



No. 09-139945- -00007-0000

Fecha: 2011-07-15 15:52:12 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 329 CTOINFORMACION Folios: 47**SEÑOR****SUPERINTENDENTE DE INDUSTRIA Y COMERCIO****E.****S.****D.****REF: Expediente 09-139-945****TÍTULO SOLICITADO: FORMAS AMORFAS ESTABILIZADAS DE
MESILATO DE IMATINIB.****PUBLICACIÓN: Gaceta 624 de 20/01/2011, N° de publicación 1118.****SOLICITANTE: NOVARTIS AG.****PRIORIDAD: EP 07109816.4 de 07/06/2007
US 60/974,197 de 21/09/2007****APODERADO: CARLOS REYNALDO OLARTE GARCIA.****TRÁMITE: SUSTENTACION DE OPOSICIÓN**

JOSÉ LUIS REYES VILLAMIZAR, mayor de edad, identificado como aparece al pie de mi firma, abogado en ejercicio, titular de la tarjeta profesional número 44655 del Consejo Superior de la Judicatura, obrando en calidad de apoderado de la sociedad **TECNOQUÍMICAS S.A.**, dentro del trámite de la referencia, en ejercicio de lo dispuesto por el artículo 42 inciso 2° de la Decisión 486 de 2000, por medio del presente escrito, procedo a sustentar y complementar la oposición presentada el 02 de Febrero de 2009, en los siguientes términos:

I. RATIFICACIÓN

Comendidamente me permito insistir en todos y cada uno de los argumentos planteados en la oposición referida, los cuales, como se dijo en su momento, demuestran que la solicitud de la referencia carece de los requisitos de

patentabilidad establecidos por los artículos 14, 16 y 18 de la Decisión 486 y que como tal, no merece recibir el beneficio patentario:

- Ante la reivindicación de una forma amorfa estabilizada de mesilato de Imatinib en la reivindicación 1 de la solicitud colombiana en trámite, es relevante señalar que cualquier persona medianamente versada en la material reconoce que los sólidos pueden existir, de acuerdo con su estructura u ordenamiento interno, en formas cristalinas o amorfas. En las formas amorfas las partículas componentes no presentan una disposición interna ordenada, sino que se encuentran distribuidas al azar, por el contrario, en las formas cristalinas se presenta un arreglo interno ordenado y regular de las moléculas, que implica la apreciación de formas geométricas definidas. Un polimorfo es una fase -o arreglo- cristalino sólido de un compuesto conocido, dado por el sometimiento de la molécula a diversas condiciones de ambiente, temperatura, tiempo o acción de solventes, otras como presión, velocidad de cristalización, concentración de saturación, e inclusive, la influencia de sustancias extrañas y campos de fuerza exteriores al cristal¹. A esta característica de algunas sustancias, que pueden organizar de manera diversa sus moléculas en estado sólido, se le reconoce como polimorfismo. El polimorfismo, en los términos de la Farmacia Práctica de Remington, es “la capacidad de cualquier elemento o compuesto de cristalizar en más de un sistema cristalino”; así mismo se reconoce que el descubrimiento del polimorfismo como propiedad de las entidades químicas se atribuye al farmacéutico Martín Enrique Klaproth en 1798, y la tesis según la cual los mismos elementos químicos pueden adoptar formas sólidas diversas – polimorfos - y mostrar propiedades físicas diferentes, se atribuye a Louis Jacques Thénard (1777-1857) y Jean Baptiste Biot (1774-1862)².
- El polimorfismo es una característica para tener en cuenta en el desarrollo de una formulación farmacéutica (en especial para los principios activos), puesto que los diferentes polimorfos de una sustancia pueden llegar a tener diferente densidad, capacidad para fluir, compresibilidad y solubilidad, entre otras características fisicoquímicas, con lo cual pueden traer variaciones considerables en la parte tecnológica y biofarmacéutica al momento de usar

¹ J. Garrido. Forma y estructura de los Cristales, (obra citada), capítulo V, página 204

uno u otro polimorfo de la misma sustancia en el proceso de elaboración del medicamento. Por esta razón es una característica que se evalúa dentro de los ensayos de preformulación y formulación, especialmente dentro de lo que se conoce como las consideraciones fisicoquímicas de la etapa de preformulación³.

- El polimorfismo es una propiedad inherente a la materia en su estado sólido y su reporte es el simple hallazgo de algo que ya se sabía podía ser hallado y no la invención de algo nuevo. Esto puede confirmarse a través de la consulta a las diversas publicaciones científicas⁴ y textos de tecnología farmacéutica⁵ que exponen a profundidad este tema.
- La reivindicación textual de concentraciones (dosis) de mesilato de Imatinib, contraviene lo dispuesto en la Decisión 486 de 2000 que literalmente refiere a que *"No serán patentables (...) d) los métodos terapéuticos o quirúrgicos para el tratamiento humano o animal, así como los métodos de diagnóstico aplicados a los seres humanos o a animales."* Dicha mención de dosificaciones tiene el mismo efecto que las reivindicaciones sobre métodos de tratamiento médico, dado que la concentración, en este caso directamente referido a la dosificación de la formulación farmacéutica, no pertenece a la categoría de producto o proceso, sino que hace referencia la forma en la que un producto se utiliza terapéuticamente, y por lo tanto no hace parte de las actividades industriales sino de las actividades médicas. En otras palabras la dosificación o los cambios en la dosificación dentro de un producto farmacéutico no tiene naturaleza inventiva, ya que no cumplen con el estándar de aplicabilidad industrial, dado que dichas modificaciones solo tienen efectos en el organismo (verificables a nivel clínico) y no efectos técnicos.
- Cualquier persona medianamente versada en la elaboración de productos farmacéuticos debe reconocer que la formación de complejos entre fármacos y diversos ligandos es una estrategia de formulación ampliamente conocida y descrita en el estado de la técnica para modificar algunas características

² A. R. Verna, P. Krishna – "Polytypism in crystals". John Wiley and Son Inc., New York 1966.

³ Vila Jato J.L. Tecnología Farmacéutica. Volumen I. Páginas 42 a 49.

⁴ Doelker E. Crystalline modifications and polymorphism changes during drug manufacture. Ann Pharm Fr. 2002 May;60(3):161-76.

⁵ Vila Jato. J.L. Tecnología Farmacéutica. Volumen I. Páginas 44 a 48.

fisicoquímicas de los principios activos a ser formulados, como por ejemplo el coeficiente de reparto, la carga eléctrica, el tamaño molecular, el coeficiente de difusión, la solubilidad y la velocidad de disolución. De la misma manera dicha persona medianamente versada en la formulación de productos farmacéuticos debe reconocer que las ciclodextrinas (CD) forman complejos de inclusión en los que la disposición espacial desempeña un papel tan importante como la afinidad química con el fármaco; forman una estructura troncocónica con una cavidad interior; ésta cavidad es apolar, mientras que la superficie de la ciclodextrina es muy hidrófila debido a que los grupos hidroxilos se orientan hacia el exterior. Es así como las ciclodextrinas facilitan la disolución en agua de fármacos poco solubles al incorporarlos en su cavidad interna⁶. Dichos complejos se pueden obtener en medio líquido por precipitación, evaporación, atomización, liofilización del solvente, o en medio sólido por amasado, molienda o calentamiento, que es la manera que se obtienen en lo descrito en el capítulo reivindicatorio de la solicitud en cuestión, específicamente en la reivindicación 3.

- La solicitud en cuestión revela también una dispersión sólida, específicamente en sus reivindicaciones 3 y 4, también se puede afirmar que dicha técnica es una estrategia tecnológica de formulación ampliamente reconocida. Cualquier persona medianamente versada en la producción de formulaciones farmacéuticas debe reconocer que la formación de dichas dispersiones del fármaco en el seno de un portador se puede realizar mediante técnicas de fusión, disolución-dsecación o una mezcla de ambas⁷.
- La utilización de complejos de ciclodextrinas o la formación de dispersiones sólidas de cualquier principio activo no puede sustentar nivel inventivo alguno, especialmente cuando dichas estrategias se utilizan para obtener formulaciones convencionales para la administración oral, como lo son las cápsulas y las tabletas, formulaciones que también están ampliamente descritas en el estado de la técnica.
- La publicación internacional WO 2004/106326 publicada el 09 de Diciembre de 2004; la publicación científica titulada ***“Cyclodextrin/Imatinib Complexation:***

⁶ Vila Jato J.L. Tecnología Farmacéutica. Volumen I. páginas 197 a 201.

⁷ Vila Jato. J.L. Tecnología Farmacéutica. Volumen I. Páginas 201 a 202.

Binding Mode And Charge Dependent Stabilities⁸” y la publicación científica titulada ***“Improving Drug Solubility For Oral Delivery Using Solid Dispersions”*** revelan que la formulación de formas amorfas de imatinib de manera estable, la complejación de Imatinib con ciclodextrinas y la inclusión de Imatinib en formulaciones tipo dispersión solida, no pueden soportar novedad ni nivel inventivo alguno, puesto que existe suficiente información en el estado de la técnica como para guiar a cualquier persona medianamente versada en la producción de formas farmacéuticas para obtener lo descrito en las reivindicaciones de la solicitud colombiana en trámite.

II. COMPLEMENTO DE INFORMACIÓN

En complemento de los argumentos presentados oportunamente en la oposición correspondiente, se presentan nuevos argumentos relacionados a la tesis de falta de novedad y de nivel inventivo, veamos:

La patente americana US 2006/275372 publicada el 07 de Diciembre de 2006 revela:

The present invention is directed to a nanoparticulate compositions of imatinib mesylate, or a salt or derivative thereof, having improved pharmacokinetic profiles and reduced fed/fasted variability. The nanoparticulate imatinib mesylate particles of the composition have an effective average particle size of less than about 2000 nm and are useful in the treatment of chronic myeloid leukemia, gastrointestinal stromal tumors and related diseases.

(...)

[0034] As used herein with reference to stable imatinib mesylate nanoparticulate particles, “stable” connotes, but is not limited to one or more of the following parameters: (1) the particles do not appreciably flocculate or agglomerate due to interparticle attractive forces or otherwise significantly increase in particle size over time; (2) that the physical structure of the particles is not altered over time, such as by conversion from an amorphous phase to a crystalline phase; (3) that the particles are chemically stable; and/or (4) where the imatinib mesylate has not been subject to a heating step at or above the melting point of the imatinib mesylate in the preparation of the nanoparticles of the present invention.

(...)

⁸ Béni S, Szakács Z, Csernák O, Barcza L, Noszá B. Eur J Pharm Sci. 2007 Feb;30(2):167-74. Epub 2006 Nov 7.

[0144] Solid dosage forms for oral administration include, but are not limited to, capsules, tablets, pills, powders, and granules. In such solid dosage forms, the active agent is admixed with at least one of the following: (a) one or more

(...)

EXAMPLE 1

[0151] The purpose of this example was to prepare a composition comprising a nanoparticulate imatinib mesylate or a salt or derivative thereof.

[0152] An aqueous dispersion of 5% (w/w) imatinib mesylate, combined with one or more surface stabilizers, such as hydroxypropyl cellulose (HPC-SL) and dioctylsulfosuccinate (DOSS), could be milled in a 10 ml chamber of a NanoMill® 0.01 (NanoMill Systems, King of Prussia, Pa.; see e.g., U.S. Pat. No. 6,431,478), along with 500 micron PolyMill® attrition media (Dow Chemical Co.) (e.g., at an 89% media load). In an exemplary process, the mixture could be milled at a speed of 2500 rpms for 60 minutes.

[0153] Following milling, the particle size of the milled imatinib mesylate particles can be measured, in deionized distilled water, using a Horiba LA-910 particle size analyzer. For a successful composition, the initial mean and/or D50 milled imatinib mesylate particle size is expected to be less than 2000 nm.

Como se puede apreciar claramente, en esta anterioridad se revela la obtención de una dispersión acuosa de nanopartículas de mesilato de Imatinib, lo que anticipa el “principio de formulación” mencionado por la solicitud Colombiana en trámite, específicamente en sus reivindicaciones 1 y 2, en especial en la reivindicación 2, cuando se hace referencia a dispersiones sólidas.

Por su parte la publicación internacional WO 2006/121941 publicada el 16 de noviembre de 2006 revela:

The present invention relates to modified release pharmaceutical compositions that contain a therapeutic compound, e.g., imatinib or a pharmaceutically acceptable salt thereof and a release retardant. The amount of the therapeutic compound in the pharmaceutical composition can be at least 50% by weight of the composition. The balance of the pharmaceutical composition can be made up of at least one release retardant. In a particular aspect of the present invention the release retardant is a water-soluble, water swellable and/or water insoluble polymer. Particularly useful as such polymers are ethylcellulose, hydroxypropyl cellulose and/or hydroxypropyl methyl cellulose. In yet another aspect the release retardant can be a non-polymeric release retardant. In a particular aspect, the non-polymeric release retardant is hydrogenated castor oil. The aforementioned compositions can be milled or granulated and compressed into monolithic tablets or encapsulated into capsules.

(...)

(B) A method of making a modified release pharmaceutical composition comprising the step of granulating imatinib or any of its salts with a release retardant and optionally a release modifier in an extruder while heating to a temperature below the melting temperature of imatinib or its salt, to form melt granules;

• In particular said method, wherein the melt granules are once again introduced into the extruder, to further granulate with or without release retardant or release modifier or plasticizer, at a temperature less than the melting point of imatinib or the imatinib salt employed.

Como se puede apreciar claramente, en esta anterioridad se revela la obtención de extrudidos de mesilato de Imatinib con polímero u otros excipientes, lo que anticipa el “principio de formulación” mencionado por la solicitud Colombiana en trámite, específicamente en sus reivindicaciones 1 y 2, en especial en la reivindicación 2, cuando se hace referencia a co-molienda con excipientes seleccionados.

Por todo lo anterior, le solicito Señor Superintendente, que analice los argumentos citados con el rigor y detenimiento habituales y que decrete, además de la negación de la solicitud en comento, el archivo del citado expediente.

III. ANEXOS

- Copia de la patente americana US 2006/275372 publicada el 07 de Diciembre de 2006 y la publicación internacional WO 2006/121941 publicada el 16 de noviembre de 2006.

Señor Superintendente,



JOSE LUIS REYES VILLAMIZAR

C.C. 79.152.473 de Usaquén

T.P. 44655 del C. S de la J.



US 20060275372A1

(19) **United States**

(12) **Patent Application Publication**
Jenkins et al.

(10) **Pub. No.: US 2006/0275372 A1**

(43) **Pub. Date: Dec. 7, 2006**

(54) **NANOPARTICULATE IMATINIB MESYLATE FORMULATIONS**

(75) Inventors: **Scott Jenkins**, Downingtown, PA (US);
Gary G. Liversidge, West Chester, PA (US)

Correspondence Address:
ELAN DRUG DELIVERY, INC.
C/O FOLEY & LARDNER LLP
3000 K STREET, N.W.
SUITE 500
WASHINGTON, DC 20007-5109 (US)

(73) Assignee: **Elan Pharma International Limited**

(21) Appl. No.: **11/446,565**

(22) Filed: **Jun. 5, 2006**

Related U.S. Application Data

(60) Provisional application No. 60/687,146, filed on Jun. 3, 2005.

Publication Classification

(51) **Int. Cl.**
A61K 31/506 (2006.01)
A61K 9/14 (2006.01)

(52) **U.S. Cl.** **424/489; 977/906; 514/252.18**

(57) **ABSTRACT**

The present invention is directed to a nanoparticulate compositions of imatinib mesylate, or a salt or derivative thereof, having improved pharmacokinetic profiles and reduced fed/fasted variability. The nanoparticulate imatinib mesylate particles of the composition have an effective average particle size of less than about 2000 nm and are useful in the treatment of chronic myeloid leukemia, gastrointestinal stromal tumors and related diseases.

NANOPARTICULATE IMATINIB MESYLATE FORMULATIONS

CROSS-REFERENCE TO RELATED PATENT APPLICATIONS

[0001] This application claims the benefit under 35 U.S.C. §119(e) of U.S. provisional application No. 60/687,146, filed on Jun. 3, 2005, which is incorporated by reference herein in its entirety.

FIELD

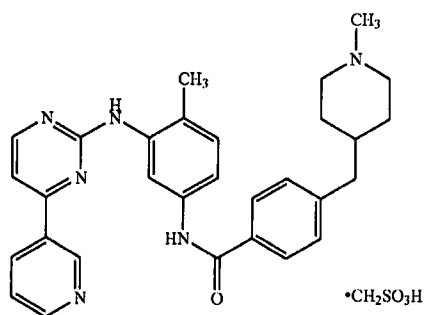
[0002] The invention relates generally to compounds and compositions useful in the treatment of chronic myeloid leukemia, gastrointestinal stromal tumors and related diseases. More specifically, the invention relates to nanoparticulate imatinib mesylate compositions. The nanoparticulate imatinib mesylate compositions have an effective average particle size of less than about 2000 nm.

BACKGROUND

A. Background Regarding Imatinib Mesylate

[0003] Imatinib mesylate, chemically known as 4-[(4-Methyl-1-piperazinyl)methyl]-N-[4-methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]-phenyl]benzamide methane-sulfonate, has a molecular formula of $C_{29}H_{31}N_7O_4S$, and a molecular weight of 589.7.

[0004] Imatinib mesylate has the chemical structure shown below:



[0005] Imatinib mesylate is a white to off-white to brownish or yellowish tinged crystalline powder. Imatinib mesylate is soluble in aqueous buffers $\leq$ pH 5.5 and slightly soluble to insoluble in neutral to alkaline aqueous buffers. In non-aqueous solvents, imatinib mesylate is freely soluble to very slightly soluble in dimethyl sulfoxide, methanol and ethanol, but is insoluble in n-octanol, acetone and acetonitrile.

[0006] Imatinib mesylate is commercially available under the trade name Gleevec® as film-coated tablets, manufactured by Novartis Pharma Stein AG (Stein, Switzerland), and distributed by Novartis Pharmaceuticals Corporation (East Hanover, N.J.). Gleevec® is available in strengths containing imatinib mesylate in amounts equivalent to 100 mg or 400 mg of imatinib free base. Gleevec® contains inactive ingredients that include colloidal silicon dioxide; croscopidone; hydroxypropyl methylcellulose; magnesium

stearate; and microcrystalline cellulose with tablet coatings having ferric oxide, red; ferric oxide, yellow; hydroxypropyl methylcellulose; polyethylene glycol and talc.

[0007] Imatinib mesylate is indicated for the treatment of Philadelphia chromosome positive chronic myeloid leukemia (CML) and Kit (CD117) positive unresectable and/or metastatic malignant gastrointestinal stromal tumors (GIST).

[0008] Gleevec® is generally prescribed in dosages of 400 mg/day for adult patients in chronic phase CML and 600 mg/day for adult patients in accelerated phase or blast crisis. Additionally Gleevec® is recommended at dosages of 400 mg/day or 600 mg/day for adult patients with unresectable and/or metastatic, malignant GIST. Gleevec® is generally prescribed to be administered orally, with a meal and a large glass of water, with doses of 400 mg or 600 mg administered once daily, and dosages of 800 mg administered as 400 mg twice a day.

[0009] Imatinib mesylate compounds have been disclosed, for example, in U.S. Pat. No. 5,521,184 to Zimmermann for "Pyrimidine Derivatives and Processes for the Preparation Thereof" and United States Patent Application No. 2004/0127571 to Bhalla et al. for "Method of Treating Leukemia with a Combination of Suberoylanilide Hydroxamic Acid and Imatinib Mesylate". Both of these references are hereby incorporated by reference.

[0010] Imatinib mesylate has high therapeutic value in the treatment of chronic myeloid leukemia, gastrointestinal stromal tumors, and related diseases. However, because conventional, non-nanoparticulate imatinib mesylate tablets are only very slightly soluble in water at 37° C., the dissolution of conventional imatinib mesylate tablets is reduced in the fasting state as compared to the fed state. Thus, imatinib mesylate has limited bioavailability in the fasting state as compared to the fed state, which limits the therapeutic outcome for all treatments requiring imatinib mesylate.

B. Background Regarding Nanoparticulate Active Agent Compositions

[0011] Nanoparticulate active agent compositions, first described in U.S. Pat. No. 5,145,684 ("the '684 patent"), are particles consisting of a poorly soluble therapeutic or diagnostic agent having adsorbed onto the surface thereof a non-crosslinked surface stabilizer. The '684 patent does not describe nanoparticulate compositions of imatinib mesylate.

[0012] Methods of making nanoparticulate active agent compositions are described in, for example, U.S. Pat. Nos. 5,518,187 and 5,862,999, both for "Method of Grinding Pharmaceutical Substances;" U.S. Pat. No. 5,718,388, for "Continuous Method of Grinding Pharmaceutical Substances;" and U.S. Pat. No. 5,510,118 for "Process of Preparing Therapeutic Compositions Containing Nanoparticles."

[0013] Nanoparticulate active agent compositions are also described, for example, in U.S. Pat. No. 5,298,262 for "Use of Ionic Cloud Point Modifiers to Prevent Particle Aggregation During Sterilization;" U.S. Pat. No. 5,302,401 for "Method to Reduce Particle Size Growth During Lyophilization;" 38 U.S. Pat. No. 5,318,767 for "X-Ray Contrast Compositions Useful in Medical Imaging;" U.S. Pat. No. 5,326,552 for "Novel Formulation For Nanoparticulate X-Ray

Blood Pool Contrast Agents Using High Molecular Weight Non-ionic Surfactants;" U.S. Pat. No. 5,328,404 for "Method of X-Ray Imaging Using Iodinated Aromatic Propanedioates;" U.S. Pat. No. 5,336,507 for "Use of Charged Phospholipids to Reduce Nanoparticle Aggregation;" U.S. Pat. No. 5,340,564 for "Formulations Comprising Olin 10-G to Prevent Particle Aggregation and Increase Stability;" U.S. Pat. No. 5,346,702 for "Use of Non-Ionic Cloud Point Modifiers to Minimize Nanoparticle Aggregation During Sterilization;" U.S. Pat. No. 5,349,957 for "Preparation and Magnetic Properties of Very Small Magnetic-Dextran Particles;" U.S. Pat. No. 5,352,459 for "Use of Purified Surface Modifiers to Prevent Particle Aggregation During Sterilization;" U.S. Pat. No. 5,399,363 and 5,494,683, both for "Surface Modified Anticancer Nanoparticles;" U.S. Pat. No. 5,401,492 for "Water Insoluble Non-Magnetic Manganese Particles as Magnetic Resonance Enhancement Agents;" U.S. Pat. No. 5,429,824 for "Use of Tyloxapol as a Nanoparticle Stabilizer;" U.S. Pat. No. 5,447,710 for "Method for Making Nanoparticle X-Ray Blood Pool Contrast Agents Using High Molecular Weight Non-ionic Surfactants;" U.S. Pat. No. 5,451,393 for "X-Ray Contrast Compositions Useful in Medical Imaging;" U.S. Pat. No. 5,466,440 for "Formulations of Oral Gastrointestinal Diagnostic X-Ray Contrast Agents in Combination with Pharmaceutically Acceptable Clays;" U.S. Pat. No. 5,470,583 for "Method of Preparing Nanoparticle Compositions Containing Charged Phospholipids to Reduce Aggregation;" U.S. Pat. No. 5,472,683 for "Nanoparticle Diagnostic Mixed Carbamic Anhydrides as X-Ray Contrast Agents for Blood Pool and Lymphatic System Imaging;" U.S. Pat. No. 5,500,204 for "Nanoparticle Diagnostic Dimers as X-Ray Contrast Agents for Blood Pool and Lymphatic System Imaging;" U.S. Pat. No. 5,518,738 for "Nanoparticle NSAID Formulations;" U.S. Pat. No. 5,521,218 for "Nanoparticle Iododipamide Derivatives for Use as X-Ray Contrast Agents;" U.S. Pat. No. 5,525,328 for "Nanoparticle Diagnostic Diatrizoxy Ester X-Ray Contrast Agents for Blood Pool and Lymphatic System Imaging;" U.S. Pat. No. 5,543,133 for "Process of Preparing X-Ray Contrast Compositions Containing Nanoparticles;" U.S. Pat. No. 5,552,160 for "Surface Modified NSAID Nanoparticles;" U.S. Pat. No. 5,560,931 for "Formulations of Compounds as Nanoparticle Dispersions in Digestible Oils or Fatty Acids;" U.S. Pat. No. 5,565,188 for "Polyalkylene Block Copolymers as Surface Modifiers for Nanoparticles;" U.S. Pat. No. 5,569,448 for "Sulfated Non-ionic Block Copolymer Surfactant as Stabilizer Coatings for Nanoparticle Compositions;" U.S. Pat. No. 5,571,536 for "Formulations of Compounds as Nanoparticle Dispersions in Digestible Oils or Fatty Acids;" U.S. Pat. No. 5,573,749 for "Nanoparticle Diagnostic Mixed Carboxylic Anhydrides as X-Ray Contrast Agents for Blood Pool and Lymphatic System Imaging;" U.S. Pat. No. 5,573,750 for "Diagnostic Imaging X-Ray Contrast Agents;" U.S. Pat. No. 5,573,783 for "Redispersible Nanoparticle Film Matrices With Protective Overcoats;" U.S. Pat. No. 5,580,579 for "Site-specific Adhesion Within the GI Tract Using Nanoparticles Stabilized by High Molecular Weight, Linear Poly(ethylene Oxide) Polymers;" U.S. Pat. No. 5,585,108 for "Formulations of Oral Gastrointestinal Therapeutic Agents in Combination with Pharmaceutically Acceptable Clays;" U.S. Pat. No. 5,587,143 for "Butylene Oxide-Ethylene Oxide Block Copolymers Surfactants as Stabilizer Coatings for Nanoparticle Compo-

sitions;" U.S. Pat. No. 5,591,456 for "Milled Naproxen with Hydroxypropyl Cellulose as Dispersion Stabilizer;" U.S. Pat. No. 5,593,657 for "Novel Barium Salt Formulations Stabilized by Non-ionic and Anionic Stabilizers;" U.S. Pat. No. 5,622,938 for "Sugar Based Surfactant for Nanocrystals;" U.S. Pat. No. 5,628,981 for "Improved Formulations of Oral Gastrointestinal Diagnostic X-Ray Contrast Agents and Oral Gastrointestinal Therapeutic Agents;" U.S. Pat. No. 5,643,552 for "Nanoparticle Diagnostic Mixed Carbonic Anhydrides as X-Ray Contrast Agents for Blood Pool and Lymphatic System Imaging;" U.S. Pat. No. 5,718,388 for "Continuous Method of Grinding Pharmaceutical Substances;" U.S. Pat. No. 5,718,919 for "Nanoparticles Containing the R(-)Enantiomer of Ibuprofen;" U.S. Pat. No. 5,747,001 for "Aerosols Containing Beclomethasone Nanoparticle Dispersions;" U.S. Pat. No. 5,834,025 for "Reduction of Intravenously Administered Nanoparticle Formulation Induced Adverse Physiological Reactions;" U.S. Pat. No. 6,045,829 "Nanocrystalline Formulations of Human Immunodeficiency Virus (HIV) Protease Inhibitors Using Cellulosic Surface Stabilizers;" U.S. Pat. No. 6,068,858 for "Methods of Making Nanocrystalline Formulations of Human Immunodeficiency Virus (HIV) Protease Inhibitors Using Cellulosic Surface Stabilizers;" U.S. Pat. No. 6,153,225 for "Injectable Formulations of Nanoparticle Naproxen;" U.S. Pat. No. 6,165,506 for "New Solid Dose Form of Nanoparticle Naproxen;" U.S. Pat. No. 6,221,400 for "Methods of Treating Mammals Using Nanocrystalline Formulations of Human Immunodeficiency Virus (HIV) Protease Inhibitors;" U.S. Pat. No. 6,264,922 for "Nebulized Aerosols Containing Nanoparticle Dispersions;" U.S. Pat. No. 6,267,989 for "Methods for Preventing Crystal Growth and Particle Aggregation in Nanoparticle Compositions;" U.S. Pat. No. 6,270,806 for "Use of PEG-Derivatized Lipids as Surface Stabilizers for Nanoparticle Compositions;" U.S. Pat. No. 6,316,029 for "Rapidly Disintegrating Solid Oral Dosage Form;" U.S. Pat. No. 6,375,986 for "Solid Dose Nanoparticle Compositions Comprising a Synergistic Combination of a Polymeric Surface Stabilizer and Dioctyl Sodium Sulfosuccinate;" U.S. Pat. No. 6,428,814 for "Bioadhesive Nanoparticle Compositions Having Cationic Surface Stabilizers;" U.S. Pat. No. 6,431,478 for "Small Scale Mill;" and U.S. Pat. No. 6,432,381 for "Methods for Targeting Drug Delivery to the Upper and/or Lower Gastrointestinal Tract;" U.S. Pat. No. 6,592,903 for "Nanoparticle Dispersions Comprising a Synergistic Combination of a Polymeric Surface Stabilizer and Dioctyl Sodium Sulfosuccinate;" U.S. Pat. No. 6,582,285 for "Apparatus for sanitary wet milling;" U.S. Pat. No. 6,656,504 for "Nanoparticle Compositions Comprising Amorphous Cyclosporine;" U.S. Pat. No. 6,742,734 for "System and Method for Milling Materials;" U.S. Pat. No. 6,745,962 for "Small Scale Mill and Method Thereof;" U.S. Pat. No. 6,811,767 for "Liquid droplet aerosols of nanoparticle drugs;" and U.S. Pat. No. 6,908,626 for "Compositions having a combination of immediate release and controlled release characteristics;" U.S. Pat. No. 6,969,529 for "Nanoparticle compositions comprising copolymers of vinyl pyrrolidone and vinyl acetate as surface stabilizers;" U.S. Pat. No. 6,976,647 for "System and Method for Milling Materials;" all of which are specifically incorporated by reference. In addition, U.S. Patent Publication No. 20020012675 A1, for "Controlled Release Nanoparticle Compositions;" U.S. Patent Publication No. 20050276974

for "Nanoparticulate Fibrate Formulations;" U.S. Patent Publication No. 20050238725 for "Nanoparticulate compositions having a peptide as a surface stabilizer;" U.S. Patent Publication No. 20050233001 for "Nanoparticulate megestrol formulations;" U.S. Patent Publication No. 20050147664 for "Compositions comprising antibodies and methods of using the same for targeting nanoparticulate active agent delivery;" U.S. Patent Publication No. 20050063913 for "Novel metaxalone compositions;" U.S. Patent Publication No. 20050042177 for "Novel compositions of sildenafil free base;" U.S. Patent Publication No. 20050031691 for "Gel stabilized nanoparticulate active agent compositions;" U.S. Patent Publication No. 20050019412 for "Novel glipizide compositions;" U.S. Patent Publication No. 20050004049 for "Novel griseofulvin compositions;" U.S. Patent Publication No. 20040258758 for "Nanoparticulate topiramate formulations;" U.S. Patent Publication No. 20040258757 for "Liquid dosage compositions of stable nanoparticulate active agents;" U.S. Patent Publication No. 20040229038 for "Nanoparticulate meloxicam formulations;" U.S. Patent Publication No. 20040208833 for "Novel fluticasone formulations;" U.S. Patent Publication No. 20040195413 for "Compositions and method for milling materials;" U.S. Patent Publication No. 20040156895 for "Solid dosage forms comprising pullulan;" U.S. Patent Publication No. 20040156872 for "Novel nimesulide compositions;" U.S. Patent Publication No. 20040141925 for "Novel triamcinolone compositions;" U.S. Patent Publication No. 20040115134 for "Novel nifedipine compositions;" U.S. Patent Publication No. 20040105889 for "Low viscosity liquid dosage forms;" U.S. Patent Publication No. 20040105778 for "Gamma irradiation of solid nanoparticulate active agents;" U.S. Patent Publication No. 20040101566 for "Novel benzoyl peroxide compositions;" U.S. Patent Publication No. 20040057905 for "Nanoparticulate beclomethasone dipropionate compositions;" U.S. Patent Publication No. 20040033267 for "Nanoparticulate compositions of angiogenesis inhibitors;" U.S. Patent Publication No. 20040033202 for "Nanoparticulate sterol formulations and novel sterol combinations;" U.S. Patent Publication No. 20040018242 for "Nanoparticulate nystatin formulations;" U.S. Patent Publication No. 20040015134 for "Drug delivery systems and methods;" U.S. Patent Publication No. 20030232796 for "Nanoparticulate polycosanol formulations & novel polycosanol combinations;" U.S. Patent Publication No. 20030215502 for "Fast dissolving dosage forms having reduced friability;" U.S. Patent Publication No. 20030185869 for "Nanoparticulate compositions having lysozyme as a surface stabilizer;" U.S. Patent Publication No. 20030181411 for "Nanoparticulate compositions of mitogen-activated protein (MAP) kinase inhibitors;" U.S. Patent Publication No. 20030137067 for "Compositions having a combination of immediate release and controlled release characteristics;" U.S. Patent Publication No. 20030108616 for "Nanoparticulate compositions comprising copolymers of vinyl pyrrolidone and vinyl acetate as surface stabilizers;" U.S. Patent Publication No. 20030095928 for "Nanoparticulate insulin;" U.S. Patent Publication No. 20030087308 for "Method for high throughput screening using a small scale mill or microfluidics;" U.S. Patent Publication No. 20030023203 for "Drug delivery systems & methods;" U.S. Patent Publication No.

20020179758 for "System and method for milling materials; and U.S. Patent Publication No. 20010053664 for "Apparatus for sanitary wet milling," describe nanoparticulate active agent compositions and are specifically incorporated by reference.

[0014] Surface modified nanoparticles and compositions thereof useful for treating cancer and other neoplastic diseases have been described, for example, in U.S. Pat. Nos. 5,399,363 and 5,494,683, both for "Surface Modified Anti-cancer Nanoparticles".

[0015] Amorphous small particle compositions are described, for example, in U.S. Pat. No. 4,783,484 for "Particulate Composition and Use Thereof as Antimicrobial Agent;" U.S. Pat. No. 4,826,689 for "Method for Making Uniformly Sized Particles from Water-Insoluble Organic Compounds;" U.S. Pat. No. 4,997,454 for "Method for Making Uniformly-Sized Particles From Insoluble Compounds;" U.S. Pat. No. 5,741,522 for "Ultrasmall, Non-aggregated Porous Particles of Uniform Size for Entrapping Gas Bubbles Within and Methods;" and U.S. Pat. No. 5,776,496, for "Ultrasmall Porous Particles for Enhancing Ultrasound Back Scatter."

[0016] There is a need in the art for imatinib mesylate formulations which overcome the fed/fasted absorption variability, along with other problems, observed with conventional imatinib mesylate dosage forms. The present invention, which overcomes such problems, relates to a nanoparticulate composition comprising imatinib mesylate, or a salt or derivative thereof for the treatment of chronic myeloid leukemia, gastrointestinal stromal tumors and related diseases.

SUMMARY

[0017] The compositions disclosed herein typically include nanoparticulate imatinib mesylate, or a salt or derivative thereof, having an effective average particle size of less than about 2000 nm and at least one surface stabilizer. The surface stabilizer is typically adsorbed on or associated with the surface of the nanoparticulate imatinib mesylate particles. Optionally, the compositions may include a pharmaceutically acceptable carrier and any suitable excipients.

[0018] The nanoparticulate compositions of imatinib mesylate, or a salt or derivative thereof, disclosed herein may be effective in the treatment of a number of disease or conditions, including but not limited to chronic myeloid leukemia, gastrointestinal stromal tumors and related diseases.

[0019] A preferred dosage form of the invention is a solid dosage form, although any pharmaceutically acceptable dosage form can be utilized.

[0020] Another aspect of the invention is directed to pharmaceutical compositions comprising particles of a nanoparticulate imatinib mesylate, or a salt or derivative thereof, at least one surface stabilizer, and a pharmaceutically acceptable carrier, as well as any desired excipients.

[0021] One embodiment of the invention encompasses a nanoparticulate imatinib mesylate composition, wherein the pharmacokinetic profile of the nanoparticulate imatinib mesylate is not affected by the fed or fasted state of a subject ingesting the composition.

[0022] In yet another embodiment, the invention encompasses a nanoparticulate imatinib mesylate composition, wherein administration of the composition to a subject in a fasted state is bioequivalent to administration of the composition to a subject in a fed state.

[0023] Another embodiment of the invention is directed to nanoparticulate imatinib mesylate compositions comprising one or more additional compounds useful in the treatment of chronic myeloid leukemia, gastrointestinal stromal tumors, and related diseases.

[0024] This invention further discloses a method of making the nanoparticulate imatinib mesylate composition. Such a method comprises contacting the nanoparticulate imatinib mesylate, or a salt or derivative thereof, with at least one surface stabilizer for a time and under conditions sufficient to provide a nanoparticulate imatinib mesylate composition having an effective average particle size of less than about 2000 nm. The one or more surface stabilizers can be contacted with a nanoparticulate imatinib mesylate, either before, during, or after size reduction of the imatinib mesylate particle.

[0025] The present invention is also directed to methods of treatment including but not limited to, the treatment of chronic myeloid leukemia, gastrointestinal stromal tumors and related diseases, using the novel nanoparticulate imatinib mesylate compositions disclosed herein. Such methods comprise administering to a subject a therapeutically effective amount of a nanoparticulate imatinib mesylate, or a salt or derivative thereof. Other methods of treatment using the nanoparticulate compositions of the invention are known to those of skill in the art.

[0026] Both the foregoing general description and the following detailed description are exemplary and explanatory and are intended to provide further explanation of the invention as claimed. Other objects, advantages, and novel features will be readily apparent to those skilled in the art from the following detailed description of the invention.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

[0027] The present invention is directed to nanoparticulate compositions comprising an imatinib mesylate, or a salt or derivative thereof. The compositions comprise an imatinib mesylate, or a salt or derivative thereof, and preferably at least one surface stabilizer adsorbed on or associated with the surface of the drug. The imatinib mesylate, or a salt or derivative thereof, particles have an effective average particle size of less than about 2000 nm.

[0028] Advantages of the nanoparticulate imatinib mesylate compositions of the invention as compared to a conventional, non-nanoparticulate composition of the same imatinib mesylate formulation, include, but are not limited to: (1) smaller tablet size or other solid dosage form size; (2) smaller doses of drug required to obtain the same pharmacological effect; (3) increased bioavailability; (4) substantially similar pharmacokinetic profiles of the imatinib mesylate compositions when administered in the fed versus the fasted state; (5) bioequivalency of the imatinib mesylate compositions; (6) an increased rate of dissolution for the imatinib mesylate compositions; (7) the imatinib mesylate nanoparticles of the present invention redisperse upon addi-

tion thereof to a solution; and (8) the imatinib mesylate compositions can be used in conjunction with other active agents useful in the treatment of chronic myeloid leukemia, gastrointestinal stromal tumors and related diseases.

[0029] The present invention also includes nanoparticulate imatinib mesylate compositions, or a salt or derivative thereof, together with one or more non-toxic physiologically acceptable carriers, adjuvants, or vehicles, collectively referred to as carriers. The compositions can be formulated for parenteral injection (e.g., intravenous, intramuscular, or subcutaneous), oral administration in solid, liquid, or aerosol form, vaginal, nasal, rectal, ocular, local (powders, ointments, or drops), buccal, intracisternal, intraperitoneal, or topical administration, and the like.

[0030] A preferred dosage form of the invention is a solid dosage form, although any pharmaceutically acceptable dosage form can be utilized. Exemplary solid dosage forms include, but are not limited to, tablets, capsules, sachets, lozenges, powders, pills, or granules, and the solid dosage form can be, for example, a fast melt dosage form, controlled release dosage form, lyophilized dosage form, delayed release dosage form, extended release dosage form, pulsatile release dosage form, mixed immediate release and controlled release dosage form, or a combination thereof. A solid dose tablet formulation is preferred.

[0031] The present invention is described herein using several definitions, as set forth below and throughout the application.

[0032] The term "effective average particle size of less than about 2000 nm," as used herein, means that at least about 50% of the nanoparticulate imatinib mesylate particles have a size of less than about 2000 nm, by weight (or by other suitable measurement technique, such as by number, volume, etc.) when measured by, for example, sedimentation flow fractionation, photon correlation spectroscopy, light scattering, disk centrifugation, and other techniques known to those of skill in the art.

[0033] As used herein, "about" will be understood by persons of ordinary skill in the art and will vary to some extent on the context in which it is used. If there are uses of the term which are not clear to persons of ordinary skill in the art given the context in which it is used, "about" will mean up to plus or minus 10% of the particular term.

[0034] As used herein with reference to stable imatinib mesylate nanoparticulate particles, "stable" connotes, but is not limited to one or more of the following parameters: (1) the particles do not appreciably flocculate or agglomerate due to interparticle attractive forces or otherwise significantly increase in particle size over time; (2) that the physical structure of the particles is not altered over time, such as by conversion from an amorphous phase to a crystalline phase; (3) that the particles are chemically stable; and/or (4) where the imatinib mesylate has not been subject to a heating step at or above the melting point of the imatinib mesylate in the preparation of the nanoparticles of the present invention.

[0035] The term "conventional" or "non-nanoparticulate active agent" shall mean an active agent which is solubilized or which has an effective average particle size of greater than about 2000 nm. Nanoparticulate active agents as defined herein have an effective average particle size of less than about 2000 nm.

[0036] The phrase "poorly water soluble drugs" as used herein refers to those drugs that have a solubility in water of less than about 30 mg/ml, less than about 20 mg/ml, less than about 10 mg/ml, or less than about 1 mg/ml.

[0037] As used herein, the phrase "therapeutically effective amount" shall mean that drug dosage that provides the specific pharmacological response for which the drug is administered in a significant number of subjects in need of such treatment. It is emphasized that a therapeutically effective amount of a drug that is administered to a particular subject in a particular instance will not always be effective in treating the conditions/diseases described herein, even though such dosage is deemed to be a therapeutically effective amount by those of skill in the art.

A. Preferred Characteristics of the Nanoparticulate Imatinib Mesylate Compositions of the Invention

[0038] 1. Increased Bioavailability

[0039] The nanoparticulate imatinib mesylate, or a salt or derivative thereof, formulations of the invention are proposed to exhibit increased bioavailability, and require smaller doses as compared to prior conventional imatinib mesylate formulations.

[0040] In one embodiment of the invention, the nanoparticulate imatinib mesylate composition, upon administration to a mammal, produces therapeutic results at a dosage which is less than that of a non-nanoparticulate dosage form of the same imatinib mesylate composition.

[0041] 2. Improved Pk Profiles

[0042] The invention also preferably provides compositions comprising nanoparticulate imatinib mesylate, or a derivative or salt thereof, having a desirable pharmacokinetic profile when administered to mammalian subjects. The desirable pharmacokinetic profile of the compositions comprising imatinib mesylate, or a salt or derivative thereof, preferably includes, but is not limited to: (1) a C_{max} for imatinib mesylate, when assayed in the plasma of a mammalian subject following administration, that is preferably greater than the C_{max} for a non-nanoparticulate formulation of the same imatinib mesylate, administered at the same dosage; and/or (2) an AUC for imatinib mesylate, when assayed in the plasma of a mammalian subject following administration, that is preferably greater than the AUC for a non-nanoparticulate formulation of the same imatinib mesylate, administered at the same dosage; and/or (3) a T_{max} for imatinib mesylate, when assayed in the plasma of a mammalian subject following administration, that is preferably less than the T_{max} for a non-nanoparticulate formulation of the same imatinib mesylate, administered at the same dosage.

[0043] In one embodiment, a composition comprising a nanoparticulate imatinib mesylate exhibits in comparative pharmacokinetic testing with a non-nanoparticulate formulation of the same imatinib mesylate, administered at the same dosage, a T_{max} not greater than about 90%, not greater than about 80%, not greater than about 70%, not greater than about 60%, not greater than about 50%, not greater than about 30%, not greater than about 25%, not greater than about 20%, not greater than about 15%, not greater than about 10%, or not greater than about 5% of the T_{max} exhibited by the non-nanoparticulate imatinib mesylate formulation.

[0044] In another embodiment, the composition comprising a nanoparticulate imatinib mesylate exhibits in comparative pharmacokinetic testing with a non-nanoparticulate formulation of the same imatinib mesylate, administered at the same dosage, a C_{max} which is at least about 50%, at least about 100%, at least about 200%, at least about 300%, at least about 400%, at least about 500%, at least about 600%, at least about 700%, at least about 800%, at least about 900%, at least about 1000%, at least about 1100%, at least about 1200%, at least about 1300%, at least about 1400%, at least about 1500%, at least about 1600%, at least about 1700%, at least about 1800%, or at least about 1900% greater than the C_{max} exhibited by the non-nanoparticulate imatinib mesylate formulation.

[0045] In yet another embodiment, the composition comprising a nanoparticulate imatinib mesylate exhibits in comparative pharmacokinetic testing with a non-nanoparticulate formulation of the same imatinib mesylate, administered at the same dosage, an AUC which is at least about 25%, at least about 50%, at least about 75%, at least about 100%, at least about 125%, at least about 150%, at least about 175%, at least about 200%, at least about 225%, at least about 250%, at least about 275%, at least about 300%, at least about 350%, at least about 400%, at least about 450%, at least about 500%, at least about 550%, at least about 600%, at least about 750%, at least about 700%, at least about 750%, at least about 800%, at least about 850%, at least about 900%, at least about 950%, at least about 1000%, at least about 1050%, at least about 1100%, at least about 1150%, or at least about 1200% greater than the AUC exhibited by the non-nanoparticulate imatinib mesylate formulation.

[0046] In one embodiment of the invention, the T_{max} of imatinib mesylate, when assayed in the plasma of the mammalian subject, is less than about 6 to about 8 hours. In other embodiments of the invention, the T_{max} of imatinib mesylate is less than about 6 hours, less than about 5 hours, less than about 4 hours, less than about 3 hours, less than about 2 hours, less than about 1 hour, or less than about 30 minutes after administration.

[0047] The desirable pharmacokinetic profile, as used herein, is the pharmacokinetic profile measured after the initial dose of imatinib mesylate or a salt or derivative thereof. The compositions can be formulated in any way as described herein and as known to those of skill in the art.

[0048] 3. The Pharmacokinetic Profiles of the Imatinib Mesylate Compositions of the Invention are not Affected by the Fed or Fasted State of the Subject Ingesting the Compositions

[0049] The invention encompasses imatinib mesylate compositions wherein the pharmacokinetic profile of imatinib mesylate is not substantially affected by the fed or fasted state of a subject ingesting the composition. This means that there is no substantial difference in the quantity of drug absorbed or the rate of drug absorption when the nanoparticulate imatinib mesylate compositions are administered in the fed versus the fasted state.

[0050] For conventional imatinib mesylate formulations, i.e., GLEEVEC®, the absorption of imatinib mesylate is increased when administered with food. This difference in absorption observed with conventional imatinib mesylate

formulations is undesirable. The imatinib mesylate formulations of the invention overcome this problem, as the imatinib mesylate formulations reduce or preferably substantially eliminate significantly different absorption levels when administered under fed as compared to fasting conditions.

[0051] Benefits of a dosage form which substantially eliminates the effect of food include an increase in subject convenience, thereby increasing subject compliance, as the subject does not need to ensure that they are taking a dose either with or without food. This is significant, as with poor subject compliance an increase in the medical condition for which the drug is being prescribed may be observed.

[0052] 4. Bioequivalency of Imatinib Mesylate Compositions of the Invention When Administered in the Fed Versus the Fasted State

[0053] The invention also provides a nanoparticulate imatinib mesylate composition in which the administration of the composition to a subject in a fasted state is bioequivalent to administration of the composition to a subject in a fed state.

[0054] The difference in absorption of the imatinib mesylate compositions of the invention, when administered in the fed versus the fasted state, preferably is less than about 60%, less than about 55%, less than about 50%, less than about 45%, less than about 40%, less than about 35%, less than about 30%, less than about 25%, less than about 20%, less than about 15%, less than about 10%, less than about 5%, or less than about 3%.

[0055] In one embodiment of the invention, the invention encompasses compositions comprising at least one nanoparticulate imatinib mesylate composition, wherein administration of the composition to a subject in a fasted state is bioequivalent to administration of the composition to a subject in a fed state, in particular as defined by C_{max} and AUC guidelines given by the U.S. Food and Drug Administration and the corresponding European regulatory agency (EMA). Under U.S. FDA guidelines, two products or methods are bioequivalent if the 90% Confidence Intervals (CI) for AUC and C_{max} are between 0.80 to 1.25 (T_{max} measurements are not relevant to bioequivalence for regulatory purposes). To show bioequivalency between two compounds or administration conditions pursuant to Europe's EMA guidelines, the 90% CI for AUC must be between 0.80 to 1.25 and the 90% CI for C_{max} must be between 0.70 to 1.43.

[0056] 5. Dissolution Profiles of the Imatinib Mesylate Compositions of the Invention

[0057] The nanoparticulate imatinib mesylate compositions, or a salt or derivative thereof, of the invention are proposed to have unexpectedly dramatic dissolution profiles. Rapid dissolution of an administered active agent is preferable, as faster dissolution generally leads to faster onset of action and greater bioavailability. To improve the dissolution profile and bioavailability of the imatinib mesylate it would be useful to increase the drug's dissolution so that it could attain a level close to 100%.

[0058] The imatinib mesylate compositions of the invention preferably have a dissolution profile in which within about 5 minutes at least about 20% of the composition is

dissolved. In other embodiments of the invention, at least about 30% or at least about 40% of the imatinib mesylate composition is dissolved within about 5 minutes. In yet other embodiments of the invention, at least about 40%, at least about 50%, at least about 60%, at least about 70%, or at least about 80% of the imatinib mesylate composition is dissolved within about 10 minutes. Finally, in another embodiment of the invention, preferably at least about 70%, at least about 80%, at least about 90%, or at least about 100% of the imatinib mesylate composition is dissolved within about 20 minutes.

[0059] Dissolution is preferably measured in a medium which is discriminating. Such a dissolution medium will produce two very different dissolution curves for two products having very different dissolution profiles in gastric juices; i.e., the dissolution medium is predictive of in vivo dissolution of a composition. An exemplary dissolution medium is an aqueous medium containing the surfactant sodium lauryl sulfate at 0.025 M. Determination of the amount dissolved can be carried out by spectrophotometry. The rotating blade method (European Pharmacopoeia) can be used to measure dissolution.

[0060] 6. Redispersibility Profiles of the Imatinib Mesylate Compositions of the Invention

[0061] An additional feature of the imatinib mesylate, or a salt or derivative thereof, compositions of the invention is that the compositions redisperse such that the effective average particle size of the redispersed imatinib mesylate particles is less than about 2 microns. This is significant, as if upon administration the imatinib mesylate compositions of the invention did not redisperse to a substantially nanoparticulate size, then the dosage form may lose the benefits afforded by formulating the imatinib mesylate into a nanoparticulate particle size.

[0062] This is because nanoparticulate active agent compositions benefit from the small particle size of the active agent; if the active agent does not redisperse into the small particle sizes upon administration, then "clumps" or agglomerated active agent particles are formed, owing to the extremely high surface free energy of the nanoparticulate system and the thermodynamic driving force to achieve an overall reduction in free energy. With the formation of such agglomerated particles, the bioavailability of the dosage form may fall.

[0063] Moreover, the nanoparticulate imatinib mesylate compositions of the invention exhibit dramatic redispersion of the nanoparticulate imatinib mesylate composition particles upon administration to a mammal, such as a human or animal, as demonstrated by reconstitution/redispersion in a biorelevant aqueous media such that the effective average particle size of the redispersed imatinib mesylate composition particles is less than about 2 microns. Such biorelevant aqueous media can be any aqueous media that exhibit the desired ionic strength and pH, which form the basis for the biorelevance of the media. The desired pH and ionic strength are those that are representative of physiological conditions found in the human body. Such biorelevant aqueous media can be, for example, aqueous electrolyte solutions or aqueous solutions of any salt, acid, or base, or a combination thereof, which exhibit the desired pH and ionic strength.

[0064] Biorelevant pH is well known in the art. For example, in the stomach, the pH ranges from slightly less

than 2 (but typically greater than 1) up to 4 or 5. In the small intestine the pH can range from 4 to 6, and in the colon it can range from 6 to 8. Biorelevant ionic strength is also well known in the art. Fasted state gastric fluid has an ionic strength of about 0.1 M while fasted state intestinal fluid has an ionic strength of about 0.14. See e.g., Lindahl et al., "Characterization of Fluids from the Stomach and Proximal Jejunum in Men and Women," *Pharm. Res.*, 14 (4): 497-502 (1997).

[0065] It is believed that the pH and ionic strength of the test solution is more critical than the specific chemical content. Accordingly, appropriate pH and ionic strength values can be obtained through numerous combinations of strong acids, strong bases, salts, single or multiple conjugate acid-base pairs (i.e., weak acids and corresponding salts of that acid), monoprotic and polyprotic electrolytes, etc.

[0066] Representative electrolyte solutions can be, but are not limited to, HCl solutions, ranging in concentration from about 0.001 to about 0.1 N, and NaCl solutions, ranging in concentration from about 0.001 to about 0.1 M, and mixtures thereof. For example, electrolyte solutions can be, but are not limited to, about 0.1 N HCl or less, about 0.01 N HCl or less, about 0.001 N HCl or less, about 0.1 M NaCl or less, about 0.01 M NaCl or less, about 0.001 M NaCl or less, and mixtures thereof. Of these electrolyte solutions, 0.01 M HCl and/or 0.1 M NaCl, are most representative of fasted human physiological conditions, owing to the pH and ionic strength conditions of the proximal gastrointestinal tract.

[0067] Electrolyte concentrations of 0.001 N HCl, 0.01 N HCl, and 0.1 N HCl correspond to pH 3, pH 2, and pH 1, respectively. Thus, a 0.01 N HCl solution simulates typical acidic conditions found in the stomach. A solution of 0.1 M NaCl provides a reasonable approximation of the ionic strength conditions found throughout the body, including the gastrointestinal fluids, although concentrations higher than 0.1 M may be employed to simulate fed conditions within the human GI tract.

[0068] Exemplary solutions of salts, acids, bases or combinations thereof, which exhibit the desired pH and ionic strength, include but are not limited to phosphoric acid/phosphate salts+sodium, potassium and calcium salts of chloride, acetic acid/acetate salts+sodium, potassium and calcium salts of chloride, carbonic acid/bicarbonate salts+sodium, potassium and calcium salts of chloride, and citric acid/citrate salts+sodium, potassium and calcium salts of chloride.

[0069] In other embodiments of the invention, the redispersed particles of imatinib mesylate, or a salt or derivative thereof, (redispersed in water, a biorelevant media, or any other suitable media) have an effective average particle size of less than about 1900 nm, less than about 1800 nm, less than about 1700 nm, less than about 1600 nm, less than about 1500 nm, less than about 1400 nm, less than about 1300 nm, less than about 1200 nm, less than about 1100 nm, less than about 1000 nm, less than about 900 nm, less than about 800 nm, less than about 700 nm, less than about 650 nm, less than about 600 nm, less than about 550 nm, less than about 500 nm, less than about 450 nm, less than about 400 nm, less than about 350 nm, less than about 300 nm, less than about 250 nm, less than about 200 nm, less than about 150 nm, less than about 100 nm, less than about 75 nm, or less than about 50 nm, as measured by light-

scattering methods, microscopy, or other appropriate methods. Such methods suitable for measuring effective average particle size are known to a person of ordinary skill in the art.

[0070] Redispersibility can be tested using any suitable means known in the art. See e.g., the example sections of U.S. Pat. No. 6,375,986 for "Solid Dose Nanoparticulate Compositions Comprising a Synergistic Combination of a Polymeric Surface Stabilizer and Dioctyl Sodium Sulfosuccinate."

[0071] 7. Imatinib Mesylate Compositions Used in Conjunction with Other Active Agents

[0072] The imatinib mesylate, or a salt or derivative thereof, compositions of the invention can additionally comprise one or more compounds useful in the treatment of chronic myeloid leukemia, gastrointestinal stromal tumors and related diseases, or the imatinib mesylate compositions can be administered in conjunction with such a compound. Examples of such compounds include, but are not limited to, anti-cancer agents such as mitotic inhibitors, alkylating agents, anti-metabolites, intercalating antibiotics, growth factor inhibitors, cell cycle inhibitors, enzymes, topoisomerase inhibitors, biological response modifiers, anti-hormones, and anti-androgens. For example, additional compounds may include gefitinib, pertuzamib, paclitaxel, cisplatin, carboplatin, gemcitabine, bevacizumab, temozolomide, sunitinib, leflunomide, docetaxel, imatinib, lapatinib, caneritinib, doxorubicin, vatalanib, sorafenib, leucovorin, capecitabine, cetuximab, and combinations thereof.

B. Nanoparticulate Imatinib Mesylate Compositions

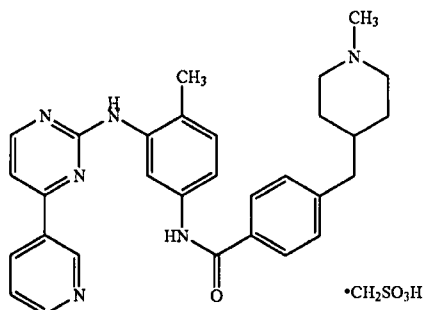
[0073] The invention provides compositions comprising particles of imatinib mesylate, or a salt or derivative thereof, and at least one surface stabilizer. The surface stabilizers preferably are adsorbed on, or associated with, the surface of the imatinib mesylate particles. Surface stabilizers especially useful herein preferably physically adhere on, or associate with, the surface of the nanoparticulate imatinib mesylate particles, but do not chemically react with the imatinib mesylate particles or itself. Individually adsorbed molecules of the surface stabilizer are essentially free of intermolecular cross-linkages.

[0074] The present invention also includes imatinib mesylate, or a salt or derivative thereof, compositions together with one or more non-toxic physiologically acceptable carriers, adjuvants, or vehicles, collectively referred to as carriers. The compositions can be formulated for parenteral injection (e.g., intravenous, intramuscular, or subcutaneous), oral administration in solid, liquid, or aerosol form, vaginal, nasal, rectal, ocular, local (powders, ointments or drops), buccal, intracisternal, intraperitoneal, or topical administration, and the like.

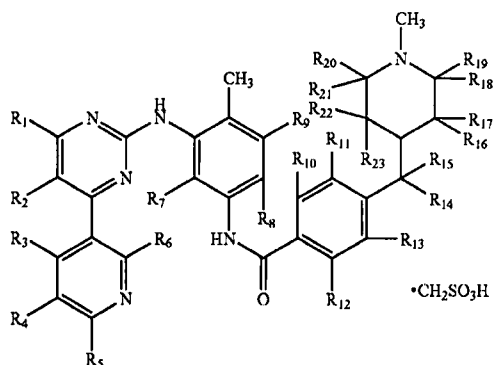
[0075] 1. Imatinib Mesylate Derivatives

[0076] The compositions of the invention comprise imatinib mesylate, an imatinib mesylate derivative or a salt thereof. The particles of imatinib mesylate, or a salt or derivative thereof, can be in a crystalline phase, a semi-crystalline phase, an amorphous phase, a semi-amorphous phase, or a combination thereof.

[0077] Imatinib mesylate has the molecular formula (formula I):



[0078] Imatinib mesylate derivatives may include any compound of formula II:



[0079] In some embodiments, imatinib mesylate derivatives may include a compound having formula II, where each substituent R^1-R^{23} , may be the same or different, and is selected, independently from each other, from a group consisting of:—H; —OH; —F; —Cl; —Br; —I; —NH₂; alkyl- and dialkylamino; linear or branched C₁₋₆ alkyl, C₂₋₆ alkenyl and alkynyl; aralkyl; linear or branched C₁₋₆ alkoxy; aryloxy; aralkoxy; -(alkylene)oxy(alkyl); —CN; —NO₂; —COOH; —COO(alkyl); —COO(aryl); —C(O)NH(C₁₋₆ alkyl); —C(O)NH(aryl); sulfonyl; (C₁₋₆ alkyl)sulfonyl; arylsulfonyl; sulfamoyl, (C₁₋₆ alkyl)sulfamoyl; (Calkyl)thio; (C₁₋₆ alkyl)sulfonamide; arylsulfonamide; —NHNH₂, —NHOH; aryl; and heteroaryl; and where each alkyl, alkenyl, alkynyl, aryl, and heteroaryl moiety may be optionally substituted with one or more groups independently selected from the group consisting of —OH; —F; —Cl; —Br; —I; —NH₂; alkyl- and dialkylamino; linear or branched C₁₋₆ alkyl, C₂₋₆ alkenyl and alkynyl; aralkyl; linear or branched C₁₋₆ alkoxy, aryloxy, aralkoxy; -(alkylene)oxy(alkyl); —CN, —NO₂, —COOH, —COO(alkyl), —COO(aryl); —C(O)NH(C₁₋₆ alkyl); —C(O)NH(aryl); sulfonyl; (C₁₋₆ alkyl)sulfonyl; arylsulfonyl; sulfamoyl, (C₁₋₆ alkyl)sulfamoyl; (C₁₋₆ alkyl)thio; (C₁₋₆ alkyl)sulfonamide; arylsulfonamide; —NHNH₂; and —NHOH.

[0080] 2. Surface Stabilizers

[0081] Combinations of more than one surface stabilizer can be used in the invention. Useful surface stabilizers which can be employed in the invention include, but are not limited to, known organic and inorganic pharmaceutical excipients. Such excipients include various polymers, low molecular weight oligomers, natural products, and surfactants. Exemplary surface stabilizers include nonionic, ionic, anionic, cationic, and zwitterionic compounds or surfactants.

[0082] Representative examples of surface stabilizers include hydroxypropyl methylcellulose (now known as hypromellose), hydroxypropylcellulose, polyvinylpyrrolidone, sodium lauryl sulfate, dioctylsulfosuccinate, gelatin, casein, lecithin (phosphatides), dextran, gum acacia, cholesterol, tragacanth, stearic acid, benzalkonium chloride, calcium stearate, glycerol monostearate, cetostearyl alcohol, cetomacrogol emulsifying wax, sorbitan esters, polyoxyethylene alkyl ethers (e.g., macrogol ethers such as cetomacrogol 1000), polyoxyethylene castor oil derivatives, polyoxyethylene sorbitan fatty acid esters (e.g., the commercially available Tween® products such as e.g., Tween® 20 and Tween® 80 (ICI Specialty Chemicals)); polyethylene glycols (e.g., Carbowax® 3550 and 934 (Union Carbide)), polyoxyethylene stearates, colloidal silicon dioxide, phosphates, carboxymethylcellulose calcium, carboxymethylcellulose sodium, methylcellulose, hydroxyethylcellulose, hypromellose phthalate, noncrystalline cellulose, magnesium aluminium silicate, triethanolamine, polyvinyl alcohol (PVA), 4-(1,1,3,3-tetramethylbutyl)-phenol polymer with ethylene oxide and formaldehyde (also known as tyloxapol, superione, and triton), poloxamers (e.g., Pluronic® F68 and F108, which are block copolymers of ethylene oxide and propylene oxide); poloxamines (e.g., Tetric® 908, also known as Poloxamine® 908, which is a tetrafunctional block copolymer derived from sequential addition of propylene oxide and ethylene oxide to ethylenediamine (BASF Wyandotte Corporation, Parsippany, N.J.)); Tetric® 1508 (T-1508) (BASF Wyandotte Corporation), Triton® X-200, which is an alkyl aryl polyether sulfonate (Rohm and Haas); Crodesta® F-110, which is a mixture of sucrose stearate and sucrose distearate (Croda Inc.); p-isononylphenoxypoly-(glycidol), also known as Olin® 10G or Surfactant® 10-G (Olin Chemicals, Stamford, Conn.); Crodestas® SL-40 (Croda, Inc.); and SA9OHCO, which is $C_{18}H_{37}CH_2(CON(CH_3)CH_2(CHOH)_4(CH_2OH)_2$ (Eastman Kodak Co.); decanoyl-N-methylglucamide; n-decyl β -D-glucopyranoside; n-decyl β -D-maltopyranoside; n-dodecyl β -D-glucopyranoside; n-dodecyl β -D-maltoside; heptanoyl-N-methylglucamide; n-heptyl- β -D-glucopyranoside; n-heptyl μ -D-thiogluconide; n-hexyl β -D-glucopyranoside; nonanoyl-N-methylglucamide; n-nonyl μ -D-glucopyranoside; octanoyl-N-methylglucamide; n-octyl- β -D-glucopyranoside; octyl β -D-thiogluconide; PEG-phospholipid, PEG-cholesterol, PEG-cholesterol derivative, PEG-vitamin A, PEG-vitamin E, lysozyme, random copolymers of vinyl pyrrolidone and vinyl acetate, such as Plasdone® S630 and the like.

[0083] Examples of useful cationic surface stabilizers include, but are not limited to, polymers, biopolymers, polysaccharides, celluloses, alginates, phospholipids, and nonpolymeric compounds, such as zwitterionic stabilizers, poly-*n*-methylpyridinium, anthryl pyridinium chloride.

cationic phospholipids, chitosan, polylysine, polyvinylimidazole, polybrene, polymethylmethacrylate trimethylammoniumbromide bromide (PMMTMABr), hexyldesyltrimethylammonium bromide (HDMAB), and polyvinylpyrrolidone-2-dimethylaminoethyl methacrylate dimethyl sulfate.

[0084] Other useful cationic stabilizers include, but are not limited to, cationic lipids, sulfonium, phosphonium, and quarternary ammonium compounds, such as stearyltrimethylammonium chloride, benzyl-di(2-chloroethyl)ethylammonium bromide, coconut trimethyl ammonium chloride or bromide, coconut methyl dihydroxyethyl ammonium chloride or bromide, decyl triethyl ammonium chloride, decyl dimethyl hydroxyethyl ammonium chloride or bromide, C_{12-15} dimethyl hydroxyethyl ammonium chloride or bromide, coconut dimethyl hydroxyethyl ammonium chloride or bromide, myristyl trimethyl ammonium methyl sulphate, lauryl dimethyl benzyl ammonium chloride or bromide, lauryl dimethyl (ethenoxy)₄ ammonium chloride or bromide, N-alkyl (C_{12-18})dimethylbenzyl ammonium chloride, N-alkyl (C_{14-18})dimethyl-benzyl ammonium chloride, N-tetradecyldimethylbenzyl ammonium chloride monohydrate, dimethyl didecyl ammonium chloride, N-alkyl and (C_{12-14}) dimethyl 1-naphthylmethyl ammonium chloride, trimethylammonium halide, alkyl-trimethylammonium salts and dialkyl-dimethylammonium salts, lauryl trimethyl ammonium chloride, ethoxylated alkyamidoalkyldialkylammonium salt and/or an ethoxylated trialkyl ammonium salt, dialkylbenzene dialkylammonium chloride, N-didecyldimethyl ammonium chloride, N-tetradecyldimethylbenzyl ammonium, chloride monohydrate, N-alkyl(C_{12-14}) dimethyl 1-naphthylmethyl ammonium chloride and dodecyldimethylbenzyl ammonium chloride, dialkyl benzene-alkyl ammonium chloride, lauryl trimethyl ammonium chloride, alkylbenzyl methyl ammonium chloride, alkyl benzyl dimethyl ammonium bromide, C_{12} , C_{15} , C_{17} trimethyl ammonium bromides, dodecylbenzyl triethyl ammonium chloride, poly-diallyldimethylammonium chloride (DADMAC), dimethyl ammonium chlorides, alkyl dimethylammonium halogenides, tricetyl methyl ammonium chloride, decyltrimethylammonium bromide, dodecyltriethylammonium bromide, tetradecyltrimethylammonium bromide, methyl triocetyl ammonium chloride (ALQUAT 336™), POLYQUAT 10™, tetrabutylammonium bromide, benzyl trimethylammonium bromide, choline esters (such as choline esters of fatty acids), benzalkonium chloride, stearylalkonium chloride compounds (such as stearyltrimonium chloride and Di-stearyldimonium chloride), cetyl pyridinium bromide or chloride, halide salts of quaternized polyoxyethylalkylamines, MIRAPOL™ and ALKAQUA™ (Alkaril Chemical Company), alkyl pyridinium salts; amines, such as alkylamines, dialkylamines, alkanolamines, polyethylenepolyamines, N,N-dialkylaminoalkyl acrylates, and vinyl pyridine, amine salts, such as lauryl amine acetate, stearyl amine acetate, alkylpyridinium salt, and alkylimidazolium salt, and amine oxides; imide azolinium salts; protonated quaternary acrylamides; methylated quaternary polymers, such as poly[diallyl dimethylammonium chloride] and poly-[N-methyl vinyl pyridinium chloride]; and cationic guar.

[0085] Such exemplary cationic surface stabilizers and other useful cationic surface stabilizers are described in J. Cross and E. Singer, *Cationic Surfactants: Analytical and Biological Evaluation* (Marcel Dekker, 1994); P. and D. Rubingh (Editor), *Cationic Surfactants: Physical Chemistry*

(Marcel Dekker, 1991); and J. Richmond, *Cationic Surfactants: Organic Chemistry*, (Marcel Dekker, 1990).

[0086] Nonpolymeric surface stabilizers are any nonpolymeric compound, such as benzalkonium chloride, a carbonium compound, a phosphonium compound, an oxonium compound, a halonium compound, a cationic organometallic compound, a quarternary phosphorous compound, a pyridinium compound, an anilinium compound, an ammonium compound, a hydroxylammonium compound, a primary ammonium compound, a secondary ammonium compound, a tertiary ammonium compound, and quarternary ammonium compounds of the formula $NR_1R_2R_3R_4^{(+)}$. For compounds of the formula $NR_1R_2R_3R_4^{(+)}$:

[0087] (i) none of R_1-R_4 are CH_3 ;

[0088] (ii) one of R_1-R_4 is CH_3 ;

[0089] (iii) three of R_1-R_4 are CH_3 ;

[0090] (iv) all of R_1-R_4 are CH_3 ;

[0091] (v) two of R_1-R_4 are CH_3 , one of R_1-R_4 is $C_6H_5CH_2$, and one of R_1-R_4 is an alkyl chain of seven carbon atoms or less;

[0092] (vi) two of R_1-R_4 are CH_3 , one of R_1-R_4 is $C_6H_5CH_2$, and one of R_1-R_4 is an alkyl chain of nineteen carbon atoms or more;

[0093] (vii) two of R_1-R_4 are CH_3 and one of R_1-R_4 is the group $C_6H_5(CH_2)_n$, where $n>1$;

[0094] (viii) two of R_1-R_4 are CH_3 , one of R_1-R_4 is $C_6H_5CH_2$, and one of R_1-R_4 comprises at least one heteroatom;

[0095] (ix) two of R_1-R_4 are CH_3 , one of R_1-R_4 is $C_6H_5CH_2$, and one of R_1-R_4 comprises at least one halogen;

[0096] (x) two of R_1-R_4 are CH_3 , one of R_1-R_4 is $C_6H_5CH_2$, and one of R_1-R_4 comprises at least one cyclic fragment;

[0097] (xi) two of R_1-R_4 are CH_3 and one of R_1-R_4 is a phenyl ring; or

[0098] (xii) two of R_1-R_4 are CH_3 and two of R_1-R_4 are purely aliphatic fragments.

[0099] Such compounds include, but are not limited to, bezalkonium chloride, benzethonium chloride, cetylpyridinium chloride, behentrimonium chloride, lauralkonium chloride, cetalkonium chloride, cetrimonium bromide, cetrimonium chloride, cethylamine hydrofluoride, chlorallylmethenamine chloride (Quaternium-15), distearyldimonium chloride (Quaternium-5), dodecyl dimethyl ethylbenzyl ammonium chloride (Quaternium-14), Quaternium-22, Quaternium-26, Quaternium-18 hectorite, dimethylaminoethylchloride hydrochloride, cysteine hydrochloride, diethanolammonium POE (10) oleyl ether phosphate, diethanolammonium POE (3) oleyl ether phosphate, tallow alkonium chloride, dimethyl dioctadecylammoniumbentonite, stearylalkonium chloride, domiphen bromide, denatonium benzoate, myristalkonium chloride, laurtrimonium chloride, ethylenediamine dihydrochloride, guanidine hydrochloride, pyridoxine HCl, iofetamine hydrochloride, meglumine hydrochloride, methylbenzethonium chloride, myrtrimonium bromide, oleyltrimonium chloride, polyqua-

temium-1, procaine hydrochloride, cocobetaine, stearylalkonium bentonite, stearylalkonium hectorite, stearyl trihydroxyethyl propylenediamine dihydrofluoride, tallowtrimonium chloride, and hexadecyltrimethyl ammonium bromide.

[0100] The surface stabilizers are commercially available and/or can be prepared by techniques known in the art. Most of these surface stabilizers are known pharmaceutical excipients and are described in detail in the *Handbook of Pharmaceutical Excipients*, published jointly by the American Pharmaceutical Association and The Pharmaceutical Society of Great Britain (The Pharmaceutical Press, 2000), specifically incorporated by reference.

[0101] The imatinib mesylate composition and surface stabilizer may be present in the pharmaceutical compositions disclosed herein at any suitable ratio (w/w). For example, in some embodiments the pharmaceutical compositions include the imatinib mesylate composition and the surface stabilizer at a ratio of about 20:1, 15:1, 10:1, 8:1, 7:1, 6:1, 5:1, 4:1, 3:1, 2:1 (w/w), or any range defined by said ratios (for example, but not limited to about 20:1-2:1, about 10:1-4:1, and about 8:1-5:1).

[0102] 3. Other Pharmaceutical Excipients

[0103] Pharmaceutical compositions according to the invention may also comprise one or more binding agents, filling agents, lubricating agents, suspending agents, sweeteners, flavoring agents, preservatives, buffers, wetting agents, disintegrants, effervescent agents, and other excipients. Such excipients are known in the art.

[0104] Examples of filling agents are lactose monohydrate, lactose anhydrous, and various starches; examples of binding agents are various celluloses and cross-linked polyvinylpyrrolidone, microcrystalline cellulose, such as Avicel® PH101 and Avicel® PH102, microcrystalline cellulose, and silicified microcrystalline cellulose (ProSolv SMCC™).

[0105] Suitable lubricants, including agents that act on the flowability of the powder to be compressed, are colloidal silicon dioxide, such as Aerosil® 200, talc, stearic acid, magnesium stearate, calcium stearate, and silica gel.

[0106] Examples of sweeteners are any natural or artificial sweetener, such as sucrose, xylitol, sodium saccharin, cyclamate, aspartame, and acesulfame. Examples of flavoring agents are Magnasweet® (trademark of MAFCO), bubble gum flavor, and fruit flavors, and the like.

[0107] Examples of preservatives are potassium sorbate, methylparaben, propylparaben, benzoic acid and its salts, other esters of parahydroxybenzoic acid such as butylparaben, alcohols such as ethyl or benzyl alcohol, phenolic compounds such as phenol, or quaternary compounds such as benzalkonium chloride.

[0108] Suitable diluents include pharmaceutically acceptable inert fillers, such as microcrystalline cellulose, lactose, dibasic calcium phosphate, saccharides, and/or mixtures of any of the foregoing. Examples of diluents include microcrystalline cellulose, such as Avicel® PH101 and Avicel® PH102; lactose such as lactose monohydrate, lactose anhydrous, and Pharmatose® DCL21; dibasic calcium phosphate such as Emcompress®; mannitol; starch; sorbitol; sucrose; and glucose.

[0109] Suitable disintegrants include lightly crosslinked polyvinyl pyrrolidone, corn starch, potato starch, maize starch, and modified starches, croscarmellose sodium, cross-povidone, sodium starch glycolate, and mixtures thereof.

[0110] Examples of effervescent agents are effervescent couples such as an organic acid and a carbonate or bicarbonate. Suitable organic acids include, for example, citric, tartaric, malic, fumaric, adipic, succinic, and alginic acids and anhydrides and acid salts. Suitable carbonates and bicarbonates include, for example, sodium carbonate, sodium bicarbonate, potassium carbonate, potassium bicarbonate, magnesium carbonate, sodium glycine carbonate, L-lysine carbonate, and arginine carbonate. Alternatively, only the sodium bicarbonate component of the effervescent couple may be present.

[0111] 4. Nanoparticulate Imatinib Mesylate Particle Size

[0112] The compositions of the invention comprise nanoparticulate imatinib mesylate, or a salt or derivative thereof, particles which have an effective average particle size of less than about 2000 nm (i.e., 2 microns), less than about 1900 nm, less than about 1800 nm, less than about 1700 nm, less than about 1600 nm, less than about 1500 nm, less than about 1400 nm, less than about 1300 nm, less than about 1200 nm, less than about 1100 nm, less than about 1000 nm, less than about 900 nm, less than about 800 nm, less than about 700 nm, less than about 600 nm, less than about 500 nm, less than about 400 nm, less than about 300 nm, less than about 250 nm, less than about 200 nm, less than about 150 nm, less than about 100 nm, less than about 75 nm, or less than about 50 nm, as measured by light-scattering methods, microscopy, or other appropriate methods.

[0113] By "an effective average particle size of less than about 2000 nm" it is meant that at least 50% of the imatinib mesylate particles have a particle size of less than the effective average, by weight (or by other suitable measurement technique, such as by volume, number etc.), i.e., less than about 2000 nm, 1900 nm, 1800 nm, etc., when measured by the above-noted techniques. In other embodiments of the invention, at least about 60%, at least about 70%, at least about 80%, at least about 90%, at least about 95%, or at least about 99% of the imatinib mesylate particles have a particle size of less than the effective average, i.e., less than about 2000 nm, 1900 nm, 1800 nm, 1700 nm, etc.

[0114] In the present invention, the value for D50 of a nanoparticulate imatinib mesylate composition is the particle size below which 50% of the imatinib mesylate particles fall, by weight (or by other suitable measurement technique, such as by volume, number etc.). Similarly, D90 is the particle size below which 90% of the imatinib mesylate particles fall, by weight (or by other suitable measurement technique, such as by volume, number etc.).

[0115] 5. Concentration of Imatinib Mesylate and Surface Stabilizers

[0116] The relative amounts of imatinib mesylate, or a salt or derivative thereof, and one or more surface stabilizers can vary widely. The optimal amount of the individual components can depend, for example, upon the particular imatinib mesylate selected, the hydrophilic lipophilic balance (HLB), melting point, and the surface tension of water solutions of the stabilizer, etc.

[0117] The concentration of the imatinib mesylate can vary from about 99.5% to about 0.001%, from about 95% to about 0.1%, or from about 90% to about 0.5%, by weight, based on the total combined dry weight of the imatinib mesylate and at least one surface stabilizer, not including other excipients.

[0118] The concentration of the at least one surface stabilizer can vary from about 0.5% to about 99.999%, from about 5.0% to about 99.9%, or from about 10% to about 99.5%, by weight, based on the total combined dry weight of the imatinib mesylate and at least one surface stabilizer, not including other excipients.

[0119] 6. Exemplary Nanoparticle Imatinib Mesylate Tablet Formulations

[0120] Several exemplary imatinib mesylate tablet formulations are given below. These examples are not intended to limit the claims in any respect, but rather to provide exemplary tablet formulations of imatinib mesylate which can be utilized in the methods of the invention. Such exemplary tablets can also comprise a coating agent.

Exemplary Nanoparticle Imatinib Mesylate Tablet Formulation #1	
Component	g/Kg
Imatinib Mesylate	about 50 to about 500
Hypromellose, USP	about 10 to about 70
Docusate Sodium, USP	about 1 to about 10
Sucrose, NF	about 100 to about 500
Sodium Lauryl Sulfate, NF	about 1 to about 40
Lactose Monohydrate, NF	about 50 to about 400
Silicified Microcrystalline Cellulose	about 50 to about 300
Crospovidone, NF	about 20 to about 300
Magnesium Stearate, NF	about 0.5 to about 5

[0121]

Exemplary Nanoparticle Imatinib Mesylate Tablet Formulation #2	
Component	g/Kg
Imatinib Mesylate	about 100 to about 300
Hypromellose, USP	about 30 to about 50
Docusate Sodium, USP	about 0.5 to about 10
Sucrose, NF	about 100 to about 300
Sodium Lauryl Sulfate, NF	about 1 to about 30
Lactose Monohydrate, NF	about 100 to about 300
Silicified Microcrystalline Cellulose	about 50 to about 200
Crospovidone, NF	about 50 to about 200
Magnesium Stearate, NF	about 0.5 to about 5

[0122]

Exemplary Nanoparticle Imatinib Mesylate Tablet Formulation #3	
Component	g/Kg
Imatinib Mesylate	about 200 to about 225
Hypromellose, USP	about 42 to about 46
Docusate Sodium, USP	about 2 to about 6

-continued	
Exemplary Nanoparticle Imatinib Mesylate Tablet Formulation #3	
Component	g/Kg
Sucrose, NF	about 200 to about 225
Sodium Lauryl Sulfate, NF	about 12 to about 18
Lactose Monohydrate, NF	about 200 to about 205
Silicified Microcrystalline Cellulose	about 130 to about 135
Crospovidone, NF	about 112 to about 118
Magnesium Stearate, NF	about 0.5 to about 3

[0123]

Exemplary Nanoparticle Imatinib Mesylate Tablet Formulation #4	
Component	g/Kg
Imatinib Mesylate	about 119 to about 224
Hypromellose, USP	about 42 to about 46
Docusate Sodium, USP	about 2 to about 6
Sucrose, NF	about 119 to about 224
Sodium Lauryl Sulfate, NF	about 12 to about 18
Lactose Monohydrate, NF	about 119 to about 224
Silicified Microcrystalline Cellulose	about 129 to about 134
Crospovidone, NF	about 112 to about 118
Magnesium Stearate, NF	about 0.5 to about 3

C. Methods of Making Nanoparticle Imatinib Mesylate Compositions

[0124] The nanoparticle imatinib mesylate, or a salt or derivative thereof, compositions can be made using, for example, milling, homogenization, precipitation, cryogenic, or template emulsion techniques. Exemplary methods of making nanoparticle active agent compositions are described in the '684 patent. Methods of making nanoparticle active agent compositions are also described in U.S. Pat. No. 5,518,187 for "Method of Grinding Pharmaceutical Substances;" U.S. Pat. No. 5,718,388 for "Continuous Method of Grinding Pharmaceutical Substances;" U.S. Pat. No. 5,862,999 for "Method of Grinding Pharmaceutical Substances;" U.S. Pat. No. 5,665,331 for "Co-Microprecipitation of Nanoparticle Pharmaceutical Agents with Crystal Growth Modifiers;" U.S. Pat. No. 5,662,883 for "Co-Microprecipitation of Nanoparticle Pharmaceutical Agents with Crystal Growth Modifiers;" U.S. Pat. No. 5,560,932 for "Microprecipitation of Nanoparticle Pharmaceutical Agents;" U.S. Pat. No. 5,543,133 for "Process of Preparing X-Ray Contrast Compositions Containing Nanoparticles;" U.S. Pat. No. 5,534,270 for "Method of Preparing Stable Drug Nanoparticles;" U.S. Pat. No. 5,510,118 for "Process of Preparing Therapeutic Compositions Containing Nanoparticles;" and U.S. Pat. No. 5,470,583 for "Method of Preparing Nanoparticle Compositions Containing Charged Phospholipids to Reduce Aggregation," all of which are specifically incorporated by reference.

[0125] The resultant nanoparticle imatinib mesylate compositions or dispersions can be utilized in solid or liquid dosage formulations, such as liquid dispersions, gels, aerosols, ointments, creams, controlled release formulations, fast

melt formulations, lyophilized formulations, tablets, capsules, delayed release formulations, extended release formulations, pulsatile release formulations, mixed immediate release and controlled release formulations, etc.

[0126] 1. Milling to Obtain Nanoparticulate Imatinib Mesylate Dispersions

[0127] Milling an imatinib mesylate, or a salt or derivative thereof, to obtain a nanoparticulate dispersion comprises dispersing the imatinib mesylate particles in a liquid dispersion medium in which the imatinib mesylate is poorly soluble, followed by applying mechanical means in the presence of grinding media to reduce the particle size of the imatinib mesylate to the desired effective average particle size. The dispersion medium can be, for example, water, safflower oil, ethanol, t-butanol, glycerin, polyethylene glycol (PEG), hexane, or glycol. A preferred dispersion medium is water.

[0128] The imatinib mesylate particles can be reduced in size in the presence of at least one surface stabilizer. Alternatively, imatinib mesylate particles can be contacted with one or more surface stabilizers after attrition. Other compounds, such as a diluent, can be added to the imatinib mesylate/surface stabilizer composition during the size reduction process. Dispersions can be manufactured continuously or in a batch mode.

[0129] 2. Precipitation to Obtain Nanoparticulate Imatinib Mesylate Compositions

[0130] Another method of forming the desired nanoparticulate imatinib mesylate, or a salt or derivative thereof, composition is by microprecipitation. This is a method of preparing stable dispersions of poorly soluble active agents in the presence of one or more surface stabilizers and one or more colloid stability enhancing surface active agents free of any trace toxic solvents or solubilized heavy metal impurities. Such a method comprises, for example: (1) dissolving the imatinib mesylate in a suitable solvent; (2) adding the formulation from step (1) to a solution comprising at least one surface stabilizer; and (3) precipitating the formulation from step (2) using an appropriate non-solvent. The method can be followed by removal of any formed salt, if present, by dialysis or diafiltration and concentration of the dispersion by conventional means.

[0131] 3. Homogenization to Obtain Nanoparticulate Imatinib Mesylate Compositions

[0132] Exemplary homogenization methods of preparing active agent nanoparticulate compositions are described in U.S. Pat. No. 5,510,118, for "Process of Preparing Therapeutic Compositions Containing Nanoparticles." Such a method comprises dispersing particles of an imatinib mesylate, or a salt or derivative thereof, in a liquid dispersion medium, followed by subjecting the dispersion to homogenization to reduce the particle size of an imatinib mesylate to the desired effective average particle size. The imatinib mesylate particles can be reduced in size in the presence of at least one surface stabilizer. Alternatively, the imatinib mesylate particles can be contacted with one or more surface stabilizers either before or after attrition. Other compounds, such as a diluent, can be added to the imatinib mesylate/surface stabilizer composition either before, during, or after the size reduction process. Dispersions can be manufactured continuously or in a batch mode.

[0133] 4. Cryogenic Methodologies to Obtain Nanoparticulate Imatinib Mesylate Compositions

[0134] Another method of forming the desired nanoparticulate imatinib mesylate, or a salt or derivative thereof, composition is by spray freezing into liquid (SFL). This technology comprises use of an organic or organoaqueous solution of imatinib mesylate with stabilizers, which is injected into a cryogenic liquid, such as liquid nitrogen. The droplets of the imatinib mesylate solution freeze at a rate sufficient to minimize crystallization and particle growth, thus forming nanostructured imatinib mesylate particles. Depending upon the choice of solvent system and processing conditions, the nanoparticulate imatinib mesylate particles can have varying particle morphology. In the isolation step, the nitrogen and solvent are removed under conditions that avoid agglomeration or ripening of the imatinib mesylate particles.

[0135] As a complementary technology to SFL, ultra rapid freezing (URF) may also be used to create equivalent nanostructured imatinib mesylate particles with greatly enhanced surface area. URF comprises an organic or organoaqueous solution of imatinib mesylate with stabilizers onto a cryogenic substrate.

[0136] 5. Emulsion Methodologies to Obtain Nanoparticulate Imatinib Mesylate Compositions

[0137] Another method of forming the desired nanoparticulate imatinib mesylate, or a salt or derivative thereof, composition is by template emulsion. Template emulsion creates nanostructured imatinib mesylate particles with controlled particle size distribution and rapid dissolution performance. The method comprises an oil-in-water emulsion that is prepared, then swelled with a non-aqueous solution comprising the imatinib mesylate and stabilizers. The particle size distribution of the imatinib mesylate particles is a direct result of the size of the emulsion droplets prior to loading with the imatinib mesylate a property which can be controlled and optimized in this process. Furthermore, through selected use of solvents and stabilizers, emulsion stability is achieved with no or suppressed Ostwald ripening. Subsequently, the solvent and water are removed, and the stabilized nanostructured imatinib mesylate particles are recovered. Various imatinib mesylate particles morphologies can be achieved by appropriate control of processing conditions.

[0138] Published International Patent Application No. WO 97/144407 to Pace et al., published Apr. 24, 1997, discloses particles of water insoluble biologically active compounds with an average size of 100 nm to 300 nm that are prepared by dissolving the compound in a solution and then spraying the solution into compressed gas, liquid or supercritical fluid in the presence of appropriate surface modifiers.

D. Methods of Using the Nanoparticulate Imatinib Mesylate Compositions of the Invention

[0139] The invention provides a method of increasing the plasma levels of an imatinib mesylate, or a salt or derivative thereof, in a subject. Such a method comprises administering to a subject an effective amount of a composition according to the invention comprising nanoparticulate imatinib mesylate compositions.

[0140] In one embodiment of the invention, the imatinib mesylate composition, in accordance with standard pharma-

cokinetic practice, preferably produces a maximum blood plasma concentration profile in less than about 6 hours, less than about 5 hours, less than about 4 hours, less than about 3 hours, less than about 2 hours, less than about 1 hour, or less than about 30 minutes after the initial dose of the composition.

[0141] The compositions of the invention are useful in the treatment of chronic myeloid leukemia, gastrointestinal stromal tumors and related diseases. The imatinib mesylate, or a salt or derivative thereof, compounds of the invention can be administered to a subject via any conventional means including, but not limited to, orally, rectally, optically, ocularly, parenterally (e.g., intravenous, intramuscular, or subcutaneous), intracisternally, pulmonary, intravaginally, intraperitoneally, locally (e.g., powders, ointments or drops), or as a buccal or nasal spray. As used herein, the term "subject" is used to mean an animal, preferably a mammal, including a human or non-human. The terms patient and subject may be used interchangeably.

[0142] Compositions suitable for parenteral injection may comprise physiologically acceptable sterile aqueous or non-aqueous solutions, dispersions, suspensions or emulsions, and sterile powders for reconstitution into sterile injectable solutions or dispersions. Examples of suitable aqueous and nonaqueous carriers, diluents, solvents, or vehicles including water, ethanol, polyols (propyleneglycol, polyethyleneglycol, glycerol, and the like), suitable mixtures thereof, vegetable oils (such as olive oil) and injectable organic esters such as ethyl oleate. Proper fluidity can be maintained, for example, by the use of a coating such as lecithin, by the maintenance of the required particle size in the case of dispersions, and by the use of surfactants.

[0143] The nanoparticulate imatinib mesylate, or a salt or derivative thereof, compositions may also comprise adjuvants such as preserving, wetting, emulsifying, and dispensing agents. Prevention of the growth of microorganisms can be ensured by various antibacterial and antifungal agents, such as parabens, chlorobutanol, phenol, sorbic acid, and the like. It may also be desirable to include isotonic agents, such as sugars, sodium chloride, and the like. Prolonged absorption of the injectable pharmaceutical form can be brought about by the use of agents delaying absorption, such as aluminum monostearate and gelatin.

[0144] Solid dosage forms for oral administration include, but are not limited to, capsules, tablets, pills, powders, and granules. In such solid dosage forms, the active agent is admixed with at least one of the following: (a) one or more inert excipients (or carriers), such as sodium citrate or dicalcium phosphate; (b) fillers or extenders, such as starches, lactose, sucrose, glucose, mannitol, and silicic acid; (c) binders, such as carboxymethylcellulose, alginates, gelatin, polyvinylpyrrolidone, sucrose, and acacia; (d) humectants, such as glycerol; (e) disintegrating agents, such as agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, certain complex silicates, and sodium carbonate; (f) solution retarders, such as paraffin; (g) absorption accelerators, such as quaternary ammonium compounds; (h) wetting agents, such as cetyl alcohol and glycerol monostearate; (i) adsorbents, such as kaolin and bentonite; and (j) lubricants, such as talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, or mixtures thereof. For capsules, tablets, and pills, the dosage forms may also comprise buffering agents.

[0145] Liquid dosage forms for oral administration include pharmaceutically acceptable emulsions, solutions, suspensions, syrups, and elixirs. In addition to an imatinib mesylate, the liquid dosage forms may comprise inert diluents commonly used in the art, such as water or other solvents, solubilizing agents, and emulsifiers. Exemplary emulsifiers are ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propyleneglycol, 1,3-butyleneglycol, dimethylformamide, oils, such as cottonseed oil, groundnut oil, corn germ oil, olive oil, castor oil, and sesame oil, glycerol, tetrahydrofurfuryl alcohol, polyethyleneglycols, fatty acid esters of sorbitan, or mixtures of these substances, and the like.

[0146] Besides such inert diluents, the composition can also include adjuvants, such as wetting agents, emulsifying and suspending agents, sweetening, flavoring, and perfuming agents.

[0147] 'Therapeutically effective amount' as used herein with respect to an imatinib mesylate, dosage shall mean that dosage that provides the specific pharmacological response for which an imatinib mesylate is administered in a significant number of subjects in need of such treatment. It is emphasized that 'therapeutically effective amount,' administered to a particular subject in a particular instance will not always be effective in treating the diseases described herein, even though such dosage is deemed a 'therapeutically effective amount' by those skilled in the art. It is to be further understood that imatinib mesylate dosages are, in particular instances, measured as oral dosages, or with reference to drug levels as measured in blood.

[0148] One of ordinary skill will appreciate that effective amounts of an imatinib mesylate can be determined empirically and can be employed in pure form or, where such forms exist, in pharmaceutically acceptable salt, ester, or prodrug form. Actual dosage levels of an imatinib mesylate in the nanoparticulate compositions of the invention may be varied to obtain an amount of an imatinib mesylate that is effective to obtain a desired therapeutic response for a particular composition and method of administration. The selected dosage level therefore depends upon the desired therapeutic effect, the route of administration, the potency of the administered imatinib mesylate, the desired duration of treatment, and other factors.

[0149] Dosage unit compositions may contain such amounts of such submultiples thereof as may be used to make up the daily dose. It will be understood, however, that the specific dose level for any particular patient will depend upon a variety of factors: the type and degree of the cellular or physiological response to be achieved; activity of the specific agent or composition employed; the specific agents or composition employed; the age, body weight, general health, sex, and diet of the patient; the time of administration, route of administration, and rate of excretion of the agent; the duration of the treatment; drugs used in combination or coincidental with the specific agent; and like factors well known in the medical arts.

[0150] The following prophetic example is given to illustrate the present invention. It should be understood, however, that the spirit and scope of the invention is not to be limited to the specific conditions or details described in this example but should only be limited by the scope of the claims that follow. All references identified herein, including U.S. patents, are hereby expressly incorporated by reference

EXAMPLE 1

[0151] The purpose of this example was to prepare a composition comprising a nanoparticulate imatinib mesylate or a salt or derivative thereof.

[0152] An aqueous dispersion of 5% (w/w) imatinib mesylate, combined with one or more surface stabilizers, such as hydroxypropyl cellulose (HPC-SL) and dioctylsulfosuccinate (DOSS), could be milled in a 10 ml chamber of a NanoMill® 0.01 (NanoMill Systems, King of Prussia, Pa.; see e.g., U.S. Pat. No. 6,431,478), along with 500 micron PolyMill® attrition media (Dow Chemical Co.) (e.g., at an 89% media load). In an exemplary process, the mixture could be milled at a speed of 2500 rpms for 60 minutes.

[0153] Following milling, the particle size of the milled imatinib mesylate particles can be measured, in deionized distilled water, using a Horiaba LA 910 particle size analyzer. For a successful composition, the initial mean and/or D50 milled imatinib mesylate particle size is expected to be less than 2000 nm.

[0154] It will be apparent to those skilled in the art that various modifications and variations can be made in the methods and compositions of the present invention without departing from the spirit or scope of the invention. Thus, it is intended that the present invention cover the modifications and variations of this invention provided they come within the scope of the appended claims and their equivalents.

1. A stable nanoparticulate composition of imatinib mesylate, or a salt or derivative thereof, comprising:

(a) particles of imatinib mesylate, or a salt or derivative thereof, having an effective average particle size of less than about 2000 nm; and

(b) at least one surface stabilizer.

2. The composition of claim 1, wherein the imatinib mesylate particles are selected from the group consisting of a crystalline phase, an amorphous phase, a semi-crystalline phase, a semi amorphous phase, and mixtures thereof.

3. The composition of claim 1, wherein the effective average particle size of the imatinib mesylate particles is selected from the group consisting of less than about 1900 nm, less than about 1800 nm, less than about 1700 nm, less than about 1600 nm, less than about 1500 nm, less than about 1400 nm, less than about 1300 nm, less than about 1200 nm, less than about 1100 nm, less than about 1000 nm, less than about 900 nm, less than about 800 nm, less than about 700 nm, less than about 600 nm, less than about 500 nm, less than about 400 nm, less than about 300 nm, less than about 250 nm, less than about 200 nm, less than about 100 nm, less than about 75 nm, and less than about 50 nm.

4. The composition of claim 1, wherein the composition is formulated:

(a) for administration selected from the group consisting of oral, pulmonary, rectal, colonic, parenteral, intracasternal, intravaginal, intraperitoneal, ocular, optic, local, buccal, nasal, and topical administration;

(b) into a dosage form selected from the group consisting of liquid dispersions, gels, aerosols, ointments, creams, lyophilized formulations, tablets, and capsules;

(c) into a dosage form selected from the group consisting of controlled release formulations, fast melt formula-

tions, delayed release formulations, extended release formulations, pulsatile release formulations, and mixed immediate release and controlled release formulations; or

(d) any combination of (a), (b), and (c).

5. The composition of claim 4, further comprising one or more pharmaceutically acceptable excipients, carriers, or a combination thereof.

6. The composition of claim 1, wherein:

(a) imatinib mesylate, or a salt or derivative thereof is present in an amount selected from the group consisting of from about 99.5% to about 0.001%, from about 95% to about 0.1%, and from about 90% to about 0.5%, by weight, based on the total combined dry weight of imatinib mesylate, or a salt or derivative thereof and at least one surface stabilizer, not including other excipients;

(b) the surface stabilizer is present in an amount selected from the group consisting of about 0.5% to about 99.999% by weight, from about 5.0% to about 99.9% by weight, and from about 10% to about 99.5% by weight, based on the total combined dry weight of imatinib mesylate, salt, or derivative thereof and at least one surface stabilizer, not including other excipients; or

(c) a combination thereof.

7. The composition of claim 1, further comprising at least one primary surface stabilizer and at least one secondary surface stabilizer.

8. The composition of claim 1, wherein the surface stabilizer is selected from the group consisting of an anionic surface stabilizer, a cationic surface stabilizer, a non-ionic surface stabilizer, a zwitterionic surface stabilizer, and an ionic surface stabilizer.

9. The composition of claim 1, wherein the surface stabilizer is selected from the group consisting of cetyl pyridinium chloride, gelatin, casein, phosphatides, dextran, glycerol, gum acacia, cholesterol, tragacanth, stearic acid, benzalkonium chloride, calcium stearate, glycerol monostearate, cetostearyl alcohol, cetomacrogol emulsifying wax, sorbitan esters, polyoxyethylene alkyl ethers, polyoxyethylene castor oil derivatives, polyoxyethylene sorbitan fatty acid esters, polyethylene glycols, dodecyl trimethyl ammonium bromide, polyoxyethylene stearates, colloidal silicon dioxide, phosphates, sodium dodecylsulfate, carboxymethylcellulose calcium, hydroxypropyl celluloses, hypromellose, carboxymethylcellulose sodium, methylcellulose, hydroxyethylcellulose, hypromellose phthalate, non-crystalline cellulose, magnesium aluminum silicate, triethanolamine, polyvinyl alcohol, polyvinylpyrrolidone, 4-(1,1,3,3-tetramethylbutyl)-phenol polymer with ethylene oxide and formaldehyde, poloxamers; poloxamines, a charged phospholipid, dioctylsulfosuccinate, dialkylesters of sodium sulfosuccinic acid, sodium lauryl sulfate, alkyl aryl polyether sulfonates, mixtures of sucrose stearate and sucrose distearate, p-isononylphenoxypoly-(glycidol), decanoyl-N-methylglucamide; n-decyl β -D-glucopyranoside; n-decyl β -D-maltopyranoside; n-dodecyl β -D-glucopyranoside; n-dodecyl β -D-maltoside; heptanoyl-N-methylglucamide; n-heptyl- β -D-glucopyranoside; n-heptyl β -D-thiogluconide; n-hexyl β -D-glucopyranoside; nonanoyl-N-methylglucamide; n-nonyl β -D-glucopyranoside; octanoyl-N-methylgluca-

amide; n-octyl- β -D-glucopyranoside; octyl β -D-thioglucopyranoside; lysozyme, PEG-phospholipid, PEG-cholesterol, PEG-cholesterol derivative, PEG-vitamin A, PEG-vitamin E, random copolymers of vinyl acetate and vinyl pyrrolidone, a cationic polymer, a cationic biopolymer, a cationic polysaccharide, a cationic cellulosic, a cationic alginate, a cationic nonpolymeric compound, a cationic phospholipids, cationic lipids, polymethylmethacrylate trimethylammonium bromide, sulfonium compounds, polyvinylpyrrolidone-2-dimethylaminoethyl methacrylate dimethyl sulfate, hexadecyltrimethyl ammonium bromide, phosphonium compounds, quaternary ammonium compounds, benzyl-di(2-chloroethyl)ethylammonium bromide, coconut trimethyl ammonium chloride, coconut trimethyl ammonium bromide, coconut methyl dihydroxyethyl ammonium chloride, coconut methyl dihydroxyethyl ammonium bromide, decyl triethyl ammonium chloride, decyl dimethyl hydroxyethyl ammonium chloride, decyl dimethyl hydroxyethyl ammonium chloride bromide, C_{12-15} dimethyl hydroxyethyl ammonium chloride, C_{12-15} dimethyl hydroxyethyl ammonium chloride bromide, coconut dimethyl hydroxyethyl ammonium chloride, coconut dimethyl hydroxyethyl ammonium bromide, myristyl trimethyl ammonium methyl sulphate, lauryl dimethyl benzyl ammonium chloride, lauryl dimethyl benzyl ammonium bromide, lauryl dimethyl (ethenoxy)₄ ammonium chloride, lauryl dimethyl (ethenoxy)₄ ammonium bromide, N-alkyl (C_{12-18}) dimethylbenzyl ammonium chloride, N-alkyl (C_{12-14}) dimethylbenzyl ammonium chloride, N-tetradecylidmethylbenzyl ammonium chloride monohydrate, dimethyl didecyl ammonium chloride, N-alkyl and (C_{12-14}) dimethyl 1-naphthylmethyl ammonium chloride, trimethylammonium halide, alkyl-trimethylammonium salts, dialkyl-dimethylammonium salts, lauryl trimethyl ammonium chloride, ethoxylated alkyamidoalkyldialkylammonium salt, an ethoxylated trialkyl ammonium salt, dialkylbenzene dialkylammonium chloride, N-didecylidmethyl ammonium chloride, N-tetradecylidmethylbenzyl ammonium, chloride monohydrate, N-alkyl(C_{12-14}) dimethyl 1-naphthylmethyl ammonium chloride, dodecylidmethylbenzyl ammonium chloride, dialkyl benzenealkyl ammonium chloride, lauryl trimethyl ammonium chloride, alkylbenzyl methyl ammonium chloride, alkyl benzyl dimethyl ammonium bromide, C_{12} trimethyl ammonium bromides, C_{15} trimethyl ammonium bromides, C_{17} trimethyl ammonium bromides, dodecylbenzyl triethyl ammonium chloride, poly-diallyldimethylammonium chloride, dimethyl ammonium chlorides, alkyl dimethylammonium halogenides, tricetyl methyl ammonium chloride, decyltrimethylammonium bromide, dodecyltriethylammonium bromide, tetradecyltrimethylammonium bromide, methyl trioctylammonium chloride, tetrabutylammonium bromide, benzyl trimethylammonium bromide, choline esters, benzalkonium chloride, stearylalkonium chloride compounds, cetyl pyridinium bromide, cetyl pyridinium chloride, halide salts of quaternized polyoxyethylalkylamines, alkyl pyridinium salts; amines, amine salts, amine oxides, imide azolinium salts, protonated quaternary acrylamides, methylated quaternary polymers, and cationic guar.

10. The composition of claim 1, wherein the composition is bioadhesive.

11. The composition of claim 1, wherein the composition does not produce significantly different absorption levels when administered under fed as compared to fasting conditions.

12. The composition of claim 1, wherein administration of the composition to a subject in a fasted state is bioequivalent to administration of the composition to a subject in a fed state.

13. A composition comprising imatinib mesylate, or a salt or a derivative thereof, wherein upon administration to a human the composition does not produce significantly different absorption levels when administered under fed as compared to fasting conditions.

14. The composition of claim 13, wherein administration of the composition to a subject in a fasted state is bioequivalent to administration of the composition to a subject in a fed state.

15. A stable nanoparticulate composition of imatinib mesylate, or a salt or derivative thereof, comprising:

(a) particles of imatinib mesylate, or a salt or derivative thereof, having an effective average particle size of less than about 2000 nm; and

(b) at least one surface stabilizer,

wherein upon administration to a mammal the composition produces therapeutic results at a dosage which is less than that of a non-nanoparticulate dosage form of the same imatinib mesylate, or salt or derivative thereof.

16. A composition of imatinib mesylate, or a salt or derivative thereof, comprising imatinib mesylate or a salt or derivative thereof wherein the composition has:

(a) a C_{max} for imatinib mesylate, or a salt or derivative thereof, when assayed in the plasma of a mammalian subject following administration that is greater than the C_{max} for a non-nanoparticulate formulation of the same imatinib mesylate, or a salt or derivative thereof, administered at the same dosage;

(b) an AUC for imatinib mesylate, or a salt or derivative thereof, when assayed in the plasma of a mammalian subject following administration that is greater than the AUC for a non-nanoparticulate formulation of the same imatinib mesylate, or a salt or derivative thereof, administered at the same dosage;

(c) a T_{max} for imatinib mesylate, or a salt or derivative thereof, when assayed in the plasma of a mammalian subject following administration that is less than the T_{max} for a non-nanoparticulate formulation of the same imatinib mesylate, or a salt or derivative thereof, administered at the same dosage; or

(d) any combination of (a), (b), and (c).

17. The composition of claim 1, additionally comprising one or more active agents useful for the treatment of chronic myeloid leukemia, gastrointestinal stromal tumors and related diseases.

18. The composition of claim 17, wherein the active agent is selected from a group consisting of mitotic inhibitors, alkylating agents, anti-metabolites, intercalating antibiotics, growth factor inhibitors, cell cycle inhibitors, enzymes, topoisomerase inhibitors, biological response modifiers, anti-hormones, and anti-androgens.

19. A method for preparing imatinib mesylate, or a salt or derivative thereof, comprising contacting particles of imatinib mesylate, or a salt or derivative thereof with at least one surface stabilizer for a time and under conditions sufficient

to provide a nanoparticulate imatinib mesylate composition having an effective average particle size of less than about 2000 nm.

20. The method of claim 19, wherein the contacting comprises grinding, wet grinding, homogenization, freezing, template emulsion, precipitation, or a combination thereof.

21. A method for treating of chronic myeloid leukemia, gastrointestinal stromal tumors and related diseases comprising administering a stable nanoparticulate composition of imatinib mesylate, or a salt or derivative thereof, comprising:

- (a) particles of imatinib mesylate, or a salt or derivative thereof, having an effective average particle size of less than about 2000 nm; and
- (b) at least one surface stabilizer.

22. The method of claim 21, wherein the effective average particle size of the particles of imatinib mesylate, or a salt or derivative thereof, is selected from the group consisting of less than about 1900 nm, less than about 1800 nm, less than about 1700 nm, less than about 1600 nm, less than about 1500 nm, less than about 1000 nm, less than about 1400 nm, less than about 1300 nm, less than about 1200 nm, less than about 1100 nm, less than about 900 nm, less than about 800 nm, less than about 700 nm, less than about 600 nm, less than about 500 nm, less than about 400 nm, less than about 300 nm, less than about 250 nm, less than about 200 nm, less than about 100 nm, less than about 75 nm, and less than about 50 nm.

* * * * *

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
16 November 2006 (16.11.2006)

PCT

(10) International Publication Number
WO 2006/121941 A2

- (51) International Patent Classification:
A61K 9/20 (2006.01) A61K 31/506 (2006.01)
A61K 9/16 (2006.01)

(21) International Application Number:
PCT/US2006/017558

(22) International Filing Date: 8 May 2006 (08.05.2006)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/679,607 10 May 2005 (10.05.2005) US

(71) Applicant (for all designated States except US): NOVAR-TIS AG [CH/CH]; Lichtstrasse 35, CH-4056 Basel (CH).

(71) Applicant (for AT only): NOVARTIS PHARMA GMBH [AT/AT]; Brunner Strasse 59, A-1230 Vienna (AT).

(72) Inventors; and

(75) Inventors/Applicants (for US only): VASANTHAVADA, Madhav [IN/US]; 15 Minuteman Court, Basking Ridge, New Jersey 07920 (US). LAKSHMAN, Jay Parthiban [US/US]; 215 Vista Drive, Cedar Knolls, New Jersey 07927 (US). TONG, Wei-Qin [US/US]; 1 Wellington Drive, Basking Ridge, New Jersey 07920 (US). SER-AJUDDIN, Abu T.M. [US/US]; 172-11 35 Avenue, Flushing, New York 11358 (US).

(74) Agent: JACKSON, Oona; NOVARTIS, Corporate Intellectual Property, One Health Plaza, Building 104, East Hanover, New Jersey 07936 (US).
- (81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declaration under Rule 4.17:
— as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))

Published:
— without international search report and to be republished upon receipt of that report

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: PHARMACEUTICAL COMPOSITIONS COMPRISING IMATINIB AND A RELEASE RETARDANT

(57) Abstract: Sustained release pharmaceutical compositions that contain imatinib or a pharmaceutically acceptable salt thereof. The pharmaceutical compositions further contain a release retardant, for example a water soluble, a water swellable and/or a water insoluble polymer. The present invention also features a particularly useful process of making such sustained release pharmaceutical compositions by using an extruder.



WO 2006/121941 A2

**PHARMACEUTICAL COMPOSITIONS COMPRISING IMATINIB AND A RELEASE
RETARDANT**

Field of the Invention

The present invention relates to sustained release pharmaceutical compositions comprising a therapeutic compound, such as imatinib, and a release retardant. The present invention also relates to processes for making such sustained release pharmaceutical compositions.

Background of the Invention

The therapeutic compound 4-[(4-methyl-1-piperazinyl)methyl]-N-[4-methyl-3-[(4-(3-pyridinyl)-2-pyrimidinyl)amino]phenyl]-benzamide, or more commonly known as imatinib, and its preparation are described in U.S. Patent No. 5,521,184.

Basic pharmaceutically active therapeutic compounds are commonly formulated into pharmaceutical preparations as an acid addition salt form, particularly as a crystalline acid addition salt. For example, imatinib is marketed in many countries as its monomethanesulfonate salt (imatinib mesylate) under the brandname GLIVEC or GLEEVEC. Two crystal forms of imatinib mesylate are described in WO 99/03854. The crystal form designated as the beta form is described as having physical properties that make it advantageous for the manufacture of solid oral pharmaceutical dosage forms, such as tablet and capsule dosage forms.

The currently marketed formulations of imatinib mesylate are 100 mg hard gelatin capsules and 100 mg and 400 mg film coated tablets. There is a need for an extended release tablet comprising imatinib, for example, to reduce peak plasma concentration and to maintain therapeutic plasma levels for a prolonged period of time.

It is an object of the present invention to provide for a sustained release formulation for imatinib. It is a further object of the present invention to provide for a sustained release formulation manufactured by using a melt granulation process. It is yet another object of the present invention to provide for the use of an extruder to implement the melt granulation process. Traditionally, extruders in a pharmaceutical context have been used for the

manufacture of solid dispersion and/or solid solutions that have required at least a partial melting of the therapeutic compound. Surprisingly, it has been found that the use of extruders can be useful in the preparation of melt granulated solid dosage forms without the need for melting any of the therapeutic compound.

Summary of the Invention

The present invention relates to modified release pharmaceutical compositions that contain a therapeutic compound, e.g., imatinib or a pharmaceutically acceptable salt thereof and a release retardant. The amount of the therapeutic compound in the pharmaceutical composition can be at least 50% by weight of the composition. The balance of the pharmaceutical composition can be made up of at least one release retardant. In a particular aspect of the present invention the release retardant is a water-soluble, water swellable and/or water insoluble polymer. Particularly useful as such polymers are ethylcellulose, hydroxypropyl cellulose and/or hydroxypropyl methyl cellulose. In yet another aspect the release retardant can be a non-polymeric release retardant. In a particular aspect, the non-polymeric release retardant is hydrogenated castor oil. The aforementioned compositions can be milled or granulated and compressed into monolithic tablets or encapsulated into capsules.

In another exemplary embodiment of the present invention, the invention features a method for making sustained release pharmaceutical compositions of imatinib or a pharmaceutically acceptable salt thereof. In a particular aspect, the therapeutic compound is melt granulated with a release retardant using an extruder. During the processing in the extruder, the heating temperature of the extruder does not exceed the melting temperature of the therapeutic compound. The result extrudate can be optionally milled and compressed into solid oral dosage forms.

Brief Description of the Drawings

The accompanying drawings, which are incorporated in and constituting a part of the specification, illustrates exemplary embodiments of the present invention.

FIG. 1 shows a chart depicting the dissolution profiles for exemplary embodiments in accordance with the present invention as disclosed in Examples 1, 2 and 3.



FIG. 2 shows a chart depicting the dissolution profiles for present invention as disclosed in Examples 4, 5, 6 and 7.

Detailed Description of the Invention

The present invention relates to sustained release solid dosage forms of a therapeutic compound which comprises granules of the therapeutic compound with a release retardant and to a process for preparing such dosage forms. The sustained release solid dosage forms may optionally further comprise plasticizers, release modifier, disintegrants, and/or lubricants.

As used herein the term "pharmaceutical composition" means a mixture (e.g., a solid dispersion) and/ or solution (e.g., a solid solution) containing a therapeutic compound to be administered to a mammal, e.g., a human in order to prevent, treat or control a particular disease or condition affecting the mammal. The term "pharmaceutical composition" as used herein, for example, also encompasses an intimate physical mixture formed at high temperature and pressure.

As used herein the term "pharmaceutically acceptable" refers to those compounds, materials, compositions and/or dosage forms, which are, within the scope of sound medical judgment, suitable for contact with the tissues of mammals, especially humans, without excessive toxicity, irritation, allergic response and other problem complications commensurate with a reasonable benefit/risk ratio.

As used herein the term "therapeutic compound" means any compound, substance, drug, medicament, or active ingredient having a therapeutic or pharmacological effect, and which is suitable for administration to a mammal, e.g., a human, in a composition that is particularly suitable for oral administration. Particularly useful as a therapeutic compound in the present invention is imatinib and pharmaceutically acceptable salts thereof.

As used herein the term "imatinib" refers to the free base of imatinib or a pharmaceutically acceptable salt thereof (e.g., imatinib mesylate).

Pharmaceutically acceptable salts of imatinib include, but are not limited to, pharmaceutically acceptable acid addition salts. Examples include inorganic acids, such as hydrochloric acid, sulfuric acid or a phosphoric acid, or with suitable organic carboxylic or sulfonic acids, for example aliphatic mono- or di-carboxylic acids, such as trifluoroacetic

acid, acetic acid, propionic acid, glycolic acid, succinic acid, maleic acid, fumaric acid, hydroxymaleic acid, malic acid, tartaric acid, citric acid or oxalic acid, or amino acids such as arginine or lysine, aromatic carboxylic acids, such as benzoic acid, 2-phenoxy-benzoic acid, 2-acetoxy-benzoic acid, salicylic acid, 4-aminosalicylic acid, aromatic-aliphatic carboxylic acids, such as mandelic acid or cinnamic acid, heteroaromatic carboxylic acids, such as nicotinic acid or isonicotinic acid, aliphatic sulfonic acids, such as methane-, ethane- or 2-hydroxyethane-sulfonic acid, or aromatic sulfonic acids, for example benzene-, p-toluene- or naphthalene-2-sulfonic acid. Other examples of acid addition salts include tartrate salt, such as a (*D*)(-) tartrate salt or a (*L*)(+) tartrate salt, a hydrochloride salt, a citrate salt, a malate salt, particularly a *D*-malate salt, a fumarate salt, a succinate salt, a benzoate salt, a benzenesulfonate salt, a pamoate salt, a formate salt, a malonate salt, a 1,5-naphthalenedisulfonate salt, a salicylate salt, a cyclohexanesulfamate salt, a lactate salt, particularly a (*S*)-lactate salt, a mandelate salt, particularly an (*R*)(-) mandelate salt, a glutarate salt, an adipate salt, a squarate salt, a vanillate salt, an oxaloacetate salt, an ascorbate salt, particularly an (*L*)-ascorbate salt and a sulfate salt.

In one exemplary embodiment, the acid addition salt is selected from the group consisting of imatinib ascorbate, imatinib formate, imatinib malonate, imatinib oxaloacetate, imatinib squarate and imatinib vanillate.

The monomethanesulfonic acid addition salt of imatinib and an exemplary crystal form thereof, e.g. the beta-crystal form, are described in PCT patent application WO99/03854 published on January 28, 1999. Imatinib mesylate has an aqueous solubility of >1,300 mg/mL at pH of less than 5.5.

The therapeutic compound(s) is present in the pharmaceutical compositions of the present invention in a therapeutically effective amount or concentration. Such a therapeutically effective amount or concentration is known to one of ordinary skill in the art as the amount or concentration varies with the therapeutic compound being used and the indication which is being addressed. For example, in accordance with the present invention, the therapeutic compound especially imatinib, may be present in an amount of about 50% to about 99% by weight of pharmaceutical composition. In one embodiment, the therapeutic compound, especially imatinib, may be present in an amount by weight of about 62% to about 99% by weight of the pharmaceutical composition. In one embodiment, the therapeutic compound, especially imatinib, may be present in an amount by weight of about 75% to about 99% by weight of the pharmaceutical composition.

As used herein, the term "immediate release" refers to the rapid release of the majority of the therapeutic compound, e.g., greater than about 50%, about 60%, about 70%, about 80%, or about 90% within a relatively short time, e.g., within 1 hour, 40 minutes, 30 minutes or 20 minutes after oral ingestion. Particularly useful conditions for immediate release are release of at least or equal to about 80% of the therapeutic compound within thirty minutes after oral ingestion. The particular immediate release conditions for a specific therapeutic compound will be recognized or known by one of ordinary skill in the art.

As used herein, the term "sustained release", or modified release, refers to the gradual but continuous or sustained release over a relatively extended period of the therapeutic compound content after oral ingestion. The release will continue over a period of time and may continue through until and after the pharmaceutical composition reaches the intestine. Sustained release may also refer to delayed release in which release of the therapeutic compound does not start immediately when the pharmaceutical composition reaches the stomach but is delayed for a period of time, for instance, until when the pharmaceutical composition reaches the intestine when the increasing pH is used to trigger release of the therapeutic compound from the pharmaceutical composition.

As used herein the term "release retardant" refers to any material or substance that slows the release of a therapeutic compound from a pharmaceutical composition when orally ingested. Various sustained release systems, as known in the art, can be accomplished by the use of a release retardant, e.g., a diffusion system, a dissolution system and/or an osmotic system. A release retardant can be a polymer or non-polymer.

As used herein the term "polymer" refers to a polymer or mixture of polymers that has a glass transition temperature, softening temperature or melting temperature less than 212°C. The glass transition temperature is the temperature at which such polymer's characteristics change from that of highly viscous to that of relatively less viscous mass. Types of polymers include, but are not limited to, water-soluble, water-swellaable, water insoluble polymers and combinations of the foregoing.

Examples of polymers include, but are not limited to:

homopolymers and copolymers of N-vinyl lactams, e.g., homopolymers and copolymers of N-vinyl pyrrolidone (e.g., polyvinylpyrrolidone), copolymers of N-vinyl pyrrolidone and vinyl acetate or vinyl propionate;

cellulose esters and cellulose ethers (e.g., methylcellulose and ethylcellulose) hydroxyalkylcelluloses (e.g., hydroxypropylcellulose), hydroxyalkylalkylcelluloses (e.g., hydroxypropylmethylcellulose), cellulose phthalates (e.g., cellulose acetate phthalate and hydroxypropylmethylcellulose phthalate) and cellulose succinates (e.g., hydroxypropylmethylcellulose succinate or hydroxypropylmethylcellulose acetate succinate);

high molecular polyalkylene oxides such as polyethylene oxide and polypropylene oxide and copolymers of ethylene oxide and propylene oxide;

polyacrylates and polymethacrylates (e.g., methacrylic acid/ethyl acrylate copolymers, methacrylic acid/methyl methacrylate copolymers, butyl methacrylate/2-dimethylaminoethyl methacrylate copolymers, poly(hydroxyalkyl acrylates), poly(hydroxyalkyl methacrylates));

polyacrylamides;

vinyl acetate polymers such as copolymers of vinyl acetate and crotonic acid, partially hydrolyzed polyvinyl acetate;

polyvinyl alcohol; and

oligo- and polysaccharides such as carrageenans, galactomannans and xanthan gum, or mixtures of one or more thereof.

As used herein, the term "plasticizer" refers to a material that may be incorporated into the pharmaceutical composition, especially the internal phase, in order to decrease the glass transition temperature and the melt viscosity of a polymer by increasing the free volume between polymer chains. Plasticizers, for example, include, but are not limited to, water; citrate esters (e.g., triethylcitrate, triacetin); low molecular weight poly(alkylene oxides) (e.g., poly(ethylene glycols), poly(propylene glycols), poly(ethylene/propylene glycols)); glycerol, pentaerythritol, glycerol monoacetate, diacetate or triacetate; propylene glycol; sodium diethyl sulfosuccinate; and the therapeutic compound itself. The plasticizer can be present in concentration from about 0% to 15%, e.g., 0.5% to 5% by weight of the pharmaceutical composition. Examples of plasticizers can also be found in *The Handbook of Pharmaceutical Additives*, Ash et al., Gower Publishing (2000).

As used herein the term "non-polymeric release retardant" refers to substances or a mixtures of substances, non-polymeric in nature, that are solid or semi-solid at room

temperature (about 25°C) and with melting points (or melting ranges) less than or approximately equal to the melting range of imatinib or a pharmaceutically acceptable salt thereof.

Particularly useful as non-polymeric release retardants are hydrophobic non-polymeric release retardants. As used herein, the term "hydrophobic", with respect to the release retardant, refers to being more compatible with oil than with water. A substance with hydrophobic properties is insoluble or almost insoluble in water but is easily soluble in oil or other nonpolar solvents.

Examples of hydrophobic non-polymeric release retardants include, but are not limited to, esters, hydrogenated oils, natural waxes, synthetic waxes, hydrocarbons, fatty alcohols, fatty acids, monoglycerides, diglycerides, triglycerides and mixtures thereof.

Examples of esters, such as glyceryl esters include, but are not limited to, glyceryl monostearate, e.g., CAPMUL GMS from Abitec Corp. (Columbus, OH); glyceryl palmitostearate; acetylated glycerol monostearate; sorbitan monostearate, e.g., ARLACEL 60 from Uniqema (New Castle, DE); and cetyl palmitate, e.g., CUTINA CP from Cognis Corp. (Düsseldorf, Germany), magnesium stearate and calcium stearate.

Examples of hydrogenated oils include, but are not limited to, hydrogenated castor oil; hydrogenated cottonseed oil; hydrogenated soybean oil; and hydrogenated palm oil. An example of oil includes sesame oil.

Examples of waxes include, but are not limited to, carnauba wax, beeswax and spermaceti wax. Examples of hydrocarbons include, but are not limited to, microcrystalline wax and paraffin. Examples of fatty alcohols, i.e., higher molecular weight nonvolatile alcohols that have from about 14 to about 31 carbon atoms include, but are not limited to, cetyl alcohol, e.g., CRODACOL C-70 from Croda Corp. (Edison, NJ); stearyl alcohol, e.g., CRODACOL S-95 from Croda Corp; lauryl alcohol; and myristyl alcohol. Examples of fatty acids which may have from about 10 to about 22 carbon atoms include, but are not limited to, stearic acid, e.g., HYSTRENE 5016 from Crompton Corp. (Middlebury, CT); decanoic acid; palmitic acid; lauric acid; and myristic acid.

As used herein the term "release modifier" refers to substance or mixture of substances that would help to provide either enhancement or retardation in release profile as a function of pH. Release modifier could be polymeric or non-polymeric in nature, solid or

3b

semi-solid at room temperature (25°C), and with melting points less than or approximately equal to melting range of imatinib or a pharmaceutically acceptable salt thereof. A release modifier, for example, would help in enhanced drug release at higher pH conditions, where the solubility of imatinib or its salt is lower than that in acid condition.

Examples of polymeric release modifiers include, but are not limited to, water soluble polymers that exhibit charge in their dissolved state, as a function of pH. Examples are methacrylate polymers, polymers containing quaternary ammonium or acetate groups.

Particularly useful non-polymeric release modifiers include, but are not limited to, water soluble surface active agents. More specifically, the surfactants could exhibit charge in their dissolved state, as a function of pH. Examples of such surfactants are sodium lauryl sulfate, and block-co-polymers with ionizable groups.

As used herein, the term "melt granulation" refers to the following compounding process that comprises the steps of:

- (a) forming a mixture of a therapeutic compound with at least one release retardant, e.g. a release retarding polymer, and optionally, a plasticizer or a release modifier;
- (b) granulating the mixture using an extruder or other suitable equipment, for example a jacketed high shear mixer, while heating the mixture to a temperature above the softening temperature of the release retardant; as used herein, the "softening temperature" refers to the temperature at which the release retardant experiences a change in the rate of viscosity decrease as a function of temperature; and
- (c) cooling the granules to a temperature less than 50°C, for example to room temperature (25°C),.

As described in this embodiment, the term granules shall be used interchangeably with melt granules. "Melt granules" as used herein also refers to any form of solid or semi-solid mass exiting the extruder. For example, melt granules could be noodle-shaped mass, powder or aggregation of powder.

The heating and mixing of the therapeutic compound and the release retardant to form an internal phase of granules may be accomplished, e.g., by the use of a fluidized bed granulator, an extruder or a vessel supplied with high-shear mixing means. The release retardant, e.g., can be present in an amount from about 1% to about 50% by weight of the

composition. In one embodiment, the release retardant may be present in an amount from about 3 to about 25% by weight of the composition. The therapeutic compound may be present in an amount from about 50% to about 99% by weight of the composition. In one embodiment, the therapeutic compound may be present in an amount of about 60% to about 97%.

The resulting granules are, for example, particles of the therapeutic compound coated or substantially coated by the release retardant, or alternatively, particles of the therapeutic compound embedded or substantially embedded with or within the release retardant.

Particularly useful for effecting the melt granulation process is an extruder. In general, an extruder includes a rotating screw(s) within a stationary barrel with a die located at one end of the barrel. Along the entire length of the screw, distributive mixing of the materials (e.g., the therapeutic compound, release retarding material, and any other needed excipients) is provided by the rotation of the screw(s) within the barrel. Conceptually, the extruder can be divided into at least three sections: a feeding section; a heating section and a metering section. In the feeding section, the raw materials are fed into the extruder, e.g. from a hopper. The raw materials can be directly added to the hopper without the need of a solvent. In the heating section, the raw materials are heated to a temperature greater than the softening temperature of the release retarding material. After the heating section is a metering section in which the mixed materials are extruded through a die into a particular shape, e.g., granules or noodles. Types of extruders particularly useful in the present invention are single-, twin- and multi-screw extruders, optionally configured with kneading paddles.

Once the granules are obtained, the granules may be formulated into oral forms, e.g., solid oral dosage forms, such as tablets, pills, lozenges, caplets, capsules or sachets, by adding additional conventional excipients which comprise an external phase of the pharmaceutical composition. Examples of such excipients include, but are not limited to, disintegrants, plasticizers, binders, lubricants, glidants, stabilizers, fillers and diluents. One of ordinary skill in the art may select one or more of the aforementioned excipients with respect to the particular desired properties of the solid oral dosage form by routine experimentation and without any undue burden. The amount of each excipient used may vary within ranges conventional in the art. The following references which are all hereby incorporated by reference discloses techniques and excipients used to formulate oral

dosage forms. See *The Handbook of Pharmaceutical Excipients*, 4th edition, Rowe et al., Eds., American Pharmaceuticals Association (2003); and *Remington: the Science and Practice of Pharmacy*, 20th edition, Gennaro, Ed., Lippincott Williams & Wilkins (2003).

Examples of pharmaceutically acceptable disintegrants include, but are not limited to, starches; clays; celluloses; alginates; gums; cross-linked polymers, e.g., cross-linked polyvinyl pyrrolidone or crospovidone, e.g., POLYPLASDONE XL from International Specialty Products (Wayne, NJ); cross-linked sodium carboxymethylcellulose or croscarmellose sodium, e.g., AC-DI-SOL from FMC; and cross-linked calcium carboxymethylcellulose; soy polysaccharides; and guar gum. The disintegrant may be present in an amount from about 0% to about 10% by weight of the composition. In one embodiment, the disintegrant is present in an amount from about 0.1% to about 1.5% by weight of composition.

Examples of pharmaceutically acceptable binders include, but are not limited to, starches; celluloses and derivatives thereof, for example, microcrystalline cellulose, e.g., AVICEL PH from FMC (Philadelphia, PA), hydroxypropyl cellulose hydroxyethyl cellulose and hydroxylpropylmethyl cellulose METHOCEL from Dow Chemical Corp. (Midland, MI); sucrose; dextrose; corn syrup; polysaccharides; and gelatin. The binder may be present in an amount from about 0% to about 50%, e.g., 10-40% by weight of the composition.

Examples of pharmaceutically acceptable lubricants and pharmaceutically acceptable glidants include, but are not limited to, colloidal silica, magnesium trisilicate, starches, talc, tribasic calcium phosphate, magnesium stearate, aluminum stearate, calcium stearate, magnesium carbonate, magnesium oxide, polyethylene glycol, powdered cellulose and microcrystalline cellulose. The lubricant may be present in an amount from about 0% to about 10% by weight of the composition. In one embodiment, the lubricant may be present in an amount from about 0.1% to about 1.5% by weight of composition. The glidant may be present in an amount from about 0.1% to about 10% by weight.

Examples of pharmaceutically acceptable fillers and pharmaceutically acceptable diluents include, but are not limited to, confectioner's sugar, compressible sugar, dextrates, dextrin, dextrose, lactose, mannitol, microcrystalline cellulose, powdered cellulose, sorbitol, sucrose and talc. The filler and/or diluent, e.g., may be present in an amount from about 15% to about 40% by weight of the composition.

26

To make pharmaceutical compositions of the present invention, a therapeutic compound and a release retardant are blended in a ratio in a range of 99:1 to 1:1 (on a dry weight basis) prior to, or upon addition into the hopper of an extruder. Optionally, a plasticizer is added to the internal phase.

The mixture is heated to a temperature above the softening temperature, melting temperature, or glass transition temperature of the release retardant; however, the heating temperature does not exceed the melting temperature of the therapeutic compound. As the mixture is being heated, it is also being kneaded by the screw(s) of the extruder. The mixture is maintained at the elevated temperature and blended for a time sufficient to form a granulated product. After the mixture is conveyed down the entire length of the barrel, a granulated product is obtained, the granulated mixture is cooled.

After cooling, the granules may be milled and subsequently screened through a sieve. The granules (which constitute the internal phase of the pharmaceutical composition) are then combined with solid oral dosage form excipients (the external phase of the pharmaceutical composition), i.e., fillers, binders, disintegrants and lubricants. The combined mixture may be further blended, e.g., through a V-blender, and subsequently compressed or molded into a tablet, for example a monolithic tablet, or encapsulated by a capsule.

Once the tablets are obtained, they can be optionally coated with a functional or non-functional coating as known in the art. Examples of coating techniques include, but are not limited to, sugar coating, film coating, microencapsulation and compression coating. Types of coatings include, but are not limited to, enteric coatings, sustained release coatings, controlled-release coatings.

The utility of all the pharmaceutical compositions of the present invention may be observed in standard clinical tests in, for example, known indications of drug dosages giving therapeutically effective blood levels of the therapeutic compound; for example using dosages in the range of 2.5-1000 mg of therapeutic compound per day for a 75 kg mammal, e.g., adult and in standard animal models.

The pharmaceutical composition, e.g., in form of a tablet or a powder suitable for tablet formulation will suitably contain at least 400 mg of the therapeutic compound. In one embodiment, the tablet formulation will contain about 800mg of therapeutic compound.

Such unit dosage forms are suitable for administration one to two times daily depending upon the particular purpose of therapy, the phase of therapy and the like.

The present invention provides a method of treatment of a subject suffering from a disease, condition or disorder treatable with a therapeutic compound comprising administering a therapeutically effective amount of a pharmaceutical composition of the present invention to a subject in need of such treatment.

Additionally, the present invention provides the use of a composition according to the present invention comprising imatinib mesylate in the manufacture of a medicament for the treatment and/or prevention of conditions, such as malignant or non-malignant proliferative disorders; inhibition of angiogenesis; leukemias such as chronic myelomonocytic leukemia, chronic myeloid leukemia or acute lymphocytic leukemia, gliomas, glioblastoma multiforme, sarcomas; tumors of prostate, colon, breast, lung, or ovary, atherosclerosis, thrombosis; sclerodermitis; psoriasis, restenosis, fibrosis; asthma, prevention of transplantation induced disorders, e.g. obliterative bronchiolitis; prevention of cell invasion by certain bacteria, like *Porphyromonas gingivalis*; of multi-drug resistance, hypereosinophilic syndrome, gastrointestinal stromal tumors (GIST), dermatofibrosarcoma protuberans, systemic mastocytosis or, more generally, Philadelphia positive myeloproliferative disorders.

In summary, the present invention relates, but is not limited, to the following aspects:

- (A) A pharmaceutical composition comprising imatinib or any of its salts and a release retardant, especially comprising between about 50% by weight Imatinib, more particular between about 62% and about 99 % by weight of Imatinib;
- In particular said pharmaceutical composition, wherein said composition comprises at least 400 mg of imatinib mesylate;
 - In particular said pharmaceutical composition, wherein said release retardant is a polymer, especially wherein said polymer has a glass transition temperature less than the melting point of imatinib mesylate, optionally further comprises a plasticizer;
 - In particular said pharmaceutical composition, wherein said release retardant is a non-polymeric release retardant, in particular wherein said non-polymeric release retardant melts at a temperature less than the melting point of imatinib or the imatinib

38

salt employed and/or wherein said non-polymeric release retardant is hydrogenated castor oil;

- In particular said pharmaceutical composition, wherein the pharmaceutical composition comprises at least one release retardant selected from the group consisting of water soluble, water insoluble and water swellable cellulose polymers, acrylic polymers, polysaccharides and polyols;
- In particular said pharmaceutical composition, wherein the pharmaceutical composition comprises at least one release retardant selected from the group consisting of hydroxypropyl cellulose, hydroxypropylmethyl cellulose, ethylcellulose and methacrylate polymers;
- In particular said pharmaceutical composition, further comprising a release modifier.
- In particular said pharmaceutical composition, where the drug release from the pharmaceutical composition is not greater than 80% at 1 hour, and not less than 80% at 10 hours, when tested using USP I basket apparatus at 50rpm in 900mL of 0.1N hydrochloric acid at 37°C.
- In particular said pharmaceutical composition, where the drug release from the pharmaceutical composition is not greater than 80% at 2 hours and not less than 80% at 8 hours, when tested using USP I basket apparatus at 50rpm in 900mL of 0.1N hydrochloric acid at 37°C.
- In particular said pharmaceutical composition, wherein the composition provides, in healthy humans, a mean plasma concentration value not exceeding 3.5µg Imatinib/mL, when dosed 2 hours after a light breakfast.

(B) A method of making a modified release pharmaceutical composition comprising the step of granulating imatinib or any of its salts with a release retardant and optionally a release modifier in an extruder while heating to a temperature below the melting temperature of imatinib or its salt, to form melt granules;

- In particular said method, wherein the melt granules are once again introduced into the extruder, to further granulate with or without release retardant or release modifier or plasticizer, at a temperature less than the melting point of imatinib or the imatinib salt employed;

32

- In particular said method, further comprising cooling of said melt granules to a desired temperature, which is less than melt granulation process temperature.
- In particular said method, further comprising compressing the melt granules into a tablet, e.g. wherein melt granules manufactured separately using different release retardants and/or release modifiers and/or plasticizers at different compositions are blended and compressed into a tablet.
- In particular said method, wherein said extruder is a twin-screw extruder, and, more especially, wherein the release retardant is a polymer, more specifically hydroxypropyl cellulose;
- In particular said method, wherein said composition comprises at least 50% imatinib by weight of the composition.

The following examples are illustrative, but do not serve to limit the scope of the invention described herein. The examples are meant only to suggest a method of practicing the present invention.

Quantities of ingredients, represented by percentage by weight of the pharmaceutical composition, used in each example are set forth below.

Example 1

<u>Ingredient</u>	<u>Percentage (w/w)</u>	<u>Amount per tablet (mg)</u>
Internal phase		
imatinib mesylate	89%	956
hydroxypropyl methylcellulose	5%	53
hydroxypropyl cellulose	5%	53
External phase		
magnesium stearate	1%	10
Total		1072

The internal phase ingredients: imatinib mesylate, hydroxypropyl methylcellulose available as METHOCEL K 100M Premium CR from Dow Chemical Co. (Midland, Michigan), hydroxypropyl cellulose available as KLUCEL HF Pharm from Hercules Chemical Co. (Wilmington, Delaware) are combined and blended in a bin blender for about two hundred rotations. Subsequent to blending, the internal phase is introduced into the feed section, or hopper, of a twin screw extruder. A suitable twin screw extruder is the PRISM 16 mm pharmaceutical twin screw extruder available from Thermo Electron Corp. (Waltham, Massachusetts).

Located at the end of the twin screw extruder is a die with a bore of approximately three mm. The twin screw extruder is configured with five individual barrel zones, or sections. Starting from the hopper to the die, the zones are respectively heated to the following temperatures: 40°C, 70°C, 110°C, 150°C and 185°C.

As the material progresses through the extruder, the speed of the screws is gradually increased to 150 rpm and the volumetric feed rate is adjusted to deliver between about twelve to fifteen grams of material per minute.

The extrudate, or granules, from the extruder are then cooled to room temperature by allowing them to stand from approximately fifteen to twenty minutes. The cooled granules, are subsequently sieved through an 18 mesh screen (i.e., a one mm screen).

For the external phase, the magnesium stearate is first passed through an 18 mesh screen. The magnesium stearate is then blended with the obtained granules from the internal blender in a bin blender for approximately sixty rotations. The resulting final blend is compressed into tablets using a conventional rotary tablet press (e.g., Manesty Beta Press). The resulting tablets are monolithic and have a hardness in the range of 15 kP to 33 kP.

Example 2

<u>Ingredient</u>	<u>Percentage (w/w)</u>	<u>Amount per tablet (mg)</u>
Internal phase		
imatinib mesylate	94%	956
hydroxypropyl cellulose	5%	50

40

External phase		
magnesium stearate	1%	10
Total		1016

The tablets of Example 2 are made using the same method as disclosed for Example 1; however, no hydroxypropyl methylcellulose is added to the internal phase.

Example 3

<u>Ingredient</u>	<u>Percentage (w/w)</u>	<u>Amount per tablet (mg)</u>
Internal phase		
imatinib mesylate	94%	956
hydroxypropyl methylcellulose	4%	40
hydrogenated castor oil	1%	10
External phase		
magnesium stearate	1%	10
Total		1016

The tablets of Example 3 are made using the same method as disclosed in Example 1; however, hydrogenated castor oil available as CUTINA HR from Cognis Corp. (Düsseldorf, Germany) is added to the internal phase.

Example 4

<u>Ingredient</u>	<u>Percentage (w/w)</u>	<u>Amount per tablet (mg)</u>
Internal phase		
imatinib mesylate	89%	956
hydroxypropyl methylcellulose	5%	53

ethylcellulose	5%	53
External phase		
magnesium stearate	1%	10
Total		1072

The tablets of Example 4 are manufactured using the method described in Example 1. In the present, hydroxypropyl cellulose is replaced by ethyl cellulose.

Example 5

<u>Ingredient</u>	<u>Percentage (w/w)</u>	<u>Amount per tablet (mg)</u>
Internal phase		
Imatinib mesylate	89%	956
ethylcellulose	10%	106
External phase		
magnesium stearate	1%	10
Total		1072

The tablets of Example 5 are manufactured using the method described in example 4, however, hydroxypropylmethylcellulose is replaced by ethylcellulose.

Example 6

<u>Ingredient</u>	<u>Percentage (w/w)</u>	<u>Amount per tablet (mg)</u>
Internal phase		
imatinib mesylate	84%	956

52

ethylcellulose	10%	168
Sodium lauryl sulfate	5%	84
External phase		
magnesium stearate	1%	12
Total		1221

The tablets of Example 6 are manufactured using the method described in eExample 1. However, a release modifier – sodium lauryl sulfate, is incorporated in the internal phase.

Example 7

Melt granules A

<u>Ingredient</u>	<u>Percentage (w/w)</u>	<u>Amount per tablet (mg)</u>
Internal phase		
imatinib mesylate	89%	956
Hydroxypropylcellulose	10%	106
External phase		
magnesium stearate	1%	10
Total		1072

Melt granules B

<u>Ingredient</u>	<u>Percentage (w/w)</u>	<u>Amount per tablet (mg)</u>
Internal phase		
imatinib mesylate	89%	956
ethylcellulose	10%	106

External phase		
magnesium stearate	1%	10
Total		1072

Melt granules A and melt granules B are manufactured separately and are combined prior to compression. The ratio of melt granules A to melt granules B is 85:15.

Example 8

FIG. 1 is a chart showing the dissolution profile for tablets for each of the three Examples 1-3. The tablets are placed in 900 mL of 0.1N HCl (pH 1.2) using USP Apparatus II rotating at 100 rpm and at 37°C. The in vitro release profiles of the compositions described in Examples 4, 5, 6 and 7 is shown in FIG 2. The charts show that the Examples of the present invention have a sustained release profile.

It is understood that while the present invention has been described in conjunction with the detailed description thereof that the foregoing description is intended to illustrate and not limit the scope of the invention, which is defined by the scope of the following claims. Other aspects, advantages and modifications are within the scope of the claims.

What is Claimed:

1. A pharmaceutical composition comprising imatinib or any of its salts and a release retardant.
2. The pharmaceutical composition of Claim 1, comprising between about 50% by weight imatinib.
3. The pharmaceutical composition of Claim 2, wherein said composition comprises between about 62% and about 99 % by weight of imatinib.
4. The pharmaceutical composition of Claim 1, wherein said composition comprises at least 400 mg of imatinib mesylate.
5. The pharmaceutical composition of Claim 1, wherein said release retardant is a polymer.
6. The pharmaceutical composition of Claim 5, wherein said polymer has a glass transition temperature less than the melting point of imatinib mesylate.
7. The pharmaceutical composition of Claim 6, further comprising a plasticizer.
8. The pharmaceutical composition of Claim 1, wherein said release retardant is a non-polymeric release retardant.
9. The pharmaceutical composition of Claim 8, wherein said non-polymeric release retardant melts at a temperature less than the melting point of imatinib or the imatinib salt employed.
10. The pharmaceutical composition of Claim 8, wherein said non-polymeric release retardant is hydrogenated castor oil.
11. The pharmaceutical composition of Claim 1, wherein the pharmaceutical composition comprises at least one release retardant selected from the group consisting of water soluble, water insoluble and water swellable cellulose polymers, acrylic polymers, polysaccharides and polyols.
12. The pharmaceutical composition of Claim 1, wherein the pharmaceutical composition comprises at least one release retardant selected from the group consisting of hydroxypropyl cellulose, hydroxypropylmethyl cellulose, ethylcellulose and methacrylate polymers.
13. The pharmaceutical composition according to any one of Claims 1 to 12, further comprising a release modifier.
14. A method of making a modified release pharmaceutical composition comprising the step

of granulating imatinib or any of its salts with a release retardant and optionally a release modifier in an extruder while heating to a temperature below the melting temperature of imatinib or its salt, to form melt granules.

15. The method of claim 14, wherein the melt granules are once again introduced into the extruder, to further granulate with or without release retardant or release modifier or plasticizer, at a temperature less than the melting point of imatinib or the imatinib salt employed.

16. The method of claim 14, further comprising cooling of said melt granules to a desired temperature, which is less than melt granulation process temperature.

17. The method of Claim 14, further comprising compressing the melt granules into a tablet.

18. The method of Claim 17, wherein melt granules manufactured separately using different release retardants and/or release modifiers and/or plasticizers at different compositions are blended and compressed into a tablet.

19. The method of Claim 14, wherein said extruder is a twin-screw extruder.

20. The method of Claim 15, wherein the release retardant is a polymer.

21. The method of Claim 20, wherein said polymer is hydroxypropyl cellulose.

22. The method of Claim 14, wherein said composition comprises at least 50% imatinib by weight of the composition.

23. The pharmaceutical composition according to any one of claims 1 to 13, where the drug release from the pharmaceutical composition is not greater than 80% at 1 hour, and not less than 80% at 10 hours, when tested using USP I basket apparatus at 50rpm in 900mL of 0.1N hydrochloric acid at 37°C.

24. The pharmaceutical composition according to any one of claims 1 to 13, where the drug release from the pharmaceutical composition is not greater than 80% at 2 hours and not less than 80% at 8 hours, when tested using USP I basket apparatus at 50rpm in 900mL of 0.1N hydrochloric acid at 37°C.

25. The pharmaceutical composition according to any one of claims 1 to 13, wherein the composition provides, in healthy humans, a mean plasma concentration value not exceeding 3.5µg Imatinib/mL, when dosed 2 hours after a light breakfast.

46

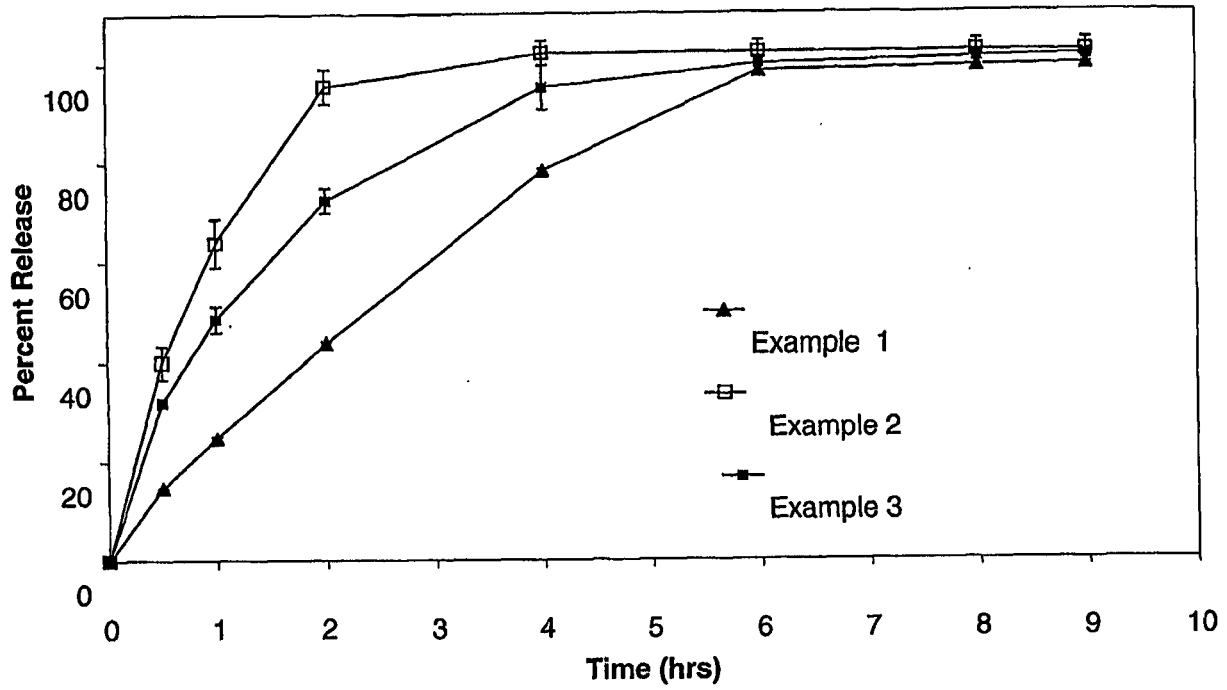


Figure 1

