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(74) Agent: **MAZZA, Michael, J.**; Sedgwick, Detert, Moran & Arnold LLP, One Market Plaza, Steuart Tower, 8th Floor, San Francisco, CA 94105 (US).

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(71) Applicant (*for all designated States except US*): **NEKTAR THERAPEUTICS** [US/US]; 150 Industrial Road, San Carlos, CA 94070 (US).

(72) Inventors; and

(75) Inventors/Applicants (*for US only*): **GREEN, Jennifer, Anne** [GB/GB]; 1 Brichlands Grove, Wilsden, Bradford BD15 0HD (GB). **DAINTREE, Linda, Sharon** [GB/GB]; 7 Fern Valley Chase, Todmorden, West Yorkshire OL14 7 HB (GB). **KORDIKOWSKI, Andreas** [DE/GB]; 6 Birchdale, Bingley, West Yorkshire BD 16 4SE (GB). **DUDDU, Sarma** [US/US]; 624 Dory Lane, Redwood City, California 94065 (US). **ZHANG, Jiang** [CN/US]; 106 Riconada Avenue, Palo Alto, California 94301 (US). **PALAKODATY, Srinivas** [IN/US]; 115 Goldhunter Court, Foster City, California 94404 (US). **TONG, Maurine** [US/US]; 2768 Westberry Drive, San Jose, California 95132 (US).

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(54) Title: NON-CRYSTALLINE FORMULATION COMPRISING CLOPIDOGREL

(57) Abstract: One or more embodiments of the invention provide various novel formulation, and tablet dosage forms, comprising clopidogrel, and particles comprising clopidogrel, that are non-crystalline, stable flowable, non-sticky and/or otherwise improvements over known clopidogrel formulations. One or more embodiments of the invention further provide methods for preparing the formulation, methods for preparing the tablet dosage form, and to methods, of administering the tablet dosage and/or formulation comprising clopidogrel. The clopidogrel-containing formulations may be administered to a user to treat platelet aggregation and/or thrombosis, and related conditions.

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United States Patent Application for:
Stable Non-crystalline Formulation Comprising Clopidogrel

RELATED APPLICATION

[0001] This application relates to U.S. Provisional Application No. 60/640,315, filed December 30, 2004, from which priority is claimed under 35 USC §119(e), and which is incorporated herein by reference in its entirety.

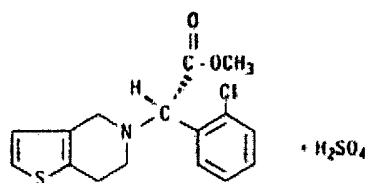
BACKGROUND OF THE INVENTION

[0002] One or more embodiments of the present invention relates to a formulation comprising clopidogrel, to co-formulations of clopidogrel with excipients, to methods for preparing the formulations, pharmaceutical compositions comprising the formulations and to their use in medical treatment. One or more embodiments of the present invention relates more particularly to co-formulations of clopidogrel with one or more oligomeric and/or polymeric excipients, and to methods of making and methods of delivering, which result in desired, especially improved or enhanced, solubility and/or dissolution characteristics and/or handling characteristics, resulting in desired, especially improved or enhanced, bioavailability and/or pharmacokinetics. Also provided are pharmaceutical compositions comprising the formulation, methods of administering the pharmaceutical compositions and methods of treating patients with the pharmaceutical compositions.

Description of Related Art

[0003] Clopidogrel, methyl (+)-(S)- α -(2-chlorophenyl)-6, 7-dihydrothieno[3,2-c] pyridine-5(4H)-acetate, is a well known pharmaceutical agent. U.S. Patent 4,529,596, to *Aubert et al.* which is incorporated herein by reference in its entirety, describes the blood-platelet aggregation inhibiting and the antithrombotic properties of some thieno [3,2-c] pyridine derivatives, such as clopidogrel, and the effectiveness of the compounds in treating or inhibiting platelet aggregation and/or for treating or inhibiting thrombosis. Clopidogrel has also been determined to be effective in preventing second ischemic events, as described in U.S. Patent 5,576,328, to *Herbert et al.* which is incorporated herein by reference in its entirety.

[0004] Clopidogrel is commercially available in the United States from Sanofi Synthelabo in partnership with the Bristol Myers Squibb Company in New York, New York under the tradename PLAVIX®. According to the Sanofi and Bristol Myers Squibb product description, PLAVIX® is clopidogrel bisulfate and is an inhibitor of ADP-induced platelet aggregation acting by direct inhibition of adenosine diphosphate (ADP) binding to its receptor and of the subsequent ADP-mediated activation of the glycoprotein GPIIb/IIIa complex. Clopidogrel bisulfate in PLAVIX® is chemically methyl (+)-(S)- α -(2-chlorophenyl)-6, 7-dihydrothieno [3,2-c] pyridine-5(4H)-acetate sulfate (1:1). The empirical formula of clopidogrel bisulfate is $C_{16}H_{16}Cl NO_2S \cdot H_2SO_4$ and its structural formula is:



[0005] PLAVIX® is available as orally administrable filmed-coated tablets containing 97.875 mg of clopidogrel bisulfate which is the molar equivalent of 75 mg of clopidogrel base. The PLAVIX® tablets are said to also contain the following ingredients: hydrogenated castor oil, hydroxypropylcellulose, mannitol, microcrystalline cellulose and polyethylene glycol 6000 as inactive ingredients. The pink film coating is said to contain ferric oxide, hydroxypropyl methylcellulose 2910, lactose monohydrate, titanium dioxide and triacetin. The tablets are polished with Carnauba wax.

[0006] In the PLAVIX® tablets, the clopidogrel bisulfate is in a crystalline form. Crystalline polymorphic Forms I and II are described in U.S. Patent 6,429,210 and U.S. Patent 6,504,030 both to *Bousquet et al.*, both of which are incorporated herein by reference in their entireties. These patents describe various methods for making the crystalline polymorphic forms of clopidogrel bisulfate.

[0007] The existing crystalline forms of clopidogrel have disadvantages. While the crystalline polymorphic forms are relatively physically stable in that they do not easily convert to another form during storage or processing, the crystalline forms may be less bioactive than non-crystalline forms, such as amorphous forms. Non-crystalline forms of

active agents generally have increased dissolution rates over crystalline forms. Accordingly, the non-crystalline forms may have increased bioavailability when administered to a user because of their ability to dissolve faster in the GI tract, as recognized in the art. This increased bioavailability can allow for the active agent to be taken up faster for systemic delivery. Also, the increased bioactivity can allow for a reduction in the amount of the active agent that needs to be administered to the user.

[0008] Prior art attempts to formulate non-crystalline (amorphous) clopidogrel have met with limited success. Amorphous clopidogrel of the prior art may have limited physical and/or chemical stability, and/or less than desirable micromeritic properties, such as flowability and handling properties. Pure amorphous forms are thermodynamically less favored, thus under normal storage conditions, they tend to alter their form and convert to one or more crystalline forms. Because the degree of crystalline conversion at a particular time during storage is often unknown, it is difficult to assure that dosages are administered in a consistent solid form. As a result, the clopidogrel must either be administered immediately after formulation or a sufficient amount of storage time must pass so that full conversion to a crystalline form takes place, in which case the advantages of having the clopidogrel in amorphous form are lost. In addition, non-crystalline forms of active agents such as clopidogrel may be difficult to process into stable pharmaceutical compositions, such as tablets. Clopidogrel formulations of the prior art, especially in amorphous form, may be mechanically unstable, due at least in part to clopidogrel's hygroscopicity. Mechanical instability causes the clopidogrel to be relatively intolerant of changes in moisture and temperature, which may adversely affect flowability, dispersability and dispensability of a particulate form, and resulting in increased difficulties in downstream processing, such as mixing and/or tableting. In particular, when formulated processed as a powder, the hygroscopicity of prior art amorphous clopidogrel can result in the powder becoming very sticky at ambient temperatures, and therefore difficult to process.

[0009] Therefore, in view of the foregoing, there is a need to solve one or more of these disadvantages of prior art forms of clopidogrel.

Summary of the Invention

[0010] One or more embodiments of the present invention satisfies one or more of these needs. The invention provides various novel formulations comprising clopidogrel that are non-crystalline, more stable, and/or otherwise improvements over known clopidogrel formulations.

[0011] In one aspect of the invention, a solid, non-crystalline formulation comprises clopidogrel wherein the formulation is physically stable.

[0012] In another aspect of the invention, a solid, non-crystalline formulation comprises clopidogrel wherein the formulation maintains its non-crystalline form when stored at 25°C and 60% relative humidity for a period of at least 1 week, more preferably at least 1 month, more preferably at least one year.

[0013] In another aspect of the invention, a solid, non-crystalline formulation comprises clopidogrel wherein the formulation maintains its non-crystalline form when stored at 40°C and 75% relative humidity for a period of at least 1 week, more preferably at least 1 month, more preferably at least three months.

[0014] In one aspect of the invention, a solid non-crystalline formulation comprises clopidogrel wherein the formulation exhibits at least one of the characteristics of acceptable, or parity, dissolution, solubility, stability, shelf life or bioavailability, when compared to a commercially-available formulation.

[0015] In one aspect of the invention, a solid, non-crystalline formulation comprises clopidogrel and an excipient, wherein the formulation exhibits at least one of the characteristics of enhanced dissolution, solubility, stability, shelf life, bioavailability, or tableting ease or manufacturing cost-effectiveness.

[0016] In another aspect of the invention, a solid, non-crystalline formulation comprises particles, wherein the particles-comprise clopidogrel and an excipient.

[0017] In another aspect of the invention, a solid, non-crystalline formulation comprises particles, wherein the particles comprise clopidogrel and an excipient, and wherein the excipient comprises a co-polymer of vinyl pyrrolidone and vinyl acetate.

[0018] In another aspect of the invention, a solid, non-crystalline formulation comprises particles, wherein the particles comprise clopidogrel and an excipient, and wherein the excipient comprises a co-polymer of vinyl pyrrolidone and vinyl acetate, wherein a ratio of vinyl pyrrolidone:vinyl acetate is between about 8:2 to 2:8, such as 6:4.

[0019] In another aspect of the invention, a solid, non-crystalline formulation comprises particles, wherein the particles comprise clopidogrel and an excipient, and wherein the excipient comprises a polymer or co-polymer comprising a hydroxyl propyl (alkyl) cellulose, such as HPC and/or HPMC.

[0020] In another aspect of the invention, a solid, non-crystalline formulation comprises particles, wherein the particles comprise clopidogrel and an excipient, and wherein the excipient comprises a polymer or co-polymer comprising a cellulose, alkyl cellulose, cellulose acetate, and/or derivatives thereof such as cellulose acetate trimellitate (CAT) and/or cellulose acetate phthalate (CAP).

[0021] In another aspect of the invention, a solid, non-crystalline formulation comprises particles, wherein the particles comprise clopidogrel and an excipient, and wherein the excipient comprises a polyoxyalkylene polymer or co-polymer surfactant, such as a PLURONIC®.

[0022] In another aspect of the invention, a solid, non-crystalline formulation comprises particles, wherein the particles comprise clopidogrel and an excipient, and wherein the excipient comprises a lipid, or a lipid-based material.

[0023] In another aspect of the invention, a solid, non-crystalline formulation comprises particles, wherein the particles comprise clopidogrel and a surface-modifying agent, wherein a particle surface is more hydrophobic than a particle surface in the absence of the surface modifying agent.

[0024] In another aspect of the invention, a solid, non-crystalline formulation comprises particles, wherein the particles comprise clopidogrel and a stabilizing excipient, wherein the formulation is more physically stable than a formulation without the stabilizing excipient.

[0025] In another aspect of the invention, a solid, non-crystalline formulation comprises particles, wherein the particles comprise clopidogrel and a stabilizing excipient, wherein the

formulation when stored at 40°C and 75% relative humidity converts to a crystalline form more slowly than a formulation without the stabilizing excipient.

[0026] In another aspect of the invention, a solid, non-crystalline formulation comprises particles, wherein the particles comprise clopidogrel and a stabilizing excipient, wherein the formulation has a higher glass transition temperature than a formulation without the stabilizing excipient.

[0027] In another aspect of the invention, a solid, non-crystalline formulation comprises particles, wherein the particles comprise clopidogrel and a stabilizing excipient, wherein the formulation has a glass transition temperature of above about 40°C.

[0028] In another aspect of the invention, a solid, non-crystalline formulation comprises particles, wherein the particles comprise clopidogrel and a stabilizing excipient or a surface modifying agent, or both, wherein the formulation has a lower hygroscopicity than a formulation without the stabilizing excipient, or the surface modifying agent, or both.

[0029] In another aspect of the invention, a solid formulation comprises a tablet dosage form, wherein the tablet comprises non-crystalline clopidogrel and a stabilizing excipient.

[0030] In another aspect of the invention, a method of treating platelet aggregation and/or thrombosis comprises administering to a user a non-crystalline formulation comprising clopidogrel.

[0031] In another aspect of the invention, a method of treating platelet aggregation and/or thrombosis comprises administering to a user a non-crystalline formulation comprising clopidogrel following storage of the non-crystalline formulation.

[0032] In another aspect of the invention, a method of treating platelet aggregation and/or thrombosis comprises administering to a user a particulate formulation wherein the particles comprise non-crystalline clopidogrel and an excipient.

[0033] In another aspect of the invention, a method of treating platelet aggregation and/or thrombosis comprises administering to a user a non-crystalline, particulate formulation wherein the particles comprise clopidogrel and a stabilizing excipient.

[0034] In another aspect of the invention, a method of making a formulation comprising clopidogrel comprises providing a liquid containing clopidogrel and spray drying the liquid under conditions appropriate to produce particles comprising non-crystalline clopidogrel which exhibits acceptable solubility and/or bioavailability.

[0035] In another aspect of the invention, a method of making a formulation comprising clopidogrel comprises providing a liquid comprising clopidogrel and contacting liquid with a supercritical or near critical fluid to remove the solvent from the liquid to produce particles comprising non-crystalline clopidogrel.

[0036] In another aspect of the invention, a method of making a formulation comprising clopidogrel comprises providing an aqueous liquid containing clopidogrel and an excipient and removing the aqueous liquid to produce particles comprising clopidogrel and the excipient.

[0037] In another aspect of the invention, a method of making a formulation comprising clopidogrel comprises providing an aqueous liquid containing clopidogrel and an excipient and removing the aqueous liquid to produce particles comprising non-crystalline clopidogrel and the excipient wherein the particles exhibit at least one of the characteristics of parity or enhanced dissolution, solubility, stability, shelf life, or bioavailability when compared to a commercially-available product, or tableting ease or manufacturing cost-effectiveness.

[0038] In another aspect of the invention, a method of making a formulation comprising clopidogrel comprises providing an organic solvent containing clopidogrel and removing the organic solvent to produce particles comprising clopidogrel.

[0039] In another aspect of the invention, a method of making a formulation comprising clopidogrel comprises providing an organic solvent containing clopidogrel and an excipient and removing the organic solvent to produce particles comprising clopidogrel and the excipient.

[0040] In another aspect of the invention, a method of making a formulation comprising clopidogrel comprises spray drying a liquid containing clopidogrel and an excipient to produce particles comprising non-crystalline clopidogrel and the excipient.

[0041] In another aspect of the invention a method of making a formulation comprising clopidogrel comprises providing a liquid containing clopidogrel free base and adding an acid. The liquid is then removed to form a non-crystalline clopidogrel acid salt.

[0042] In another aspect of the invention a method of making a formulation comprising clopidogrel comprises providing water and adding to the water clopidogrel free acid and a sulfuric acid. The water is then removed to form non-crystalline bisulfate.

[0043] In another aspect of the invention a method of making an immediate-release tablet comprising non-crystalline clopidogrel comprises forming an intimate mixture of clopidogrel and excipient, and compacting into a tablet.

[0044] In another aspect of the invention, any two or more of the above aspects are combined.

DRAWINGS

[0045] These features, aspects, and advantages of the present invention will become better understood with regard to the following description, appended claims, and accompanying drawings which illustrate exemplary features of the invention. However, it is to be understood that each of the features can be used in the invention in general, not merely in the context of a particular example or drawing, and the invention includes any combination of these features, where:

[0046] Figure 1 is a graph showing an X-ray powder diffraction (XRPD) profile for a prior art form of clopidogrel bisulfate in its crystalline polymorphic Form 2;

[0047] Figure 2 is a schematic block diagram of one embodiment of a spray-drying process according to the present invention;

[0048] Figure 3 is a schematic diagram of an embodiment of an apparatus for carrying out a spray-drying process according to the present invention;

[0049] Figure 4 is a schematic diagram of one embodiment of an apparatus for carrying out a particle precipitation process according to the present invention;

[0050] Figure 5 is a graph showing an X-ray powder diffraction (XRPD) profile for a particulate formulation comprising pure non-crystalline clopidogrel bisulfate produced by removing an aqueous solvent from a solution using a supercritical particle precipitation process in accordance with one or more aspects of the present invention, the diffraction pattern obtained immediately after preparation;

[0051] Figure 6A is a DSC thermogram of the specific heat as a function of temperature for another version of particles comprising non-crystalline clopidogrel and a stabilizing excipient (cellulose acetate trimellitate), in a 1:1 ratio, produced using a supercritical particle precipitation process in accordance with one or more aspects of the present invention, the thermogram obtained immediately after preparation;

[0052] Figure 6B is a graph showing an X-ray powder diffraction (XRPD) profile for the formulation comprising particles of non-crystalline clopidogrel and a stabilizing excipient (cellulose acetate trimellitate) analyzed in Figure 6A, after exposure to 40°C/75% relative humidity (RH) for two weeks;

[0053] Figure 6C is a thermal gravimetric analysis (TGA) of the formulation analyzed in Figure 6A, after exposure to 40°C/75% relative humidity (RH) for two weeks;

[0054] Figure 7 is a graph showing an X-ray powder diffraction (XRPD) profile for a particulate formulation comprising non-crystalline clopidogrel bisulfate and excipient (ethyl cellulose) produced by removing an aqueous solvent from a solution using a supercritical particle precipitation process in accordance with one or more aspects of the present invention, the formulation analyzed after exposure to 40°C/75% RH for two weeks;

[0055] Figure 8 is a thermal gravimetric analysis (TGA) of the formulation analyzed in Figure 7, also after exposure to 40°C/75% RH for two weeks, showing changes in water content of the formulation during storage;

[0056] Figure 9A is a DSC thermogram of the specific heat as a function of temperature for particles comprising non-crystalline clopidogrel bisulfate and a stabilizing excipient mixture comprising CAT and HPMC in a ratio of 5:4:1, the particles produced by removing an aqueous solvent from a solution using a supercritical particle precipitation process in accordance with one or more aspects of the present invention;

[0057] Figure 9B is a graph showing an X-ray powder diffraction (XRPD) profile for the particles comprising non-crystalline clopidogrel bisulfate and CAT and HPMC of Figure 9A, the graph showing the profile after the formulation was exposed to 75% relative humidity at 40° for two weeks;

[0058] Figure 9C is a thermal gravimetric analysis (TGA) for the particles comprising the formulation analyzed in Figure 9A, the analysis obtained after the formulation was exposed to 75% relative humidity at 40° for two weeks;

[0059] Figure 10 is an X-ray powder diffraction (XRPD) profile for another version of particles of the present invention, comprising pure non-crystalline clopidogrel bisulfate, produced by spray-drying, in accordance with one or more aspects of the present invention;

[0060] Figure 11A is an X-ray powder diffraction (XRPD) profile for another version of particles of the present invention, comprising non-crystalline clopidogrel bisulfate, and a stabilizing excipient comprising HPC in a ratio of 1:1, produced by spray-drying, in accordance with one or more aspects of the present invention;

[0061] Figure 11B is an X-ray powder diffraction (XRPD) profile for the particles analyzed in Figure 11A, after the formulation was exposed to 75% relative humidity at 40° for two weeks; and

[0062] Figure 12 is an X-ray powder diffraction (XRPD) profile for another version of particles of the present invention, comprising non-crystalline clopidogrel bisulfate, PVP and a PLURONIC® surfactant polymer, in a ratio of 1:1:0.1, produced by spray-drying in accordance with one or more aspects of the present invention.

DETAILED DESCRIPTION OF SPECIFIC EMBODIMENTS

[0063] One or more embodiments of the present invention relates to a formulation comprising clopidogrel, to a method of making a formulation comprising clopidogrel, and to a method of administering a formulation comprising clopidogrel. One or more embodiments of the present invention further relates to a pharmaceutical composition comprising clopidogrel, to a method of making a pharmaceutical composition comprising clopidogrel, and to a method of administering a pharmaceutical composition comprising clopidogrel. Although the invention is illustrated in the context of a particulate formulation,

the present invention can be used in other forms and for purposes other than for those specifically disclosed, and the invention should not be limited to the examples provided herein.

Definitions

[0064] Before describing the present invention in detail, it is to be understood that the invention is not limited to the particularly exemplified apparatus, systems, methods, or processes disclosed herein, which may, of course, vary. It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments of the invention only, and is not intended to limit the scope of the invention in any manner.

[0065] All publications, patents and patent applications cited herein, whether *supra* or *infra*, are hereby incorporated by reference in their entirety to the same extent as if each individual publication, patent or patent application was specifically and individually indicated to be incorporated by reference.

[0066] It must be noted that, as used in this specification and the appended claims, the singular forms “a,” “an” and “the” include the plural unless the content clearly dictates otherwise.

[0067] Reference herein to “one embodiment”, “one version” or “one aspect” shall include one or more such embodiments, versions or aspects, unless otherwise clear from the context.

[0068] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which the invention pertains. A number of methods and materials similar or equivalent to those described herein can be used in the practice of the present invention.

[0069] Amount of ingredients, materials or substances are listed as the ranges or levels of ingredients in the descriptions, which follow hereto.

[0070] The use of the term “about” or “approximately” to modify a numerical range or series means that all numerals in the range or series are so modified, unless otherwise clear from the context that only certain numerals are to be modified.

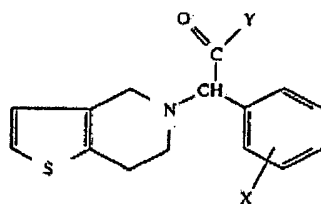
[0071] "Therapeutically-effective amount" means that amount of active present in the composition that is needed to provide the desired level of drug in the subject to be treated to yield the expected physiological response.

[0072] "Drug" means any compound or composition which induces a desired pharmacologic and/or physiologic effect, when administered appropriately to the target organism (human or animal). Clopidogrel is one example of a drug.

[0073] The term "vehicle" means a fluid which dissolves a solid or solids, to form a solution, or which forms a suspension of a solid or solids which do not dissolve or have a low solubility in the fluid. The vehicle can be composed of one or more fluids.

[0074] As used herein, a 'co-formulation' refers to two or more substances formulated at substantially the same time and/or formulated so that a particle comprising a co-formulation contains the two or more substances. For example, a co-formulation may comprise a solid dispersion of a first substance and a second substance, such as an intimate mixture of an active substance and an excipient. In some versions, the intimate mixture may comprise an active agent, especially a pharmaceutically-active agent, such as clopidogrel, dispersed in a "matrix" of a carrier material, especially an excipient, such as an oligomeric and/or polymeric excipient. The co-formulations of one or more embodiments of the present invention with an excipient may advantageously modify the solubility and/or dissolution characteristics of the active substance. Unless otherwise clear from the context, a formulation includes a co-formulation.

[0075] By "clopidogrel" it is meant the compound chemically methyl (+)-(S)- α -(2-chlorophenyl)-6, 7-dihydrothieno[3,2-c]pyridine-5(4H)-acetate, and comprises all compounds having any of the following chemical formulas:



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in which Y represents hydroxyl, an OR group wherein R is a straight or branched lower alkyl radical, or



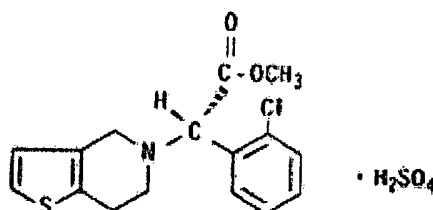
in which R₁ and R₂ are each independent of each other and represent hydrogen or a straight or branched lower alkyl group; or R₁ and R₂ form together with the nitrogen atom to which they are attached a heterocycle selected from the group consisting of pyrrolidino, piperidino, morpholino, piperazino, N-lower alkyl piperazino and N-benzyl piperazino; and X represents hydrogen, a halogen or a lower alkyl radical; and their addition salts with pharmaceutically acceptable mineral or organic acids if Y represents OR groups or



or with mineral bases if Y represents OH, including both enantiomeric forms or their mixture.

[0076] and which have ADP-induced platelet aggregation inhibiting properties, and/or are useful as platelet aggregation inhibiting agents and/or antithrombosis agents. The clopidogrel compound may be in its free compound (base) form or in the form of any pharmaceutically acceptable salt, ester, or prodrug of clopidogrel. The term "pharmaceutically acceptable salts" comprises anionic salts, such as sulfate, chloride and phosphate salts, and the like, and combinations thereof.

[0077] "Clopidogrel bisulfate" includes any of the sulfate salts of clopidogrel, for example, as shown by the structural formula:



[0078] By “crystalline” it is meant any solid which gives a wide angle x-ray powder diffraction pattern showing one or more characteristic peaks that result from the solid’s three dimensional structure, including pure compounds and mixtures which show such peaks. The x-ray powder diffraction may be performed by any suitable instrument, such as a D5000 XRD (Siemens, Germany) between 2 and 40° 2 θ , at a scan rate of 0.02 degrees per second.

[0079] By “non-crystalline” it is meant any solid which does not give rise to one or more characteristic peaks in wide angle x-ray powder diffraction indicative of crystallinity as defined above. This includes amorphous materials, which are disordered at the molecular level, and liquid crystals, such as frozen thermotropic liquid crystals, which can be distinguished from amorphous materials because they exhibit birefringence under polarized light, and microcrystalline forms which do not give rise to one or more characteristic peaks in wide angle x-ray diffraction. “Non-crystalline” also includes pure amorphous materials and amorphous mixtures of materials. In the case of a mixture, this includes molecular solid dispersions, which are comparable to liquid solutions in that there is a single phase which is disordered at the molecular level, non-molecular solid dispersions, which have one or more distinct amorphous phases, and to other homogeneous or non-homogeneous mixtures, provided there is no crystallinity as defined above.

[0080] One or more embodiments of the present invention provide an improved formulation comprising clopidogrel. Among other improvements, the clopidogrel-containing formulation described herein offers improvements over prior art formulations containing crystalline clopidogrel in that the present formulation provides clopidogrel in a form where it has a dissolution rate which provides a desired, especially a commercially-desired, bioavailability. Additionally or alternatively, one or more embodiments of the present formulation is advantageous over known pure amorphous forms of clopidogrel in that the one or more embodiments have improved mechanical stability and/or processability and/or improved physical stability and/or improved chemical stability, allowing the present formulation to be stored over longer periods of time and/or allowing the formulation more time for being processed into a solid dosage form, such as a tablet.

[0081] Solid clopidogrel is conventionally present in one or more of its stable crystalline polymorphic forms. For example, as disclosed in U.S. Patent 6,429,210 and U.S. Patent 6,504,030, clopidogrel may be processed to be in one or more crystalline polymorphic forms. These crystalline polymorphic forms may be characterized by analyzing the X-ray powder diffraction pattern of the solid material. Figure 1 shows the X-ray powder diffraction pattern disclosed in U.S. Patent 6,429,210 for crystalline polymorphic Form 2 of clopidogrel. Form 2 may be characterized by having the powder diffraction angles disclosed in the patent. Commercially available clopidogrel, supplied by Sai Life Sciences Limited in Hyderabad, India, has been tested and analyzed and has been determined to be at least partially in crystalline form.

[0082] As discussed above, the crystalline form of clopidogrel has proven to be stable and effective. However, non-crystalline forms of clopidogrel may have advantages over one or more crystalline forms of clopidogrel. Accordingly, in one or more versions of the present invention, a formulation comprising clopidogrel is provided in non-crystalline form. In one or more embodiments of a non-crystalline formulation of clopidogrel of the present invention, a desired dissolution rate may be attained while maintaining the efficacy of the clopidogrel, thereby providing an improved form of the pharmaceutical agent. In one or more embodiments, the desired dissolution rate and/or profile is substantially equal to, or parity with a commercially-available product, such as PLAVIX® 75 mg tablets. In other embodiments, the desired dissolution rate and/or profile is better than a commercially-available product, such as PLAVIX® 75 mg tablets. In other embodiments of the non-crystalline clopidogrel, and process for making herein, the result is a particulate material with desirable micromeritic properties, such as a free-flowing and/or non-sticky powder with good handling qualities enabling easy post processing, such as tablet processing.

[0083] In one or more versions, the non-crystalline formulation is produced by spray drying. During the spray drying process the clopidogrel is dissolved or suspended within a liquid. This mixture is then passed through a nozzle, or other atomizer, which introduces droplets of the mixture into a chamber. As the droplets dry, the liquid is removed thereby producing solid particles comprising non-crystalline clopidogrel. The particles are then

collected, such as by filtration or cyclone separation, to provide a particulate composition that may be administered to a user or further processed into a dosage form.

[0084] By “spray drying” it is meant the process of producing a particulate solid from a solution, slurry, emulsion, or suspension, or the like, of the clopidogrel in a liquid, such as an aqueous or organic liquid, by atomizing the liquid to form droplets and drying the droplets to form a particulate solid. Generally, the particles have a moisture content of less than about 10% by weight water, preferably less than about 5% by weight water and sometimes less than about 3% by weight water, and may be from about 3% to about 5%. The drying conditions are suitably chosen to provide the desired moisture levels. The particle size (mass mean diameter) may be tailored to be a particular size as dictated by the end usage. For tableting, the size may be about 10 to about 500 μm , and in one or more versions is in the range of about 10 to about 200 μm , or about 20 to about 100 μm , or about 20 to about 50 μm . Smaller particle sizes, for example about 10 μm or less, or larger particle sizes, for example about 500 or greater, may have applications in additional or alternative dosage forms.

[0085] During the spray drying process, atomization of the liquid may be performed using a conventional atomizer such as a centrifugal, sonic, pressure and/or rotary atomizer. In one or more versions, a rotary atomizer is used in which the liquid flows over the wheel surface as a thin film, and is sheared away into discrete droplets. Other suitable atomizers include two-fluid atomizers, wherein liquid and atomization gas stream are delivered concurrently. Typically, the atomization gas is pressurized to high pressure for delivery through an atomization nozzle. Often the gas is air although other gases such as nitrogen may also be used. An example of a suitable spray drying method is a method as described in *The Spray Drying Handbook*, by Keith Masters, Longman Publishing, 5th Ed., September 1991, the contents of which is incorporated herein by reference in its entirety. Other spray-drying references include US 6,592,904 and/or WO 03/037303, the contents of which are incorporated herein by reference in their entireties.

[0086] In one or more embodiments of the present invention, and referring to Figure 2, a spray-drying process comprises an atomization operation 10 that produces droplets of a liquid medium, which are subsequently dried in a drying operation 20. The drying

operation 20 may be a single drying chamber or a multi-stage operation. Drying of the liquid droplets results in formation of the discrete particles that form the dry powder compositions which are then collected in a separation operation 30. Each of these unit operations is described in greater detail below.

[0087] The atomization process 10 may utilize any one of several conventional forms of atomizers. The atomization process increases the surface area of the starting liquid. Due to atomization there is an increase in the surface energy of the liquid, the magnitude of which is directly proportional to the surface area increase. The source of this energy increase depends on the type of atomizer used. Any atomizer (rotary, centrifugal, sonic, pressure, two fluid) which is capable of producing droplets with a mass median diameter of less than about 100 microns, is suitable.

[0088] If a two fluid atomizer is used, the atomization gas may be nitrogen which has been filtered or otherwise cleaned to remove particulates and other contaminants. Alternatively, other gases, such as air may be used. The atomization gas will be pressurized for delivery through the atomization nozzle, typically to a pressure above 5 psig, preferably being above 10 psig. The atomization conditions, including atomization gas flow rate, atomization gas pressure, liquid flow rate, and the like, are controlled to produce liquid droplets having a desired particle diameter as known to the art.

[0089] The feedstock for the process may be a solution, suspension, colloidal system, or other dispersion of an active agent in a suitable solvent, or co-solvent system, and is preferably a homogenous solution. The active agent comprises a drug, pharmaceutical, compound, formulation or co-formulation, which is desired to be spray-dried. In one embodiment, the active agent is present as a solution in water. Alcohol/water co-solvent systems according to this invention may also be employed. Other suitable solvents include, but are not limited to, alcohols such as methanol, ketones such as acetone, polar aprotic solvents, hydrogenated hydrocarbons such as methylene chloride, hydrocarbons such as cyclohexane, and mixtures thereof. The total dissolved solids, including the insoluble active agent and other carriers, excipients, etc., that may be present in the final dried particle, may be present at a wide range of concentrations, typically being present at from about 0.1% by weight to about 50% by weight, and often about 1% to about 25% by

weight. It will thus be understood that the term "feedstock" as used herein is used broadly and encompasses mixtures such as solutions, slurries, suspensions, emulsions, microemulsions, multiple emulsions, and reverse emulsions.

[0090] The drying operation 20 is performed next to evaporate liquid from the droplets produced by the atomization operation 10. In some embodiments, the drying comprises introducing energy to the droplets, typically by mixing the droplets with a heated gas which causes evaporation of the water or other liquid medium. In some embodiments, the mixing is done in a spray dryer or equivalent chamber where a heated gas stream has been introduced. In some embodiments, the heated gas stream may flow concurrently with the atomized liquid; in other embodiments a counter-current flow, cross-current flow, or other flow pattern of the heated gas is employed. It is also possible to perform the drying operation in multiple stages as described, for example, in more detail in WO 01/00312 the disclosure of which is incorporated by reference in its entirety, and in particular with regard to drying apparatus, steps methods and conditions.

[0091] The drying rate may be controlled based on a number of variables, including the droplet size distribution, the inlet temperature of the gas stream, the outlet temperature of the gas stream, the inlet temperature of the liquid droplets, and the manner in which the atomized spray and hot drying gas are mixed. In one embodiment, the drying gas stream has an inlet temperature of at least about 70°C, and may be at least about 120°C, at least about 135°C, at least about 145°C, and may often be over about 175°C, or even as high as about 200°C, depending on the active agent being dried. At least in part, the inlet temperature of the heated gas drying stream depends on the lability of the active agent being treated. The outlet temperature is usually in the range of about 50-100°C. The drying gas may be moved through the system using conventional blowers or compressors.

[0092] The separation operation 30 is selected to achieve high efficiency collection of the particles produced by the drying operation 20. Any of several conventional separation operations may be used, although in some cases they could be modified to assure collection of a specified particle size range. In one or more embodiments, separation is achieved using a cyclone separator. Other separators, such as filters, for example, a membrane medium (bag filter), a sintered metal fiber filter, or the like may also be used. The

separation operation should achieve collection of at least about 70% of all particles, and in some embodiments collects more than about 85%, more than about 90%, or even more than about 95% of such particles.

[0093] Referring now to Figure 3, one embodiment of a spray-dryer system is described. The system includes a spray dryer 50, which may be a commercial spray dryer such as those available from suppliers such as Buchi, Niro, APV, Yamato Chemical Company, Okawara Kakoki Company, and others. The spray dryer 50 is provided with a feedstock as described above through a supply pump 52, filter 54, and supply line 56. The supply line 56 is connected to an atomizer 57. Atomizing air is supplied from a compressor 58, a filter 60, and line 62 to the atomizer 57. Drying air is also provided to the spray dryer 50 through a heater 65 and a filter 66.

[0094] In this embodiment, dried particles from the spray dryer 50 are carried by the air flow through conduit 70 to a separator 72. In one embodiment, the separator 72 comprises a cyclone. Alternatively, the separator 72 may be a filter, with filter media such as bag filters, cloth filters, and cartridge filters. The dried particles comprising powder are collected in a particle collection canister 76, which may be periodically be removed and replaced. The dry powder in the canister 76 may be used for packaging in unit dosage or other forms. The carrier gas passes out from the top of the separator 72 through line 80 and an exhaust fan 84.

[0095] As one alternative to spray drying, the liquid may be removed from the solution, slurry, emulsion, or suspension by other known techniques. For example, the liquid may be removed by freeze drying (lyophilization), vacuum drying, spray freeze drying, evaporation, bubble drying, or the like. In one or more embodiments, spray drying is often advantageous in terms of its efficiency and reproducibility.

[0096] In other embodiments of the present invention, the non-crystalline formulation may be produced by contacting the liquid containing the clopidogrel with an anti-solvent. For example, in one version, the liquid may comprise one or more organic solvents in which the clopidogrel is dissolved or suspended. The liquid may be contacted by a compressed gas, such as a supercritical or near supercritical anti-solvent gas, to rapidly remove the organic

solvent and thereby extract particles comprising clopidogrel. In one particular version, the anti-solvent gas may be supercritical carbon dioxide, for example.

[0097] A solvent removal process using a supercritical or near-critical fluid involves contacting a solution or suspension containing clopidogrel in a fluid (the “clopidogrel solution/suspension”) with a compressed fluid (generally a supercritical or near-critical fluid) anti-solvent under conditions which allow the anti-solvent to extract the fluid from the clopidogrel solution/suspension and to cause particles comprising clopidogrel to precipitate from the solution/suspension. The conditions are such that the fluid mixture formed between the anti-solvent and the extracted fluid is still in a compressed (generally supercritical or near-critical) state. The anti-solvent fluid should generally be a nonsolvent for the clopidogrel and be miscible with the fluid. In the context of this or any other solvent removal process, a solution may be construed to include a suspension or dispersion.

[0098] In one or more versions, the solvent removal process is a supercritical fluid particle formation process, such as the process known as the “SEDSTM” (Solution Enhanced Dispersion by Supercritical fluids) process of Nektar Therapeutics in San Carlos, California and in Bradford, United Kingdom. In one version, this process involves using the anti-solvent fluid substantially simultaneously both to extract the vehicle from, and to disperse, the clopidogrel solution/suspension. In this context, ‘disperse’ refers generally to the transfer of kinetic energy from one fluid to another, usually implying the formation of droplets, or of other analogous fluid elements, of the fluid to which the kinetic energy is transferred. Examples of Nektar Therapeutics’ supercritical fluid processes are described in PCT Publications WO 95/01221, WO 96/00610, WO 98/36825, WO 99/44733, WO 99/59710, WO 01/03821, WO 01/15664, WO 02/38127 and WO 03/008082. Other suitable processes are described in PCT Publications WO 99/52507, WO 99/52550, WO 00/30612, WO 00/30613, WO 00/67892 and WO 02/058674. All of these publications (as well as any corresponding US publications) are incorporated herein by reference in their entireties, and with specific reference to supercritical fluid processing methods, materials and apparatus. The target solution/suspension and the anti-solvent are preferably contacted with one another in the manner described in WO 95/01221 and/or WO 96/00610, being co-introduced into a particle formation vessel using a fluid inlet which allows the mechanical

energy (typically the shearing action) of the anti-solvent flow to facilitate intimate mixing and dispersion of the fluids at the point where they meet. The target solution/suspension and the anti-solvent preferably meet and enter the particle formation vessel at substantially the same point, for instance via separate passages of a multi-passage coaxial nozzle. Alternatively, or additionally, the supercritical fluid process may be of the type described in WO 03/008082, which is incorporated herein by reference in its entirety, in which the target solution/suspension and the anti-solvent enter the vessel at separate, although close, locations.

[0099] Reference to an anti-solvent fluid being in a compressed state means that, at the relevant operating temperatures, it is above its vapor pressure, preferably above atmospheric pressure, more preferably from about 50 to 250 bar. The anti-solvent fluid is preferably a fluid which is a gas at atmospheric pressure and ambient temperature. Preferably, "compressed" means close to, at or more preferably above the critical pressure P_c for the fluid concerned. The anti-solvent is preferably a supercritical or near-critical fluid or may alternatively be a compressed liquid. A "supercritical fluid" is a fluid at or above its critical pressure (P_c) and its critical temperature (T_c) simultaneously. A "near-critical fluid" is either (a) above its T_c but slightly below its P_c or (b) above its P_c but slightly below its T_c or (c) slightly below both its P_c and T_c . The terms "compressed fluid", "supercritical fluid" and "near-critical fluid" each encompass a mixture of fluid types, so long as the overall mixture is in the compressed, supercritical or near-critical state respectively.

[00100] Various anti-solvents, solvents, and process conditions may be used. The anti-solvent used is preferably supercritical, near-critical or liquid CO_2 , especially supercritical CO_2 . Preferred solvents include one or more of methanol, ethanol, isopropyl alcohol, acetone, tetrahydrofuran, ethylacetate, dimethylformamide, dichloromethane, MeCN (acetonitrile), N,N-dimethylacetamide (DMA). Hydroxylic solvents are preferred. The processing conditions are preferably chosen to produce particles of desired sizes and/or to reduce residual solvent levels. If clopidogrel is co-formulated with an excipient, and the SEDSTM particle precipitation process is used, the excipient is preferably soluble or miscible with the solvent. Excipients with varying degrees of hydrophilicity may thus be suitable depending upon the solvent employed in the SEDSTM process.

[00101] By "sonic velocity" and "supersonic velocity" is meant respectively that the velocity of the anti-solvent fluid as it enters the vessel is the same as or greater than the velocity of sound in that fluid at that point. By "near-sonic velocity" is meant that the anti-solvent velocity on entry into the vessel is slightly lower than, but close to, the velocity of sound in that fluid at that point--for instance its "Mach number" M (the ratio of its actual speed to the speed of sound) is greater than about 0.8, preferably greater than about 0.9 or about 0.95. Generally speaking, in the method of the invention, the Mach number for the anti-solvent fluid on entering the particle formation vessel may be between about 0.8 and about 1.5, preferably between about 0.9 and about 1.3.

[00102] In one or more embodiments, the method of the present invention comprises a method for forming a substance, or co-forming two or more substances, in particulate form, the method comprising introducing into a particle formation vessel (a) a solution or suspension of the target substance in a fluid vehicle (the "target solution/suspension") and (b) a compressed fluid anti-solvent for the substance, and allowing the anti-solvent fluid to extract the vehicle from the target solution/suspension so as to form particles of the target substance, wherein (i) the pressure in the particle formation vessel is P_1 which is preferably greater than the critical pressure P_c of the anti-solvent, (ii) the anti-solvent is introduced through a restricted inlet so as to have a back pressure of P_2 , where P_2 is greater than P_1 , (iii) the temperature in the particle formation vessel is T_1 which is preferably greater than the critical temperature T_c of the anti-solvent, (iv) the anti-solvent is introduced into the vessel at a temperature T_2 , where T_2 is greater than T_1 , (v) T_1 and T_2 are such that Joule-Thomson cooling of the anti-solvent as it enters the vessel does not reduce the anti-solvent temperature to below that required of it at the point of particle formation (and are preferably such that the anti-solvent temperature does not fall below T_c within the vessel) and (vi) P_1 , P_2 , T_1 and T_2 are such that the anti-solvent fluid has a sonic, near-sonic or supersonic velocity as it enters the particle formation vessel.

[00103] Although not intending to be bound by theory, it is believed that in the method of the invention, a so-called "Mach disk" is generated in the anti-solvent flow downstream of the second fluid inlet means. In this region the fluid velocity will change abruptly to sub-sonic thus generating shock waves in the fluids present (in effect a

continuous, low volume, supersonic boom). These shock waves are thought to aid mixing and dispersion of the target solution/suspension with the anti-solvent. Moreover they will propagate in the direction of the anti-solvent flow, rather than in a counter-current sense.

[00104] The arrangement of the first and second inlet means will preferably be such that the Mach disk is generated upstream (in the direction of anti-solvent flow) of the point of entry of the target solution/suspension into the particle formation vessel. It should occur in line with the longitudinal axis of the second inlet means, i.e., in line with the direction of anti-solvent flow.

[00105] The near-sonic, sonic or supersonic anti-solvent velocity is ideally achieved, in one or more methods of the present invention, by the use of appropriate anti-solvent flow rates, back pressures and/or operating temperatures, and preferably without the aid of mechanical, electrical and/or magnetic input such as for example from impellers, impinging surfaces especially within the anti-solvent introducing means, electrical transducers and the like. Introducing the anti-solvent via a convergent nozzle, ideally as a single fluid stream, may also help in the achievement of appropriate fluid velocities.

[00106] The use of near-sonic, sonic or supersonic anti-solvent velocities can allow achievement of smaller particle sizes and narrower size distributions in a supercritical or near-critical fluid-based particle formation processes. In particular it can allow the formation of small micro- or even nano-particles, for instance of volume mean diameter less than about 5 microns, preferably less than 2 microns, more preferably less than about 1 micron. Such particulate products preferably have narrow size distributions, such as with a standard deviation of 2.5 or less, more preferably 2.0 or less, most preferably 1.9 or even 1.8 or less.

[00107] The use of near-sonic, sonic or supersonic anti-solvent velocities also appears to lead to more efficient vehicle extraction, thus potentially yielding particles with lower residual solvent levels, less agglomeration and generally improved handling properties.

[00108] Preferably the two fluids meet immediately downstream of the point of anti-solvent entry. "Immediately" in this context implies a sufficiently small time interval

(between the anti-solvent entering the particle formation vessel and its contact with the target solution/suspension) as preferably still to allow transfer of mechanical energy from the anti-solvent to the solution/suspension so as to achieve dispersion. Nevertheless, there is still preferably a short interval of time between anti-solvent entry and fluid contact so as to eliminate, or substantially eliminate or at least reduce, the risk of apparatus blockage due to particle formation at the point of anti-solvent entry. The timing of the fluid contact will depend on the natures of the fluids, the target substance and the desired end product, as well as on the size and geometry of the particle formation vessel and the apparatus used to introduce the fluids and on the fluid flow rates. The contact may occur within about 0.0001 to about 50 milliseconds, or within about 0.001 to about 25 milliseconds. The contact preferably occurs within about 0.001 to about 20 milliseconds, such as within about 0.01 to about 10 milliseconds, of the anti-solvent entering the particle formation vessel.

[00109] At the point where the target solution/suspension and the anti-solvent meet, the angle between their axes of flow may be from about 0 degrees (i.e., the two fluids are flowing in parallel directions) to about 180 degrees (i.e., oppositely-directed flows). In one embodiment of the present invention, they meet at a point where they are flowing in approximately perpendicular directions, i.e., the angle between their axes of flow is from about 70 to about 110 degrees, more preferably from about 80 to about 100 degrees, such as about 90 degrees. In another embodiment of the present invention, the flows of target solution/suspension and the anti-solvent meet at a point where they are flowing in approximately parallel directions, i.e., the angle between their axes of flow is from about 0 to about 70 degrees, more preferably from about 0 to about 30 degrees, such as about 0 degrees.

[00110] When carrying out one or more embodiments of the present invention, the particle formation vessel temperature and pressure may be controlled so as to allow particle formation to occur at or substantially at the point where the target solution/suspension meets the anti-solvent fluid. The conditions in the vessel must generally be such that the anti-solvent fluid, and the solution which is formed when it extracts the vehicle, both remain in the compressed (preferably supercritical or near-critical, more preferably supercritical) form whilst in the vessel. For the supercritical, near-critical or compressed

solution, this means that at least one of its constituent fluids (usually the anti-solvent fluid, which in general will be the major constituent of the mixture) should be in a compressed state at the time of particle formation. There should at that time be a single-phase mixture of the vehicle and the anti-solvent fluid, otherwise the particulate product might be distributed between two or more fluid phases, in some of which it might be able to redissolve. This is why the anti-solvent fluid needs to be miscible or substantially miscible with the vehicle.

[00111] The flow rate of the anti-solvent fluid relative to that of the target solution/suspension, and its pressure and temperature, should be sufficient to allow it to accommodate the vehicle, so that it can extract the vehicle and hence cause particle formation. The anti-solvent flow rate will generally be higher than that of the target solution/suspension--typically, the ratio of the target solution/suspension flow rate to the anti-solvent flow rate (both measured at or immediately prior to the two fluids coming into contact with one another) will be about 0.001 or greater, preferably from about 0.01 to about 0.2, more preferably from about 0.03 to about 0.1. The anti-solvent flow rate will also generally be chosen to ensure an excess of the anti-solvent over the vehicle when the fluids come into contact, to minimize the risk of the vehicle re-dissolving and/or agglomerating the particles formed.

[00112] Figure 4 shows one embodiment of an apparatus suitable for carrying out methods in accordance with the present invention. Reference numeral 101 denotes a particle formation vessel, within which the temperature and pressure can be controlled by means of a heating jacket 102 and back a pressure regulator 103. The vessel 101 contains a particle collection device (not shown) such as a filter, filter basket or filter bag. A fluid inlet assembly 104 allows introduction of a compressed (typically supercritical or near-critical) fluid anti-solvent from source 105 and one or more target solutions/suspensions from sources such as 106 and 107. The elements labeled 108 are pumps, and 109 is a cooler. A recycling system 110 allows solvent recovery.

[00113] The fluid inlet assembly 104 may for example take the forms shown in U.S. Patent 6,063,138 and/or U.S. Patent 5,851,435, the disclosures of which are incorporated by reference in their entireties, and in particular with regard to apparatus, steps, methods and conditions. The fluid inlet assembly 104 includes a nozzle (not shown) for introduction

of the anti-solvent fluid. The nozzle may comprise a single passage of circular cross section, with a circular outlet, or may alternatively comprise a multi-component nozzle, with anti-solvent introduced through one or more of its passages and the remaining passages either closed off or else used to introduce additional reagents. (For example, a multi-passage nozzle of the type described in WO-95/01221 and/or corresponding U.S. Patent 5,851,453 or WO-96/00610 may be used). Such nozzles have two or more concentric (coaxial) passages, the outlets of which are typically separated by a short distance to allow a small degree of internal mixing to take place between fluids introduced through the respective passages before they exit the nozzle. The anti-solvent could for instance be introduced through the inner passage of such a nozzle, traversing a small "mixing" zone as it exits that inner passage and then passing through the main nozzle outlet into the particle formation vessel).

[00114] The opening at the outlet end (tip) of the nozzle may have a diameter in the range of about 0.05 to about 2 mm, preferably between about 0.1 and about 0.3 mm, typically about 0.2 mm. The outlet end of the nozzle may be tapered depending upon the desired velocity of the fluids introduced through the nozzle; an increase in the angle may be used, for instance, to increase the velocity of the supercritical fluid introduced through the nozzle and hence to increase the amount of physical contact between the supercritical fluid and the vehicle.

[00115] Figure 5 shows an X-ray powder diffraction pattern of pure non-crystalline clopidogrel bisulfate particles produced by supercritical fluid processing of clopidogrel bisulfate dissolved in an organic solution. By "pure non-crystalline clopidogrel bisulfate" it is meant that a majority of the particles consist of clopidogrel bisulfate. As can be seen, there are no characteristic peaks. Thus, it can be determined that the formulated particles are non-crystalline. Polarized light photomicrography of the non-crystalline clopidogrel bisulfate formulation reveals no signs of crystallinity. This pure non-crystalline formulation may be administered to a user immediately, may be formulated immediately into a stable form, may be stored under controlled environments, or may be allowed to convert to another solid state form.

[00116] The pure non-crystalline clopidogrel, as shown in Figure 5, produced by supercritical fluid processing in accordance with one or more embodiments of the present invention may be physically stable. It has been found that in accordance with one or more embodiments of the present invention, clopidogrel which has been obtained by supercritical fluid processing from solution, such as a solution comprising an organic solvent, is initially non-crystalline, and may retain substantially its non-crystalline character for a period of time, especially when stored under cool and/or dry conditions. In one or more versions, the cool conditions comprise a storage temperature of about 10°C or less, and the dry conditions comprise a relative humidity of about 25% or less.

[00117] Accordingly, in one or more versions of the present invention, a non-crystalline formulation comprising clopidogrel is formulated so as to improve its physical stability. For example, the improved stability may be provided by combining the non-crystalline clopidogrel with a stabilizing excipient. The stabilizing excipient is provided in a sufficient quantity to reduce the tendency of the non-crystalline clopidogrel to convert to a crystalline form. The clopidogrel and a stabilizing excipient may be formulated together by conventional methods such as blending the two ingredients together. Preferably, the stabilizing excipient is in intimate contact with the non-crystalline clopidogrel. The stabilizing excipient may be either non-crystalline or crystalline, as long as it serves to maintain the clopidogrel in a non-crystalline form. Formulation or co-formulation of the non-crystalline clopidogrel with one or more excipients and/or surface modifying agents as described in the one or more embodiments, versions or aspects herein may permit manipulation of the surface composition and/or topology to provide desired, especially improved, pharmaceutical and/or micromeritic properties.

[00118] In one or more versions, the formulation is made up of particles, and the particles comprise non-crystalline clopidogrel and an excipient, i.e. both the clopidogrel and the stabilizing excipient are present in the same formulated particle. By providing the stabilizing excipient and the clopidogrel in the same particle, the excipient and the clopidogrel are in greater contact and the stabilizing excipient is better able to assert its stabilizing influence on the clopidogrel. In one or more versions, the clopidogrel and the excipient are formulated so that there is provided a solid dispersion of one component in

another, such as an intimate mixture of clopidogrel dispersed in a matrix of the stabilizing excipient, or a solid solution of the components, whereby an intimate association results. In one or more versions, the particles comprising non-crystalline clopidogrel and excipient may be formulated by adding the excipient to the liquid in the product methods described above. For example, clopidogrel and a stabilizing excipient may be dissolved or suspended in an aqueous or organic solvent and the particles may be formed by removing the solvent by spray drying, freeze drying, spray freeze drying, evaporation, supercritical fluid extraction, or other solvent removal technique.

[00119] The stabilizing excipient may be any excipient that serves to reduce the conversion of non-crystalline clopidogrel to crystalline clopidogrel when compared to non-crystalline clopidogrel in the absence of the stabilizing excipient. For example, the excipient may comprise one or more polymeric or oligomeric excipients, such as polyvinylpyrrolidone (PVP), polyvinyl acetate (PVA), vinylpyrrolidone/vinyl acetate copolymer (PVP-VA), vinylpyrrolidone/vinyl acetate copolymer in a VP:VA of 60:40 (PVP-VA 64), poly ethylene oxide (PEO), cellulose, starch, hydroxypropyl cellulose (HPC), hydroxyl propyl methyl cellulose (HPMC), and their copolymers and derivatives; carbohydrates; polyols; sugars; oligo saccharides such as cyclodextrins; proteins, peptides and amino acids; lipids and modified lipids such as lipid-PEG and lipid-sugar esters; salts; citric acid; citrates; known glass formers; or the like. Some stabilizing excipients are described in U.S. Patent 6,582,728, and in PCT WO 01/15664, the entire disclosures of which are incorporated herein by reference in their entirety, and in particular those portions relating to excipients. In one or more embodiments, the excipient is selected to be non-hygroscopic, such as being hydrophobic, and wherein the resultant formulation or co-formulation with clopidogrel is relatively non-hygroscopic. In one or more embodiments, the selection of excipient is based, at least in part, on the hydrophobicity or hydrophilicity of the excipient, considering the solvent removal process and type of solvent used therein. Thus, in one or more embodiments, for example, the excipient is selected to be non or minimally hygroscopic, and also to be sufficiently soluble in the solvent or solvent mixture from which the formulation or co-formulation is precipitated. Additionally, it is preferred that the excipient's solubility be compatible with, and especially optimal for processing by, the particular solvent removal process employed. In one or more embodiments, the

excipient is selected such that at any given environmental condition(s), such as a particular relative humidity, the excipient will absorb less moisture than the clopidogrel absent the excipient.

[00120] In other embodiments of the present invention, the excipient is alternatively or additionally a surface modifying agent, such that when formulated or co-formulated with the clopidogrel and produced as a particle or powder, the surface of the particle, in particular, is hydrophobic. This may provide desired or advantageous micromeritic and/or mechanical properties, such as desired and/or improved, flowability, dispersibility or dispensibility, or combinations thereof. In one or more embodiment, lipid and lipid derivatives, including lipid carbohydrate esters are suitable to provide such advantageous micromeritic and/or mechanical properties. Such lipid and lipid derivatives often tend to remain on the surface of the particle produced therewith, thus can be used to impart surface hydrophobicity. In one or more embodiments, the surface modification agents alternatively or additionally permit desired surface topologies to be attained. In particular, a surface modification agent may improve flowability by reducing the particles' surface hydrophilicity.

[00121] Examples of other polymeric or oligomeric excipients for formulation with clopidogrel according to the invention include other celluloses and cellulose derivatives, such as alkyl (for example, methyl or ethyl) cellulose, hydroxyalkyl celluloses (such as hydroxypropylmethyl cellulose, hydroxypropylmethyl cellulose phthalate, hydroxyethyl cellulose, hydroxypropyl cellulose), cellulose acetate and derivatives thereof, such as cellulose acetate mellitate, cellulose acetate phthalate, cellulose acetate propionate, carboxymethylcellulose, sodium carboxymethyl cellulose, microcrystalline cellulose, microfine cellulose) or mixtures thereof; traditional "natural" source materials, their derivatives and their synthetic analogues, such as acacia, tragacanth, alginates (for instance calcium alginate), alginic acid, starch, agar, carrageenan, xanthan gum, chitosan, gelatin, guar gum, pectin, amylase or lecithin; homo- and co-polymers of hydroxy acids such as lactic and glycolic acids; hydrated silicas, such as bentonite or magnesium aluminium silicate; polymeric surfactants, such as polyoxyethylene or polyoxypropylene, or polyalkylene oxides such as polyethylene oxides; phospholipids, such as DMPC

(dimyristoyl phosphatidyl choline), DMPG (dimyristoyl phosphatidyl glycerol) or DSPC (distearyl phosphatidyl choline); carbohydrates, such as lactose, sucrose, dextrans, cyclodextrins or cyclodextrin derivatives; mannitol; dendrimeric polymers, such as those based on 3,5 hydroxy benzyl alcohol; poly(ϵ -caprolactones), DL-lactide-co-caprolactones and their derivatives; poly(orthoester)s and poly(orthoester)/poly(ethylene glycol) copolymers, including block copolymers, such as are described in US-5,968,543 and US-5,939,453, the entire disclosures of which are incorporated herein by reference in their entireties, and in particular those portions relating to polymers and/or excipients. Surfactant polymers and co-polymers such as polyoxyalkylenes, for example, polyoxyethylenes and/or polyoxypropylenes are suitable. A particular class of polyoxyalkylene co-polymers are the PLURONIC® surfactants, marketed by BASF, especially PLURONIC® F-127. Derivatives of such polymers, such as polymers with incorporated esters of short chain α -hydroxy acids or glycolic-co-lactic acid copolymers; or mixtures thereof, are additionally suitable.

[00122] Preferred excipients, especially when the liquid removal process comprises spray-drying, are those which have a T_g of above about 40°C, and preferably above about 50°C. In some versions, the T_g may be above about 55 or 60 or 65 or 70°C. Particularly preferred excipients, especially when the liquid removal process comprises spray-drying, are those which, when formulated or co-formulated with the clopidogrel in accordance with one or more embodiments of the present invention herein, result in a formulation or co-formulation T_g of above about 40°C, and preferably above about 50°C. In some versions, the formulation T_g may be above about 55 or 60 or 65 or 70°C. It should be noted that the T_g is only one possible determinant of the desired physical qualities of the resulting particles, and other determinants, such as hygroscopicity, empirical physical stability, chemical stability, powder flowability, handling properties, and micromeritic properties may be important as well. In one or more embodiments copolymers are preferred excipients. Such copolymers may comprise block, alternating, random, graft, branched, substituted and combinations thereof. Copolymers of vinyl pyrrolidone with vinyl acetate and/or vinyl alcohol are particularly preferred. It is additionally preferred that a ratio of vinyl pyrrolidone:vinyl acetate be about 60:40, or in ratios such as about 80:20, 70:30, 50:50, 30:70, 40:60 and 20:80.

[00123] In one or more versions of the formulation according to the invention, an oligomeric or polymeric stabilizing excipient is present in an amount by weight sufficient, following formulation with clopidogrel, to provide improved stability to the non-crystalline clopidogrel. In one or more embodiments, the improved stability comprises physical stability which is at least comparable to that attained by a crystalline form of clopidogrel. In one or more embodiments, the improved stability comprises chemical stability which is at least comparable to that attained by a crystalline form of clopidogrel. In other embodiments, the improved stability comprises a formulation which maintains its non-crystalline form when stored at about 25°C and about 60% relative humidity for a period of at least one week, preferably at least one month, more preferably at least three months. In some embodiments, the formulation maintains its non-crystalline form when stored at about 25°C and about 60% relative humidity for a period of at least about one year. In other embodiments, the improved stability comprises a formulation which maintains its non-crystalline form when stored at about 40°C and about 75% relative humidity for a period of at least one week, more preferably at least one month, more preferably at least three months.

[00124] Generally, in terms of weight percentage, the excipient may be present at a concentration in the range of from about 1 to 99.9% w/w, or from about 5% to 70%, or from about 10% to 50% w/w of the formulation. The clopidogrel may be present in the complementary (to the excipient) amount, and in one or more versions is present in an amount of between about 0.1 to 99.9% by weight, or is present from about 1 to 50%, typically from about 5 to 25% by weight.

[00125] The formulation according to the invention is preferably in particulate form, especially in the form of fine particles having a volume mean diameter (VMD) of about 5 to about 200 μm preferably about 10 μm to about 100 μm more preferably from about 10 μm to about 50 μm , or about 15 μm to about 30 μm . In some embodiments, particle sizes are about 20 or 22 μm , or in a range thereof. Particle sizes may be measured for instance using a laser diffraction sensor such as the HelosTM system available from Sympatec GmbH, Germany (which provides a geometric projection equivalent (mass mean diameter, MMD)). Volume mean diameters may be obtained using commercially available software packages.

[00126] Following formulation with at least one excipient, the clopidogrel will have improved physical stability with respect to reversion to crystalline form, for at least one week, more preferably at least one month, and most preferably at least three months. By “stable” is meant that over the specified time period, there is no significant change in the X-ray diffraction (XRD) pattern of the formulation and, where measurable, in its differential scanning calorimetry (DSC) profile. Preferably there is no significant change in the dissolution profile of the clopidogrel formulation over time. Preferably there is little or no (for example less than about 10%, preferably less than about 5%, more preferably less than about 1%) change in degree of crystallinity of the clopidogrel within the formulation with respect to the initial amount. Particularly preferably, there is no detectable crystalline clopidogrel present in the formulation either before or after storage. Stability may be assessed by storing the formulation according to the invention at ambient temperature, for example from about 18 to about 25°C, or from about 20 to about 23°C, such as about 22°C, or at the accepted industrial standard temperature of about 25 °C, and at up to about 20% or 30% or 40% or 60% or even 75% relative humidity (RH). In one particular assessment, the temperature is about 25°C and the relative humidity is about 60%. Higher storage temperatures and/or humidity conditions may be used, in conventional manner, to establish shelf life for longer term storage under ambient conditions. Conventional thermal cycling procedures such as freeze/thaw cycling, may be employed in some circumstances, for example, stability assessment of non-solid formulations. For example, an accelerated storage assessment may be performed at about 40°C and about 75% relative humidity. The formulation according to the invention is preferably stable, for the periods mentioned above, when stored at about 25°C and up to about 60% RH for a period of at least one year, more preferably at least eighteen months, and most preferably at least twenty-four months. Even more preferably, the formulation is considered stable when stored at about 40°C, most preferably at about 40°C and up to about 75% RH for a period of at least about one year, more preferably at least about eighteen months, and most preferably at least about twenty-four months. As a general guide, a formulation tested as stable under accelerated storage conditions for three months will be stable under ambient storage conditions for at least about two years.

[00127] The degree of crystallinity of the formulation may be assessed by conventional techniques, for example using X-ray powder diffraction (XRPD) techniques, particularly high resolution X-ray powder diffraction using a synchrotron radiation source. Levels of non-crystalline or amorphous phase may also be assessed by reference to its moisture uptake at any given temperature and humidity.

[00128] Bioavailability may be assessed, according to standard procedures, with reference to the release profile of the active substance, with time, into the patient's bloodstream. It may be measured for example as either the maximum plasma concentration of active achieved following administration (C_{max}), or as the area under the plasma concentration curve (AUC) integrated from time zero (the point of administration) to a suitable endpoint or to infinity. Bioavailability can also be estimated using standard dissolution rate tests.

[00129] The formulations according to one or more embodiments of the present invention may be further formulated into a pharmaceutical composition. A pharmaceutical composition according to the invention may take the form of any delivery form conventional in the art. The composition may take the form of a solid composition such as a powder, granulate or tablet, for example, or a liquid form such as a solution or suspension (including more viscous forms such as pastes and gels) suitable for oral delivery. Alternatively, pharmaceutical compositions according to the invention may be presented in a form suitable for topical application (for instance as a gel or paste), as a solution or suspension for injection or as a suppository.

[00130] Pharmaceutical compositions according to one or more embodiments of the invention may comprise additional active substances and/or excipients, which may or may not be included along with the clopidogrel and the excipient as part of the formulation of the invention. In one or more embodiments, the formulation comprising clopidogrel and excipient may provide a bioequivalent at least substantially equal to that of a commercially available product, such as PLAVIX® tablets. Additional ingredients may be dry-blended in with the tablet formulation. The pharmaceutical compositions according to the invention may include other additives such as those typically used in pharmaceutical dosage

formulations, for instance flavorings and sweeteners, colors, bulking agents, tablet lubricants and disintegrating agents.

[00131] The non-crystalline form of clopidogrel may be formed by adding the clopidogrel to a liquid and removing the liquid in a manner that produces particles comprising non-crystalline clopidogrel, such as by using one or more of the solvent removal or solid extraction techniques discussed herein. In one or more versions, the free compound, e.g. base, of clopidogrel is the starting material for the process embodiments herein. The commercially-available form of clopidogrel may be the free-base form. To improve solubility, the free-base can be reacted with a molar equivalent of an acid, for example sulfuric acid, to produce a clopidogrel acid salt. This clopidogrel acid salt may then be introduced into a liquid, such as by dissolving the clopidogrel in the liquid, and the liquid may be removed, using one or more process embodiments described herein and in a manner which produces the desired form of clopidogrel, such as non-crystalline clopidogrel. Alternatively, the clopidogrel free base and the acid can both be added to a liquid in a manner where the reaction to clopidogrel takes place in the liquid, and the liquid can then be removed to produce the particles of clopidogrel. In another version, the clopidogrel free base may be in solution in a liquid, such as a mother liquor from the synthesis process, and the acid may be added to this liquid, and the liquid may then be removed to produce non-crystalline clopidogrel. When an excipient is to be included in the produced particles, the excipient may be added to the solution containing the clopidogrel or the clopidogrel free base and the acid. In an alternative version, a crystalline form of clopidogrel may be used as the starting material that is added to the liquid. The crystalline clopidogrel, for example, is dissolved in the solvent and the solvent is removed by a process that produces the non-crystalline clopidogrel.

Tablet Dosage Form

[00132] A non-crystalline form of clopidogrel and excipient may be made by a solvent extraction process as described herein, for example, a supercritical particle precipitation process, or by spray-drying, a solution of clopidogrel and excipient, such as a cellulose acetate trimellitate, in accordance with one or more embodiments of the present invention. The resulting powder may then be formulated, with additional excipients, into an

appropriately-sized tablet dosage form, for example, containing 75 mg of clopidogrel per tablet. A dry granulation process, such as roller compaction, may be used to make the granules. Alternatively or additionally, a wet granulation process as known in the art, may be used to make the granules. In either case, the granules can then be compressed into tablets, also by means as known in the art. In one or more embodiments, a tablet dissolution profile is preferably comparable to (at least parity or near parity with) a commercially-available dosage form, especially 75 mg PLAVIX®. In other embodiments, a tablet dissolution profile is preferably better than commercially-available dosage form, especially 75 mg PLAVIX®. The tablet formulations may be made as described herein to be preferably chemically and physically stable for at least one year, preferably two years at room temperature, and/or preferably stable for at least one year under accelerated storage conditions. The formulations additionally may be scaled to production-sized batches.

[00133] The following examples illustrate the formation of non-crystalline and/or stable versions of a formulation comprising clopidogrel. These examples are not intended to limit the scope of the invention.

EXAMPLE 1

[00134] A first example according to the present invention involves the formulation of pure clopidogrel by removing a solvent to produce solid particles comprising clopidogrel. In some embodiments, commercially available clopidogrel comprises a crystalline powder which, as a consequence of its low pH, is only sparingly soluble in water (e.g. a 1% solution, at a pH of less than about 2). Aqueous solubility may be improved by increasing the pH, such as by adding a pH adjusting agent, for example NaOH to adjust to pH 3 or greater. The clopidogrel may also be dissolved, for example, in low concentrations in an aqueous solvent or in higher concentrations in a solvent containing a liquid in which clopidogrel is more soluble than it is in water. For example, non-aqueous solvents may include organic solvents, such as nitriles, acetonitrile, alcohols such as ethanol, isopropanol, methanol, other short chain alcohols, esters, ethers, and other low boiling point solvents. The solution may then be removed to produce particles comprising pure clopidogrel, which may have beneficial pharmaceutical and/or micromeritic properties. Additionally, the particles of pure clopidogrel may be processed under conditions which

result in a physical stability acceptable for certain purposes. The solvent removal may be performed, for example, by spray-drying, freeze-drying, spray-freeze drying, vacuum drying, evaporation, and supercritical fluid extraction. In one version, the clopidogrel is prepared under conditions, such as by being formed sufficiently quickly, that produce the clopidogrel in a form that is at least partially non-crystalline for at least a period of time. Additionally or alternatively, instead of dissolving the clopidogrel, solid particles of the clopidogrel may be suspended in a liquid, such as an aqueous liquid, and the suspension may be dried to produce solid particles comprising clopidogrel.

[00135] The solvent removal process is performed under conditions selected to result in the formation of a desired form of clopidogrel, such as a non-crystalline form. Such conditions generally comprise those that result in the formation of at least a partially non-crystalline form of clopidogrel, and having at least one of the properties of a free-flowing powder, a non-sticky powder, a reduced hygroscopicity, a wet T_g of above about 40°C, or a dry T_g of the clopidogrel (without any residual solvents) of above about 90°C. Preferred is the formation of at least a partially non-crystalline form of clopidogrel having at two or more of the foregoing properties.

EXAMPLE 2

[00136] Example 2 is a specific version of Example 1, in which a supercritical fluid is used to produce a pure non-crystalline clopidogrel by removing the solvent, such as an organic solvent, from a solution of clopidogrel.

[00137] Specifically, the non-crystalline clopidogrel of Example 2 can be made by performing the following steps:

1. Starting with the commercially available clopidogrel, the material is dissolved in an organic solvent, such as methanol and optionally acetone at about 1-20% solids content, preferably at about 5-10% solids content.
2. The solution is contacted with a supercritical fluid or near critical fluid anti-solvent which removes the solvent from the solution of clopidogrel, resulting in a free-flowing, non-sticky powder having good handling and/or post processing qualities.

[00138] The solvent of this example can be removed by other organic solvent removal processes, such as evaporation, freeze-drying, spray-freeze drying, bubble drying or vacuum drying. The solvent of this example may alternatively or additionally comprise other organic solvents. For example, for the SEDS™ process, the desired solutes are dissolved or dispersed in a solvent and or solvent mixture which is miscible with carbon dioxide. Solvent choice comprises, for example, one or more of methanol, ethanol, propan-2-ol, 1-propanol, 2-methyl-1 propanol, butanol, dimethylsulfoxide, dichloromethane, toluene, hexane, ethyl ether, heptane, chloroform, acetone, ethyl acetate, toluene, acetonitrile, isopropyl acetate, methyl acetate, methylethylketone, methylisobutylketone, tetrahydrofuran, cyclohexane, N,N-dimethylformamide and dimethylacetanilide.

EXAMPLE 3

[00139] In this Example, a supercritical process is used to produce particles comprising non-crystalline clopidogrel and a stabilizing excipient. In this version, a non-crystalline form of clopidogrel can be produced that remains non-crystalline over a period of time, especially a commercially-preferred period of time, and/or exhibits desired micromeritic properties, such as desired or improved flowability. The stabilizing excipient can be any excipient that increases the physical stability of the non-crystalline clopidogrel when compared to a formulation of non-crystalline clopidogrel substantially absent the excipient.

[00140] Specifically, the non-crystalline clopidogrel bisulfate and excipient of Example 3 can be made by performing the following steps:

1. Starting with the commercially available crystalline clopidogrel, the material is dissolved in an organic solvent, such as methanol and optionally acetone at a solids content of about 1-20%, preferably at about 5-10% solids content.
2. The stabilizing excipient is then added to the solution in a weight ratio of stabilizing excipient to clopidogrel of from about 0.1:10 to about 10:0.1, preferably from about 1:10 to about 10:1, more preferably from about 1:4 to about 4:1, and most preferably about 1:1.

3. The solution is contacted with a supercritical fluid or near critical fluid anti-solvent which removes the liquid from the solution of clopidogrel and stabilizing excipient, resulting in a free-flowing powder.

[00141] The solvent of this example can be removed by other organic solvent removal processes, such as evaporation, freeze-drying, spray-freeze drying, bubble drying or vacuum drying. The solvent of this example may alternatively or additionally comprise other organic solvents. For example, for the SEDS™ process, the desired solutes are dissolved or dispersed in a solvent and or solvent mixture which is miscible with carbon dioxide. Solvent choice comprises, for example, one or more of methanol, ethanol, propan-2-ol, 1-propanol, 2-methyl-1 propanol, butanol, dimethylsulfoxide, dichloromethane, toluene, hexane, ethyl ether, heptane, chloroform, acetone, ethyl acetate, toluene, acetonitrile, isopropyl acetate, methyl acetate, methylethylketone, methylisobutylketone, tetrahydrofuran, cyclohexane, N,N-dimethylformamide and dimethylacetanilide.

[00142] The stabilizing excipient may be selected to be any excipient that increases the physical stability of the non-crystalline clopidogrel when compared to a formulation of non-crystalline clopidogrel substantially absent the excipient. Additionally or alternatively, the stabilizing excipient may be selected to be any excipient that provided improved micromeritic properties, such as powder flowability, good or improved handling qualities (including non-stickiness) and good or improved post processing qualities, such as ease of tableting. The increase in physical stability may be in terms of the formulations storage life before crystallization and/or may be in terms of its glass transition temperature at a particular relative humidity and/or other physical stability determinants. In one or more versions, the stabilizing excipient is selected that has a higher glass transition temperature than the non-crystalline clopidogrel. In other versions, the stabilizing excipient may be selected so that it has a lower hygroscopicity than the non-crystalline clopidogrel. It is preferred that the excipient, and resulting formulation or co-formulation possess a lower hygroscopicity than the clopidogrel absent the excipient. In one or more embodiments, the lowered hygroscopicity is preferred for the resultant mechanical stability and/or micromeritic properties conferred thereby. In other versions, the stabilizing excipient may be selected so that it has both a higher glass transition temperature than that of the non-

crystalline clopidogrel and a lower hygroscopicity than that of the non-crystalline clopidogrel. In one or more embodiments, suitable stabilizing excipients comprise PVPVA, ethyl cellulose, Eudragit E, hydroxypropyl cellulose and hydroxypropyl beta cyclodextrin and mixtures of the above. Additional stabilizing excipients include cellulose polymers especially enteric cellulose polymers such as cellulose acetate phthalate, cellulose acetate mellitate, cellulose acetate propionate, hydroxypropyl methylcellulose phthalate etc.

EXAMPLE 4

[00143] Example 4 is another version of Example 3. The following steps are carried out under ambient conditions:

1. Starting with the crystalline material, preferably clopidogrel bisulfate, the salt is dissolved in organic solvent at 1-20%, preferably at 5-10% solids content. The solvent may be any organic solvent in which the clopidogrel is sufficiently soluble and which is compatible with SEDS™ processing. In one or more versions, the organic solvent is a mixture of methanol and acetone. In one or more versions, a ratio of methanol:acetone may be between about 1:1 to 1:10, such as about 1:3 v/v.
2. One or more excipients, such as a cellulose, an alkyl cellulose, a modified cellulose or combinations thereof, are added into the solution made from step 1. In one or more versions, it is preferred that the excipient has a lower hygroscopicity and/or a higher T_g than that of the clopidogrel, and be partially or completely miscible with the clopidogrel in the amorphous state. In one or more versions, a specific example of an excipient is a cellulose acetate trimellitate and/or a cellulose acetate phthalate, both of which are very hydrophobic. Other excipients and excipient-mixtures may also be used as long as they possess at least one of the properties described herein. A weight ratio of cellulose acetate trimellitate to clopidogrel bisulfate may be in the range of about 0.1:10 to about 10:0.1 preferably about 1:3 to 3:1, more preferably about 1:1.
3. The solution is contacted with a supercritical fluid or near critical fluid anti-solvent which removes the liquid from the solution of clopidogrel and stabilizing excipient, resulting in a free-flowing powder.

4. The resultant solution can also be made into powder using various technologies known to the field, such as by drying, freeze-drying (sublimation), super critical fluid processing (extraction), and spray freeze-drying. Additionally, other pharmaceutically acceptable salt, ester, and prodrugs of clopidogrel can also be used as the starting material.

EXAMPLE 5

[00144] Example 5 is another specific version of Example 3. The following steps were carried out under ambient conditions:

[00145] 6 g cellulose acetate trimellitate (CAT) was added slowly to a solution containing 25 mL methanol and 75 mL of acetone. The CAT was dissolved by stirring at about 60 RPM.

[00146] 6 g clopidogrel bisulfate was added to the solution made from step 1, and dissolved by stirring at about 60 RPM. The orders of step 1 and 2 are not critical and can be reversed.

[00147] The resultant solution was processed into a powder using a SEDS™ process as described herein. Additionally, processing was conducted using a BExMiN-2 nozzle with a 200 μ m tip for the CO₂ line and a 125 μ m tip for the solution line. The conditions used (at pilot plant scale) were a reactor vessel pressure of about 85 bar, a reactor vessel temperature of about 40°C, a CO₂ flow (the anti-solvent) of about 12-12.5 kg·hr⁻¹ and a solution flow of about 4 ml·min⁻¹. The operating conditions may be varied, as known to the art, for commercial scale production.

[00148] The particles were analyzed and found to be non-crystalline. Figure 6A shows favorable T_g values of the powder of this Example, with a T_g onset value of 46.1 °C and midpoint of 57.6 °C. The particles remained stable after being exposed to about 75% relative humidity at about 40°C for two weeks, as shown by the XRDP of Figure 6B. Figure 6C is a TGA analysis showing water absorption of the powder after storage for 2 weeks at 40°C and 75% RH. The powder of this Example remained flowable after exposure to ambient conditions. In other words the formulation has an improved handlability for down stream processing such as tableting.

EXAMPLE 6

[00149] Example 6 is another version of Example 3. The following steps are carried out under ambient conditions:

[00150] 6 g cellulose acetate phthalate (CAP) is added slowly to a solution containing 25 mL methanol and 75 mL of acetone. The CAP is dissolved by stirring at about 60 RPM.

[00151] 6 g clopidogrel bisulfate is added to the solution made from step 1, and dissolved by stirring at about 60 RPM. The orders of step 1 and 2 are not critical and can be reversed.

[00152] The resultant solution is processed into a powder using a SEDS™ process as described herein. In one or more embodiments, processing is conducted using a BExMiN-2 nozzle with a 200μm tip for the CO₂ line and a 125μm tip for the solution line. The conditions used (at pilot plant scale) are reactor vessel pressure of about 85 bar, a reactor vessel temperature of about 40°C, a CO₂ flow (the anti-solvent) of about 12-12.5 kg·hr⁻¹ and a solution flow of about 4 ml·min⁻¹. In one or more embodiments, the result is a free flowing and/or non-sticky powder with a wet T_g of above about 40°C, or a dry T_g above about 90° or both. The operating conditions may be varied, as known to the art, for commercial scale production.

EXAMPLE 7

[00153] Example 7 represents another version of Example 3. In the production of Example 7, the following steps were carried out:

1. 5% w/v crystalline clopidogrel and 5% w/v ethyl cellulose (4 cps) were added slowly to a solution containing acetone:ethanol (85:15 v/v). The components were dissolved by stirring at about 60 RPM.
2. The solution was processed using a SED™ process using a nozzle with a 200μm tip for the CO₂ line and a 125μm tip for the solution line. The conditions used (at pilot plant scale) were reactor vessel pressure of about 85 bar, reactor vessel temperature of about 40°C, CO₂ (anti-solvent) flow of about 12-12.5kg·hr⁻¹ and a solution flow of about 6 ml·min⁻¹.

[00154] Figure 7 is a graph showing an X-ray powder diffraction (XRPD) profile for the particulate formulation comprising non-crystalline clopidogrel bisulfate and ethyl cellulose of this Example, after exposure to 40°C/75% relative humidity (RH) for two weeks. It can be seen that the formulation is stable, as no crystallinity peaks appear. Figure 8 is a thermal gravimetric analysis (TGA) of the formulation, also after exposure to 40°C/75% relative humidity (RH) for two weeks.

EXAMPLE 8

[00155] Example 8 represents a specific version of Example 5. In the production of Example 8, the following steps were carried out under ambient conditions. The process is similar to that of Example 5, except that an additional excipient, comprising HPMCPH55 was added to the clopidogrel bisulfate and cellulose acetate trimellitate.

1. 4.8 g cellulose acetate trimellitate and 1.2 g HPMCPH55 were added slowly to a solution containing 25 ml methanol and 75 ml acetone. The excipients were dissolved by stirring at about 60 RPM.
2. 6 g clopidogrel bisulfate was added to the solution made from step 1, and dissolved by stirring at about 60 RPM. The order of steps 1 and 2 are not critical and can be swapped.
3. The solution was processed using a SEDS™ process using a nozzle with a 200µm tip for the CO₂ line and a 125µm tip for the solution line. The conditions used (at pilot plant scale) were reactor vessel pressure of about 85 bar, reactor vessel temperature of about 40°C, anti solvent (CO₂) flow rate of about 12-12.5 kg·hr⁻¹ and a solution flow of about 4 ml·min⁻¹.

[00156] The particles comprising non-crystalline clopidogrel and stabilizing excipient made in accordance with Example 8 have been analyzed and have been found to be non-crystalline with improved physical stability. Figure 9A is a DSC a graph of the specific heat as a function of temperature for the non-crystalline clopidogrel particles of this Example. An X-ray powder diffraction pattern of the powder particles, after storage for two weeks at 75% relative humidity at 40°C, is shown in Figure 9B. The X-ray pattern shows the powder to be non-crystalline in that no crystallinity-indicative peaks are present.

Figure 9C is a TGA analysis showing water absorption of the non-crystalline clopidogrel particles of this Example, also after storage for 2 weeks at 75%RH and 40°C.

EXAMPLE 9

[00157] Example 9 represents another version of Example 3. In the production of Example 9, the following steps are carried out:

1. 4.5 g hydroxypropyl beta cyclodextrin and 0.5 g ethyl cellulose (as excipients) are added slowly to a solution containing 50 mL methanol plus 50 mL acetone. The excipients are dissolved by sonication and/or stirring at about 60 RPM.
2. 5 g crystalline clopidogrel is added to the solution made from step 1, and dissolved by sonication and/or stirring at about 60 RPM. The order of steps 1 and 2 may be reversed.
3. The solution is processed using a SED™ process using a nozzle with a 200µm tip for the CO₂ line and a 125µm tip for the solution line. The conditions used (at pilot plant scale) are reactor vessel pressure of about 85 bar, reactor vessel temperature of about 40°C, CO₂ (antisolvent) flow of about 12-12.5 kg·hr⁻¹ and a solution flow of about 4 ml·min⁻¹. In one or more embodiments, the result is a free flowing powder and/or non-sticky with a wet T_g of above about 40°C, or a dry T_g above about 90°C or both.

[00158] In this version, the stabilizing excipient comprises hydroxypropyl beta cyclodextrin in combination with ethyl cellulose, at a weight ratio of excipient mixture to clopidogrel in the range of from 0.10:10 to 10:0.10, more preferably from 1:10 to 10:1, and most preferably 1:1. This mixture of hydroxypropyl beta cyclodextrin with ethyl cellulose is advantageous in stabilizing the non-crystalline clopidogrel. In addition, hydroxypropyl beta cyclodextrin is relatively hygroscopic while ethyl cellulose is not very hygroscopic, therefore a mixture of ethyl cellulose with hydroxypropyl beta cyclodextrin reduces the water uptake of the cyclodextrin molecule and consequently, of the formulation. Furthermore, the mixture of hydroxypropyl beta cyclodextrin with ethyl cellulose is relatively non-sticky, i.e. it is not a strong binder, therefore the resultant powder is relatively non-sticky. The weight ratio of hydroxypropyl beta cyclodextrin to ethyl cellulose in the mixture may be from 19:1 to 1:4, more preferably from 10:1 to 1:1, most preferably about 4:1.

EXAMPLE 10

[00159] Example 10 represents a specific version of Example 9. In the production of Example 10, the following steps are carried out:

1. 3.5 g hydroxypropyl beta cyclodextrin and 1.5 g ethyl cellulose (as excipients) are added slowly to a solution containing 50 mL methanol plus 50 mL acetone. The excipients are dissolved by sonication and or stirring at about 60 RPM.
2. 5 g crystalline clopidogrel is added to the solution made from step 1, and dissolved by sonication and/or stirring at about 60 RPM. Note that order of step 1 and 2 may be reversed.
3. The solution is processed using a SEDS™ process using a nozzle with a 200µm tip for the CO₂ line and a 125µm tip for the solution line. The conditions used (at pilot plant scale) were reactor vessel pressure of about 85 bar, reactor vessel temperature of about 40°C, CO₂ (anti-solvent) flow of about 12-12.5 kg·hr⁻¹ and a solution flow of about 4 ml·min⁻¹. In one or more embodiments, the result is a free flowing and/or non-sticky powder with a wet T_g of above about 40°C, or a dry T_g above about 90°C or both.

EXAMPLE 11

[00160] Example 11 represents another specific version of Example 4. In the production of Example 11, the following steps are carried out:

1. Ethyl cellulose is added slowly to a solution containing an organic solvent, for example, methanol and acetone in a 1:1 ratio. The excipient is dissolved by sonication and or stirring at about 60 RPM.
2. Crystalline clopidogrel, in a weigh ratio to the ethyl cellulose of between about 1:10 to 10:1, preferably about 1:1, is added to the solution made from step 1, and dissolved by sonication and/or stirring at about 60 RPM. The order of steps 1 and 2 may be reversed.
3. The solution is processed using a SEDS™ process using a nozzle with a 200µm tip for the CO₂ line and a 125µm tip for the solution line. The conditions used (at pilot plant scale) are reactor vessel pressure of about 85 bar, a reactor vessel temperature of about 40°C, a CO₂ (anti-solvent) flow of about 12-12.5 kg·hr⁻¹ and a solution flow of about 4

ml·min⁻¹. In one or more embodiments, the result is a free flowing and/or non-sticky powder, having a wet T_g of above about 40°C or a dry T_g above about 90°C or both.

EXAMPLE 12

[00161] Example 12 represents a specific version of Example 4. In the production of Example 12, the following steps are carried out:

1. Polyvinylpyrrolidone is added slowly to a solution containing methanol and acetone in a 1:1 ratio. The excipient is dissolved by sonication and or stirring at about 60 RPM.
2. Crystalline clopidogrel is added to the solution made from step 1, and dissolved by sonication and/or stirring at about 60 RPM. Note that order of step 1 and 2 may be reversed.
3. The solution is processed using a SEDSTM process using a nozzle with a 200μm tip for the CO₂ line and a 125μm tip for the solution line. The conditions used (at pilot plant scale) were reactor vessel pressure of about 85 bar, reactor vessel temperature of about 40°C, CO₂ (anti-solvent) flow of about 12-12.5 kg·hr⁻¹ and a solution flow of about 4 ml·min⁻¹. In one or more embodiments, the result is a free flowing and/or non-sticky powder with a wet T_g of above about 40°C, or a dry T_g above about 90°C, or both.

EXAMPLE 13

[00162] Example 13 is a specific version of Example 4. In this Example, a supercritical particle precipitation process is used to produce particles comprising non-crystalline clopidogrel and a stabilizing excipient, wherein the stabilizing excipient comprises a non-sugar, non-carbohydrate, especially non-sugar polymeric or oligomeric excipient. Using this version, a non-crystalline form of clopidogrel can be produced that remains stable with respect to the non-crystalline form over a period of time. In addition, because carbohydrate or sugar excipients tend to be hygroscopic, the particles produced in accordance with these and other Examples are less hygroscopic than particles comprising non-crystalline clopidogrel and a sugar. In this version, the stabilizing excipient can be any non-sugar, non-carbohydrate excipient that increases the physical stability of the non-crystalline clopidogrel when compared to a formulation of non-crystalline clopidogrel substantially absent the excipient.

[00163] Specifically, the non-crystalline clopidogrel and excipient of Example 13 can be made by performing the following steps:

1. Starting with a commercially available crystalline clopidogrel, the material is dissolved in water at about 0.01 to 20%, more preferably at about 0.1 to 20%, and more preferably at about 5-10% solid content. Particularly at the higher solid content ranges, solubility enhancers may be preferred. At lower concentrations, the clopidogrel is sufficiently soluble to be dissolved using an energy input comprising mechanical agitation, sonication, vigorous stirring or the like. Alternatively, a solvent in which the clopidogrel is more soluble, such as ethanol, may comprise the solvent.
2. A stabilizing non-sugar excipient, such as a PVP, or a PVP/VA copolymer is added to the solution of step 1 solution in a weight ratio of stabilizing excipient:clopidogrel of from about 0.1:10 to 10:0.1, more preferably from about 1:10 to 10:1, and most preferably about 1:1. Steps 1 and 2 may be reversed or combined.
3. The solution is then contacted, in a particle precipitation process, by supercritical carbon dioxide which removes the solvent to produce particles comprising clopidogrel. The starting material may be one or more of the crystalline polymorphs of clopidogrel. The process is performed under conditions selected to result in the formation of a non-crystalline form of clopidogrel. Such conditions generally comprise a reactor vessel temperature of about 35-80°C and a reactor vessel pressure of about 85-200 bar. In functional terms, it is preferred that the formation of a non-crystalline form of clopidogrel comprise a free-flowing and/or non-sticky powder and/or having a T_g above about 40°C, or a dry T_g of above about 90°C, or both.

[00164] The stabilizing excipient may be selected to comprise any excipient that increases the physical stability of the non-crystalline clopidogrel when compared to a formulation of non-crystalline clopidogrel substantially absent the excipient. This increase in physical stability may comprise a longer storage life of the formulation before crystallization, or may comprise a higher formulation glass transition temperature (T_g) at a particular relative humidity, or may comprise a lower hygroscopicity, or may comprise other physical stability determinants, or combinations thereof. In one or more versions, the stabilizing excipient is selected that has a higher glass transition temperature than that of the

non-crystalline clopidogrel, and the resulting formulation thus has a higher T_g than that of the non-crystalline clopidogrel. In other versions, the stabilizing excipient may be selected so that it has a lower hygroscopicity than the non-crystalline clopidogrel, and the resulting formulation thus has a lower hygroscopicity than that of the non-crystalline clopidogrel. In other versions, the stabilizing excipient may be selected so that it has both a higher glass transition temperature than that of the non-crystalline clopidogrel and a lower hygroscopicity than that of the non-crystalline clopidogrel (such as clopidogrel). Useful excipients comprise polyvinylpyrrolidone (PVP), polyvinyl acetate (PVA), vinylpyrrolidone/vinyl acetate copolymer (PVP-VA), sodium citrate, citric acid, ethyl cellulose, and mixtures thereof. Other stabilizing excipients that may be used comprise vinylpyrrolidone/vinyl acetate copolymer, such as PVP-VA 64, poly ethylene oxide (PEO), cellulose, starch, hydroxypropyl cellulose (HPC), hydroxyl propyl methyl cellulose (HPMC), and their copolymers and derivatives; proteins, peptides and amino acids; lipids and modified lipids such as lipid-PEG esters; salts; citric acid; citrates; known non-sugar glass formers; or the like.

EXAMPLE 14

[00165] Example 14 represents another version of Example 4. In the production of Example 14, the following steps are carried out:

1. Starting with a commercially available clopidogrel, the material is dissolved in water at 1-25% solids content.
2. Hydroxypropyl cellulose (HPC) is then added to the solution in a weight ratio of from about 0.1:10 to 10:0.1, more preferably from about 1:10 to 10:1, more preferably from about 1:1 to about 6:1 and most preferably about 1:1.
3. The solution is then contacted, in a particle precipitation process, by supercritical carbon dioxide which removes the solvent to produce particles comprising clopidogrel. The starting material may be one or more of the crystalline polymorphs of clopidogrel. The process is performed under conditions selected to result in the formation of a non-crystalline form of clopidogrel. Such conditions generally comprise a reactor vessel temperature of about 35-80°C and a reactor vessel pressure of about 85-200 bar. In functional terms, it is

preferred that the formation of a non-crystalline form of clopidogrel comprise a free-flowing, non-sticky powder and/or having a T_g above about 40°C, or a dry T_g of above about 90°C, or both.

[00166] The solvent of this, or any other, example can be removed by other aqueous solvent removal processes, such as freeze drying, spray freeze drying, evaporation, bubble drying or vacuum drying. The solvent of this example may alternatively or additionally comprise solvents other than water, such as organic solvents. For example, suitable solvents comprise ethanol, iso-propanol, methanol, other short chain alcohols, esters, ethers, and other low boiling point solvents.

EXAMPLE 15

[00167] Example 15 represents yet another version of Example 4. In the production of Example 15, the following steps are carried out:

1. Starting with a commercially available clopidogrel, the material is dissolved in water at 1-25% solids content.
2. Ethyl cellulose is then added to the solution in a weight ratio of from about 0.1:10 to 10:0.1, more preferably from about 1:10 to 10:1, more preferably from about 1:1 to about 6:1 and most preferably about 1:1.
3. The solution is then contacted, in a particle precipitation process, by supercritical carbon dioxide which removes the solvent to produce particles comprising clopidogrel. The starting material may be one or more of the crystalline polymorphs of clopidogrel. The process is performed under conditions selected to result in the formation of a non-crystalline form of clopidogrel. Such conditions generally comprise a reactor vessel temperature of about 35-80°C and a reactor vessel pressure of about 85-200 bar. In functional terms, it is preferred that the formation of a non-crystalline form of clopidogrel comprise a free-flowing and/or non-sticky powder and/or having a T_g above about 40°C, or a dry T_g of above about 90°C, or both.

[00168] The solvent of this example can be removed by other aqueous solvent removal processes, such as freeze drying, spray freeze drying, evaporation, or vacuum drying. The solvent of this example may alternatively or additionally comprise solvents

other than water, such as organic solvents. For example, suitable solvents comprise ethanol, iso-propanol, methanol, other short chain alcohols, esters, ethers, and other low boiling point solvents.

[00169] An alternative solvent removal process in accordance with one or more embodiments of the present invention comprises a spray-drying process for making particles comprising non-crystalline clopidogrel. One or more embodiments of the spray drying process are as described herein and/or as described in U.S. Patent 6,051,256, the entire disclosure of which is incorporated by reference and with particular reference to spray-drying methods, conditions and apparatus. The starting material may be one of more of the crystalline polymorphs of clopidogrel.

[00170] A pure clopidogrel formulation made by a spray-drying process was analyzed by X-ray diffraction, and found to be non-crystalline, as shown by Figure 10. However, after accelerated storage for one week at 40°C and 75% RH, the formulation began showing signs of crystallinity.

EXAMPLE 16

[00171] Example 16 represents a spray-drying process for making a pure, non-crystalline clopidogrel. Specifically, the non-crystalline clopidogrel of Example 16 can be made by performing the following steps:

1. Starting with a commercially available clopidogrel, the material is dissolved in a solvent comprising an alcohol, such as ethanol or methanol, or water, or combinations thereof, at a solids content of about 0.01 to 20%, preferably about 0.1 to 20% and more preferably about 5-10%.
2. The solution is spray-dried, for example, in a Buchi spray dryer with a solution feed rate at about 5 ml/min, an inlet temperature of about 100°C and an outlet temperature of about 60°C. For example, in one version, the solution is spray dried in a conventional Buchi 190 spray dryer at a solution feed rate of about 5-10 ml/min and with an inlet temperature of about 100-120°C. The conditions may be adjusted for other spray dryers and/or other sized spray dryers, wherein a residual moisture level comprises about 3-5%. In one or more embodiments, the preferred processing conditions result in the formation of a non-

crystalline form of clopidogrel comprising a free-flowing, non-sticky powder and/or having a T_g above about 40°C, or a dry T_g of the particles (without any residual solvents) of above about 70°C, or both. Alternatively, or additionally, another solvent removal technique may be used.

3. The particles are collected and are placed in a dry box.

[00172] The solution of step 1 can alternatively or additionally be made into powder using technologies known in the art, such as by freeze-drying, spray-freeze drying, vacuum drying, evaporation, bubble drying or extraction. This process can be performed in solvents other than water, such as organic solvents. For example, useful solvents comprise ethanol, iso-propanol, methanol, other short chain alcohols, esters, ethers, and other low boiling point solvents. Non-aqueous solvents, such as alcohols, and particularly ethanol and/or methanol, are often selected, as the pH dependant solubility of clopidogrel in aqueous solvents is thereby mitigated.

EXAMPLE 17

[00173] In this Example, a spray drying process is used to produce particles comprising non-crystalline clopidogrel and a stabilizing excipient. In this version, the stabilizing excipient can be any excipient that increases the physical stability of the non-crystalline clopidogrel when compared to a formulation of non-crystalline clopidogrel substantially without the excipient. In one version, the stabilizing excipient comprises a cellulose polymer, for example a hydroxy propyl (alkyl) cellulose, such as HPC, HPMC or mixtures thereof. In one or more versions HPMCPH55 is preferred.

[00174] Specifically, the non-crystalline clopidogrel and excipient of this Example can be made by performing the following steps:

1. Starting with the commercially available clopidogrel, the material is dissolved in water at 0.1 to 20%, preferably at 5-15%, solids content.
2. A hydroxy propyl (alkyl) cellulose excipient is then added to the solution in a weight ratio of hydroxy propyl (alkyl) cellulose to clopidogrel of between about 1:10 to 10:1 and preferably about 1:1.

3. The solution of step 2 is spray-dried, under conditions appropriate to form a free-flowing non-crystalline powder comprising particles of clopidogrel and hydroxy propyl (alkyl) cellulose.

[00175] The weight ratio of a hydroxy propyl (alkyl) cellulose or other stabilizing excipient to clopidogrel comprises from about 0.1:10 to 10:0.1, preferably from about 1:10 to 10:1, and more preferably about 1:1. The solvent of this example can be removed by other solvent removal processes, such as evaporation, freeze-drying, spray-freeze drying, bubble drying, vacuum drying or supercritical particle precipitation processes. The solvent of this example may alternatively or additionally comprise solvents other than water. For example, ethanol, isopropanol, methanol, other short chain alcohols, esters, ethers, and other low boiling point solvents, and mixtures thereof, may be used.

[00176] In one or more versions, the hydroxy propyl (alkyl) cellulose may be replaced by or supplemented with another stabilizing excipient. The stabilizing excipient may be selected to be any excipient that increases the physical stability of the non-crystalline clopidogrel when compared to a formulation of non-crystalline clopidogrel substantially absent the excipient. This increase in physical stability may in terms of the formulation's storage life before crystallization and/or may be in terms of its glass transition temperature at a particular relative humidity and/or other physical stability determinants. In one or more versions, the stabilizing excipient is selected that has a higher glass transition temperature than the non-crystalline clopidogrel. In other versions, the stabilizing excipient may be selected so that it has a lower hygroscopicity (and the resultant formulation or co-formulation has a lower hygroscopicity) than that of the non-crystalline clopidogrel. In other versions, the stabilizing excipient is selected to have both a higher glass transition temperature, and a lower hygroscopicity than the non-crystalline clopidogrel. Examples of stabilizing-effective excipients comprise one or more of: PVP-VA, PVP-VA at different VP:VA ratios, for example VP:VA between 80:20 to 20:80, inclusive, such as VP:VA 60:40 and VP:VA 20:80; CaCl₂, arginine, tris, sodium citrate and citric acid, HPMC, ethyl cellulose, derivatives thereof, mixtures thereof, and combinations of any of the foregoing. Sugars and sugar polymers can also very effective as a stabilizer against crystallization.

[00177] HPC and HPMC have been determined to be particularly advantageous. PVP-VA is also advantageous in that it is very non-hygroscopic, and the glass transition temperature of PVP-VA remains relatively high (about 50°C) after exposure to ambient conditions because of this relatively low hygroscopic nature. Moreover, the vinyl pyrrolidone side chains tend to interact with the structure of the clopidogrel to help prevent crystallization. In addition, PVP-VA is relatively nonsticky which allows for easier tablet formulation processing.

EXAMPLE 18

[00178] Example 18 represents a specific version of Example 17. In the production of Example 18, the following steps were carried out under ambient conditions:

1. 3 g HPC was slowly added to, and dissolved in 100 mL water with stirring.
2. 3 g clopidogrel, and sufficient ethanol to dissolve, were added to the solution of step 1, and dissolved with stirring. The order of steps 1 and 2 may be reversed.

[00179] The resultant solution was spray dried into powders by introducing the solution into a Buchi model 190 spray-drier, under conditions to make a free-flowing amorphous powder including an outlet gas temperature of about 50-60°C.

[00180] The particles comprising non-crystalline clopidogrel and HPC made in accordance with Example 18 have been analyzed and have been found to be non-crystalline with improved physical stability. An X-ray powder diffraction pattern of the powder particles is shown in Figure 11A. The X-ray pattern shows the powder to be non-crystalline in that no crystallinity-indicative peaks are present. The powder particles were then stored for two weeks at 75% relative humidity and 40°C. After this storage, the particles were X-rayed again and the X-ray powder diffraction pattern is shown in Figure 11B. As can be seen, there is no indication of the conversion of the non-crystalline form to a crystalline form. Polarized light micrographs reveal no crystallation.

EXAMPLE 19

[00181] Example 19 represents another specific version of Example 18. In the production of Example 19, the following steps are carried out under ambient conditions:

1. Starting with a commercially available crystalline clopidogrel, the material is dissolved in water at about 0.01 to 20%, more preferably at about 0.1 to 20%, and more preferably at about 5-10% solid content. Particularly at the higher solid content ranges, solubility enhancers may be preferred. At lower concentrations, the clopidogrel is sufficiently soluble to be dissolved using an energy input comprising mechanical agitation, sonication, vigorous stirring or the like. Alternatively, a solvent in which the clopidogrel is more soluble, such as ethanol, may comprise the solvent.
2. A stabilizing non-sugar excipient, such as a PVP, or a PVP/VA copolymer is added to the solution of step 1 solution in a weight ratio of stabilizing excipient:clopidogrel of from about 0.1:10 to 10:0.1, more preferably from about 1:10 to 10:1, and most preferably about 1:1. Steps 1 and 2 may be reversed or combined.

[00182] The solution is spray dried under conditions selected to result in the formation of an at least partially non-crystalline form of clopidogrel. For example, in one version, the solution is spray dried in a conventional Buchi 190 spray dryer at a solution feed rate of about 5-10 ml/min and with an inlet temperature of about 100-120°C. The conditions may be adjusted for other spray dryers and/or other sized spray dryers, wherein in one or more embodiments, a residual moisture level is about 2-9%, preferably about 3-5%. In one or more embodiments, the preferred processing conditions result in the formation of a non-crystalline form of clopidogrel comprising a free-flowing powder and/or having a T_g above about 40°C, or a dry T_g of the particles (without any residual solvents) of above about 70°C, or both. Alternatively or additionally, other solvent removal techniques may be used.

[00183] The particles made by Example 19 may be advantageous over pure non-crystalline forms. The powder of non-crystalline clopidogrel and PVP-VA formulation remains flowable after exposure to ambient conditions, while the pure non-crystalline clopidogrel powder sticks and agglomerates. Accordingly, the non-crystalline clopidogrel and PVP-VA containing powder formulation may have an improved flowability for downstream process such as tablet formation.

EXAMPLE 20

[00184] Example 20 represents a specific version of Example 19, with two excipients. In the production of Example 20, the following steps were carried out under ambient conditions:

1. 3 g of PVPVA 64 and 0.3 g of PLURONIC® F-127 (a block co-polymer of polyoxyethylene and polyoxypropylene, marketed by BASF) were added and dissolved with slow stirring in 100 mL of water.
2. 3 g of clopidogrel bisulfate was added into the solution made from step 1, and dissolved under constant stirring at about 60 RPM.
3. Sufficient ethanol was added into the solution made from step 2 to dissolve the solids. Steps 1, 2 and 3 may be performed in any order.
4. The resultant solution was spray dried into a powder form by introducing the solution into a Buchi 190 spray-dryer, under conditions to make the amorphous powder, including setting the outlet gas temperature of about 50-60°C.

[00185] In this version, the PLURONIC® F-127 is an additional excipient, and serves as a surface modifying agent and/or as an additional stabilizing agent. Alternatively or additionally, other surface modifying agents could be used. Alternatively or additionally, other agents, such as anti-oxidants can be introduced, such as vitamins such as vitamin C and/or vitamin E, methionine, lipoic acid, and the like. Other additional agents, such as surfactants and zein (a maize protein) may be added, to form a solution or a suspension. One of the reasons for doing so may be to tailor the properties of the powder, such as increasing the surface hydrophobicity, which can provide desired or improved processability and/or non-stickiness when exposed to humid environments, and a desired dissolution rate when reconstituted into a solution.

[00186] The particles produced in accordance with Example 20 have been tested and analyzed. An X-ray diffraction pattern of the powder immediately after preparation is

shown in Figure 12. In addition, the particles remained stable after being exposed to 75% relative humidity at 40°C for one week.

EXAMPLE 21

[00187] In any of the above examples, the free base of clopidogrel may be used as the starting material instead of the crystalline clopidogrel bisulfate. The free base may be obtained as such from a commercial source, or as an intermediate in a synthetic process, or may be produced from clopidogrel, as known to the art. To the free base, a molar equivalent of an acid, such as sulfuric acid, may be added to form the acid salt.

EXAMPLE 22

[00188] This Example illustrates a method of the present invention for producing a non-crystalline clopidogrel powder, and a pharmaceutical composition of the present invention, comprising the non-crystalline clopidogrel.

[00189] The following steps are carried out: an aqueous solution of clopidogrel and polyvinylpyrrolidone vinyl acetate copolymer, at a VP:VA ratio of 60:40 is made by dissolving approximately equal weights of clopidogrel and PVPVA in water. The ratio of clopidogrel:polyvinylpyrrolidone vinyl acetate copolymer is about 1:1 (w/w). The solution is processed into particles by spray-drying using a rotary atomizer and a Niro spray dryer. The feed solution is about 15% solids (clopidogrel and polyvinylpyrrolidone vinyl acetate) in water. The spray dryer conditions are an inlet temperature of about 100-180°C, and outlet temperature of about 60-70°C. The resulting powder is then processed into tablet form.

EXAMPLE 23

[00190] This Example illustrates one method (roller compaction process) by which a tablet dosage formulation may be made in accordance with one or more embodiments of the present invention.

[00191] Clopidogrel:PVPVA (1:1) made in accordance with one or more embodiments herein and Microcrystalline cellulose (as Avicel pH 102) are sifted through a sieve and collected in a container. Lactose DCL 15 and Aerosil (a silicone dioxide), is mixed and sifted through a sieve, and collected in a container. The sifted ingredients of are

charged into a drum blender and mixed. Magnesium stearate is sifted through a sieve and add to the blend in the drum blender and mixed. The mass is compacted and sized. Sifted magnesium stearate is added to sized granules of in the blender and mixed. The blend is compressed into tablets, and coated.

[00192] Alternatively direct compaction, as known in the art, may be used to provide a dense powder with good handling properties. The compacted powder may then be further processed into a desired form, such as a tablet.

EXAMPLE 24

[00193] Any of the above examples may be administered to a patient (human or animal), for a condition treatable thereby, and particularly to treat a patient having platelet aggregation and/or thrombosis. For example, the formulations described herein may be formulated into a tablet containing 75 mg or more of clopidogrel. This amount may be altered in order to achieve a desired therapeutic profile.

Analytical Methods

[00194] The analytical techniques employed in some of the examples are more fully described below.

X-ray powder diffraction (XRD/XRPD)

[00195] XRD/XRPD is used to characterize the nature of a sample or samples. An amorphous sample is indicated by the lack of diffraction peaks in the diffraction pattern which is characteristic of crystalline materials. Samples are analysed (on a D5000 XRD (Siemens, Germany) between 2 and 40° 2 θ , at a scan rate of 0.02 degrees per second, unless indicated otherwise.

Differential scanning calorimetry (DSC)

[00196] DSC is used to determine glass transition temperatures. This technique provides a measure of the glass transition characteristics of amorphous materials. In addition, the absence of a melting point is indicative of the lack of three dimensional order

characteristic of crystalline materials. A Perkin-Elmer™ DSC 7 (Perkin-Elmer Ltd, UK) is used. 1-5 mg samples are examined in sealed, crimped aluminium pans, under an atmosphere of nitrogen. Samples are measured using a TA DSC-2920 instrument (TA Instruments, New Castle, Delaware). About 5-10 mg sample is packed into an aluminum DSC pan and gently tapped to get the powder to form a uniform layer on the bottom of the pan (Catalog numbers 900 793.901 for pans and 900 794.901 for lids). The DSC pan is hermetically sealed using a sample encapsulation press (part # 900680.902). Helium is used as the DSC purge gas at 30 ml/min. A Refrigerated Control System (RCS) provides the heat sink for the DSC, with helium as the circuit gas run at about 110 ml/min. In modulated DSC experiments, the sample is first cooled to about 0°C, held isothermally for 10 minutes, and then heated at 2°C/minute to about 200°C. The heating rate is modulated by superimposing a sinusoidal heating profile at $\pm 0.318^\circ\text{C}/\text{min}$.

Dynamic Vapor Sorption

[00197] The moisture sorption isotherm of a powder at 25°C is measured using a dynamic vapor sorption (DVS) instrument made by Surface Measurement Systems, UK. Sample masses between 5 and 20 mg are used. Samples were loaded in a dry box to avoid moisture sorption. In the first step of the experimental run, the sample is dried at 25°C and 0%RH for at least 300 minutes, in an attempt to bring the sample to near zero wt% water. Then, the instrument is programmed to increase the RH in steps of 5% RH from 0% to 90% RH and decrease the RH in steps of 5%RH from 90% to 0% RH. A criterion of $dm/dt = 0.0001\%/min$ is chosen for the system to hold at each RH step before proceeding to the next RH step.

Materials

[00198] Crystalline clopidogrel was obtained, for example from Sai Life Sciences, LTD. of Hyderabad, India.

[00199] PVPVA is commercially available from BASF, for example, under the trademark Kollidone®.

[00200] HPC/HPMC is commercially available from Dow Chemical for example, under the trademark Methocel®.

[00201] Other chemicals, reagents and materials were obtained from various commercial sources, such as Sigma.

[00202] Although the present invention has been described in considerable detail with regard to certain preferred versions thereof, other versions are possible, and alterations, permutations and equivalents of the version shown will become apparent to those skilled in the art upon a reading of the specification. Furthermore, certain terminology has been used for the purposes of descriptive clarity, and not to limit the present invention. Therefore, any appended claims should not be limited to the description of the preferred versions contained herein and should include all such alterations, permutations, and equivalents as fall within the true spirit and scope of the present invention.

IN THE CLAIMS

1. A particulate composition comprising non-crystalline clopidogrel, wherein the composition is in the form of a free-flowing powder, and is physically and chemically stable for at least one month at 25° C and 65% RH.
2. A pharmaceutical or nutraceutical composition comprising a formulation according to claim 1.
3. The composition of claim 1 wherein the clopidogrel is produced by the steps of
 - (a) preparing a solution comprising clopidogrel and solvent;
 - (b) removing the solvent from the solution of step (a);wherein a plurality of particles, in the form of a free-flowing, non-sticky powder, result.
4. The composition of claim 3 wherein the solvent removal step further comprises the steps of
 - (i) atomizing the solution comprising clopidogrel and solvent; and
 - (ii) removing the solvent, under supercritical conditions, to produce non-crystalline clopidogrel.
5. The composition of claim 4 wherein the solution of clopidogrel and solvent further comprises an excipient, and wherein the resulting particles comprise clopidogrel and excipient.
6. The composition of claim 1 wherein the non-crystalline clopidogrel is produced by the steps of
 - (a) preparing a solution comprising clopidogrel and solvent;
 - (b) atomizing the solution comprising clopidogrel and solvent; and
 - (c) spray-drying the clopidogrel and solvent solution;wherein a plurality of particles, in the form of a free-flowing non-sticky powder, result.
7. The composition of claim 6 wherein the solution of clopidogrel and solvent further comprises an excipient, and wherein the resulting particles comprise clopidogrel and excipient.

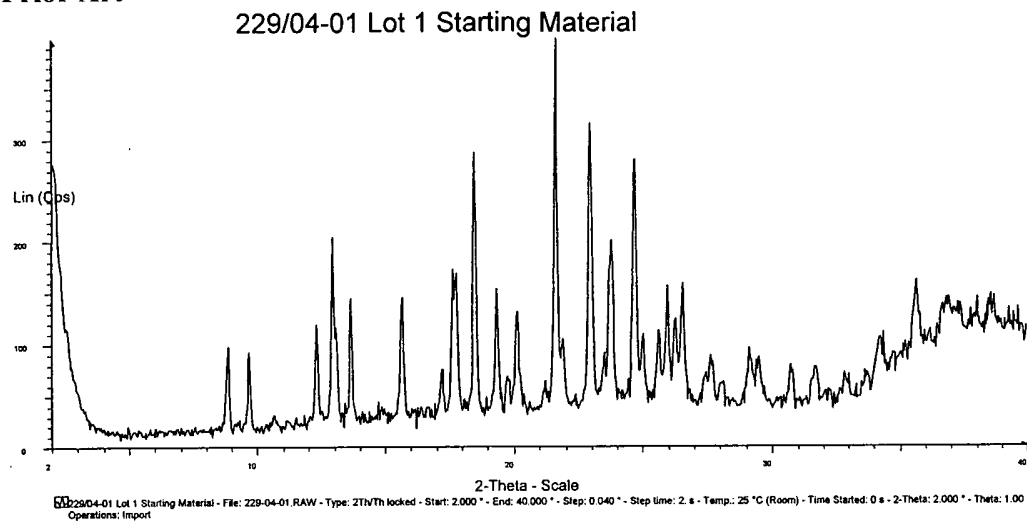
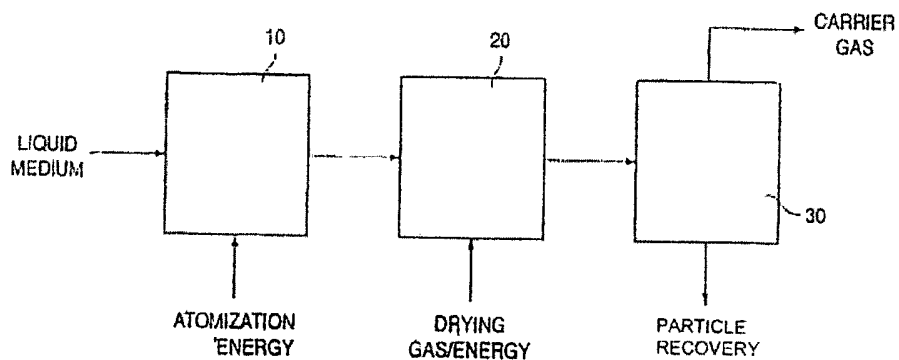
8. The composition of claim 7 wherein the excipient comprises PVP, PVPVA, HMPC, HPC, alkyl celluloses, derivatives thereof, polyoxyalkylene polymers and co-polymers, lipids and lipid derivatives, and mixtures thereof.
9. The composition of claim 1 wherein the non-crystalline clopidogrel is produced by the steps of
 - (a) providing a free-compound form of clopidogrel;
 - (b) combining the free-compound form of clopidogrel with a substantially equimolar amount of an acid and adding thereto to a solvent; and
 - (c) removing the solvent to form a non-crystalline clopidogrel acid salt.
10. A composition comprising non-crystalline clopidogrel and an excipient.
11. The composition of claim 10 in the form of a free-flowing, non-sticky powder.
12. The composition of claim 11 wherein the excipient is oligomeric or polymeric.
13. The composition of claim 12 wherein the excipient has at least one of a higher T_g , a lower hygroscopicity, or greater hydrophobicity, compared to the clopidogrel alone.
14. The composition of claim 13 wherein the excipient comprises PVP, PVPVA, HMPC, HPC, alkyl celluloses, derivatives thereof, polyoxyalkylene polymers and co-polymers, lipids and lipid derivatives, and mixtures thereof.
15. The composition of claim 10 wherein the composition comprising non-crystalline clopidogrel and excipient is produced by a supercritical particle extraction process from a target solution/suspension comprising clopidogrel, an excipient and a solvent, and wherein a free-flowing, non-sticky powder results.
16. The composition of claim 15 which has been made by co-precipitating the clopidogrel and the excipient from a common solvent or solvent mixture using a compressed fluid anti-solvent, and wherein the anti-solvent comprises CO_2 , and the solvent comprises a hydroxylic solvent.

17. The composition of claim 16, wherein the process further comprises contacting the target solution with a compressed fluid anti-solvent under conditions which allow the anti-solvent simultaneously both to disperse the target solution and to extract the vehicle from it so as to cause particles of clopidogrel and excipient to precipitate as a co-formulation.
18. The formulation according to claim 17 wherein the excipient is a polymer or co-polymer comprising vinyl pyrrolidone, HMPC, HPC, alkyl celluloses, derivatives thereof, polyoxyalkylene polymers and co-polymers, lipids and lipid derivatives, and mixtures thereof.
19. A pharmaceutical or nutraceutical composition comprising a formulation according to claim 18.
20. The composition of claim 10 comprising a surface modifying agent, and wherein the composition is in the form of a free flowing, non-sticky powder, and exhibits at least one of good dispersibility, good dispensability or good flowability.
21. A formulation comprising a non-crystalline methyl (+)-(*S*)- α -(2-chlorophenyl)-6, 7-dihydrothieno[3,2-c]pyridine-5(4*H*)-acetate compound and an excipient, the formulation prepared by a method comprising
 - providing a target solution comprising solution or suspension of methyl (+)-(*S*)- α -(2-chlorophenyl)-6, 7-dihydrothieno[3,2-c]pyridine-5(4*H*)-acetate, and
 - contacting the target solution with a compressed fluid anti-solvent under conditions which allow the anti-solvent to extract fluid from the target solution so as to cause particles of the formulated methyl (+)-(*S*)- α -(2-chlorophenyl)-6, 7-dihydrothieno[3,2-c]pyridine-5(4*H*)-acetate, and excipient to precipitate as a free-flowing powder.
22. The formulation of claim 21 wherein the excipient comprises an oligomer or polymer.
23. The formulation of claim 22 wherein the the excipient comprises a hydrophobic polymer.

24. The formulation of claim 22 wherein the the excipient comprises PVP, PVPVA, HMPC, HPC, alkyl celluloses, derivatives thereof, polyoxyalkylene polymers and co-polymers, lipids and lipid derivatives, and mixtures thereof.
25. The formulation of claim 22, wherein a ratio of clopidogrel to excipient is about 1:1.
26. A particulate co-formulation comprising an clopidogrel and excipient, the co-formulation prepared by a gas anti-solvent precipitation method comprising
providing a target solution comprising solution or suspension of clopidogrel and excipient in at least one fluid; and
contacting the target solution with a compressed fluid anti-solvent under conditions which allow the anti-solvent to simultaneously both to extract the target solution from the fluid, and to disperse the target solution it so as to cause particles of the coformulated non-crystalline clopidogrel and excipient to precipitate from the fluid.
27. The co-formulation of claim 26 wherein the excipient is a hydrophobic polymer.
28. The co-formulation of claim 26 wherein, the excipient comprises a PVP, PVPVA, HMPC, HPC, alkyl cellulose, derivatives thereof, polyoxyalkylene polymers and co-polymers, lipids and lipid derivatives, and a combination thereof.
29. The co-formulation of claim 28 wherein a ratio of clopidogrel to polymer is about 1:1.
30. A method of preparing a particulate co-formulation comprising clopidogrel and a stabilizing excipient, the method comprising
(a) providing a solution or suspension of clopidogrel and a stabilizing excipient in a solvent;
and
(b) removing the liquid from the solution or suspension so as to cause particles of the formulated clopidogrel and stabilizing excipient to precipitate, wherein a plurality of particles result, the particles the form of a free-flowing, non-sticky powder, and having a hygroscopicity less than that of the clopidogrel substantially absent the excipient.

31. The method of claim 30 wherein the excipient comprises PVP, PVPVA, HMPC, HPC, alkyl cellulose, derivatives thereof, polyoxyalkylene polymers and co-polymers, lipids and lipid derivatives, and mixtures thereof.
32. A solid, non-crystalline formulation comprising particles of clopidogrel and a stabilizing excipient, wherein the formulation is more physically stable than a formulation without the stabilizing excipient.
33. A solid, non-crystalline formulation comprising clopidogrel and a stabilizing excipient, wherein the formulation when stored at 40°C and 75% relative humidity converts to a crystalline form more slowly than a formulation without the stabilizing excipient.
34. A solid, non-crystalline formulation comprising particles of clopidogrel and a stabilizing excipient, wherein the formulation has a lower hygroscopicity than a formulation without the stabilizing excipient.
35. A solid, non-crystalline formulation comprising particles, wherein the particles comprise clopidogrel and a surface-modifying agent, wherein a particle surface is more hydrophobic than a particle surface in the absence of the surface modifying agent.

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Prior Art**Fig 1****Fig 2**

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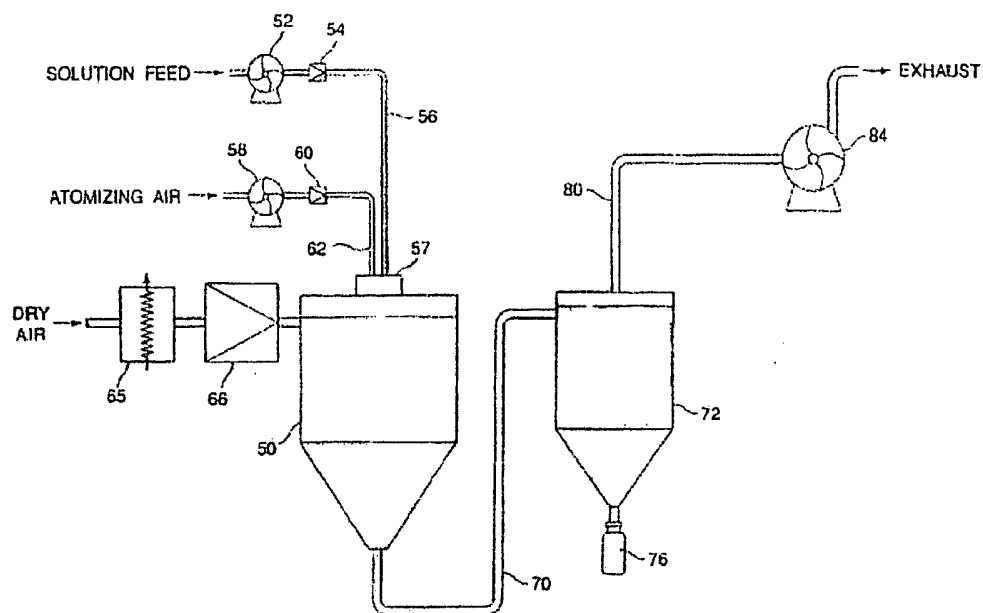


Fig 3

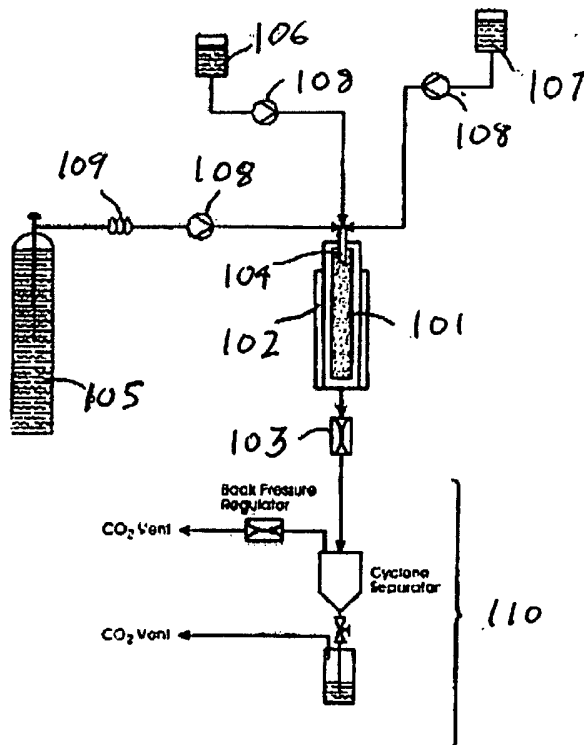


Fig 4

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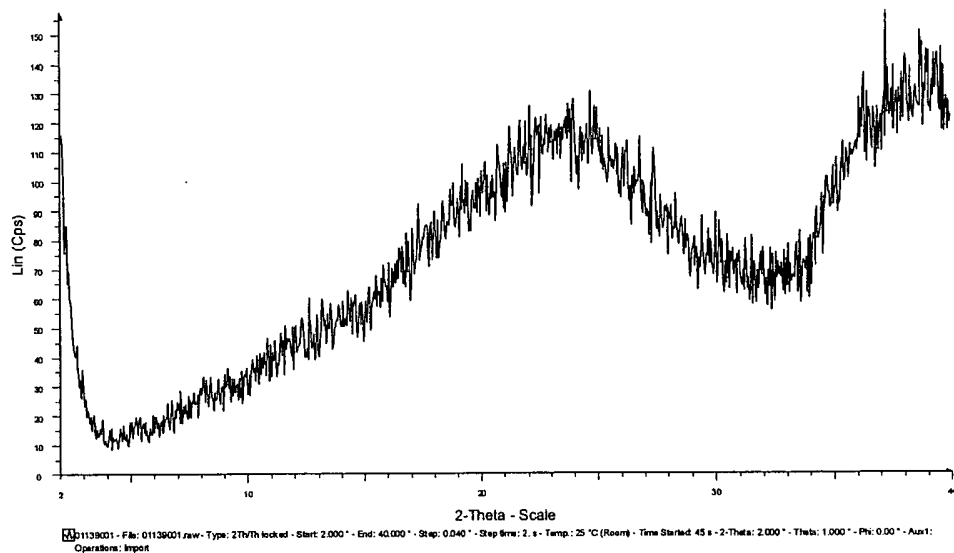


Fig 5

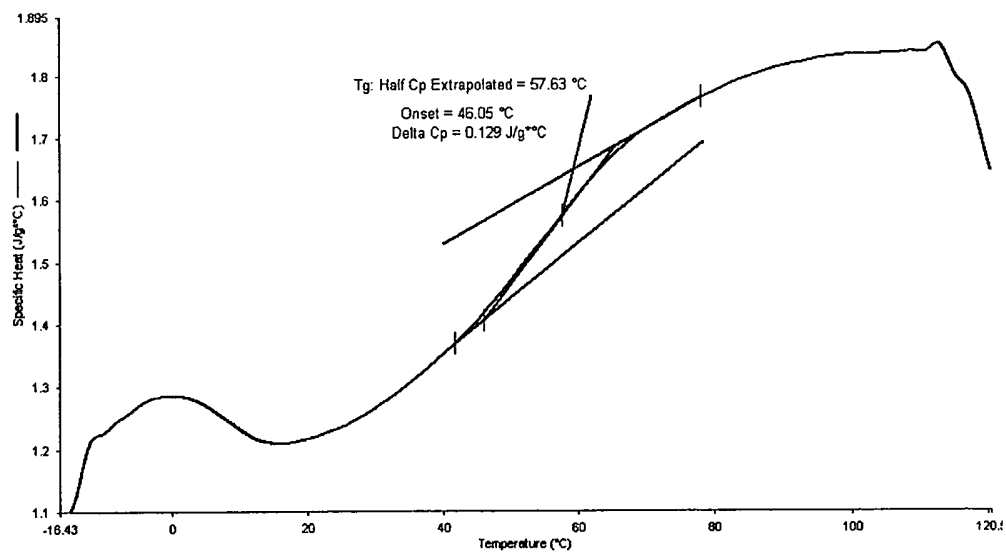


Fig 6A

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SS00243 40/75 T = 2 weeks

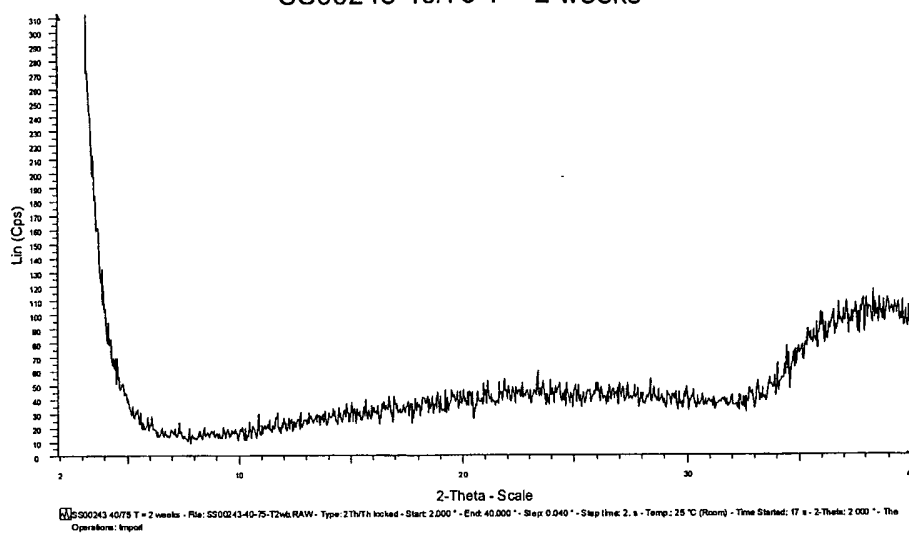


Fig 6B

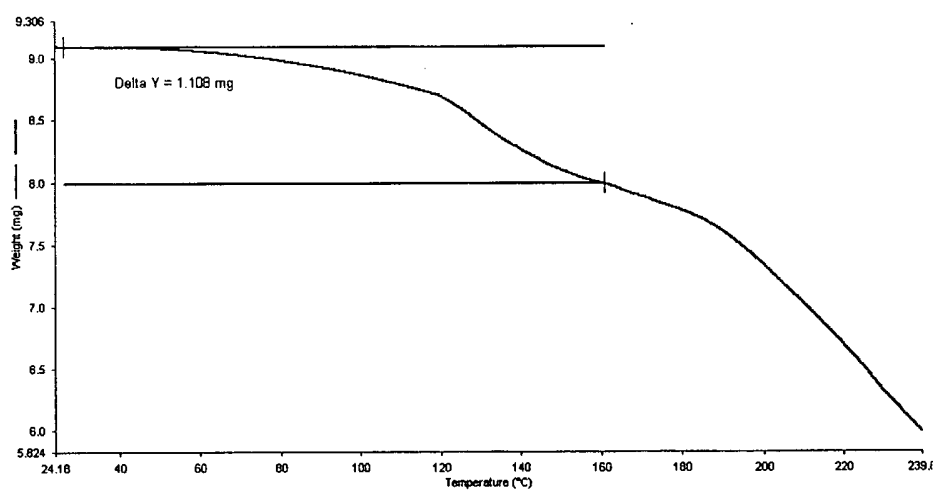


Fig 6C

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SS00218 40/75 T = 2 weeks

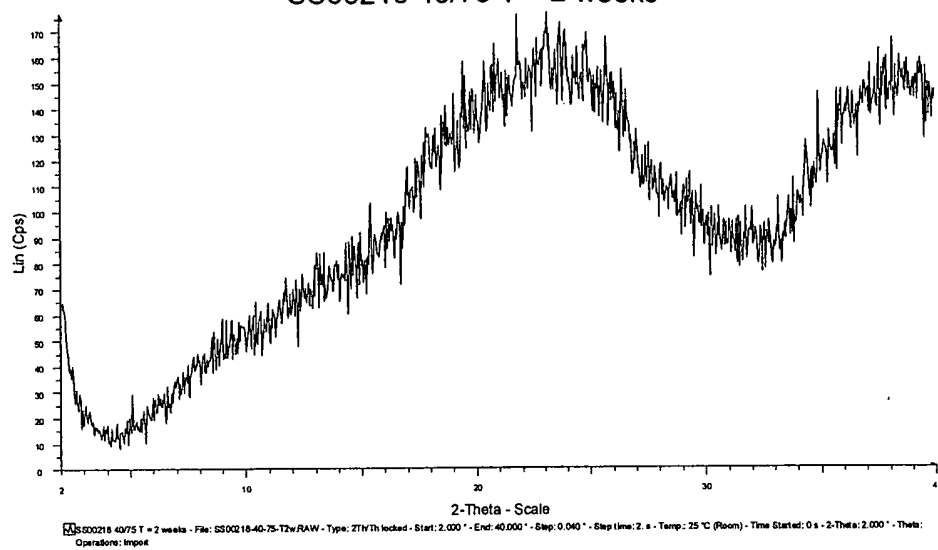


Fig 7

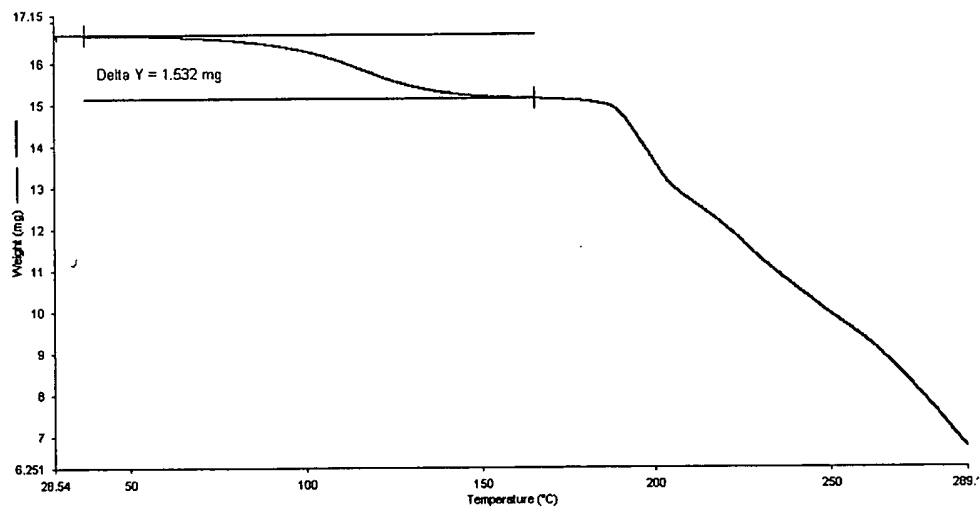


Fig 8

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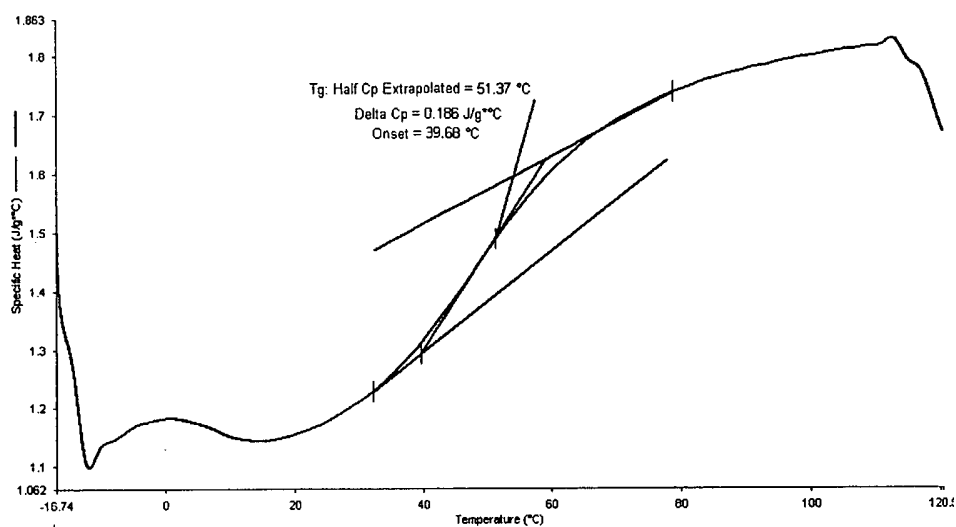


Fig 9A

SS00251 T = 2 weeks

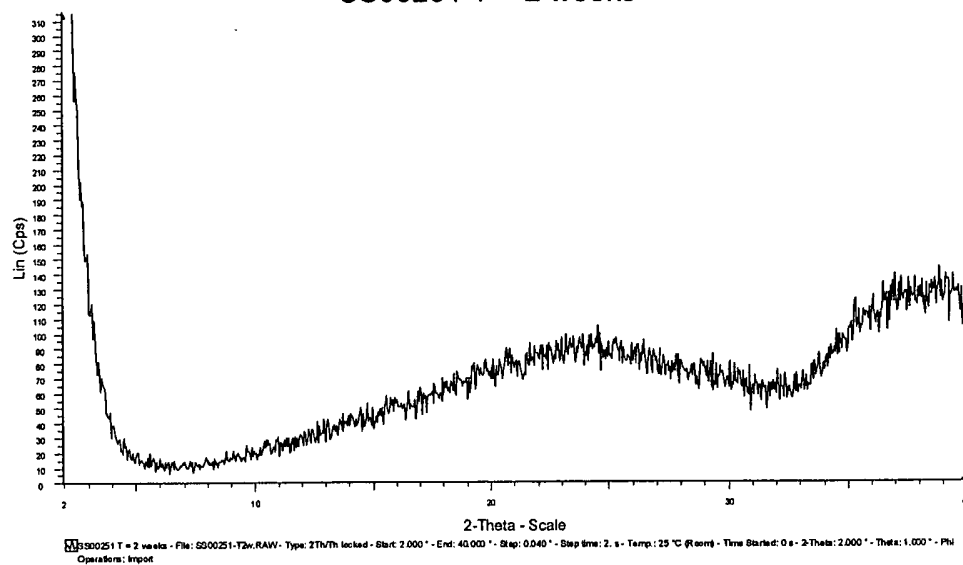


Fig 9B

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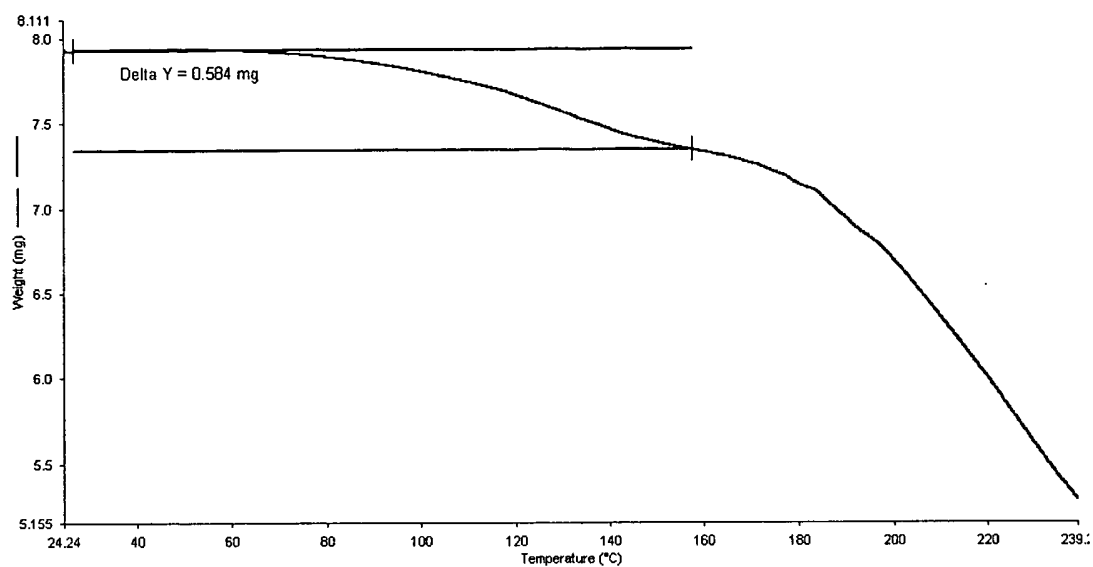


Fig 9C

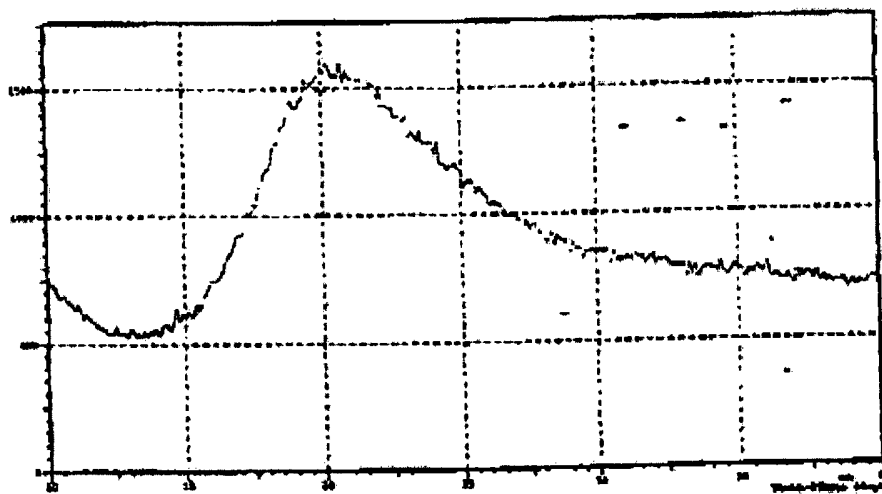


Fig 10

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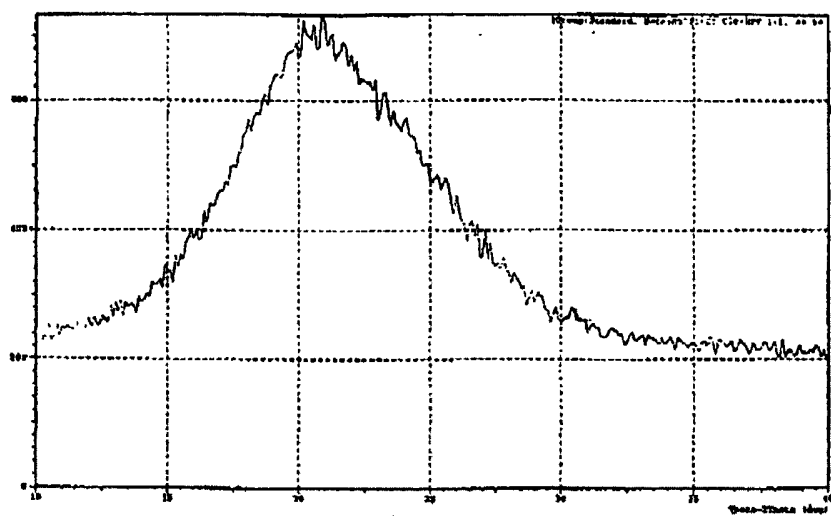


Fig 11A

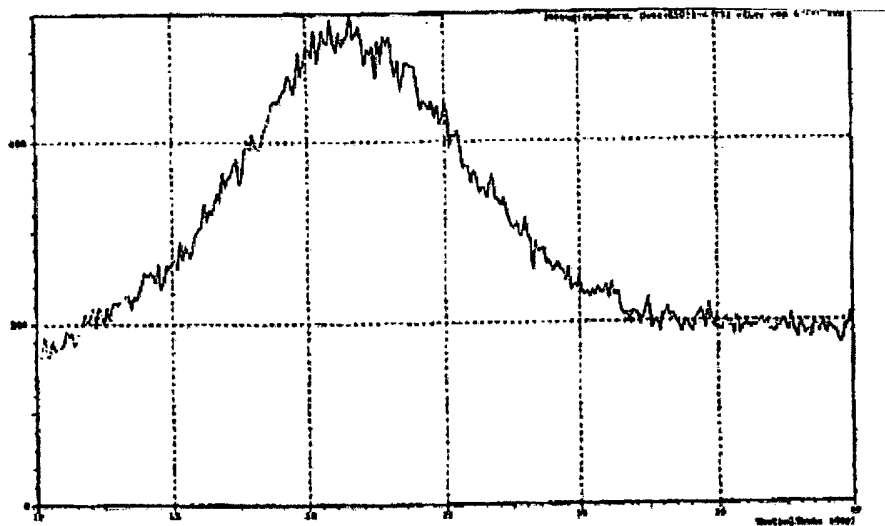


Fig 11B

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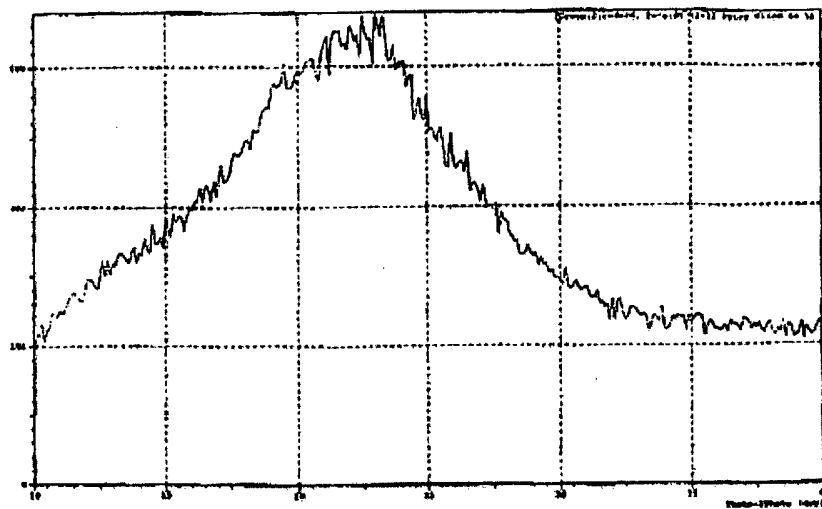


Fig 12

INTERNATIONAL SEARCH REPORT

International application No
/US2005/047424

A. CLASSIFICATION OF SUBJECT MATTER

INV. A61K31/4365 C07D495/04 C08G65/333

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

A61K C07D C08G

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 2005/117866 A (IVAX CORPORATION; IVAX PHARMACEUTICALS S.R.O; KAZNANOV, VLADIMIR; VEVE) 15 December 2005 (2005-12-15) claims 1-29; examples 1-10	1,2,10, 19,21, 26,30, 32-35
P,X	WO 2005/063708 A (CADILA HEALTHCARE LIMITED; LOHRAY, BRAJ, BHUSHAN; LOHRAY, VIDYA, BHUSH) 14 July 2005 (2005-07-14) page 1; claims 1-24; examples 1-23	1,2,10, 19,21, 26,30, 32-35
X	WO 2004/106344 A (CADILA HEALTHCARE LIMITED; LOHRAY, BRAJ, BHUSHAN; LOHRAY, VIDYA, BHUSH) 9 December 2004 (2004-12-09) page 1 - page 3; claims 1-30 ----- -/--	1,2,10, 19,21, 26,30, 32-35

☒ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

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Date of the actual completion of the international search

25 April 2006

Date of mailing of the international search report

08/05/2006

Name and mailing address of the ISA/

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Kardas-Llorens, E

INTERNATIONAL SEARCH REPORT

International application No

/US2005/047424

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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X	WO 2004/081015 A (HETERO DRUGS LIMITED; PARTHASARADHI, REDDY, BANDI; RATHNAKAR, REDDY, K) 23 September 2004 (2004-09-23) page 1 - page 2; claims 1-14 -----	1,2,10, 19,21, 26,30, 32-35
X	GB 2 393 181 A (* CIPLA LIMITED) 24 March 2004 (2004-03-24) page 1 - page 8; claims 1-26; examples 1-7 -----	1,2,10, 19,21, 26,30, 32-35

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

/US2005/047424

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