitussives; antiviral agents; antidepressants; azaspirodecanediones; barbiturates; benzodiazepines; benzothiadiazides; beta-adrenergic agonists; beta-adrenergic antagonists; selective adrenergic antagonists; selective agonists; bile salts; butyrophenones; calcium channel blockers; catecholamines and sympathomimetic drugs; cholinergic agonists; cholinesterase reactivators; cognitive enhancers, such as, piracetam; dermatological agents; diphenylbutylpiperidines; diuretics; ergot alkaloids; oestrogens; ganglionic blocking agents; ganglionic stimulating agents; glucocorticoid steroids, such as, dexamethasone and prednisolone; agents for control of gastric acidity and treatment of peptic ulcers; haematopoietic agents; histamines; antihistamine; HMG-CoA reductase inhibitors, e.g. statins, such as, atorvastatin, fluvastatin, lovastatin, pitavastatin, pravastatin, rosuvastatin and simvastatin; 5-hydroxytryptamine antagonists; hypnotics and sedatives; immunosuppressive agents; laxatives; methylxanthines; monoamine oxidase inhibitors; neuromuscular blocking agents; nutrients or dietary supplements, such as, vitamin B1, vitamin B6 and retinol; organic nitrates; opioid analgesics and antagonists; pancreatic enzymes; phenothiazines; progestins; prostaglandins; agents for the treatment of psychiatric disorders; retinoids; sodium channel blockers; thrombolytic agents; thyroid agents; tricyclic antidepressants; tyrosine kinase inhibitors, such as, axitinib, crizotinib, dasatinib, erlotinib, gefitinib, imatinib, lapatinib, nilotinib, pazopanib, regorafenib, ruxolitinib, sorafenib, sunitinib, vandetanib and vemurafenib; drugs from the group comprising danazol, acyclovir,

dapsone, indinavir, lopinavir, nifedipine, nitrofurantion, phentytoin, ritonavir, saquinavir, sulfamethoxazole, valproic acid, trimethoprin, acetazolamide, azathioprine, iopanoic acid, nalidixic acid, nevirapine, praziquantel, rifampicin, albendazole, amitrptyline, artemether, lumefantrine, chloropromazine, clofazimine, efavirenz, iopinavir, folic acid, glibenclamide, haloperidol, ivermectin, mebendazole, niclosamide, pyrantel, pyrimethamine, sulfadiazine, sulfasalazine, triclabendazole, and cinnarizine; and combinations thereof.

~~29. The method according to claim 28 wherein the pharmaceutically active compound is an HMG-CoA reductase inhibitor, e.g. a statin, such as, atorvastatin.~~

~~30. The method according to claim 28 wherein the pharmaceutically active compound is an HMG-CoA reductase inhibitor in amorphous form, e.g. a statin, such as, atorvastatin.~~

~~31~~15. The method according to claim ~~28~~14 wherein the pharmaceutically active compound is an antihypertensive agent, such as, telmisartan.

~~32~~16. The method according to claim ~~28~~14 wherein the pharmaceutically active compound is an antihypertensive agent in amorphous form, such as, telmisartan.

~~33. The method according to any one of the preceding claims wherein the volumetric ratio of solution to antisolvent is from about 1:0.5 to about 1:50.~~

~~34. The method according to any one of the preceding claims wherein the solution solvents and antisolvents include, but shall not be limited to, for example, alcohols, aliphatic and alicyclic alkanes, ethers, esters, hydrocarbons, ketones, water, and the like.~~

~~35. The method according to claim 34 wherein the solution solvents and antisolvents include, but shall not be limited to, for example, ethanol, water, hexane, glycerol, t-butanol, isopropanol, ethyl acetate, and the like.~~

~~36. The method according to any one of the preceding claims wherein the solution solvent comprise a mixture of two or more solvents.~~

~~37. The method according to any one of claims 1 to 35 wherein the antisolvent comprises a mixture of two or more antisolvents.~~

~~38. The method according to any one of the preceding claims wherein the solution solvent and/or the antisolvent may additionally comprise one or more surfactants or co-surfactants.~~

~~39. The method according to claim 38 wherein the surfactants may be selected from one or more of non-ionic surfactants, anionic surfactants, cationic surfactants and zwitterionic surfactants; and combinations thereof.~~

~~40~~17. The method according to claim ~~15~~9 wherein the apparatus includes an insert.

~~41. The method according to claim 15 wherein the apparatus does not include an insert.~~

~~42. The method according to claim 15 wherein the particle outlet is generally at a second end of the tubular sleeve.~~

~~43. The method according to claim 15 wherein the particle outlet is generally at a side branch of the tubular sleeve.~~

~~44. The method according to claims 15 wherein the first inlet is a second phase first inlet and the second inlet is a first phase inlet.~~

~~45. The method according to claims 15 wherein the first inlet is a first phase inlet and the second inlet is a second phase inlet.~~

~~46. The method according to claim 15 wherein the tubular membrane is located centrally within the outer sleeve, such that the spacing between the membrane and the sleeve comprises an annulus, of equal or substantially equal dimensions at any point around the tubular membrane.~~

~~47. The method according to claim 46 wherein the spacing is from about 0.05 to about 10mm.~~

~~48. The method according to claim 40 wherein the insert is tapered.~~

~~49. The method according to claim 40 wherein the tubular membrane is located centrally within the outer sleeve, such that the spacing between the membrane and the insert comprises an annulus, of equal or substantially equal dimensions at any point around the insert.~~

~~50. The method according to claim 49 wherein the spacing is from about 0.05 to about 10mm.~~

~~51. The method according to claim 15 wherein the internal diameter of the tubular membrane is from about 1mm to about 10mm.~~

~~52. The method according to claim 15 wherein the crossflow apparatus comprises a plurality of tubular membranes.~~

~~53. The method according to claim 52 wherein each membrane has an insert located inside it.~~

~~54. The method according to claims 52 or 53 wherein a plurality of membranes is grouped as a cluster of membranes positioned alongside each other.~~

~~55. The method according to claim 15 wherein the inlet and outlet ends of the outer sleeve will generally be provided with a seal assembly.~~

~~56. The method according to claim 55 wherein the seal assembly on the inlet and outlet ends of the outer sleeve are the same.~~

~~57. The method according to claims 55 or 56 wherein the seal assembly comprises a tubular ferrule provided with a flange at each end; and wherein a first flange located at the end adjacent to the outer sleeve (when coupled) is provided with a circumferential internal recess which acts as a seat for an O-ring seal, wherein the O-ring seal allows a loose fit as the membrane slides through the O-rings.~~

~~58. The method according to claim 57 wherein the O-ring seal is adapted to be located around the end of the insert and within a recess in the outer sleeve.~~

~~59. The method according to claim 15 wherein the membrane pores are laser drilled.~~

~~60. The method according to claim 59 wherein the membrane pores are substantially uniform in pore diameter, pore shape and pore depth.~~

~~61. The method according to claim 60 wherein the membrane pores are generally uniformly spaced.~~

~~62. The method according to any one of claims 59 to 61 wherein the pores have a diameter of from about 1 μm to about 100 μm.~~

~~63. The method according to any one of claims 59 to 62 wherein the shape of the pores is substantially tubular.~~

64. The method according to any one of claims 59 to 63 wherein the interpore distance is from about 1 μm to about 5,000 μm.

65. The method according to any one of claims 59 to 64 wherein the surface porosity of the membrane may be from about 0.001% to about 20% of the surface area of the membrane.

66. The method according to any one of claims 59 to 65 wherein the pores are in a patterned arrangement.

67. The method according to claim 66 wherein the patterned arrangement is a square, triangular, linear, circular or rectangular arrangement.

68. The method according to claim 67 wherein the patterned arrangement is a square arrangement.

69. The method according to claim 15 wherein the membrane comprises a material selected from glass; ceramic; metal; polymer/plastic or silicon.

70. The method according to claim 69 wherein the membrane comprises a metal.

71. The method according to claim 70 wherein the metal is stainless steel.

72. The method according to claim 15 wherein the furcation plate is a bi-furcation plate or a tri-furcation plate.

~~73. The method according to claim 72 wherein the furcation plate is a tri-furcation plate.~~

~~74. The method according to claim 53 wherein the number of orifices provided in the insert is from 2 to 6.~~

~~75. The method according to claim 74 wherein the number of orifices provided in the insert is three.~~

~~76. The method according to any one of claims 53 to 75 wherein the chamfered region on the insert comprises a shallow chamfer.~~

~~77. The method according to any one of the preceding claims wherein the membrane emulsification technique comprises the use of laminar flow.~~

~~78~~18. The method according to any one of the preceding claims wherein the method is a continuous process.

~~79. The method according to claim 78 wherein the apparatus comprises a continuous crossflow emulsification apparatus (CXF).~~

~~80. The method according to any one of the preceding claims wherein the solid particles of the compound have a narrow size distribution.~~

~~81~~19. A solid particle prepared by the method according to any one of claims 1 to ~~80~~18.

~~82~~20. A solid particle according to claim ~~81~~19 wherein the particle comprises an active agent.

~~83~~21. A solid particle according to claims ~~81 or 82~~19 or 20 wherein the solid particles are in crystalline form or amorphous form, or a combination thereof.

~~84. A solid particle according to any one of claims 81 to 82 wherein the solid comprises crystalline particles of an active agent.~~

~~85. A solid particle according to any one of claims 81 to 82 wherein the solid comprises amorphous particles of an active agent.~~

~~86. A solid particle according to any one of the claims 81 to 85 wherein the compound is of low bioavailability.~~

~~87. A solid particle according to claim 86 wherein the compound lies within Class II or IV of the Biopharmaceutics Classification System (BCS).~~

~~88. A solid particle according to claim 87 wherein the compound lies within Class II of the BCS.~~

~~89. A solid particle according to claim 87 wherein the compound lies within Class IV of the BCS.~~

~~90~~22. A solid particle according to any one of claims ~~81 to 89~~19 to 21 wherein the active agent is selected from one or more of antifungal agents, such as, itraconazole fluoconazole, terconazole, ketoconazole and saperconazole; anti-infective agents, such as griseofulvin and griseoverdin; antibiotics, such as, amoxicillin, azithromycin, cephalexin, cefixime, cefoperazone, ceftriaxone, ciprofloxacin, clarithromycin, clavulanic acid, clindamycin, doxycycline, erythromycin, gentamycin, levofloxacin, meropenem, metronidazole, neomycin, norfloxacin, ofloxacin, ornidazole, oxytctracycline, piperacillin, rifampicin, streptomycin, sulbactam, sulfadiazine, tazobactam, tetracycline and tinidazole; anti malaria drugs, such as, atovaquone and artesunate; protein kinase inhibitors, such as, afatinib, axitinib, bosutinib, cetuximab.crizotinib, dasatinib, erlotinib, fostamatinib, gefitinib, ibrutinib, imatinib, zemurasenib, lapatinib, lenvatinib, mubritinib and nilotinib; immune system modulators, such as, cyclosporine; cardiovascular drugs, such as, digoxin and spironolactone; sterols or steroids, such as, betamethasone; ACE inhibitors, such as, captopril, enalapril, ramipril, quinapril, perindopril, lisinopril, and fosinopril; adenohypophyseal hormones; adrenergic antagonists, such as, phentolamine, phenoxybenzamine, tamsulosin, propranolol, atenolol, metoprolol, timolol and acebutolol; adrenocortical steroids; inhibitors of the biosynthesis of adrenocortical steroids; alpha-adrenergic agonists, such as methoxamine, phenylephrine, methyldopa, norepinephrine; alpha-adrenergic antagonists, such as, phentolamine and phenoxybenzamine; analgesics, such as, aspirin and paracetamol; antipyretics and anti-inflammatory agents, such as, diclofenac, ibuprofen, naproxen and ketoprofen;

androgens, local anaesthetics, such as, lidocaine; antiaddictive agents; antiandrogens; antiarrhythmic agents, such as, verapamil and diltiazem; antiasthmatic agents, such as, beclomethasone, budesonide, fluticasone, reproterol, salbutamol and salmeterol; anticholinergic agents, such as, ipratropium and oxybutynin; anticholinesterase agents, such as, donepezil; anticoagulants, such as, dabigatran, rivaroxaban, apixaban, edoxaban and betrixaban; antidiabetic agents, such as, metformin; antidiarrheal agents; antidiuretics; antiemetic and prokinetic agents; antiepileptic agents, such as carbamazepine, gabapentin oxcarbazepine; antiestrogens; antifungal agents; antihypertensive agents, such as, losartan, olmesartan, telmisartan and valsartan; antimicrobial agents; antimigraine agents, such as, zolmitriptan; antimuscarinic agents; antineoplastic agents; antiparasitic agents; antiparkinsons agents, such as, carbidopa and levodopa; antiplatelet agents; antiprogestins; antithyroid agents; antitussives; antiviral agents; antidepressants; azaspirodecanediones; barbiturates; benzodiazepines; benzothiadiazides; beta-adrenergic agonists; beta-adrenergic antagonists; selective adrenergic antagonists; selective agonists; bile salts; butyrophenones; calcium channel blockers; catecholamines and sympathomimetic drugs; cholinergic agonists; cholinesterase reactivators; cognitive enhancers, such as, piracetam; dermatological agents; diphenylbutylpiperidines; diuretics; ergot alkaloids; oestrogens; ganglionic blocking agents; ganglionic stimulating agents; glucocorticoid steroids, such as, dexamethasone and prednisolone; agents for control of gastric acidity and treatment of peptic ulcers; haematopoietic agents; histamines; antihistamine; HMG-CoA reductase inhibitors, e.g. statins, such as, atorvastatin, fluvastatin, lovastatin, pitavastatin, pravastatin, rosuvastatin and simvastatin; 5-hydroxytryptamine antagonists; hypnotics and sedatives; immunosuppressive agents; laxatives; methylxanthines; monoamine oxidase inhibitors; neuromuscular blocking

agents; nutrients or dietary supplements, such as, vitamin B1, vitamin B6 and retinol; organic nitrates; opioid analgesics and antagonists; pancreatic enzymes; phenothiazines; progestins; prostaglandins; agents for the treatment of psychiatric disorders; retinoids; sodium channel blockers; thrombolytic agents; thyroid agents; tricyclic antidepressants; tyrosine kinase inhibitors, such as, axitinib, crizotinib, dasatinib, erlotinib, gefitinib, imatinib, lapatinib, nilotinib, pazopanib, regorafenib, ruxolitinib, sorafenib, sunitinib, vandetanib and vemurafenib; drugs from the group comprising danazol, acyclovir, dapsone, indinavir, lopinavir, nifedipine, nitrofurantion, phentytoin, ritonavir, saquinavir, sulfamethoxazole, valproic acid, trimethoprin, acetazolamide, azathioprine, iopanoic acid, nalidixic acid, nevirapine, praziquantel, rifampicin, albendazole, amitrptyline, artemether, lumefantrine, chloropromazine, clofazimine, efavirenz, iopinavir, folic acid, glibenclamide, haloperidol, ivermectin, mebendazole, niclosamide, pyrantel, pyrimethamine, sulfadiazine, sulfasalazine, triclabendazole, and cinnarizine; and combinations thereof.

~~91. A composition comprising a solid particle according to any one of claims 81 to 90 and a pharmaceutically acceptable excipient, carrier or diluent.~~

~~92. A method, solid particle or composition as herein described with reference to the accompanying description.~~