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(54) **Title**: HIGHLY PURE IMATINIB OR A PHARMACEUTICALLY ACCEPTABLE SALT THEREOF

(57) **Abstract**: Provided herein are impurities of imatinib, N-acetylpiperazine, N-acetylamino, N- chloromethylamino, formamide, 4-methylbenzamide and '2.24 RRt' impurities, and processes for the preparation and isolation thereof. Provided further herein is a highly pure imatinib or a pharmaceutically acceptable salt thereof substantially free of at least one, or two, or more, of the N-acetylpiperazine, N-acetylamino, N-chloromethylamino, formamide, 4-methylbenzamide, and '2.24 RRt' impurities, processes for the preparation, and pharmaceutical compositions comprising highly pure imatinib or a pharmaceutically acceptable salt thereof substantially free of impurities. Disclosed also herein is a process for preparing substantially pure α-form of imatinib mesylate.

HIGHLY PURE IMATINIB OR A PHARMACEUTICALLY ACCEPTABLE SALT THEREOF

CROSS REFERENCE TO RELATED APPLICATION

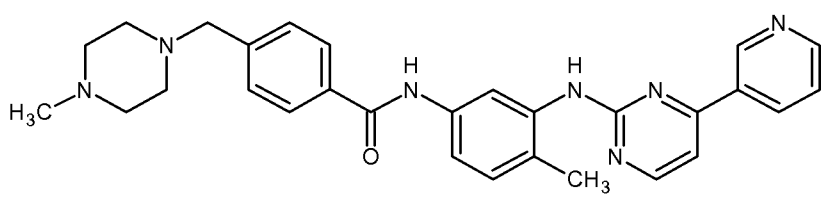
This application claims the benefit of priority to Indian provisional application No. 251/CHE/2010, filed on February 2, 2010, which is incorporated herein by reference in its entirety.

FIELD OF THE DISCLOSURE

[0001] Disclosed herein are impurities of imatinib or a pharmaceutically acceptable salt thereof, and processes for the preparation and isolation thereof. Disclosed further herein is a highly pure imatinib or a pharmaceutically acceptable salt thereof substantially free of impurities, processes for the preparation, and pharmaceutical compositions comprising highly pure imatinib or a pharmaceutically acceptable salt thereof substantially free of impurities. Disclosed also herein is a process for preparing a substantially pure α-form of imatinib mesylate.

BACKGROUND

[0002] U.S. Patent No. 5,521,184 discloses a variety of N-phenyl-2-pyrimidine-amine derivatives, processes for their preparation, pharmaceutical compositions comprising the derivatives, and method of use thereof. These compounds are useful in the treatment of tumoral diseases. Among them, imatinib, 4-[(4-methyl-1-piperazinyl)methyl]-N-[4-methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]phenyl]benzamide, is a protein-tyrosine kinase inhibitor, especially useful in the treatment of various types of cancers that can also be used for the treatment of atherosclerosis, thrombosis, restenosis, or fibrosis. Imatinib can also be used for the treatment of non-maligant diseases. Imatinib is usually administered orally in the form of a suitable salt, e.g., in the form of imatinib mesylate. Imatinib is sold by Novartis as Gleevec™ capsules containing imatinib mesylate equivalent to 100 mg of imatinib free base. Imatinib is represented by the following structural formula I:



---------- I

[0003] Various processes for the preparation of imatinib and related compounds are disclosed in U.S. Patent No. 5,521,184; U.S. Patent Application Nos. 2006/0149061, 2007/0197545, 2008/0207904; and PCT Publication Nos. WO 2003/066613, WO 2004/074502, WO 2004/108699, WO 2006/061332 and WO 2006/071130.

[0004] As per the process described in the U.S. Patent No. 5,521,184 (hereinafter referred to as the '184 patent), imatinib is prepared by the reaction of 2-methyl-5-nitroaniline with an aqueous solution of cyanamide in the presence of nitric acid in ethanol, to produce 2-methyl-5-nitrophenyl guanidine nitrate. This product is reacted with 3-dimethylamino-1-(3-pyridinyl)-2-propen-1-one in the presence of sodium hydroxide in isopropanol to produce N-(2-methyl-5-nitrophenyl)-4-(3-pyridinyl)-2-pyrimidineamine, followed by reduction using hydrogen in the presence of a Pd/C catalyst in ethyl acetate to produce N-(5-amino-2-methylphenyl)-4-(3-pyridinyl)-2-pyrimidineamine, which is then condensed with 4-(4-methyl-piperazinomethyl)benzoyl chloride in pyridine. The crude product obtained is then subjected to column chromatographic purifications using a solvent system containing chloroform and methanol to yield imatinib.

[0005] Imatinib obtained by the process described in the '184 patent does not have satisfactory purity for pharmaceutical use. Unacceptable amounts of impurities are generally formed along with imatinib. The yield of imatinib obtained is very poor and the process involves column chromatographic purifications. Methods involving column chromatographic purifications are generally undesirable for large-scale operations, thereby making the process commercially unfeasible. Moreover, the '184 patent involves the use of highly hazardous materials like pyridine as a solvent for the condensation of N-(5-amino-2-methylphenyl)-4-(3-pyridinyl)-2-pyrimidineamine with 4-(4-methyl-piperazinomethyl)benzoyl chloride. Use of a solvent such as pyridine in the final stage of a synthetic process is not advisable for scale up operations, since it is very difficult to remove residual traces thereof from the final product.

[0006] PCT Publication No. WO 2003/066613 (hereinafter referred to as the '613 application) describes several synthetic routes for preparing imatinib. According to one synthetic process, imatinib is prepared by the reaction of 4-(4-methyl-piperazin-1-ylmethyl)-benzoic acid methyl ester with 3-nitro-4-methyl-aniline to give N-(4-methyl-3-nitrophenyl)-4-(4-methyl-piperazin-1-ylmethyl)-benzamide, which is subsequently reduced to obtain N-(3-amino-4-methyl-phenyl)-4-(4-methyl-piperazin-1-ylmethyl)-benzamide. This product is reacted with cyanamide in a mixture of concentrated hydrochloric acid solution and n-butanol

to produce N-(3-guanidino-4-methyl-phenyl)-4-(4-methyl-piperazin-1-ylmethyl)-benzamide, which is then reacted with 3-dimethylamino-1-pyridin-3-yl-propenone to yield imatinib.

[0007] According to another synthetic process as described in the '613 application, imatinib is prepared by the reaction of 3-bromo-4-methyl-aniline with 4-(4-methyl-piperazin-1-ylmethyl)-benzoic acid methyl ester to afford N-(3-bromo-4-methyl-phenyl)-4-(4-methyl-piperazin-1-ylmethyl)-benzamide, which is reacted with 4-(3-pyridyl)-2-pyrimidine amine to yield imatinib.

[0008] PCT Publication No. WO 2004/074502 (hereinafter referred to as the '502 application) describes a process for the preparation of imatinib by the reaction of N-(2-methyl-5-aminophenyl-4-(3-pyridyl)-2-pyrimidineamine with 4-(4-methyl-piperazinomethyl)benzoyl chloride dihydrochloride in dimethylformamide to produce imatinib trihydrochloride monohydrate, which is then treated with aqueous ammonia to produce imatinib.

[0009] The process described in the '502 application also suffers from drawbacks since imatinib obtained by the process described therein does not have satisfactory purity, unacceptable amounts of impurities are formed along with imatinib, and the yield of imatinib is poor.

[0010] It is known that synthetic compounds can contain extraneous compounds or impurities resulting from their synthesis or degradation. The impurities can be unreacted starting materials, by-products of the reaction, products of side reactions, or degradation products. Generally, impurities in an active pharmaceutical ingredient (API) may arise from degradation of the API itself, or during the preparation of the API. Impurities in imatinib or any active pharmaceutical ingredient (API) are undesirable and might be harmful.

[0011] Regulatory authorities worldwide require that drug manufacturers isolate, identify and characterize the impurities in their products. Furthermore, it is required to control the levels of these impurities in the final drug compound obtained by the manufacturing process and to ensure that the impurity is present in the lowest possible levels, even if structural determination is not possible.

[0012] The product mixture of a chemical reaction is rarely a single compound with sufficient purity to comply with pharmaceutical standards. Side products and byproducts of the reaction and adjunct reagents used in the reaction will, in most cases, also be present in the product mixture. At certain stages during processing of the active pharmaceutical ingredient, the product is analyzed for purity, typically, by HPLC, TLC or GC analysis, to determine if it is suitable for continued processing and, ultimately, for use in a

pharmaceutical product. Purity standards are set with the intention of ensuring that an API is as free of impurities as possible, and, thus, are as safe as possible for clinical use. The United States Food and Drug Administration guidelines recommend that the amounts of some impurities are limited to less than 0.1 percent.

[0013] Generally, impurities are identified spectroscopically and by other physical methods, and then the impurities are associated with a peak position in a chromatogram (or a spot on a TLC plate). Thereafter, the impurity can be identified by its position in the chromatogram, which is conventionally measured in minutes between injection of the sample on the column and elution of the particular component through the detector, known as the "retention time" ("Rt"). This time period varies daily based upon the condition of the instrumentation and many other factors. To mitigate the effect that such variations have upon accurate identification of an impurity, practitioners use "relative retention time" ("RRT") to identify impurities. The RRT of an impurity is its retention time divided by the retention time of a reference marker.

[0014] It is known by those skilled in the art, the management of process impurities is greatly enhanced by understanding their chemical structures and synthetic pathways, and by identifying the parameters that influence the amount of impurities in the final product.

[0015] There is a need for highly pure imatinib or a pharmaceutically acceptable salt thereof substantially free of impurities, as well as processes for preparing thereof.

[0016] Imatinib mesylate can exist in different polymorphic forms, which differ from each other in terms of stability, physical properties, spectral data and methods of preparation.

[0017] Various polymorphic forms, including hydrated and solvated forms, of imatinib mesylate designated Forms α, β, H1, α2, δ, ε, I, II, F, G, H, I, K, IV, V, VI, VII, VIII, IX, X, XI, XIII, XIV, XV, XVI and amorphous forms are apparently disclosed in U.S. Patent Nos. 6,894,051 and 7,300,938; PCT Publication Nos. WO 2005/077933, WO 2005/095379, WO 2006/054314, WO 2006/024863, WO 2006/048890, WO 2007/023182 and WO 2007/136510.

[0018] U.S. Patent No. 6,894,051 B1 (hereinafter referred to as the '051 patent) discloses two crystalline modifications (α-form and β-form) of imatinib mesylate, processes for their preparation, and characterizes the modifications by powder X-ray diffraction (P-XRD), differential scanning calorimetry (DSC) and crystal morphology.

[0019] The processes for the preparation of the imatinib mesylate crystalline form-α described in the prior art suffer from the drawbacks since they do not consistently produce the imatinib mesylate crystalline form-α in substantially pure form. The imatinib mesylate

crystalline form-α obtained according to the prior art processes is contaminated with crystalline form-β.

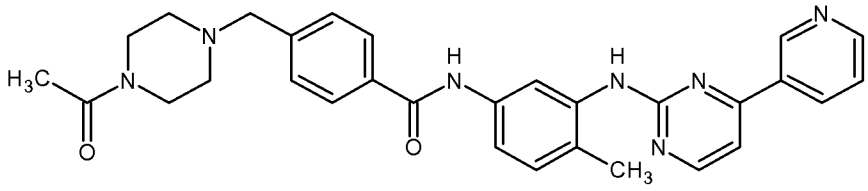
[0020] Polymorphism is defined as the ability of a substance to exist as two or more crystalline phases that have different arrangement and /or conformations of the molecule in the crystal lattice. Different polymorphs may differ in their physical properties such as melting point, solubility, X-ray diffraction patterns, and the like. Although these differences disappear once the compound is dissolved, they can appreciably influence the pharmaceutically relevant properties of the solid form, such as handling properties, dissolution rate and stability. Such properties can significantly influence the processing, shelf life, and commercial acceptance of a polymorph. It is therefore important to investigate all solid forms of a pharmaceutical compound, including all polymorphic forms, and to determine the stability, dissolution and flow properties of each polymorphic form.

[0021] Solvent medium and mode of isolation play very important roles in obtaining a polymorphic form over another.

[0022] Still, there is a strong technical and commercial desire to develop a modified process for the preparation of substantially pure α-form of imatinib mesylate.

SUMMARY

[0023] In one aspect, provided herein is an isolated N-acetylpiperazine compound, 4-[(4-acetyl-1-piperazinyl)methyl]-N-[4-methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]phenyl]benzamide, having the following structural formula A:



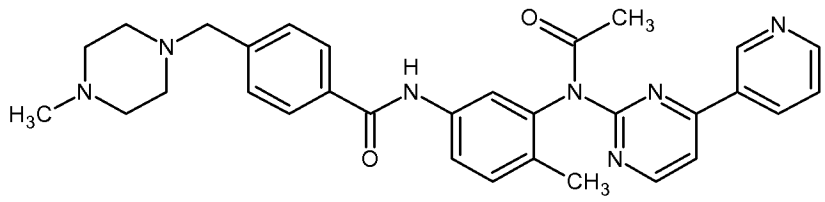
---------- A

[0024] or a pharmaceutically acceptable salt thereof.

[0025] In another aspect, provided herein is an impurity of imatinib, N-acetylpiperazine impurity, 4-[(4-acetyl-1-piperazinyl)methyl]-N-[4-methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl] amino]phenyl]benzamide, of formula A.

[0026] In another aspect, encompassed herein is a process for synthesizing and isolating the N-acetylpiperazine compound of formula A, also referred to as the "N-acetylpiperazine impurity".

[0027] In another aspect, provided herein is an isolated N-acetylamino imatinib, 4-[(4-methyl-1-piperazinyl)methyl]-N-[4-methyl-3-[[[4-(3-pyridinyl)-2-pyrimidinyl]-N-acetyl]amino]phenyl] benzamide, having the following structural formula B:



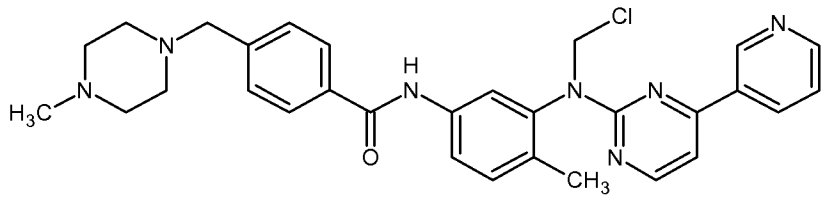
---------- B

or a pharmaceutically acceptable salt thereof.

[0028] In another aspect, provided herein is an impurity of imatinib, N-acetylamino impurity, 4-[(4-methyl-1-piperazinyl)methyl]-N-[4-methyl-3-[[[4-(3-pyridinyl)-2-pyrimidinyl]-N-acetyl] amino]phenyl]benzamide, of formula B.

[0029] In another aspect, encompassed herein is a process for synthesizing and isolating the N-acetylamino compound of formula B, also referred to as the "N-acetylamino impurity".

[0030] In another aspect, provided herein is an isolated N-chloromethylamino imatinib, 4-[(4-methyl-1-piperazinyl)methyl]-N-[4-methyl-3-[[[4-(3-pyridinyl)-2-pyrimidinyl]-N-chloromethyl] amino]phenyl]benzamide, having the following structural formula C:



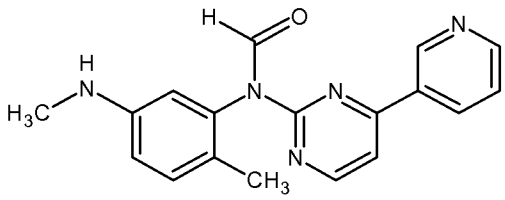
---------- C

or a pharmaceutically acceptable salt thereof.

[0031] In another aspect, provided herein is an impurity of imatinib, N-chloromethylamino impurity, 4-[(4-methyl-1-piperazinyl)methyl]-N-[4-methyl-3-[[[4-(3-pyridinyl)-2-pyrimidinyl]-N-chloromethyl] amino]phenyl]benzamide, of formula C.

[0032] In another aspect, encompassed herein is a process for synthesizing and isolating the N-chloromethylamino compound of formula C, also referred to as the "N-chloromethylamino impurity".

[0033] In another aspect, provided herein is an isolated formamide compound, N-(2-Methyl-5-methylamino-phenyl)-N-(4-pyridin-3-yl-pyrimidin-2-yl)-formamide, having the following structural formula D:



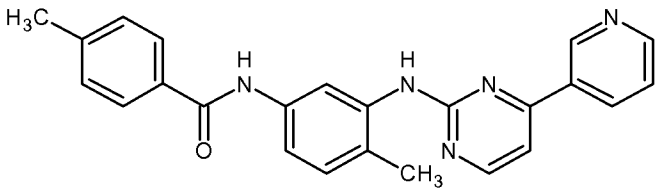
---------- D

or a pharmaceutically acceptable salt thereof.

[0034] In another aspect, provided herein is an impurity of imatinib, formamide impurity, N-(2-Methyl-5-methylamino-phenyl)-N-(4-pyridin-3-yl-pyrimidin-2-yl)-formamide, of formula D.

[0035] In another aspect, encompassed herein is a process for synthesizing and isolating the formamide compound of formula D, also referred to as the "formamide impurity".

[0036] In another aspect, provided herein is an isolated 4-methylbenzamide compound, 4-methyl-N-[4-methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]phenyl]benzamide, having the following structural formula E:



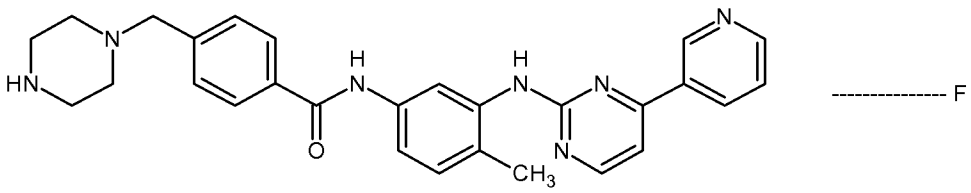
---------- E

or a pharmaceutically acceptable salt thereof.

[0037] In another aspect, provided herein is an impurity of imatinib, 4-methylbenzamide impurity, 4-methyl-N-[4-methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]phenyl]benzamide, of formula E.

[0038] In another aspect, encompassed herein is a process for synthesizing and isolating the 4-methylbenzamide compound of formula E, also referred to as the "4-methylbenzamide impurity".

[0039] In addition to the above five impurities, there is one more impurity, whose presence was observed in imatinib, the desmethyl imatinib impurity, N-[4-methyl-3-(4-pyridin-3-yl-pyrimidin-2-ylamino)-phenyl]-4-piperazin-1-ylmethyl-benzamide, having the following structural formula F:



and it is detected and resolved from imatinib by HPLC with an RRt of 0.9.

[0040] In addition to the above six impurities, there is another impurity identified at 2.24 ±0.01 RRt (hereinafter referred to as the '2.24 RRt' impurity or as the 'single maximum unknown impurity'), whose presence is observed in imatinib.

[0041] In another aspect, provided herein is a highly pure imatinib or a pharmaceutically acceptable salt thereof substantially free of at least one, or two, or more, of the N-acetylpiperazine, N-acetylamino, N-chloromethylamino, formamide, 4-methylbenzamide, and '2.24 RRt' impurities.

[0042] In yet another aspect, encompassed herein is a process for preparing the highly pure imatinib or a pharmaceutically acceptable salt thereof substantially free of at least one, or two, or more, of the N-acetylpiperazine, N-acetylamino, N-chloromethylamino, formamide, 4-methylbenzamide, and '2.24 RRt' impurities.

[0043] In still another aspect, provided herein is a highly pure imatinib or a pharmaceutically acceptable salt thereof essentially free of desmethyl imatinib impurity.

[0044] In another aspect, provided herein is a pharmaceutical composition comprising highly pure imatinib or a pharmaceutically acceptable salt thereof substantially free of at least one, or two, or more, of the N-acetylpiperazine, N-acetylamino, N-chloromethylamino, formamide, 4-methylbenzamide, and '2.24 RRt' impurities, and one or more pharmaceutically acceptable excipients.

[0045] In still another aspect, provided herein is a pharmaceutical composition comprising highly pure imatinib or a pharmaceutically acceptable salt thereof substantially free of at least one, or two, or more, of the N-acetylpiperazine, N-acetylamino, N-chloromethylamino, formamide, 4-methylbenzamide, and '2.24 RRt' impurities made by the process disclosed herein, and one or more pharmaceutically acceptable excipients.

[0046] In still further aspect, encompassed is a process for preparing a pharmaceutical formulation comprising combining highly pure imatinib or a pharmaceutically acceptable salt thereof substantially free of at least one, or two, or more, of the N-acetylpiperazine, N-acetylamino, N-chloromethylamino, formamide, 4-methylbenzamide, and '2.24 RRt' impurities with one or more pharmaceutically acceptable excipients.

[0047] In another aspect, the highly pure imatinib or a pharmaceutically acceptable salt thereof substantially free of at least one, or two, or more, of the N-acetylpiperazine, N-acetylamino, N-chloromethylamino, formamide, 4-methylbenzamide, and '2.24 RRt' impurities disclosed herein for use in the pharmaceutical compositions has a D_{90} particle size of about 1 micron to about 400 micron, and specifically about 10 microns to about 200 microns.

[0048] In another aspect, encompassed herein is a process for preparing α-form of imatinib mesylate in substantially pure form.

BRIEF DESCRIPTION OF THE DRAWINGS

[0049] Figure 1 is a powder X-ray diffraction (XRD) pattern of α-form of imatinib mesylate prepared according to the process disclosed in Example 8.

[0050] Figure 2 is a powder X-ray diffraction (XRD) pattern of α-form of imatinib mesylate prepared according to the process disclosed in Example 11.

[0051] Figure 3 is a powder X-ray diffraction (XRD) pattern of α-form of imatinib mesylate prepared according to the process disclosed in Example 12.

[0052] Figure 4 is a powder X-ray diffraction (XRD) pattern of α-form of imatinib mesylate prepared according to the process disclosed in Example 13.

[0053] Figure 5 is a powder X-ray diffraction (XRD) pattern of α-form of imatinib mesylate prepared according to the process disclosed in Example 14.

[0054] Figure 6 is a powder X-ray diffraction (XRD) pattern of α-form of imatinib mesylate prepared according to the process disclosed in Example 15.

[0055] Figure 7 is a powder X-ray diffraction (XRD) pattern of α-form of imatinib mesylate prepared according to the process disclosed in Example 17.

[0056] Figure 8 is a powder X-ray diffraction (XRD) pattern of α-form of imatinib mesylate prepared according to the process disclosed in Example 18.

[0057] Figure 9 is a powder X-ray diffraction (XRD) pattern of α-form of imatinib mesylate prepared according to the process disclosed in Example 19.

[0058] Figure 10 is a powder X-ray diffraction (XRD) pattern of α-form of imatinib mesylate prepared according to the process disclosed in Example 20.

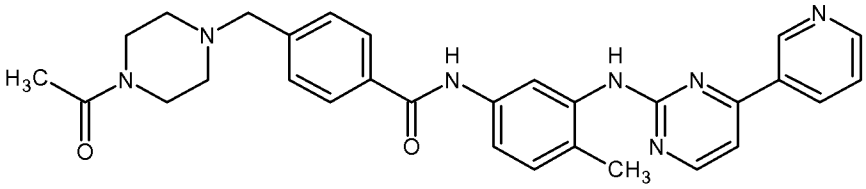
[0059] Figure 11 is a powder X-ray diffraction (XRD) pattern of α-form of imatinib mesylate prepared according to the process disclosed in Example 21.

[0060] Figure 12 is a powder X-ray diffraction (XRD) pattern of α-form of imatinib mesylate prepared according to the process disclosed in Example 22.

[0061] Figure 13 is a powder X-ray diffraction (XRD) pattern of α-form of imatinib mesylate prepared according to the process disclosed in Example 23.

DETAILED DESCRIPTION

[0062] According to one aspect, there is provided an N-acetylpiperazine compound, 4-[(4-acetyl-1-piperazinyl)methyl]-N-[4-methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]phenyl]benzamide, having the following structural formula A:



---------- A

or a pharmaceutically acceptable acid addition salt thereof.

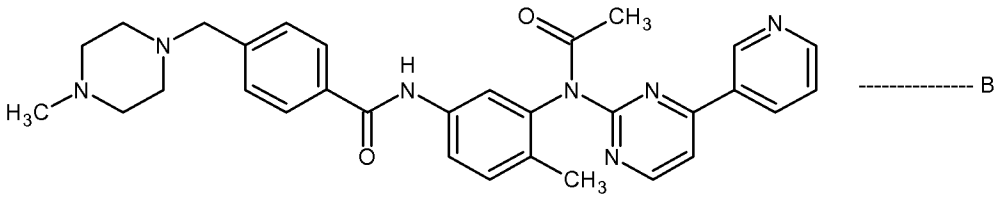
[0063] According to another aspect, there is provided an impurity of imatinib, the N-acetylpiperazine impurity, 4-[(4-acetyl-1-piperazinyl)methyl]-N-[4-methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl] amino]phenyl]benzamide, of formula A.

[0064] The N-acetylpiperazine impurity has been identified, isolated and synthesized. The N-acetylpiperazine impurity was detected and resolved from imatinib by HPLC with an RRt of 1.76. The structure of the compound of formula A was deduced with the aid of ^{1}H, ^{13}C NMR and IR spectroscopy and Liquid Chromatographic mass spectrometry (LCMS). The parent ion at 521 is consistent with the assigned structure.

[0065] The present inventors have found that the N-acetylpiperazine compound of formula A is formed as an impurity, in an amount of about 0.02% to about 0.2% as measured by HPLC, during the purification of imatinib free base with acetic anhydride in dichloromethane under specific conditions, for example, as per the process disclosed herein.

[0066] In one embodiment, the N-acetylpiperazine compound of formula A is prepared as per the process exemplified in the Example 2 as disclosed herein.

[0067] According to another aspect, there is provided an N-acetylamino imatinib, 4-[(4-methyl-1-piperazinyl)methyl]-N-[4-methyl-3-[[[4-(3-pyridinyl)-2-pyrimidinyl]-N-acetyl]amino]phenyl] benzamide, having the following structural formula B:



---------- B

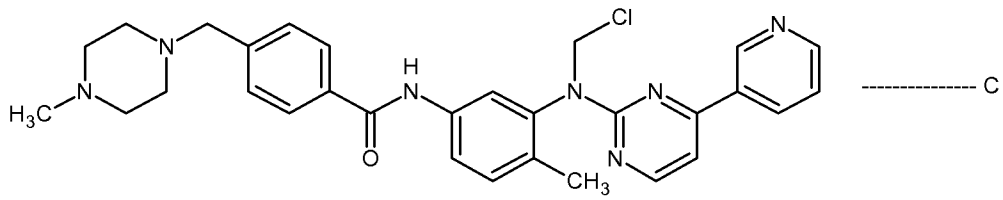
or a pharmaceutically acceptable salt thereof.

[0068] According to another aspect, there is provided an impurity of imatinib, N-acetylamino impurity, 4-[(4-methyl-1-piperazinyl)methyl]-N-[4-methyl-3-[[[4-(3-pyridinyl)-2-pyrimidinyl]-N-acetyl]amino]phenyl]benzamide, of formula B.

[0069] The N-acetylamino impurity has been identified, isolated and synthesized. The N-acetylamino impurity was detected and resolved from imatinib by HPLC with an RRt of 0.70. The structure of the compound of formula B was deduced with the aid of ^{1}H, ^{13}C NMR and IR spectroscopy and Liquid Chromatographic mass spectrometry (LCMS). The parent ion at 535 is consistent with the assigned structure.

[0070] The present inventors have found that the N-acetylamino compound of formula B is formed as an impurity, in an amount of about 6% to about 9% as measured by HPLC, during the purification of imatinib free base with acetic anhydride in dichloromethane under specific conditions, for example, as per the process exemplified in the Example 3 as disclosed herein.

[0071] According to another aspect, there is provided an N-chloromethylamino imatinib, 4-[(4-methyl-1-piperazinyl)methyl]-N-[4-methyl-3-[[[4-(3-pyridinyl)-2-pyrimidinyl]-N-chloromethyl] amino]phenyl]benzamide, having the following structural formula C:



---------- C

or a pharmaceutically acceptable salt thereof.

[0072] According to another aspect, there is provided an impurity of imatinib, N-chloromethylamino impurity, 4-[(4-methyl-1-piperazinyl)methyl]-N-[4-methyl-3-[[[4-(3-pyridinyl)-2-pyrimidinyl]-N-chloromethyl] amino]phenyl]benzamide, of formula C.

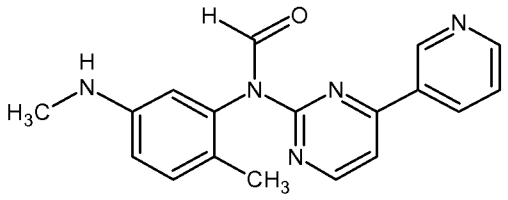
[0073] The N-chloromethylamino impurity has been identified, isolated and synthesized. The N-chloromethylamino impurity was detected and resolved from imatinib by HPLC with an RRt of 1.16. The structure of the compound of formula C was deduced with the aid of ^{1}H, ^{13}C NMR and IR spectroscopy and Liquid Chromatographic mass spectrometry (LCMS). The parent ion at 542 is consistent with the assigned structure.

[0074] According to another aspect, there is provided an isolated N-chloromethylamino impurity. N-chloromethylamino impurity formed during the synthesis of imatinib or a pharmaceutically acceptable salt thereof can be isolated by subjecting the imatinib or a pharmaceutically acceptable salt thereof that contains the N-chloromethylamino impurity to

column chromatography. The column chromatography comprises using a silica gel, as a stationary phase, and a gradient of eluents that remove N-chloromethylamino impurity from the column on which it adsorbed.

[0075] In one embodiment, the N-chloromethylamino compound of formula C is formed as an impurity, in an amount of about 0.2% to about 2% as measured by HPLC, during the purification of imatinib free base with acetic anhydride in dichloromethane under specific conditions, for example, as per the process exemplified in the Example 4 as disclosed herein.

[0076] According to another aspect, there is provided a formamide compound, N-(2-methyl-5-methylamino-phenyl)-N-(4-pyridin-3-yl-pyrimidin-2-yl)-formamide, having the following structural formula D:



---------- D

or a pharmaceutically acceptable salt thereof.

[0077] According to another aspect, there is provided an impurity of imatinib, formamide impurity, N-(2-methyl-5-methylamino-phenyl)-N-(4-pyridin-3-yl-pyrimidin-2-yl)-formamide, of formula D.

[0078] The formamide impurity has been identified, isolated and synthesized. The formamide impurity was detected and resolved from imatinib by HPLC with an RRt of 1.20. The structure of the compound of formula D was deduced with the aid of ^{1}H, ^{13}C NMR and IR spectroscopy and FAB mass spectrometry. The parent ion at 319 is consistent with the assigned structure.

[0079] The formamide compound (formula D) disclosed herein is characterized by data selected from a ^{1}H NMR (300MHz, $CDCl_3$) δ (ppm): 2.17 (s, 3H, N-Methyl), 2.32 (s, 3H, Methyl of aniline), 7.01 (s, 1H, Ar-H of aniline), 7.14 (s, 1H, Ar-H of aniline), 7.16 (d, 1H, pyrimidine), 7.18-7.20 (d, 1H, pyridine), 7.42 (s, 1H, Ar-H of aniline), 7.46 (s, 1H, Ar-H of pyrimidine), 8.38 (s, 1H, NH of N-Methyl), 8.43-8.51 (dd 2H, Ar-H of pyridine), 8.72 (s, 1H, pyridine), 9.27 (s, 1H, N-Formyl); MS: EI^{+} m/z (MH+): 319; and IR spectra on KBr having absorption bands at about 1672 cm^{-1}(N-Formyl).

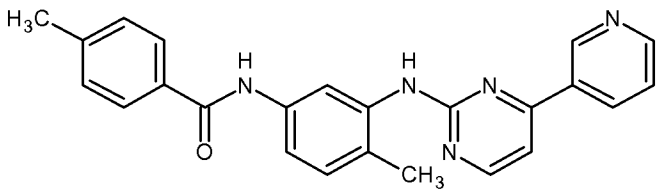
[0080] According to another aspect, there is provided an isolated formamide impurity. Formamide impurity formed during the synthesis of imatinib or a pharmaceutically acceptable salt thereof can be isolated by subjecting the imatinib or a pharmaceutically

acceptable salt thereof that contains the formamide impurity to column chromatography. The column chromatography comprises using a silica gel, as a stationary phase, and a gradient of eluents that remove formamide impurity from the column on which it adsorbed.

[0081] The present inventors have found that the formamide compound of formula D is formed as an impurity, in an amount of about 4% to about 6% as measured by HPLC, during the synthesis of imatinib free base.

[0082] In one embodiment, the formamide compound of formula D is prepared as per the process exemplified in the Example 5 as disclosed herein.

[0083] In addition to the above four impurities, there is another impurity, 4-methylbenzamide impurity, 4-methyl-N-[4-methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]phenyl]benzamide, which has the following structural formula E:



---------- E

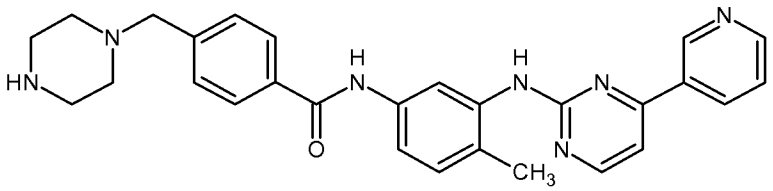
and it is detected and resolved from imatinib by HPLC with an RRt of 2.94.

[0084] The 4-methylbenzamide compound is characterized by data selected from a ^{1}H NMR (400MHz, DMSO solvent) δ (ppm): 1.73, 2.2, 2.36, 2.47, 2.482, 2.486, 3.32, 3.5, 7.17, 7.19, 7.29, 7.31, 7.39, 7.41, 7.47, 7.84, 7.86, 8.06, 8.07, 8.48, 8.49, 8.655, 8.659, 8.66, 8.67, 8.94, 9.254, 9.259, 10.09; MS: EI^+ m/z (MH+): 395.4.

[0085] The present inventors have found that the 4-methylbenzamide compound of formula E is formed as an impurity, in an amount of about 0.15% to about 2% as measured by HPLC, during the synthesis of imatinib free base due to the contamination of the key starting material 4-chloromethyl benzoic acid with p-toluic acid.

[0086] In one embodiment, the 4-methylbenzamide compound of formula E is prepared as per the process exemplified in the Example 6 as disclosed herein.

[0087] In addition to the above five impurities, there is one more impurity, whose presence was observed in imatinib, desmethyl imatinib impurity, N-[4-methyl-3-(4-pyridin-3-yl-pyrimidin-2-ylamino)-phenyl]-4-piperazin-1-ylmethyl-benzamide, having the following structural formula F:



and it is detected and resolved from imatinib by HPLC with an RRt of 0.9.

[0088] The present inventors have found that the desmethyl imatinib impurity of formula F is formed as an impurity, in an amount of about 0.04% to about 0.1% as measured by HPLC, during the synthesis of imatinib free base.

[0089] In addition to the above six impurities, there is another impurity identified at 2.24 ±0.02 RRt (hereinafter referred to as the '2.24 RRt' impurity or as the 'single maximum unknown impurity'), whose presence is observed in imatinib.

[0090] The '2.24 RRt' impurity disclosed herein is characterized by data selected from a ^{1}H NMR (400MHz, DMSO solvent) δ (ppm): 1.74, 1.77, 2.2, 2.48, 2.99, 3.7, 3.86, 4.7, 7.190, 7.198, 7.395, 7.408, 7.43, 7.45, 7.46, 7.48, 7.49, 7.51, 7.69, 7.71, 7.94, 7.96, 8.06, 8.08, 8.44, 8.46, 8.48, 8.49, 8.65, 8.66, 8.97, 9.25, 10.25; MS: EI^+ m/z (MH+): 887.3.

[0091] The present inventors have found that the '2.24 RRt' impurity is formed, in an amount of about 0.2% to about 29% as measured by HPLC, in the synthesis of imatinib free base depending upon the quantity of N-methylpiperazine used during the reaction of 4-chloromethyl-N-[4-methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]phenyl]benzamide with N-methylpiperazine, for example, as per the process exemplified in the Example 7 as disclosed herein.

[0092] Regarding the specific RRt values of impurities disclosed herein, it is well known to a person skilled in the art that the RRt values may vary from sample to sample due to, inter alia, instrument errors (both instrument to instrument variation and the calibration of an individual instrument) and differences in sample preparation. Thus, it has been generally accepted by those skilled in the art that independent measurement of an identical RRt value can differ by amounts of up to ±0.02.

[0093] Thus there is a need for a method for determining the level of impurities in imatinib samples and removing the impurities.

[0094] Extensive experimentation was carried out by the present inventors to reduce the level of the N-acetylpiperazine, N-acetylamino, N-chloromethylamino, formamide, 4-

methylbenzamide, and '2.24 RRt' impurities in imatinib. As a result, it has been found that the N-acetylpiperazine, N-acetylamino, N-chloromethylamino, formamide, 4-methylbenzamide, and '2.24 RRt' impurities formed in the preparation of the imatinib can be reduced or completely removed by the processes disclosed herein.

[0095] According to another aspect, there is provided a highly pure imatinib or a pharmaceutically acceptable salt thereof substantially free of at least one, or two, or more, of the N-acetylpiperazine, N-acetylamino, N-chloromethylamino, formamide, 4-methylbenzamide, and '2.24 RRt' impurities.

[0096] As used herein, "highly pure imatinib or a pharmaceutically acceptable salt thereof substantially free of at least one, or more, of the N-acetylpiperazine, N-acetylamino, N-chloromethylamino, formamide, 4-methylbenzamide, and '2.24 RRt' impurities" refers to imatinib or a pharmaceutically acceptable salt thereof comprising one, or more, of the N-acetylpiperazine, N-acetylamino, N-chloromethylamino, formamide, 4-methylbenzamide, and '2.24 RRt' impurities, each one, in an amount of less than about 0.2 area-% as measured by HPLC. Specifically, the imatinib, as disclosed herein, contains less than about 0.1 area-%, more specifically less than about 0.05 area-%, still more specifically less than about 0.02 area-% of one, or more, of the N-acetylpiperazine, N-acetylamino, N-chloromethylamino, formamide, 4-methylbenzamide, and '2.24 RRt' impurities, and most specifically is essentially free of one, or more, of the N-acetylpiperazine, N-acetylamino, N-chloromethylamino, formamide, 4-methylbenzamide, and '2.24 RRt' impurities.

[0097] In one embodiment, the highly pure imatinib or a pharmaceutically acceptable salt thereof disclosed herein comprises one, or more, of the N-acetylpiperazine, N-acetylamino, N-chloromethylamino, formamide, 4-methylbenzamide, and '2.24 RRt' impurities each in an amount of about 0.01 area-% to about 0.15 area-%, specifically in an amount of about 0.01 area-% to about 0.05 area-%, as measured by HPLC.

[0098] In another embodiment, the highly pure imatinib or a pharmaceutically acceptable salt thereof disclosed herein has a total purity of greater than about 99%, specifically greater than about 99.5%, more specifically greater than about 99.9%, and most specifically greater than about 99.95% as measured by HPLC. For example, the purity of the imatinib or a pharmaceutically acceptable salt thereof is about 99% to about 99.9%, or about 99.5% to about 99.99%.

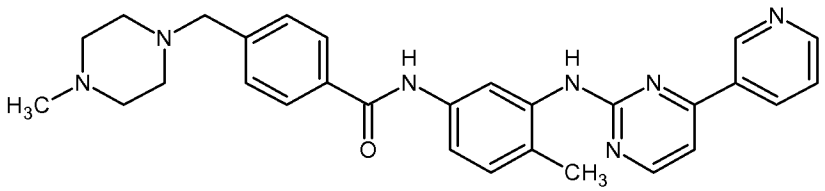
[0099] In another embodiment, the highly pure imatinib or a pharmaceutically acceptable salt thereof disclosed herein is essentially free of one, or more, of the N-acetylpiperazine, N-acetylamino, N-chloromethylamino, formamide, and '2.24 RRt' impurities.

[0100] The term "imatinib or a pharmaceutically acceptable salt thereof essentially free of at least one, or more, of the N-acetylpiperazine, N-acetylamino, N-chloromethylamino, formamide, and '2.24 RRt' impurities" refers to imatinib or a pharmaceutically acceptable salt thereof contains a non-detectable amount of one, or more, of the N-acetylpiperazine, N-acetylamino, N-chloromethylamino, formamide, and '2.24 RRt' impurities as measured by HPLC.

[0101] In another embodiment, the highly pure imatinib or a pharmaceutically acceptable salt thereof disclosed herein is essentially free of desmethyl imatinib impurity.

[0102] The term "imatinib or a pharmaceutically acceptable salt thereof essentially free of desmethyl imatinib impurity" refers to imatinib or a pharmaceutically acceptable salt thereof contains a non-detectable amount of desmethyl imatinib impurity as measured by HPLC.

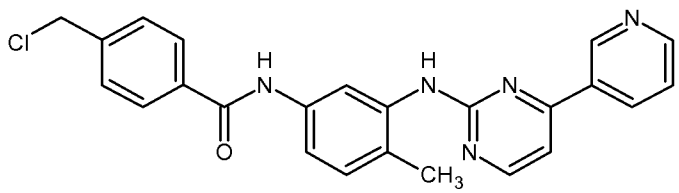
[0103] According to another aspect, there is provided a process for preparing highly pure imatinib of formula I:



---------- I

or a pharmaceutically acceptable salt thereof substantially free of at least one, or more, of the N-acetylpiperazine, N-acetylamino, N-chloromethylamino, formamide, 4-methylbenzamide, and '2.24 RRt' impurities, comprising:

a) reacting 4-chloromethyl-N-[4-methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]phenyl] benzamide of formula II:



---------- II

with N-methylpiperazine in an amide solvent to produce a first reaction mass containing imatinib free base;

b) isolating and/or recovering crude imatinib free base from the first reaction mass;

c) admixing the crude imatinib free base with water to form a first admixture;

d) acidifying the first admixture with an organic acid to produce an aqueous reaction mass;

e) admixing the aqueous reaction mass with an ester solvent to produce a second admixture;

f) combining the second admixture with a base to produce a second reaction mass;

g) isolating and/or recovering imatinib free base from the second reaction mass;

h) contacting the imatinib free base obtained in step-(b) or step-(g) with acetic anhydride in the presence of a mineral acid in a chlorinated hydrocarbon solvent to produce a third reaction mass;

i) admixing the third reaction mass with water to form a third admixture;

j) combining the third admixture with a base to produce a biphasic reaction mixture and separating the organic layer from the biphasic reaction mixture; and

k) substantially removing the solvent from the organic layer obtained in step-(j) by distillation under vacuum to produce highly pure imatinib free base substantially free impurities and optionally converting the highly pure imatinib obtained into a pharmaceutically acceptable salt thereof.

[0104] Exemplary pharmaceutically acceptable salts of imatinib include, but are not limited to, hydrochloride, hydrobromide, oxalate, maleate, fumarate, mesylate, besylate, tosylate and tartrate. A specific pharmaceutically acceptable salt of imatinib is imatinib mesylate.

[0105] In one embodiment, the amide solvent used in step-(a) is selected from the group consisting of N,N-dimethylformamide, N,N-dimethylacetamide, and mixtures thereof. A specific amide solvent is N,N-dimethylformamide.

[0106] In one embodiment, the reaction in step-(a) is carried out at a temperature of below about 10°C, specifically at a temperature of about –10°C to about 5°C for at least 30 minutes, and more specifically at about –5°C to about 5°C for about 1 hour to about 6 hours. In another embodiment, the reaction mass may be quenched with a mixture of water, ethyl acetate and a base, specifically aqueous ammonia, after completion of the reaction.

[0107] The reaction mass containing the imatinib free base obtained in step-(a) may be subjected to usual work up such as a washing, a filtration, an extraction, an evaporation, a pH adjustment, or a combination thereof.

[0108] The isolation of crude imatinib free base in step-(b) is carried out, for example, by forcible or spontaneous crystallization.

[0109] Spontaneous crystallization refers to crystallization without the help of an external aid such as seeding, cooling etc., and forcible crystallization refers to crystallization with the help of an external aid.

[0110] Forcible crystallization is initiated by methods such as cooling, seeding, partial removal of the solvent from the solution, by adding an anti-solvent to the solution, or a combination thereof.

[0111] The term "anti-solvent" refers to a solvent which when added to an existing solution of a substance reduces the solubility of the substance.

[0112] In one embodiment, the isolation is carried out by cooling the solution while stirring at a temperature of below 30°C for at least 15 minutes, specifically at about 0°C to about 30°C for about 30 minutes to about 20 hours, and more specifically at about 20°C to about 30°C for about 1 hour to about 5 hours.

[0113] The recovering in step-(b) is accomplished by techniques such as filtration, filtration under vacuum, decantation, centrifugation, or a combination thereof. In one embodiment, the imatinib free base is recovered by filtration employing a filtration media of, for example, a silica gel or celite.

[0114] The admixing in step-(c) is done in a suitable order, for example, the crude imatinib free base is added to water, or alternatively, the water is added to the crude imatinib free base. The addition is, for example, carried out drop wise or in one portion or in more than one portion. The addition is specifically carried out at a temperature of below 50°C for at least 15 minutes and more specifically at a temperature of about 15°C to about 35°C for about 20 minutes to about 2 hours. After completion of addition process, the resulting mixture is optionally stirred for at least 10 minutes, more specifically for about 30 minutes to about 10 hours, and most specifically for about 1 hour to about 4 hours, at a temperature of about 20°C to about 30°C.

[0115] Exemplary organic acids used in step-(d) include, but are not limited to, acetic acid, p-toluenesulfonic acid, methanesulfonic acid, oxalic acid, p-bromophenylsulfonic acid, carbonic acid, succinic acid, citric acid, benzoic acid, maleic acid, fumaric acid, tartaric acid, and combinations thereof. A most specific organic acid is acetic acid.

[0116] In one embodiment, the acidification in step-(d) is carried out at a temperature of below 50°C, specifically at a temperature of about 0°C to about 50°C, and more specifically at a temperature of about 15°C to about 35°C.

[0117] In another embodiment, the acidification is carried out by adjusting the pH of the reaction mixture between about 2.5 and 4.5, and specifically between about 3 and 4, with a suitable organic acid.

[0118] The aqueous reaction mass obtained in step-(d) may be subjected to usual work up such as a washing, a filtration, an extraction, an evaporation, a pH adjustment, or a

combination thereof. In one embodiment, the aqueous reaction mass obtained in step-(d) is filtered, washed with water and ethyl acetate, and followed by the separation of aqueous layer.

[0119] Exemplary ester solvents used in step-(e) include, but are not limited to, C_2 to C_6 alkyl acetates such as methyl acetate, ethyl acetate, n-propyl acetate, isopropyl acetate, n-butyl acetate, isobutyl acetate, tert-butyl acetate, ethyl formate, and mixtures thereof. A specific ester solvent is ethyl acetate.

[0120] The admixing in step-(e) is done in a suitable order, for example, the aqueous reaction mass is added to the ester solvent, or alternatively, the ester solvent is added to the aqueous reaction mass. The addition is, for example, carried out drop wise or in one portion or in more than one portion. The addition is specifically carried out at a temperature of below 50°C for at least 15 minutes and more specifically at a temperature of about 15°C to about 35°C for about 20 minutes to about 2 hours. After completion of addition process, the resulting mixture is optionally stirred for at least 10 minutes, more specifically for about 30 minutes to about 10 hours, and most specifically for about 1 hour to about 4 hours, at a temperature of about 20°C to about 30°C.

[0121] In one embodiment, the base used in step-(f) is an organic or inorganic base. Specific organic bases are triethylamine, tributylamine, diisopropylethylamine, diethylamine, tert-butyl amine, N-methylmorpholine, pyridine, 4-(N,N-dimethylamino)pyridine, and mixtures thereof. Exemplary inorganic bases include, but are not limited to, ammonia; hydroxides, alkoxides, carbonates and bicarbonates of alkali or alkaline earth metals. Specific inorganic bases are ammonia, sodium hydroxide, calcium hydroxide, magnesium hydroxide, potassium hydroxide, lithium hydroxide, sodium carbonate, potassium carbonate, lithium carbonate, sodium tert-butoxide, sodium isopropoxide, potassium tert-butoxide, and mixtures thereof; and more specifically aqueous ammonia.

[0122] Combining of the second admixture with base in step-(f) is done in a suitable order, for example, the admixture is added to the base, or alternatively, the base is added to the admixture. The addition is, for example, carried out drop wise or in one portion or in more than one portion. The addition is specifically carried out at a temperature of below 50°C for at least 15 minutes and more specifically at a temperature of about 15°C to about 35°C for about 20 minutes to about 2 hours. After completion of addition process, the resulting mixture is stirred for at least 30 minutes, more specifically for about 1 hour to about 10 hours, and most specifically for about 2 hours to about 4 hours, at a temperature of about 20°C to about 30°C to produce the second reaction mass.

[0123] The isolation and recovery of imatinib free base in step-(g) is carried out by the techniques described hereinabove.

[0124] Exemplary chlorinated hydrocarbon solvents used in step-(h) include, but are not limited to, methylene chloride, ethyl dichloride, chloroform, carbon tetrachloride, and mixtures thereof. A most specific chlorinated hydrocarbon solvent is methylene chloride.

[0125] Exemplary mineral acids used in step-(h) include, but are not limited to, hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid and nitric acid. A most specific mineral acid is sulfuric acid.

[0126] In one embodiment, the reaction in step-(h) is carried out at a temperature of below about 50°C, specifically at a temperature of about 0°C to about 35°C for at least 1 hour, and more specifically at about 20°C to about 30°C for about 2 hours to about 12 hours.

[0127] In another embodiment, the admixing in step-(i) is carried out by the methods as described above.

[0128] In one embodiment, the base used in step-(j) is selected from the group as described above. A most specific base is aqueous ammonia.

[0129] In another embodiment, the combining of the third admixture with base in step-(j) is done in a suitable order as described above. After completion of addition process, the resulting mixture is stirred for at least 10 minutes, more specifically for about 20 minutes to about 5 hours, and most specifically for about 30 minutes to about 1 hour, at a temperature of about 20°C to about 30°C to produce the biphasic reaction mixture.

[0130] The term "substantially removing" the solvent refers to at least 80%, specifically greater than about 85%, more specifically greater than about 90%, still more specifically greater than about 99%, and most specifically essentially complete (100%), removal of the solvent from the solvent solution.

[0131] In one embodiment, the distillation process in step-(k) is performed under vacuum at a temperature of below about 45°C, and more specifically at a temperature of about 15°C to about 25°C. Specifically, the solvent is removed at a pressure of about 760 mm Hg or less, more specifically at about 400 mm Hg or less, still more specifically at about 80 mm Hg or less, and most specifically from about 30 to about 80 mm Hg.

[0132] The purity of the imatinib obtained by the process disclosed herein is of greater than about 98%, specifically greater than about 98.5%, more specifically greater than about 99%, and most specifically greater than about 99.95% as measured by HPLC. For example, the purity of the imatinib disclosed herein is about 98% to about 99.95%, or about 99% to about 99.99%.

[0133] Pharmaceutically acceptable salts of imatinib in step-(k) can be prepared in high purity by using the highly pure imatinib substantially free of impurities obtained by the method disclosed herein, by known methods, or by the methods disclosed hereinafter.

[0134] Specific pharmaceutically acceptable salts of imatinib include, but are not limited to, hydrochloride, hydrobromide, oxalate, maleate, fumarate, mesylate, besylate, tosylate, and tartrate. A more specific pharmaceutically acceptable salt of imatinib is imatinib mesylate and more specifically crystalline form-α of imatinib mesylate.

[0135] The highly pure imatinib or a pharmaceutically acceptable salt thereof obtained by the above process may be further dried in, for example, a Vacuum Tray Dryer, a Rotocon Vacuum Dryer, a Vacuum Paddle Dryer or a pilot plant Rota vapor, to further lower residual solvents. Drying can be carried out under reduced pressure until the residual solvent content reduces to the desired amount such as an amount that is within the limits given by the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use ("ICH") guidelines.

[0136] In one embodiment, the drying is carried out at atmospheric pressure or reduced pressures, such as below about 200 mm Hg, or below about 50 mm Hg, at temperatures such as about 35°C to about 70°C. The drying can be carried out for any desired time period that achieves the desired result, such as times about 1 to 20 hours. Drying may also be carried out for shorter or longer periods of time depending on the product specifications. Temperatures and pressures will be chosen based on the volatility of the solvent being used and the foregoing should be considered as only a general guidance. Drying can be suitably carried out in a tray dryer, vacuum oven, air oven, or using a fluidized bed drier, spin flash dryer, flash dryer, and the like. Drying equipment selection is well within the ordinary skill in the art.

[0137] According to another aspect, there is provided a process for preparing highly pure imatinib or a pharmaceutically acceptable salt thereof substantially free of at least one, or more, of the N-acetylpiperazine, N-acetylamino, N-chloromethylamino, formamide, 4-methylbenzamide, and '2.24 RRt' impurities, comprising:

a) admixing crude imatinib free base with water to form a first admixture;
b) acidifying the first admixture with an organic acid to produce a first reaction mass;
c) admixing the first reaction mass with an ester solvent to produce a second admixture;
d) combining the second admixture with a base to produce a second reaction mass;
e) isolating and/or recovering imatinib free base from the second reaction mass;

f) contacting the imatinib free base obtained in step-(e) with acetic anhydride in the presence of a mineral acid in a chlorinated hydrocarbon solvent to produce a third reaction mass;

g) admixing the third reaction mass with water to form a third admixture;

h) combining the third admixture with a base to produce a biphasic reaction mixture and separating the organic layer from the biphasic reaction mixture; and

i) substantially removing the solvent from the organic layer obtained in step-(h) by distillation under vacuum to produce highly pure imatinib free base substantially free impurities and optionally converting the highly pure imatinib obtained into a pharmaceutically acceptable salt thereof.

[0138] The admixing in step-(a) is done in a suitable order as described above.

[0139] The organic acid used in step-(b) is selected from the group as described above. A most specific organic acid is acetic acid.

[0140] In one embodiment, the acidification in step-(b) is carried out at a temperature of below 50°C, specifically at a temperature of about 0°C to about 50°C, and more specifically at a temperature of about 15°C to about 35°C.

[0141] In another embodiment, the acidification is carried out by adjusting the pH of the reaction mixture between about 2.5 and 4.5, and specifically between about 3 and 4, with a suitable organic acid.

[0142] The first reaction mass obtained in step-(b) may be subjected to usual work up methods as described above.

[0143] The ester solvent used in step-(c) is selected from the group as described above. A specific ester solvent is ethyl acetate.

[0144] The admixing in step-(c) is done in a suitable order as described above.

[0145] In one embodiment, the base used in step-(d) is an organic or inorganic base selected from the group as described above. A most specific base is aqueous ammonia.

[0146] Combining of the second admixture with base in step-(d) is done in a suitable order as described above.

[0147] The isolation and recovery of imatinib free base in step-(e) is carried out by the techniques described hereinabove.

[0148] The chlorinated hydrocarbon solvent used in step-(f) is selected from the group as described above. A most specific chlorinated hydrocarbon solvent is methylene chloride.

[0149] The mineral acid used in step-(f) is selected from the group as described above. A most specific mineral acid is sulfuric acid.

[0150] In one embodiment, the reaction in step-(f) is carried out at a temperature of below about 50°C, specifically at a temperature of about 0°C to about 35°C for at least 1 hour, and more specifically at about 20°C to about 30°C for about 2 hours to about 12 hours.

[0151] In another embodiment, the admixing in step-(g) is carried out by the methods as described above.

[0152] In one embodiment, the base used in step-(h) is selected from the group as described above. A most specific base is aqueous ammonia.

[0153] In another embodiment, the combining of the third admixture with base in step-(h) is done in a suitable order as described above. After completion of addition process, the resulting mixture is stirred for at least 10 minutes, more specifically for about 20 minutes to about 5 hours, and most specifically for about 30 minutes to about 1 hour, at a temperature of about 20°C to about 30°C to produce the biphasic reaction mixture.

[0154] In one embodiment, the distillation process in step-(i) is performed under vacuum as described above.

[0155] Pharmaceutically acceptable salts of imatinib in step-(i) can be prepared in high purity by using the highly pure imatinib substantially free of impurities obtained by the method disclosed herein, by known methods, or by the methods disclosed hereinafter.

[0156] The highly pure imatinib or a pharmaceutically acceptable salt thereof obtained by the above process may be further dried by the methods as described above.

[0157] According to another aspect, there is provided a process for preparing highly pure imatinib or a pharmaceutically acceptable salt thereof substantially free of at least one, or more, of the N-acetylpiperazine, N-acetylamino, N-chloromethylamino, formamide, 4-methylbenzamide, and '2.24 RRt' impurities, comprising:

a) contacting crude imatinib free base with acetic anhydride in the presence of a mineral acid in a chlorinated hydrocarbon solvent to produce a reaction mass;
b) admixing the reaction mass obtained in step-(a) with water to form an admixture;
c) combining the admixture with a base to produce a biphasic reaction mixture and separating the organic layer from the biphasic reaction mixture; and
d) substantially removing the solvent from the organic layer obtained in step-(c) by distillation under vacuum to produce highly pure imatinib free base substantially free of impurities and optionally converting the highly pure imatinib obtained into a pharmaceutically acceptable salt thereof.

[0158] The chlorinated hydrocarbon solvent used in step-(a) is selected from the group as described above. A most specific chlorinated hydrocarbon solvent is methylene chloride.

[0159] The mineral acid used in step-(a) is selected from the group as described above. A most specific mineral acid is sulfuric acid.

[0160] In one embodiment, the reaction in step-(a) is carried out at a temperature of below about 50°C, specifically at a temperature of about 0°C to about 35°C for at least 1 hour, and more specifically at about 20°C to about 30°C for about 2 hours to about 12 hours.

[0161] In another embodiment, the admixing in step-(b) is carried out by the methods as described above.

[0162] In one embodiment, the base used in step-(c) is selected from the group as described above. A most specific base is aqueous ammonia.

[0163] In another embodiment, the combining of the third admixture with base in step-(c) is done in a suitable order as described above. After completion of addition process, the resulting mixture is stirred for at least 10 minutes, more specifically for about 20 minutes to about 5 hours, and most specifically for about 30 minutes to about 1 hour, at a temperature of about 20°C to about 30°C to produce the biphasic reaction mixture.

[0164] In one embodiment, the distillation process in step-(d) is performed under vacuum as described above.

[0165] Pharmaceutically acceptable salts of imatinib in step-(d) can be prepared in high purity by using the highly pure imatinib substantially free of impurities obtained by the method disclosed herein, by known methods, or by the methods disclosed hereinafter.

[0166] The highly pure imatinib or a pharmaceutically acceptable salt thereof obtained by the above process may be further dried by the methods as described above.

[0167] According to another aspect, there is provided a process preparing crystalline form-α of imatinib mesylate, comprising:

a) providing a slurry of imatinib free base in a solvent medium comprising a first solvent and a second solvent, wherein the first solvent is isopropyl alcohol and wherein the second solvent is an ether solvent or an aromatic hydrocarbon solvent;
b) heating the slurry obtained in step-(a) at a temperature above about 50°C to produce a hot slurry;
c) optionally, seeding the slurry obtained either in step-(a) or in step-(b) with a crystalline form-α of imatinib mesylate;
d) combining the hot slurry with a solution of methanesulfonic acid in isopropyl alcohol to produce a reaction mass containing imatinib mesylate; and
e) recovering crystalline form-α of imatinib mesylate in substantially pure form from the reaction mass obtained in step-(d).

[0168] In one embodiment, the crystalline form-α of imatinib mesylate obtained by the process disclosed herein is characterized by an X-ray powder diffraction pattern having peaks expressed as 2-theta at about 4.93, 10.48, 11.27, 11.92, 12.21, 13.89, 14.93, 16.53, 17.75, 18.13, 18.64, 19.12, 19.54, 19.86, 21.29, 21.66, 22.67, 23.21, 23.76, 24.93, 27.45, 28.05, 28.57 and 28.93 ± 0.2 degrees.

[0169] In another embodiment, the imatinib mesylate crystalline form-α obtained by the process disclosed herein is characterized by a powder X-ray diffraction pattern substantially in accordance with any one of the Figures 1 to 7.

[0170] The term "substantially pure α-form of imatinib mesylate" refers to the α-form of imatinib mesylate having purity greater than about 99%, specifically greater than about 99.5%, more specifically greater than about 99.8% and still more specifically greater than about 99.9% (measured by HPLC).

[0171] The crystalline form-α of imatinib mesylate obtained by the process disclosed herein is stable, consistently reproducible and has good flow properties, and is particularly suitable for bulk preparation and handling, and hence, the α-form of imatinib mesylate obtained by the process disclosed herein is suitable for formulating imatinib mesylate.

[0172] The imatinib mesylate crystalline form-α obtained by the process disclosed herein is substantially free from other crystalline forms, particularly crystalline form-β.

[0173] In one embodiment, the imatinib mesylate crystalline form-α obtained by the process disclosed herein specifically is essentially free of crystalline form-β. "Essentially free of crystalline form-β of imatinib mesylate" means that no crystalline form-β can be detected in the imatinib mesylate crystalline form-α within the limits of a powder X-ray diffractometer.

[0174] Exemplary second solvents used in step-(a) include, but are not limited to, tetrahydrofuran, 2-methyltetrahydrofuran, dioxane, diethyl ether, diisopropyl ether, methyl tert-butyl ether, methyl isobutyl ether, monoglyme, diglyme, toluene, xylene, and mixtures thereof.

[0175] Specifically, the second solvent is selected from the group consisting of methyl tert-butyl ether, tetrahydrofuran, 2-methyltetrahydrofuran, toluene, and mixtures thereof; and most specifically methyl tert-butyl ether.

[0176] Usually, about 0.1 to 5.0 volumes, specifically, about 0.5 to 2.0 volumes of the second solvent with respect to the first solvent can be used in the solvent medium.

[0177] In one embodiment, the amount of solvent medium employed in step-(a) is about 5 volumes to about 25 volumes, and specifically about 7 volumes to about 17 volumes with respect to the imatinib free base.

[0178] Step-(a) of providing a slurry of imatinib free base includes suspending imatinib in the solvent medium under stirring at below about 50°C, or obtaining an existing slurry from a previous processing step. In one embodiment, the slurry is stirred at a temperature of about 0°C to about 40°C for at least 15 minutes and more specifically at about 20°C to about 30°C for about 30 minutes to about 5 hours.

[0179] In one embodiment, the heating in step-(b) is carried out at a temperature of about 50°C to about 80°C for at least 10 minutes, specifically at a temperature of about 55°C to about 70°C for about 30 minutes to about 10 hours, and more specifically at about 55°C to about 65°C for about 1 hour to about 3 hours.

[0180] Combining of the hot slurry with a solution of methanesulfonic acid in isopropyl alcohol in step-(c) is done in a suitable order as described above. The addition is specifically carried out at a temperature of above about 50°C and more specifically at a temperature of about 55°C to about 65°C. After completion of addition process, the resulting mass is stirred for at least 30 minutes, more specifically for about 1 hour to about 10 hours, and most specifically for about 2 hours to about 4 hours, at a temperature of about 20°C to about 70°C.

[0181] The recovery of crystalline form-α of imatinib mesylate in step-(d) is accomplished by techniques such as filtration, filtration under vacuum, decantation, centrifugation, or a combination thereof. In one embodiment, the imatinib mesylate crystalline form-α is recovered by filtration employing a filtration media of, for example, a silica gel or celite.

[0182] The highly pure imatinib mesylate crystalline form-α obtained by the above process may be further dried as per the methods described hereinabove.

[0183] According to another aspect, there is provided a process preparing crystalline form-α of imatinib mesylate, comprising:

a) providing a solution of imatinib mesylate in a solvent selected from the group consisting of N,N-dimethylformamide, N,N-dimethylacetamide and mixtures thereof;
b) optionally, filtering the solution to remove insoluble matter;
c) precipitating crystalline form-α of imatinib mesylate by combining the solution obtained in step-(a) or step-(b) with an anti-solvent selected from the group consisting of t-butanol, toluene and mixtures thereof; and
d) optionally, seeding the solution in step-(c) with crystalline form-α of imatinib mesylate prior to or after the addition of anti-solvent;
e) recovering the crystalline form-α of imatinib mesylate in substantially pure form.

[0184] Step-(a) of providing a solution of imatinib mesylate includes dissolving imatinib mesylate in the solvent, or obtaining an existing solution from a previous processing step.

[0185] In one embodiment, the imatinib mesylate is dissolved in the solvent at a temperature of below about the reflux temperature of the solvent used, specifically at about 40°C to about 120°C, and still more specifically at about 50°C to about 110°C.

[0186] As used herein, "reflux temperature" means the temperature at which the solvent or solvent system refluxes or boils at atmospheric pressure.

[0187] In another embodiment, the solution in step-(a) is prepared by admixing imatinib base, methanesulfonic acid and the solvent to obtain a mixture; and stirring the mixture to obtain a solution of imatinib mesylate. In yet another embodiment, the mixture is stirred at a temperature of below about the reflux temperature of the solvent used for at least 15 minutes, specifically at about 40°C to about 120°C for about 20 minutes to about 10 hours, and still more specifically at about 50°C to about 110°C for about 30 minutes to about 5 hours.

[0188] The solution obtained in step-(a) is optionally subjected to carbon treatment or silica gel treatment. The carbon treatment or silica gel treatment is carried out by methods known in the art, for example, by stirring the solution with finely powdered carbon or silica gel at a temperature of below about 70°C for at least 15 minutes, specifically at a temperature of about 40°C to about 70°C for at least 30 minutes; and filtering the resulting mixture through hyflo to obtain a filtrate containing imatinib mesylate by removing charcoal or silica gel. Specifically, the finely powdered carbon is an active carbon. A specific mesh size of silica gel is 40-500 mesh, and more specifically 60-120 mesh.

[0189] The solution obtained in step-(a) is optionally stirred at a temperature of about 30°C to the reflux temperature of the solvent used for at least 20 minutes, and specifically at a temperature of about 40°C to the reflux temperature of the solvent used for about 30 minutes to about 4 hours.

[0190] In one embodiment, the amount of solvent used in step-(a) can range from about 2 volumes to about 10 volumes and specifically from about 3 volumes to about 5 volumes with respect to the quantity of imatinib base.

[0191] Combining of the solution with anti-solvent in step-(c) is done in a suitable order, for example, the solution is added to the anti-solvent, or alternatively, the anti-solvent is added to the solution. The addition is, for example, carried out drop wise or in one portion or in more than one portion. The addition is specifically carried out at a temperature below about the reflux temperature of the solvent used, and more specifically at a temperature of about 40°C to about 80°C. After completion of addition process, the resulting mass is stirred at a temperature of about 20°C to about 120°C for about 10 minutes to about 15 hours, and more specifically at about 40°C to about 110°C for about 30 minutes to about 5 hours.

[0192] In one embodiment, the amount of anti-solvent used in step-(c) can range from about 6 volumes to about 35 volumes and specifically from about 8 volumes to about 32 volumes with respect to the quantity of imatinib base.

[0193] The recovery of crystalline form-α of imatinib mesylate in step-(e) is accomplished by techniques such as filtration, filtration under vacuum, decantation, centrifugation, or a combination thereof. In one embodiment, the imatinib mesylate crystalline form-α is recovered by filtration employing a filtration media of, for example, a silica gel or celite.

[0194] The highly pure imatinib mesylate crystalline form-α obtained by the above process may be further dried as per the methods described hereinabove.

[0195] Further encompassed herein is the use of the highly pure imatinib or a pharmaceutically acceptable salt thereof substantially free of at least one, or more, of the N-acetylpiperazine, N-acetylamino, N-chloromethylamino, formamide, 4-methylbenzamide, and '2.24 RRt' impurities for the manufacture of a pharmaceutical composition together with a pharmaceutically acceptable carrier.

[0196] A specific pharmaceutical composition of highly pure imatinib or a pharmaceutically acceptable salt thereof substantially free of at least one, or more, of the N-acetylpiperazine, N-acetylamino, N-chloromethylamino, formamide, 4-methylbenzamide, and '2.24 RRt' impurities is selected from a solid dosage form and an oral suspension.

[0197] In one embodiment, the highly pure imatinib or a pharmaceutically acceptable salt thereof substantially free of at least one, or more, of the N-acetylpiperazine, N-acetylamino, N-chloromethylamino, formamide, 4-methylbenzamide, and '2.24 RRt' impurities has a D_{90} particle size of about 1 micron to about 400 microns, and specifically about 10 microns to about 200 microns.

[0198] In another embodiment, the particle sizes of the highly pure imatinib or a pharmaceutically acceptable salt thereof substantially free of at least one, or more, of the N-acetylpiperazine, N-acetylamino, N-chloromethylamino, formamide, 4-methylbenzamide, and '2.24 RRt' impurities are produced by a mechanical process of reducing the size of particles which includes any one or more of cutting, chipping, crushing, milling, grinding, micronizing, trituration or other particle size reduction methods known in the art, to bring the solid state form to the desired particle size range.

[0199] According to another aspect, there is provided a method for treating a patient suffering from tumoral diseases, comprising administering a therapeutically effective amount of the highly pure imatinib or a pharmaceutically acceptable salt thereof substantially free of at least one, or more, of the N-acetylpiperazine, N-acetylamino, N-chloromethylamino,

formamide, 4-methylbenzamide, and '2.24 RRt' impurities, or a pharmaceutical composition that comprises a therapeutically effective amount of highly pure imatinib or a pharmaceutically acceptable salt thereof substantially free of at least one, or more, of the N-acetylpiperazine, N-acetylamino, N-chloromethylamino, formamide, 4-methylbenzamide, and '2.24 RRt' impurities, along with pharmaceutically acceptable excipients.

[0200] According to another aspect, there is provided pharmaceutical compositions comprising highly pure imatinib or a pharmaceutically acceptable salt thereof substantially free of at least one, or more, of the N-acetylpiperazine, N-acetylamino, N-chloromethylamino, formamide, 4-methylbenzamide, and '2.24 RRt' impurities prepared according to the processes disclosed herein and one or more pharmaceutically acceptable excipients.

[0201] According to another aspect, there is provided a process for preparing a pharmaceutical formulation comprising combining highly pure imatinib or a pharmaceutically acceptable salt thereof substantially free of at least one, or more, of the N-acetylpiperazine, N-acetylamino, N-chloromethylamino, formamide, 4-methylbenzamide, and '2.24 RRt' impurities prepared according to processes disclosed herein, with one or more pharmaceutically acceptable excipients.

[0202] Yet in another embodiment, pharmaceutical compositions comprise at least a therapeutically effective amount of highly pure imatinib or a pharmaceutically acceptable salt thereof substantially free of at least one, or more, of the N-acetylpiperazine, N-acetylamino, N-chloromethylamino, formamide, 4-methylbenzamide, and '2.24 RRt' impurities. Such pharmaceutical compositions may be administered to a mammalian patient in a dosage form, e.g., solid, liquid, powder, elixir, aerosol, syrups, injectable solution, etc. Dosage forms may be adapted for administration to the patient by oral, buccal, parenteral, ophthalmic, rectal and transdermal routes or any other acceptable route of administration. Oral dosage forms include, but are not limited to, tablets, pills, capsules, syrup, troches, sachets, suspensions, powders, lozenges, elixirs and the like. The highly pure imatinib or a pharmaceutically acceptable salt thereof substantially free of at least one, or more, of the N-acetylpiperazine, N-acetylamino, N-chloromethylamino, formamide, 4-methylbenzamide, and '2.24 RRt' impurities may also be administered as suppositories, ophthalmic ointments and suspensions, and parenteral suspensions, which are administered by other routes.

[0203] The pharmaceutical compositions further contain one or more pharmaceutically acceptable excipients. Suitable excipients and the amounts to use may be readily determined by the formulation scientist based upon experience and consideration of standard procedures

and reference works in the field, e.g., the buffering agents, sweetening agents, binders, diluents, fillers, lubricants, wetting agents and disintegrants described hereinabove.

[0204] In one embodiment, capsule dosage forms contain highly pure imatinib or a pharmaceutically acceptable salt thereof substantially free of at least one, or more, of the N-acetylpiperazine, N-acetylamino, N-chloromethylamino, formamide, 4-methylbenzamide, and '2.24 RRt' impurities within a capsule which may be coated with gelatin. Tablets and powders may also be coated with an enteric coating. Suitable enteric coating agents include phthalic acid cellulose acetate, hydroxypropylmethyl cellulose phthalate, polyvinyl alcohol phthalate, carboxy methyl ethyl cellulose, a copolymer of styrene and maleic acid, a copolymer of methacrylic acid and methyl methacrylate, and like materials, and if desired, the coating agents may be employed with suitable plasticizers and/or extending agents. A coated capsule or tablet may have a coating on the surface thereof or may be a capsule or tablet comprising a powder or granules with an enteric-coating.

[0205] Tableting compositions may have few or many components depending upon the tableting method used, the release rate desired and other factors. For example, the compositions described herein may contain diluents such as cellulose-derived materials like powdered cellulose, microcrystalline cellulose, microfine cellulose, methyl cellulose, ethyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropylmethyl cellulose, carboxymethyl cellulose salts and other substituted and unsubstituted celluloses; starch; pregelatinized starch; inorganic diluents such calcium carbonate and calcium diphosphate and other diluents known to one of ordinary skill in the art. Yet other suitable diluents include waxes, sugars (e.g. lactose) and sugar alcohols such as mannitol and sorbitol, acrylate polymers and copolymers, as well as pectin, dextrin and gelatin.

[0206] Other excipients include binders, such as acacia gum, pregelatinized starch, sodium alginate, glucose and other binders used in wet and dry granulation and direct compression tableting processes; disintegrants such as sodium starch glycolate, crospovidone, low-substituted hydroxypropyl cellulose and others; lubricants like magnesium and calcium stearate and sodium stearyl fumarate; flavorings; sweeteners; preservatives; pharmaceutically acceptable dyes and glidants such as silicon dioxide.

INSTRUMENTAL DETAILS:

X-Ray Powder Diffraction (P-XRD):

[0207] The X-Ray powder diffraction was measured by an X-ray powder Diffractometer equipped with CuKα-radiations (40kV, 40 mA) in wide-angle X-ray Diffractometer of BRUKER axs, D8 ADVANCE. The sample was analyzed using the following instrument parameters: measuring range= 3-45° 2-theta; step width=0.01579°; and measuring time per step=0.11 sec.

High Performance Liquid Chromatography (HPLC):

[0208] The HPLC purity was measured by high performance liquid chromatography by using a Water's HPLC system having alliance 2695 model pump and 2487 (UV) detector with Empower Chromatography software or its equivalent under the following conditions:

Column	: Inertsil ODS 4 (250 x 4.6) mm, 5.0µ, Make: GL Sciences; C/N-5020-03946
Detector	: UV at 237nm
Injection volume	: 10.0 µL
Run time	: 50 min
Column temperature	: 35°C
Flow rate	: 1.0 ml/ min
Diluent	: Water : Acetonitrile (50: 50) (%v/v)
Elution	: Gradient

Buffer preparation:

[0209] Potassium dihydrogen phosphate (2.72 g) was taken in 1000 ml of water and pH was adjusted to 5.50 (±0.05) with 0.1N KOH solution, followed by filtration through 0.22 µm porosity membrane and degassed.

Mobile Phase-A: Buffer (100%)

Mobile Phase-B: Acetonitrile (100%).

Gradient programme:

Time (min)	(%) Mobile phase-A	(%)Mobile phase-B
0	70	30
5	70	30
35	40	60

40	40	60
41	70	30
50	70	30

[0210] The following examples are given for the purpose of illustrating the present disclosure and should not be considered as limitation on the scope or spirit of the disclosure.

EXAMPLES

Example 1

Step-I: Preparation of 4-Chloromethyl-N-[4-methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl] amino]phenyl]benzamide

[0211] Dimethylformamide (2 ml), thionyl chloride (290.4 ml), 1,4-dioxane (1000 ml) and 4-(chloromethyl)benzoic acid (200 g) were placed in a reaction flask, and the mixture was heated for 10 to 12 hours at 65-70°C. The resulting mass was distilled under vacuum at below 50°C to produce an oily mass. N-(5-Amino-2-methylphenyl)-4-(3-pyridinyl)-2-pyrimidineamine (294 g) was taken in another reaction flask, tetrahydrofuran (800 ml) was added, and the mixture was cooled to –6°C. The oily mass and pyridine (640 ml) at –5°C to 5°C were added to the resulting mixture simultaneously over a period of 1 hour to 1 hour 30 minutes. Tetrahydrofuran was added to the resulting mass portion wise (400 ml + 200 ml + 400 ml + 400 ml + 400 ml + 200 ml) followed by stirring for 1 hour at –5°C to 5°C. The reaction mass was quenched into water (9.2 L) and potassium carbonate (294 g) at 20-30°C, the flask was washed with water (1600 ml) and the reaction mass was stirred for 2 hours at 20-30°C. The resulting solid was filtered and washed with water (1600 ml). The wet material was added to acetone (3732.8 ml) and stirred for 1 hour at 20-30°C. The separated solid was filtered, washed with acetone (800 ml) and then dried in air over at 55-65°C to produce 424 g of 4-chloromethyl-N-[4-methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]phenyl]benzamide (Purity by HPLC: 95.95%).

Content of Impurities measured by HPLC:

1. 4-Methylbenzamide impurity at 2.94 RRT: 1.8%.

Step-II: Preparation of 4-[(4-Acetyl-1-piperazinyl)methyl]-N-[4-methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]phenyl]benzamide (crude Imatinib free base)

[0212] N,N-Dimethylformamide (250 ml) was added to N-methylpiperazine (1750 ml) and the mixture was cooled to –6°C to –1°C. 4-Chloromethyl-N-[4-methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl] amino]phenyl]benzamide (250 g) was added to the resulting mass at –6°C to –1°C and then stirred for 2 hours at –5°C to 5°C. The reaction mass was quenched into a mixture of water (7 L), ethyl acetate (875 ml) and aqueous ammonia (500 ml) at 20-30°C, and the resulting mass was stirred for 3 hours at 20-30°C. The resulting solid was filtered and washed with water (1250 ml).

[0213] The resulting wet solid (content of 4-methylbenzamide impurity at 2.94 RRt: 1.5% as measured by HPLC) was placed in another reaction flask, followed by the addition of water (2500 ml) and adjusting the pH of the mixture to 3.0 to 4.0 with acetic acid (125 ml). The resulting mixture was filtered through hyflow bed, washed the hyflow bed with water (250 ml) and the resulting aqueous layer was washed with ethyl acetate (1000 ml x 3). The aqueous layer was separated and followed by the addition of ethyl acetate (750 ml) and aqueous ammonia (500 ml) and stirring the resulting mixture for 3 hours at 20-30°C. The separated solid was filtered, washed with water (1250 ml) and then dried the material in air oven at 55-65°C to give 240 g of crude imatinib free base (Purity by HPLC: 99.7%).

Content of Impurities measured by HPLC:

1. 4-Methylbenzamide impurity at 2.94 RRt: 0.06%
2. '2.24 RRt' impurity: 0.06%
3. Formamide impurity at 1.20 RRt: 0.01 %
4. Desmethyl impurity at 0.9 RRt: 0.06%.

Step-III: Purification of crude imatinib free base and preparation of pure Imatinib mesylate (α-Form)

[0214] Methylene chloride (3750 ml), acetic anhydride (69 ml) and concentrated sulfuric acid (15 ml) were added to crude imatinib free base (150 g, obtained in step-II) and the mixture was stirred for 1 hour at 20-30°C. Concentrated sulfuric acid was added to the resulting mass and then stirred for 7 hours at 20-30°C. Water (1500 ml) and aqueous ammonia (300 ml) were added to the reaction mass at 20-30°C followed by stirring for 20 to 30 minutes at 20-30°C. The resulting organic layer was separated followed by distillation under vacuum at 15-25°C to produce a solid material. Isopropyl alcohol (1350 ml) and methyl tert-butyl ether (1500 ml) were added to the above solid and the resulting slurry was heated to reflux (62-63°C). A solution of methanesulfonic acid (29.2 g) in isopropyl alcohol (150 ml) were added to the resulting reaction mass at reflux (62-63°C) with stirring for 2 to 3 hours at reflux. The

separated solid was filtered, washed with isopropyl alcohol (750 ml) and then the material was dried in a vacuum oven at 20-30°C for 8 hours and further dried at 40-50°C to produce 160.5 g of imatinib mesylate in crystalline Form-α (Purity by HPLC: 99.74%).

Content of Impurities measured by HPLC:

1. 4-Methylbenzamide impurity at 2.94 RRt: 0.03%
2. '2.24 RRt' impurity: 0.06%.
3. Formamide impurity at 1.20 RRt: 0.01%.
4. Desmethyl impurity at 0.9 RRt: Not Detected

Example 2

Preparation of 4-[(4-acetyl-1-piperazinyl)methyl]-N-[4-methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]phenyl]benzamide (N-Acetylpiperazine compound or N-Acetylpiperazine impurity)

[0215] 4-[(1-Piperazinyl)methyl]-N-[4-methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]phenyl] benzamide (15 g) was added to a mixture of dichloromethane (150 ml) and triethyl amine (8.4 ml), followed by slow addition of the acetic anhydride (4.4 ml) at 20 to 25°C. The resulting mixture was stirred for 30 minutes at 20 to 25°C, water (250 ml) was added to the resulting mass, followed by stirring for 30minutes at 20 to 25°C. The resulting organic layer was separated, followed by distillation of the solvent under vacuum at 25 to 30°C to produce 14.9 g of N-acetylpiperazine compound (Purity by HPLC: 99.36%).

Example 3

Preparation of Imatinib free base containing 8% of 4-[(4-methyl-1-piperazinyl)methyl]-N-[4-methyl-3-[[[4-(3-pyridinyl)-2-pyrimidinyl]-N-acetyl]amino]phenyl]benzamide (N-acetylamino imatinib impurity)

[0216] Imatinib free base (2 g) was added to acetic anhydride (24 ml) at 25 to 28°C, and the resulting suspension was stirred for 8 to 9 hours at 25 to 28°C. Water (100 ml) was added to the reaction mixture, followed by the addition of aqueous ammonia (150 ml) and ethyl acetate (10 ml). The resulting slurry was cooled to 10 to 15°C, and the solid was filtered and washed with water (50 ml) followed by drying in air oven at 70 to 75°C for 8 to 10 hours to give 1.32 g of imatinib free base having the content of acetylamino imatinib impurity at 0.70 RRt: 8% (measured by HPLC).

Example 4

Preparation of Imatinib free base

[0217] Imatinib free base (2 g) was added to the mixture of sodium hydroxide (1 g) and dichloromethane (50 ml), and the reaction mass was stirred for 12 hours at 30°C. The resulting mass was distilled under vacuum at 35 to 40°C to produce 1 g of imatinib free base having N-chloromethylamino imatinib impurity, 4-[(4-methyl-1-piperazinyl)methyl]-N-[4-methyl-3-[[[4-(3-pyridinyl)-2-pyrimidinyl]-N-chloromethyl]amino]phenyl]benzamide, at 1.16 RRt: 1.19% (measured by HPLC).

Example 5

Preparation of N-(2-Methyl-5-methylamino-phenyl)-N-(4-pyridin-3-yl-pyrimidin-2-yl)-formamide (Formamide impurity)

[0218] A mixture of 4-(4-methyl-piperazinomethyl)benzoic acid dihydrochloride (277.1 g), dimethylsulfoxide (880 g) and carbonyl diimidazole (147 g) was stirred for 30 minutes at 25-30°C. The resulting mixture was heated at 40-45°C and followed by the addition of N-(5-amino-2-methylphenyl)-4-(3-pyridinyl)-2-pyrimidineamine (200 g). The reaction mixture was further heated at 50-55°C and maintained for 2 hours. The resulting mass was cooled to 20-25°C, followed by quenching with a mixture of water (8000 ml), ethyl acetate (720 ml), and aqueous ammonia (250 ml). The resulting slurry was stirred for 2 hours at 25-30°C for 2 hours. The separated solid was filtered, washed with water (500 ml) and then dried in an air oven at 65-70°C for 10 to 12 hours. The dried material was subjected to column chromatography to isolate the desired impurity (Yield: 6.6 g; Purity by HPLC: 99.35%).

Example 6

Preparation of 4-methyl-N-[4-methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]phenyl] benzamide (4-methylbenzamide compound or 4-methylbenzamide impurity)

[0219] 1,4-Dioxane (75 ml) and thionyl chloride (45.5 ml) were added to p-toluic acid (25 g) and the mixture was heated at 60°C for 12 hours. The resulting mass was distilled under vacuum at 50°C to produce an oily mass. The resulting oil was slowly added to a stirred suspension of (45.8 g), potassium carbonate (63 g), tetrahydrofuran (238 ml) and N-(5-Amino-2-methylphenyl)-4-(3-pyridinyl)-2-pyrimidineamine at 0°C. The resulting mass was stirred for 3 hours at 25°C and followed by quenching in a mixture of water (700 ml) and ethyl acetate (92 ml). The resulting mixture was stirred for 2 hours at 25°C and filtered the solid. The solid was washed with water (400 ml) and ethyl acetate (200 ml), and dried in an

air oven at 65°C for 8 to 10 hours to give 47.5 g of 4-methyl-N-[4-methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino] phenyl] benzamide (Purity by HPLC: 99.6%).

Example 7

Preparation of imatinib free base

[0220] N-Methylpiperazine (0.77 ml) and N,N-dimethylacetamide (6 ml) were added to 4-chloromethyl-N-[4-methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]phenyl]benzamide (2 g) at 0°C and the resulting mixture was stirred for 10 hours at 25°C. Water (60 ml), ethyl acetate (6 ml) and aqueous ammonia (6 ml) were added to the reaction mass and then stirred for 2 hours at 25°C. The separated solid was filtered, washed with water (40 ml) and then dried in an air oven at 70-75°C for 8 to 9 hours to give 1.5 g of imatinib free base (Content of '2.24 RRt' impurity: 28.26% as measured by HPLC).

Example 8

Preparation of α-Form of Imatinib mesylate

[0221] Imatinib free base (75 g) was added to a mixture of isopropyl alcohol (675 ml) and methyl tert-butyl ether (750 ml), followed by the addition of pure seeds of imatinib mesylate crystalline form-α (1.2 g). The resulting slurry was heated at 62-65°C, followed by slow addition of a solution of methane sulfonic acid (14.6 g) in isopropyl alcohol (75 ml). The resulting slurry was stirred for 3 hours to 3 hours 30 minutes and then cooled to 40 to 45°C. The separated solid was filtered and washed with isopropyl alcohol (250 ml) and then dried the solid in air oven at 75 to 80°C for 10 to 12 hours to give 81 g of imatinib mesylate crystalline form-α.

Analytical Result:

[0222] The sample of imatinib mesylate exists in crystalline Form-α and confirmed by a powder X-ray diffraction pattern substantially in accordance with Figure 1. The imatinib mesylate crystalline form-α obtained by this process does not contain crystalline form-β within the limits of detection of a powder X-ray diffractometer.

Example 9

Preparation of α-Form of Imatinib mesylate

[0223] Imatinib free base (5 g) was added to a mixture of isopropyl alcohol (20 ml) and methyl tert-butyl ether (50 ml), the slurry was heated at 55-60°C, and followed by the addition of seeds of imatinib mesylate crystalline form-α (0.1 g). A solution of methane

sulfonic acid (0.97 g) in isopropyl alcohol (5 ml) was slowly added to the resulting slurry, and the slurry was stirred for 1 hour 30 minutes to 2 hours. The separated solid was filtered, washed with isopropyl alcohol (30 ml) and the solid was dried in an air oven at 75-80°C for 10 to 12 hours to produce 5.6 g of imatinib mesylate crystalline form-α.

Analytical Result:

[0224] The sample of imatinib mesylate exists in crystalline Form-α and confirmed by powder X-ray diffraction pattern. The imatinib mesylate crystalline form-α obtained by this process does not contain crystalline form-β within the limits of a powder X-ray diffractometer.

Example 10

Preparation of α-Form of Imatinib mesylate

[0225] Imatinib free base (5 g) was added to a mixture of isopropyl alcohol (45 ml) and methyl tert-butyl ether (25 ml), the slurry was heated at 55-60°C, followed by the addition of seeds of imatinib mesylate crystalline form-α (0.1 g). A solution of methane sulfonic acid (0.97 g) in isopropyl alcohol (5 ml) was slowly added to the resulting slurry followed by further stirring the slurry for 1 hour 30 minutes to 2 hours. The separated solid was filtered, washed with isopropyl alcohol (30 ml), and then dried in an air oven at 75-80°C for 10 to 12 hours to produce 5.2 g of imatinib mesylate crystalline form-α.

Analytical Result:

[0226] The sample of imatinib mesylate exists in crystalline Form-α and confirmed by the powder X-ray diffraction pattern. The imatinib mesylate crystalline form-α obtained by this process does not contain crystalline form-β within the limits of detection of a powder X-ray diffractometer.

Example 11

Preparation of α-Form of Imatinib mesylate

[0227] Imatinib free base (5 g) was added to a mixture of isopropyl alcohol (40 ml) and methyl tert-butyl ether (50 ml), the slurry was heated at 55-60°C, followed by slow addition of a solution of methane sulfonic acid (0.97 g) in isopropyl alcohol (5 ml) and further stirring the slurry for 2 to 3 hours. The separated solid was filtered, washed with isopropyl alcohol (30 ml), and then dried in an air oven at 75-80°C for 10 to 12 hours to produce 5 g of imatinib mesylate crystalline form-α.

Analytical Result:

[0228] The sample of imatinib mesylate exists in crystalline Form-α and confirmed by a powder X-ray diffraction pattern substantially in accordance with Figure 2. The imatinib mesylate crystalline form-α obtained by this process does not contain crystalline form-β within the limits of detection of a powder X-ray diffractometer.

Example 12

Preparation of α-Form of Imatinib mesylate

[0229] Imatinib free base (5 g) was added to a mixture of toluene (10 ml) and isopropyl alcohol (95 ml), the slurry was heated at 55-60°C, followed by the addition of seeds of imatinib mesylate crystalline form-α (0.1 g). A solution of methane sulfonic acid (0.97 g) in isopropyl alcohol (5 ml) was slowly added to the resulting slurry. The resulting mixture was gradually cooled to 25-30°C and further cooled to 5-10°C. The separated solid was filtered, washed with isopropyl alcohol (30 ml), and then dried in an air oven at 75-80°C for 10 to 12 hours to produce 3.0 g of imatinib mesylate crystalline form-α.

Analytical Result:

[0230] The sample of imatinib mesylate exists in crystalline Form-α and confirmed by a powder X-ray diffraction pattern substantially in accordance with Figure 3. The imatinib mesylate crystalline form-α obtained by this process does not contain crystalline form-β within the limits of detection of a powder X-ray diffractometer.

Example 13

Preparation of α-Form of Imatinib mesylate

[0231] Imatinib free base (5 g) was added to a mixture of tetrahydrofuran (10 ml) and isopropyl alcohol (95 ml), followed by the addition of pure seeds of imatinib mesylate crystalline form-α (0.1 g). The resulting slurry was heated at 55-60°C, followed by slow addition of a solution of methane sulfonic acid (0.97 g) in isopropyl alcohol (5 ml). The resulting slurry was stirred for 2 hours to 3 hours. The separated solid was filtered and washed with isopropyl alcohol (30 ml) and then the solid was dried in an air oven at 75 to 80°C for 10 to 12 hours to give 5.2 g of imatinib mesylate crystalline form-α.

Analytical Result:

[0232] The sample of imatinib mesylate exists in crystalline Form-α and confirmed by a powder X-ray diffraction pattern substantially in accordance with Figure 4. The imatinib

mesylate crystalline form-α obtained by this process does not contain crystalline form-β within the limits of detection of a powder X-ray diffractometer.

Example 14

Preparation of α-Form of Imatinib mesylate

[0233] Imatinib free base (5 g) was added to a mixture of toluene (2.5 ml) and isopropyl alcohol (45 ml), followed by the addition of pure seeds of imatinib mesylate crystalline form-α (0.1 g). The resulting slurry was heated at 55-60°C, followed by slow addition of a solution of methane sulfonic acid (0.97 g) in isopropyl alcohol (5 ml). The resulting slurry was stirred for 2 hours to 3 hours. The separated solid was filtered and washed with isopropyl alcohol (30 ml) and then the solid was dried in an air oven at 75 to 80°C for 10 to 12 hours to give 5.5 g of imatinib mesylate crystalline form-α.

Analytical Result:

[0234] The sample of imatinib mesylate exists in crystalline Form-α and confirmed by a powder X-ray diffraction pattern substantially in accordance with Figure 5. The imatinib mesylate crystalline form-α obtained by this process does not contain crystalline form-β within the limits of detection of a powder X-ray diffractometer.

Example 15

Preparation of α-Form of Imatinib mesylate

[0235] Imatinib free base (5 g) was added to 2-methyltetrahydrofuran (25 ml), the slurry was heated at 55-60°C, followed by the addition of seeds of imatinib mesylate crystalline form-α (0.1 g). A solution of methane sulfonic acid (0.97 g) in 2-methyltetrahydrofuran (5 ml) was slowly added to the resulting slurry, followed by further stirring the slurry for 2 to 3 hours. The separated solid was filtered, washed with 2-methyltetrahydrofuran (30 ml) and then dried in an air oven at 75-80°C for 10 to 12 hours to produce 5.7 g of imatinib mesylate crystalline form-α.

Analytical Result:

[0236] The sample of imatinib mesylate exists in crystalline Form-α and confirmed by a powder X-ray diffraction pattern substantially in accordance with Figure 6. The imatinib mesylate crystalline form-α obtained by this process does not contain crystalline form-β within the limits of detection of a powder X-ray diffractometer.

Example 16

Preparation of α-Form of Imatinib mesylate

[0237] Imatinib free base (5 g) was added to a mixture of isopropyl alcohol (50 ml) and toluene (50 ml), the slurry was heated at 55-60°C, followed by slow addition of a solution of methane sulfonic acid (0.97 g) in isopropyl alcohol (10 ml). Seeds of imatinib mesylate crystalline form-α (0.2 g) were added to the resulting solution followed by further stirring the slurry for 2 hours. The separated solid was filtered, washed with toluene (20 ml), and then dried in an air oven at 75-80°C for 10 to 12 hours to produce 5.4 g of imatinib mesylate crystalline form-α.

Analytical Result:

[0238] The sample of imatinib mesylate exists in crystalline Form-α and confirmed by a powder X-ray diffraction pattern. The imatinib mesylate crystalline form-α obtained by this process does not contain crystalline form-β within the limits of detection of a powder X-ray diffractometer.

Example 17

Preparation of α-Form of Imatinib mesylate

[0239] Imatinib free base (5 g) was added to methyl tert-butyl ether (45 ml), the slurry was heated at 55-60°C, followed by the addition of seeds of imatinib mesylate crystalline form-α (0.1 g). A solution of methane sulfonic acid (0.97 g) in methyl isobutyl ether (5 ml) was slowly added to the resulting slurry followed by further stirring the slurry for 2 hours to 2 hours 30 minutes. The separated solid was filtered, washed with isopropyl alcohol (30 ml), and then dried in an air oven at 75-80°C for 10 to 12 hours to produce 4.8 g of imatinib mesylate crystalline form-α.

Analytical Result:

[0240] The sample of imatinib mesylate exists in crystalline Form-α and confirmed by a powder X-ray diffraction pattern substantially in accordance with Figure 7.

Example 18

Preparation of α-Form of Imatinib mesylate

[0241] Imatinib free base (5 g) was added to a mixture of toluene (10 ml), acetone (50 ml) and isopropyl alcohol (45 ml), the slurry was heated at 55-60°C, followed by the addition of seeds of imatinib mesylate crystalline form-α (0.1 g). A solution of methane sulfonic acid

(0.97 g) in isopropyl alcohol (5 ml) was slowly added to the resulting slurry followed by further stirring the slurry for 2 to 3 hours. The separated solid was filtered, washed with acetone (30 ml), and then dried in an air oven at 75-80°C for 10 to 12 hours to produce 5.7 g of imatinib mesylate crystalline form-α.

Analytical Result:

[0242] The imatinib mesylate crystalline form-α obtained by this process is contaminated with crystalline form-β and confirmed by a powder X-ray diffraction pattern substantially in accordance with Figure 8.

Example 19

Preparation of α-Form of Imatinib mesylate

[0243] Imatinib free base (5 g) was added to a mixture of toluene (10 ml) and acetone (95 ml), the slurry was heated at 55-60°C, followed by the addition of seeds of imatinib mesylate crystalline form-α (0.1 g). The resulting slurry was followed by slow addition of a solution of methane sulfonic acid (0.97 g) in acetone (5 ml) was slowly added to the resulting slurry followed by further stirring the slurry for 2 to 3 hours. The separated solid was filtered, washed with acetone (30 ml), and then dried in an air oven at 75-80°C for 10 to 12 hours to produce 6.3 g of imatinib mesylate crystalline form-α.

Analytical Result:

[0244] The imatinib mesylate crystalline form-α obtained by this process is contaminated with crystalline form-β and confirmed by a powder X-ray diffraction pattern substantially in accordance with Figure 9.

Example 20

Preparation of α-Form of Imatinib mesylate

[0245] Imatinib base (5 g) was added to N,N-dimethylacetamide (20 ml), followed by the addition of methane sulfonic acid (0.97 g), and heating the slurry at 55°C. The resulting mass was further heated at 110-120°C, followed by the addition of toluene (100 ml) and stirring the mixture for 2 hours at 110-120°C. The separated solid was filtered, washed with toluene (20 ml) and then dried in an air oven at 75-80°C for 10 to 12 hours to give 5.6 g of imatinib mesylate crystalline form-α.

Analytical Result:

[0246] The sample of imatinib mesylate exists in crystalline Form-α and confirmed by a powder X-ray diffraction pattern substantially in accordance with Figure 10. The imatinib

mesylate crystalline form-α obtained by this process dose not contain crystalline form-β within the limits of detection of a powder X-ray diffractometer.

Example 21

Preparation of α-Form of Imatinib mesylate

[0247] Imatinib base (5 g) was added to N,N-dimethylacetamide (15 ml), followed by the addition of methane sulfonic acid (0.97 g) and heating the slurry at 90°C. T-butanol (100 ml) was added to the resulting mass followed by stirring the mixture for 2 hours at 120°C. The separated solid was filtered, washed with t-butanol (10 ml), and then dried in an air oven at 75-80°C for 10 to 12 hours to give 5.2 g of imatinib mesylate crystalline form-α.

Analytical Result:

[0248] The sample of Imatinib mesylate exists in crystalline Form-α and confirmed by a powder X-ray diffraction pattern substantially in accordance with Figure 11. The imatinib mesylate crystalline form-α obtained by this process dose not contain crystalline form-β within the limits of detection of a powder X-ray diffractometer.

Example 22

Preparation of α-Form of Imatinib mesylate

[0249] Imatinib base (5 g) was added to N,N-dimethylacetamide (20 ml), followed by the addition of a solution of methane sulfonic acid (0.97 g) in N,N-dimethylacetamide (5 ml) and heating the slurry at 50-55°C. N-heptane (100 ml) was added to the resulting mass and seeds of imatinib mesylate crystalline form-α (0.2 g) were added. The resulting mixture was stirred for 2 hours at 50-55°C. The separated solid was filtered, washed with n-heptane (10 ml), and then dried in an air oven at 75-80°C for 10 to 12 hours to give 4 g of imatinib mesylate crystalline form-α.

Analytical Result:

[0250] The imatinib mesylate crystalline form-α obtained by this process is contaminated with crystalline form-β and confirmed by a powder X-ray diffraction pattern substantially in accordance with Figure 12.

Example 23

Preparation of α-Form of Imatinib mesylate

[0251] Imatinib base (5 g) was added to N,N-dimethylacetamide (15 ml), followed by the addition of methane sulfonic acid (0.97 g) and heating the slurry at 55-60°C. T-amyl alcohol

(50 ml) was added to the resulting mass followed by further heating the slurry for 2 hours at 115-120°C. The separated solid was filtered, washed with t-amyl alcohol (10 ml), and then dried in an air oven at 75-80°C for 10 to 12 hours to give 5.4 g of imatinib mesylate crystalline form-α.

Analytical Result:

[0252] The imatinib mesylate crystalline form-α obtained by this process is contaminated with crystalline form-β and confirmed by a powder X-ray diffraction pattern substantially in accordance with Figure 13.

[0253] Unless otherwise indicated, the following definitions are set forth to illustrate and define the meaning and scope of the various terms used to describe the invention herein.

[0254] The term "pharmaceutically acceptable" means that which is useful in preparing a pharmaceutical composition that is generally non-toxic and is not biologically undesirable and includes that which is acceptable for veterinary use and/or human pharmaceutical use.

[0255] The term "pharmaceutical composition" is intended to encompass a drug product including the active ingredient(s), pharmaceutically acceptable excipients that make up the carrier, as well as any product which results, directly or indirectly, from combination, complexation or aggregation of any two or more of the ingredients. Accordingly, the pharmaceutical compositions encompass any composition made by admixing the active ingredient, active ingredient dispersion or composite, additional active ingredient(s), and pharmaceutically acceptable excipients.

[0256] The term "therapeutically effective amount" as used herein means the amount of a compound that, when administered to a mammal for treating a state, disorder or condition, is sufficient to effect such treatment. The "therapeutically effective amount" will vary depending on the compound, the disease and its severity and the age, weight, physical condition and responsiveness of the mammal to be treated.

[0257] The term "delivering" as used herein means providing a therapeutically effective amount of an active ingredient to a particular location within a host causing a therapeutically effective blood concentration of the active ingredient at the particular location. This can be accomplished, e.g., by topical, local or by systemic administration of the active ingredient to the host.

[0258] The term "buffering agent" as used herein is intended to mean a compound used to resist a change in pH upon dilution or addition of acid of alkali. Such compounds include, by way of example and without limitation, potassium metaphosphate, potassium phosphate,

monobasic sodium acetate and sodium citrate anhydrous and dehydrate and other such material known to those of ordinary skill in the art.

[0259] The term "sweetening agent" as used herein is intended to mean a compound used to impart sweetness to a formulation. Such compounds include, by way of example and without limitation, aspartame, dextrose, glycerin, mannitol, saccharin sodium, sorbitol, sucrose, fructose and other such materials known to those of ordinary skill in the art.

[0260] The term "binders" as used herein is intended to mean substances used to cause adhesion of powder particles in granulations. Such compounds include, by way of example and without limitation, acacia, alginic acid, tragacanth, carboxymethylcellulose sodium, polyvinylpyrrolidone, compressible sugar (e.g., NuTab), ethylcellulose, gelatin, liquid glucose, methylcellulose, pregelatinized starch, starch, polyethylene glycol, guar gum, polysaccharide, bentonites, sugars, invert sugars, poloxamers (PLURONIC(TM) F68, PLURONIC(TM) F127), collagen, albumin, celluloses in non-aqueous solvents, polypropylene glycol, polyoxyethylene-polypropylene copolymer, polyethylene ester, polyethylene sorbitan ester, polyethylene oxide, microcrystalline cellulose, combinations thereof and other material known to those of ordinary skill in the art.

[0261] The term "diluent" or "filler" as used herein is intended to mean inert substances used as fillers to create the desired bulk, flow properties, and compression characteristics in the preparation of solid dosage formulations. Such compounds include, by way of example and without limitation, dibasic calcium phosphate, kaolin, sucrose, mannitol, microcrystalline cellulose, powdered cellulose, precipitated calcium carbonate, sorbitol, starch, combinations thereof and other such materials known to those of ordinary skill in the art.

[0262] The term "glidant" as used herein is intended to mean agents used in solid dosage formulations to improve flow-properties during tablet compression and to produce an anti-caking effect. Such compounds include, by way of example and without limitation, colloidal silica, calcium silicate, magnesium silicate, silicon hydrogel, cornstarch, talc, combinations thereof and other such materials known to those of ordinary skill in the art.

[0263] The term "lubricant" as used herein is intended to mean substances used in solid dosage formulations to reduce friction during compression of the solid dosage. Such compounds include, by way of example and without limitation, calcium stearate, magnesium stearate, mineral oil, stearic acid, zinc stearate, combinations thereof and other such materials known to those of ordinary skill in the art.

[0264] The term "disintegrant" as used herein is intended to mean a compound used in solid dosage formulations to promote the disruption of the solid mass into smaller particles which

are more readily dispersed or dissolved. Exemplary disintegrants include, by way of example and without limitation, starches such as corn starch, potato starch, pregelatinized, sweeteners, clays, such as bentonite, microcrystalline cellulose (e.g., Avicel(TM)), carsium (e.g., Amberlite(TM)), alginates, sodium starch glycolate, gums such as agar, guar, locust bean, karaya, pectin, tragacanth, combinations thereof and other such materials known to those of ordinary skill in the art.

[0265] The term "wetting agent" as used herein is intended to mean a compound used to aid in attaining intimate contact between solid particles and liquids. Exemplary wetting agents include, by way of example and without limitation, gelatin, casein, lecithin (phosphatides), 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., TWEEN(TM)s), polyethylene glycols, polyoxyethylene stearates colloidal silicon dioxide, phosphates, sodium dodecylsulfate, carboxymethylcellulose calcium, carboxymethylcellulose sodium, methylcellulose, hydroxyethylcellulose, hydroxyl propylcellulose, hydroxypropylmethylcellulose phthalate, noncrystalline cellulose, magnesium aluminum silicate, triethanolamine, polyvinyl alcohol, and polyvinylpyrrolidone (PVP).

[0266] The term "crude imatinib or a pharmaceutically acceptable salt thereof" as used herein refers to imatinib or a pharmaceutically acceptable salt thereof containing greater than about 0.2 area-%, more specifically greater than about 0.25 area-%, still more specifically greater than about 0.4 area-% and most specifically greater than about 1 area-% of at least one, or more, of the formamide, 4-methylbenzamide, and '2.24 RRt' impurities.

[0267] As used herein, the term, "detectable" refers to a measurable quantity measured using an HPLC method having a detection limit of 0.001 area-%.

[0268] As used herein, in connection with amount of impurities in imatinib or a pharmaceutically acceptable salt thereof, the term "not detectable" means not detected by the herein described HPLC method having a detection limit for impurities of 0.001 area-%.

[0269] As used herein, "limit of detection (LOD)" refers to the lowest concentration of analyte that can be clearly detected above the base line signal, is estimated is three times the signal to noise ratio.

[0270] The term "micronization" used herein means a process or method by which the size of a population of particles is reduced.

As used herein, the term "micron" or "μm" both are same refers to "micrometer" which is $1x10^{-6}$ meter.

As used herein, "crystalline particles" means any combination of single crystals, aggregates and agglomerates.

[0271] As used herein, "Particle Size Distribution (PSD)" means the cumulative volume size distribution of equivalent spherical diameters as determined by laser diffraction in Malvern Master Sizer 2000 equipment or its equivalent. "Mean particle size distribution, i.e., (D_{50})" correspondingly, means the median of said particle size distribution.

[0272] The important characteristics of the PSD are the (D_{90}), which is the size, in microns, below which 90% of the particles by volume are found, and the (D_{50}), which is the size, in microns, below which 50% of the particles by volume are found. Thus, a D_{90} or d(0.9) of less than 300 microns means that 90 volume-percent of the particles in a composition have a diameter less than 300 microns.

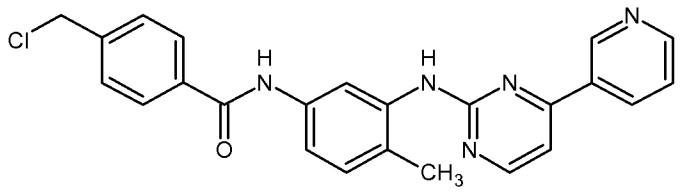
We claim:

1. Imatinib or a pharmaceutically acceptable salt thereof comprising a 4-methyl-N-[4-methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]phenyl]benzamide impurity (4-methylbenzamide impurity) in an amount of about 0.01 area-% to about 0.15 area-% as measured by HPLC.
2. Imatinib of claim 1, having a total purity of about 99.5% to about 99.99% as measured by HPLC.
3. Imatinib of claim 1, comprising the 4-methylbenzamide impurity in an amount of about 0.01 area-% to about 0.05 area-%.
4. Imatinib of claim 1, having a non-detectable amount of an N-[4-methyl-3-(4-pyridin-3-yl-pyrimidin-2-ylamino)-phenyl]-4-piperazin-1-ylmethyl-benzamide impurity (desmethyl imatinib impurity) as measured by HPLC.
5. Imatinib of claim 1, further comprising one, or more, of a 4-[(4-acetyl-1-piperazinyl)methyl]-N-[4-methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]phenyl]benzamide impurity (N-acetylpiperazine impurity), a 4-[(4-methyl-1-piperazinyl)methyl]-N-[4-methyl-3-[[[4-(3-pyridinyl)-2-pyrimidinyl]-N-acetyl]amino]phenyl]benzamide impurity (N-acetylamino impurity), a 4-[(4-methyl-1-piperazinyl)methyl]-N-[4-methyl-3-[[[4-(3-pyridinyl)-2-pyrimidinyl]-N-chloromethyl]amino]phenyl]benzamide impurity (N-chloromethylamino impurity), a N-(2-methyl-5-methylamino-phenyl)-N-(4-pyridin-3-yl-pyrimidin-2-yl)-formamide impurity (formamide impurity), and a '2.24 RRt' impurity, each, in an amount of less than 0.2 area-% as measured by HPLC.
6. Imatinib of claim 5, comprising one, or more, of the N-acetylpiperazine, N-acetylamino, N-chloromethylamino, formamide, and '2.24 RRt' impurities, each, in an amount of about 0.01 area-% to about 0.15 area-%.
7. Imatinib of claim 5, having a non-detectable amount of one, or more, of the N-acetylpiperazine, N-acetylamino, N-chloromethylamino, formamide, and '2.24 RRt' impurities as measured by HPLC.
8. Imatinib of claim 1, wherein the pharmaceutically acceptable salt of imatinib is a hydrochloride salt, a hydrobromide salt, an oxalate salt, a maleate salt, a fumarate salt, a mesylate salt, a besylate salt, a tosylate salt or a tartrate salt.
9. Imatinib of claim 1, wherein the pharmaceutically acceptable salt of imatinib is imatinib mesylate salt.

10. Imatinib or a pharmaceutically acceptable salt thereof essentially free from a desmethyl imatinib impurity, N-[4-methyl-3-(4-pyridin-3-yl-pyrimidin-2-ylamino)-phenyl]-4-piperazin-1-ylmethyl-benzamide impurity, as measured by HPLC.

11. A process for preparing highly pure imatinib or a pharmaceutically acceptable salt thereof of any one of claims 1 to 10, comprising:

a) reacting 4-chloromethyl-N-[4-methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]phenyl] benzamide of formula II:



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with N-methylpiperazine in an amide solvent to produce a first reaction mass containing imatinib free base;

b) isolating and/or recovering crude imatinib free base from the first reaction mass;

c) admixing the crude imatinib free base with water to form a first admixture;

d) acidifying the first admixture with an organic acid to produce an aqueous reaction mass;

e) admixing the aqueous reaction mass with an ester solvent to produce a second admixture;

f) combining the second admixture with a base to produce a second reaction mass;

g) isolating and/or recovering imatinib free base from the second reaction mass;

h) contacting the imatinib free base obtained in step-(b) or step-(g) with acetic anhydride in the presence of a mineral acid in a chlorinated hydrocarbon solvent to produce a third reaction mass;

i) admixing the third reaction mass with water to form a third admixture;

j) combining the third admixture with a base to produce a biphasic reaction mixture and separating the organic layer from the biphasic reaction mixture; and

k) substantially removing the solvent from the organic layer obtained in step-(j) by distillation under vacuum to produce highly pure imatinib free base substantially free impurities and optionally converting the highly pure imatinib obtained into a pharmaceutically acceptable salt thereof.

12. The process of claim 11, wherein the amide solvent used in step-(a) is selected from the group consisting of N,N-dimethylformamide, N,N-dimethylacetamide, and mixtures

thereof; wherein the organic acid used in step-(d) is selected from the group consisting of acetic acid, p-toluenesulfonic acid, methanesulfonic acid, oxalic acid, p-bromophenylsulfonic acid, carbonic acid, succinic acid, citric acid, benzoic acid, maleic acid, fumaric acid and tartaric acid; wherein the ester solvent used in step-(e) is selected from the group consisting of methyl acetate, ethyl acetate, n-propyl acetate, isopropyl acetate, n-butyl acetate, isobutyl acetate, tert-butyl acetate, ethyl formate, and mixtures thereof; wherein the base used in steps-(f) and (j) is, each independently, an organic or inorganic base selected from the group consisting of triethylamine, tributylamine, diisopropylethylamine, diethylamine, tert-butyl amine, N-methylmorpholine, pyridine, 4-(N,N-dimethylamino)pyridine, ammonia, sodium hydroxide, calcium hydroxide, magnesium hydroxide, potassium hydroxide, lithium hydroxide, sodium carbonate, potassium carbonate, lithium carbonate, sodium tert-butoxide, sodium isopropoxide, potassium tert-butoxide, and mixtures thereof; wherein the chlorinated hydrocarbon solvent used in step-(h) is selected from the group consisting of methylene chloride, ethyl dichloride, chloroform, carbon tetrachloride, and mixtures thereof; and wherein the mineral acid used in step-(h) is selected from the group consisting of hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid and nitric acid.

13. The process of claim 12, wherein the amide solvent used in step-(a) is N,N-dimethylformamide; wherein the organic acid used in step-(d) is acetic acid; wherein the ester solvent used in step-(e) is ethyl acetate; wherein the base used in steps-(f) and (j) is aqueous ammonia; wherein the chlorinated hydrocarbon solvent used in step-(h) is methylene chloride; and wherein the mineral acid used in step-(h) is sulfuric acid.

14. The process of claim 11, wherein the reaction in step-(a) is carried out at a temperature of below about 10°C; wherein the isolation in steps-(b) and (g) is, each independently, carried out by cooling, seeding, partial removal of the solvent from the solution, by adding an anti-solvent to the solution, or a combination thereof; wherein the recovering in steps-(b) and (g) is, each independently, accomplished by filtration, filtration under vacuum, decantation, centrifugation, filtration employing a filtration media of a silica gel or celite, or a combination thereof; wherein the acidification in step-(d) is carried out at a temperature of about 0°C to about 50°C; wherein the acidification in step-(d) is carried out by adjusting the pH of the reaction mixture between about 2.5 and 4.5 with an organic acid; wherein the reaction in step-(h) is carried out at a temperature of below about 50°C; wherein the distillation process in step-(k) is performed under vacuum at a temperature of below about 45°C; and wherein the highly pure imatinib a pharmaceutically acceptable

salt thereof obtained in step-(k) is further dried under vacuum or at atmospheric pressure, at a temperature of about 35°C to about 70°C.

15. The process of claim 14, wherein the reaction in step-(a) is carried out at a temperature of about –10°C to about 5°C; wherein the isolation in steps-(b) and (g) is carried out by cooling the solution while stirring at a temperature of about 0°C to about 30°C; wherein the acidification in step-(d) is carried out at a temperature of about 15°C to about 35°C; wherein the acidification in step-(d) is carried out by adjusting the pH of the reaction mixture between about 3 and 4 with an organic acid; wherein the reaction in step-(h) is carried out at a temperature of about 0°C to about 35°C; and wherein the distillation process in step-(k) is performed under vacuum at a temperature of about 15°C to about 25°C.

16. A process for preparing highly pure imatinib or a pharmaceutically acceptable salt thereof of any one of claims 1 to 10, comprising:
    a) admixing crude imatinib free base with water to form a first admixture;
    b) acidifying the first admixture with an organic acid to produce an first reaction mass;
    c) admixing the first reaction mass with an ester solvent to produce a second admixture;
    d) combining the second admixture with a base to produce a second reaction mass;
    e) isolating and/or recovering imatinib free base from the second reaction mass;
    f) contacting the imatinib free base obtained in step-(e) with acetic anhydride in the presence of a mineral acid in a chlorinated hydrocarbon solvent to produce a third reaction mass;
    g) admixing the third reaction mass with water to form a third admixture;
    h) combining the third admixture with a base to produce a biphasic reaction mixture and separating the organic layer from the biphasic reaction mixture; and
    i) substantially removing the solvent from the organic layer obtained in step-(h) by distillation under vacuum to produce highly pure imatinib free base substantially free impurities and optionally converting the highly pure imatinib obtained into a pharmaceutically acceptable salt thereof.

17. The process of claim 16, wherein the organic acid used in step-(b) is selected from the group consisting of acetic acid, p-toluenesulfonic acid, methanesulfonic acid, oxalic acid, p-bromophenylsulfonic acid, carbonic acid, succinic acid, citric acid, benzoic acid, maleic acid, fumaric acid and tartaric acid; wherein the ester solvent used in step-(c) is selected from the group consisting of methyl acetate, ethyl acetate, n-propyl acetate, isopropyl acetate, n-butyl acetate, isobutyl acetate, tert-butyl acetate, ethyl formate, and mixtures

thereof; wherein the base used in step-(d) is an organic or inorganic base selected from the group consisting of triethylamine, tributylamine, diisopropylethylamine, diethylamine, tert-butyl amine, N-methylmorpholine, pyridine, 4-(N,N-dimethylamino)pyridine, ammonia, sodium hydroxide, calcium hydroxide, magnesium hydroxide, potassium hydroxide, lithium hydroxide, sodium carbonate, potassium carbonate, lithium carbonate, sodium tert-butoxide, sodium isopropoxide, potassium tert-butoxide, and mixtures thereof; wherein the chlorinated hydrocarbon solvent used in step-(f) is selected from the group consisting of methylene chloride, ethyl dichloride, chloroform, carbon tetrachloride, and mixtures thereof; and wherein the mineral acid used in step-(f) is selected from the group consisting of hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid and nitric acid.

18. The process of claim 17, wherein the organic acid used in step-(b) is acetic acid; wherein the ester solvent used in step-(c) is ethyl acetate; wherein the base used in step-(d) is aqueous ammonia; wherein the chlorinated hydrocarbon solvent used in step-(f) is methylene chloride; and wherein the mineral acid used in step-(f) is sulfuric acid.

19. A process for preparing highly pure imatinib or a pharmaceutically acceptable salt thereof of any one of claims 1 to 10, comprising:
    a) contacting crude imatinib free base with acetic anhydride in the presence of a mineral acid in a chlorinated hydrocarbon solvent to produce a reaction mass;
    b) admixing the reaction mass obtained in step-(a) with water to form an admixture;
    c) combining the admixture with a base to produce a biphasic reaction mixture and separating the organic layer from the biphasic reaction mixture; and
    d) substantially removing the solvent from the organic layer obtained in step-(c) by distillation under vacuum to produce highly pure imatinib free base substantially free impurities and optionally converting the highly pure imatinib obtained into a pharmaceutically acceptable salt thereof.

20. The process of claim 19, wherein the chlorinated hydrocarbon solvent used in step-(a) is selected from the group consisting of methylene chloride, ethyl dichloride, chloroform, carbon tetrachloride, and mixtures thereof; and wherein the mineral acid used in step-(a) is selected from the group consisting of hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid and nitric acid.

21. The process of claim 20, wherein the chlorinated hydrocarbon solvent used in step-(a) is methylene chloride; and wherein the mineral acid used in step-(a) is sulfuric acid.

22. A process preparing crystalline form-α of imatinib mesylate, comprising:

a) providing a slurry of imatinib free base in a solvent medium comprising a first solvent and a second solvent, wherein the first solvent is isopropyl alcohol and wherein the second solvent is an ether solvent or an aromatic hydrocarbon solvent;

b) heating the slurry obtained in step-(a) at a temperature of above about 50°C to produce a hot slurry;

c) optionally, seeding the slurry obtained either in step-(a) or in step-(b) with a crystalline form-α of imatinib mesylate;

d) combining the hot slurry with a solution of methanesulfonic acid in isopropyl alcohol to produce a reaction mass containing imatinib mesylate; and

e) recovering crystalline form-α of imatinib mesylate in substantially pure form from the reaction mass obtained in step-(d).

23. The process of claim 22, wherein the second solvent used in step-(a) is selected from the group consisting of tetrahydrofuran, 2-methyltetrahydrofuran, dioxane, diethyl ether, diisopropyl ether, methyl tert-butyl ether, methyl isobutyl ether, monoglyme, diglyme, toluene, xylene, and mixtures thereof; wherein the second solvent in step-(a) is used in an amount of about 0.1 to 5.0 volumes with respect to the first solvent; and wherein the amount of solvent medium employed in step-(a) is about 5 volumes to about 25 volumes with respect to the imatinib free base.

24. The process of claim 23, wherein the second solvent used in step-(a) is methyl tert-butyl ether; wherein the second solvent in step-(a) is used in an amount of about 0.5 to 2.0 volumes with respect to the first solvent; and wherein the amount of solvent medium employed in step-(a) is about 7 volumes to about 17 volumes with respect to the imatinib free base.

25. A process preparing crystalline form-α of imatinib mesylate, comprising:

a) providing a solution of imatinib mesylate in a solvent selected from the group consisting of N,N-dimethylformamide, N,N-dimethylacetamide and mixtures thereof;

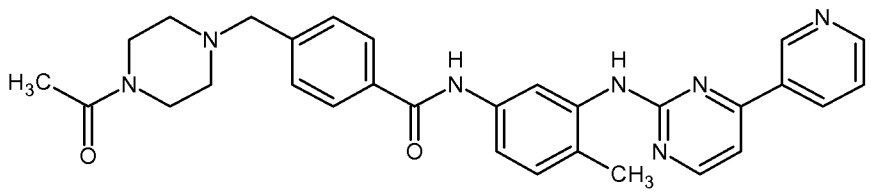
b) optionally, filtering the solution to remove insoluble matter;

c) precipitating crystalline form-α of imatinib mesylate by combining the solution obtained in step-(a) or step-(b) with an anti-solvent selected from the group consisting of t-butanol, toluene and mixtures thereof; and

d) optionally, seeding the solution in step-(c) with crystalline form-α prior to or after the addition of anti-solvent;

e) recovering the crystalline form-α of imatinib mesylate in substantially pure form.

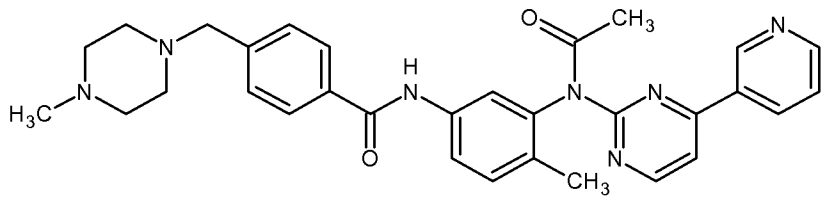
26. The process of claim 25, wherein the amount of solvent used in step-(a) is about 2 volumes to about 10 volumes with respect to the quantity of imatinib base; and wherein the amount of anti-solvent used in step-(c) is about 6 volumes to about 35 volumes with respect to the quantity of imatinib base.
27. The process of claim 26, wherein the amount of solvent used in step-(a) is about 3 volumes to about 5 volumes with respect to the quantity of imatinib base; and wherein the amount of anti-solvent used in step-(c) is about 8 volumes to about 32 volumes with respect to the quantity of imatinib base.
28. An isolated N-acetylpiperazine compound, 4-[(4-acetyl-1-piperazinyl)methyl]-N-[4-methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]phenyl]benzamide, of formula A:



---------- A

or a pharmaceutically acceptable acid addition salt thereof.

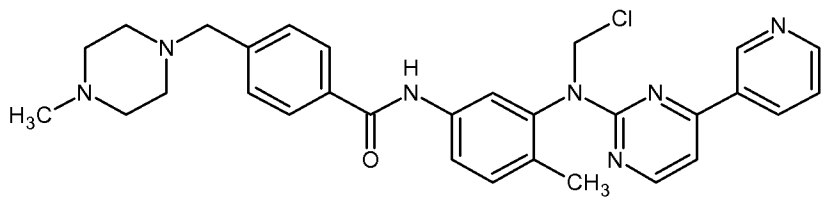
29. An isolated N-acetylamino compound, 4-[(4-methyl-1-piperazinyl)methyl]-N-[4-methyl-3-[[[4-(3-pyridinyl)-2-pyrimidinyl]-N-acetyl]amino]phenyl]benzamide, of formula B:



---------- B

or a pharmaceutically acceptable salt thereof.

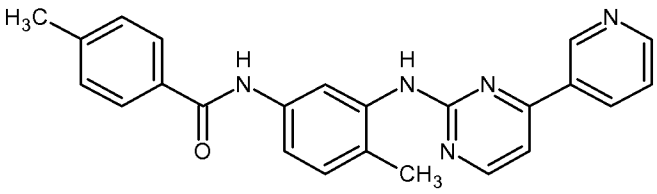
30. An isolated N-chloromethylamino compound, 4-[(4-methyl-1-piperazinyl)methyl]-N-[4-methyl-3-[[[4-(3-pyridinyl)-2-pyrimidinyl]-N-chloromethyl]amino]phenyl]benzamide, of formula C:



---------- C

or a pharmaceutically acceptable salt thereof

31. An isolated 4-methylbenzamide impurity, 4-methyl-N-[4-methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]phenyl]benzamide, of formula E:



---------- E

32. A pharmaceutical composition comprising highly pure imatinib or a pharmaceutically acceptable salt thereof of any one of claims 1 to 10, and one or more pharmaceutically acceptable excipients.
33. The pharmaceutical composition of claim 32, wherein the imatinib or a pharmaceutically acceptable salt thereof has a D90 particle size of about 1 micron to about 400 microns.
34. The pharmaceutical composition of claim 33, wherein the D_{90} particle size is about 10 microns to about 200 microns.
35. A method for treating a patient suffering from tumoral diseases, comprising administering a pharmaceutical composition comprising highly pure imatinib or a pharmaceutically acceptable salt thereof of claim 32.

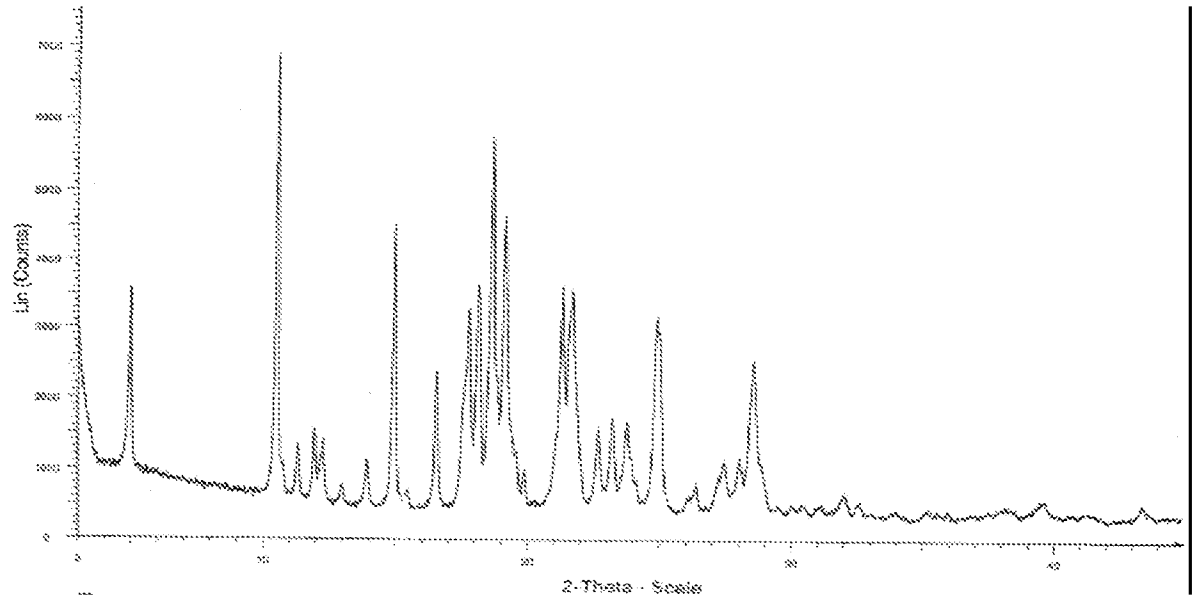


Figure 1: Powder X-ray diffraction (XRD) pattern of α-form of imatinib mesylate prepared according to the process disclosed in Example 8

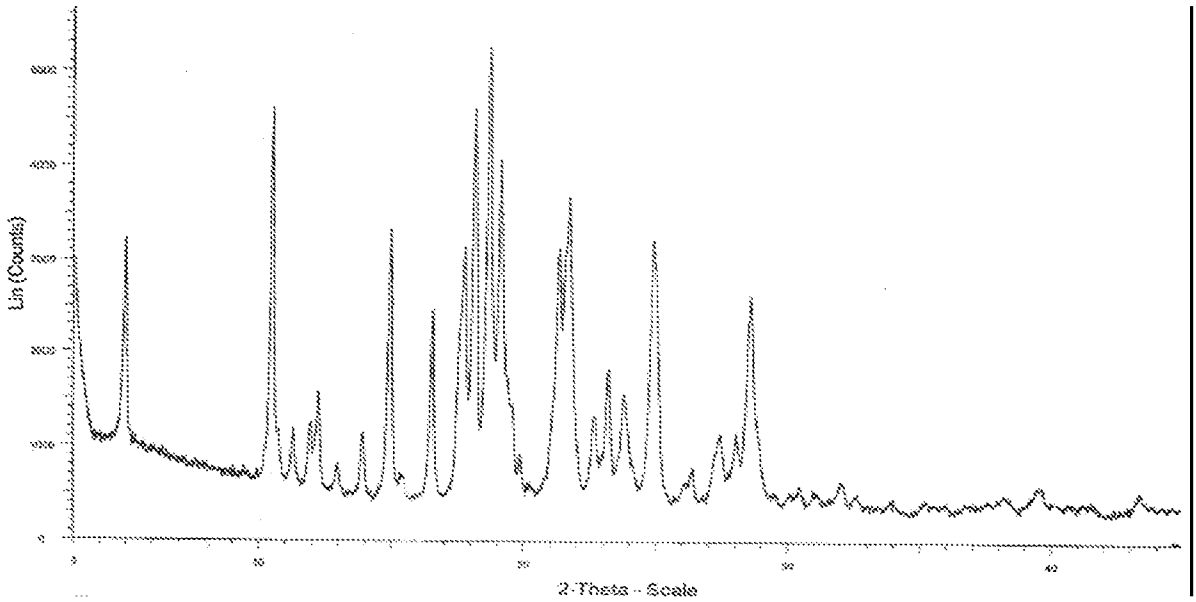


Figure 2: Powder X-ray diffraction (XRD) pattern of α-form of imatinib mesylate prepared according to the process disclosed in Example 11

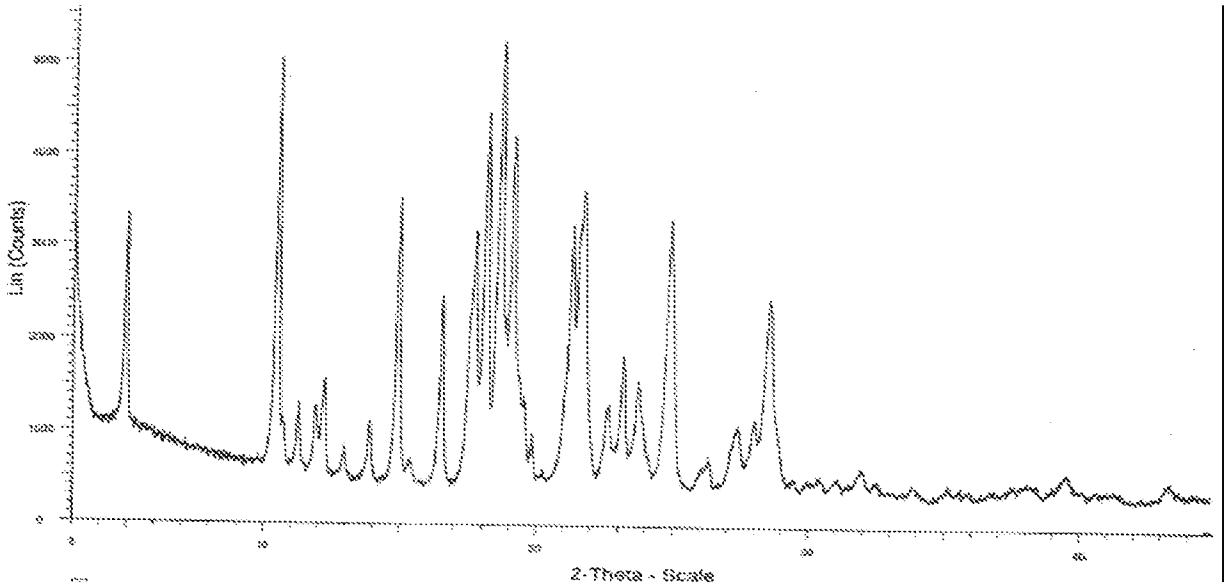


Figure 3: Powder X-ray diffraction (XRD) pattern of α-form of imatinib mesylate prepared according to the process disclosed in Example 12

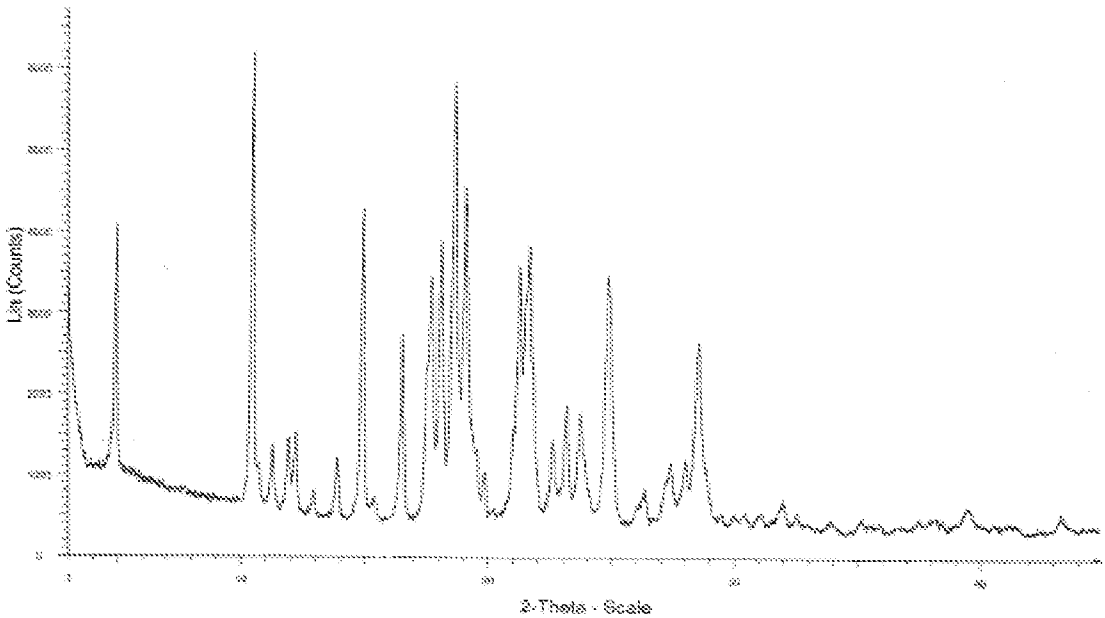


Figure 4: Powder X-ray diffraction (XRD) pattern of α-form of imatinib mesylate prepared according to the process disclosed in Example 13

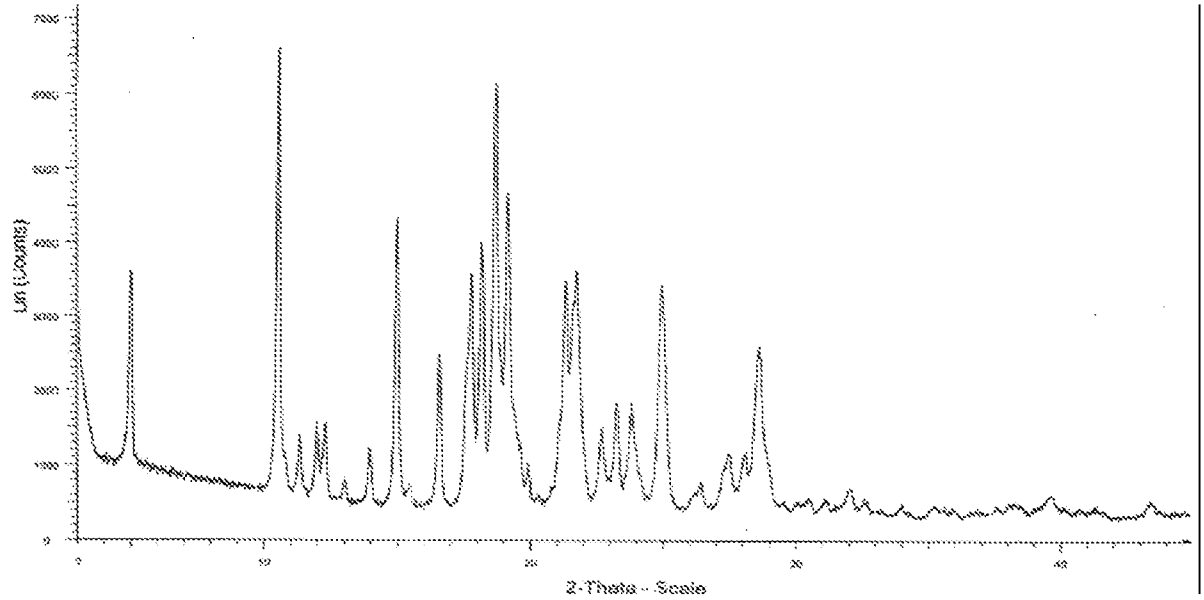


Figure 5: Powder X-ray diffraction (XRD) pattern of α-form of imatinib mesylate prepared according to the process disclosed in Example 14

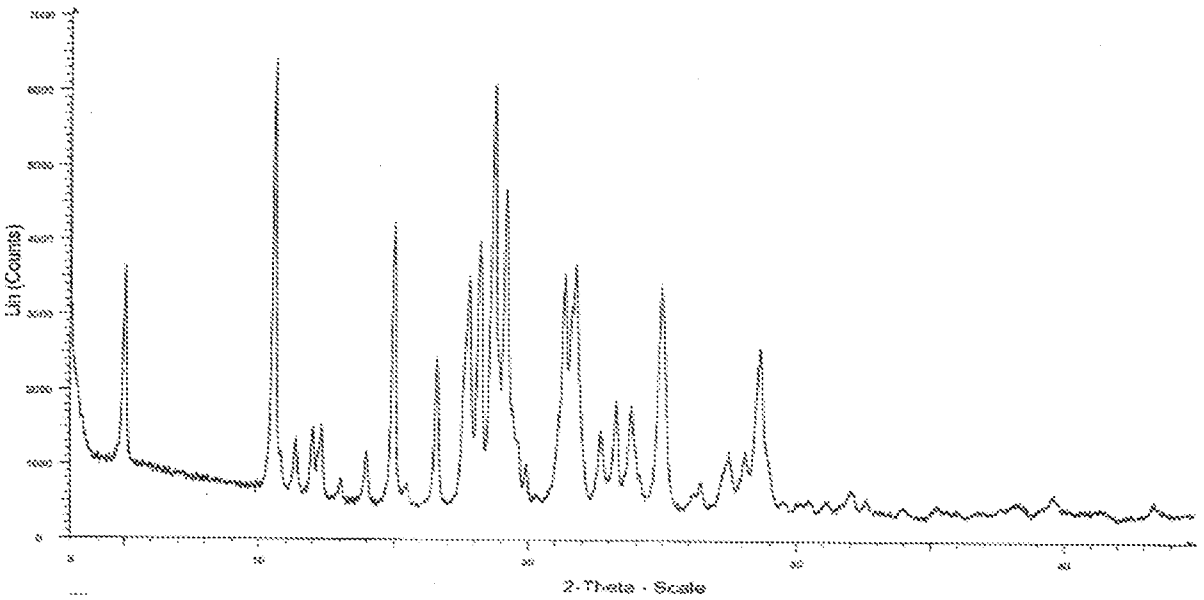


Figure 6: Powder X-ray diffraction (XRD) pattern of α-form of imatinib mesylate prepared according to the process disclosed in Example 15

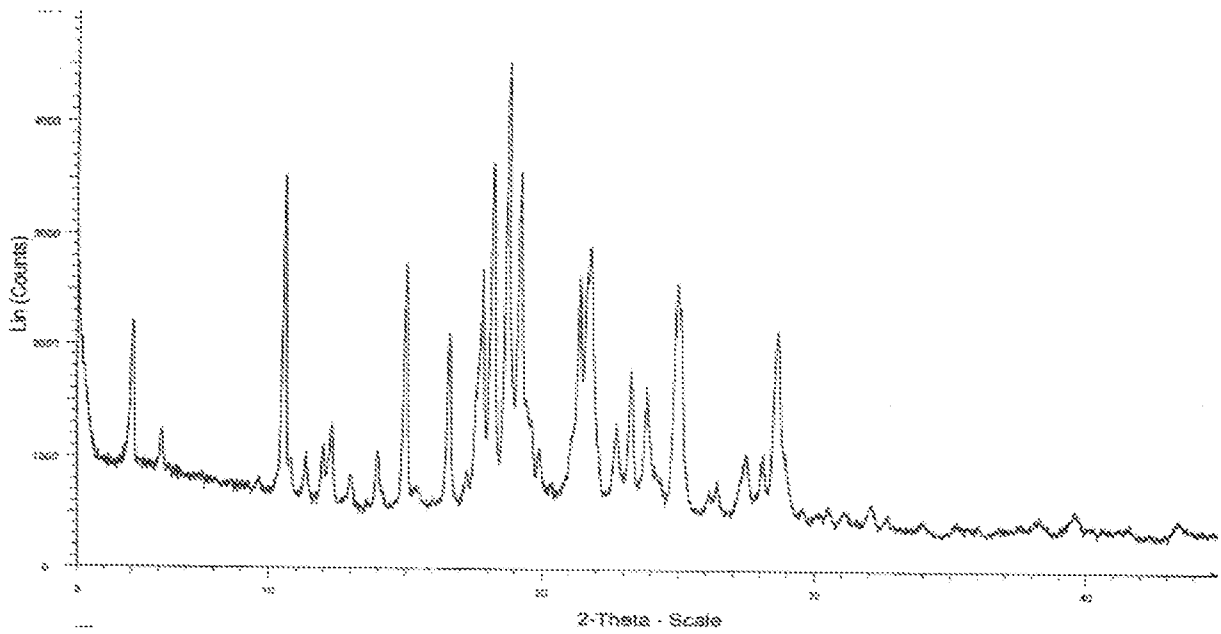


Figure 7: Powder X-ray diffraction (XRD) pattern of α-form of imatinib mesylate prepared according to the process disclosed in Example 17

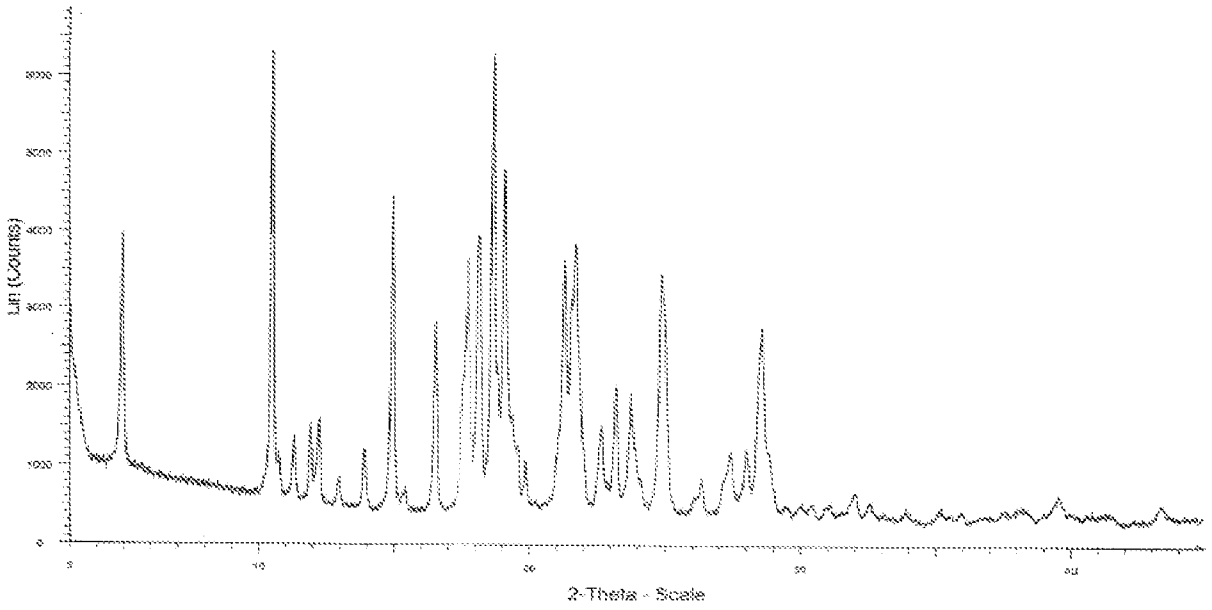


Figure 8: Powder X-ray diffraction (XRD) pattern of α-form of imatinib mesylate prepared according to the process disclosed in Example 18

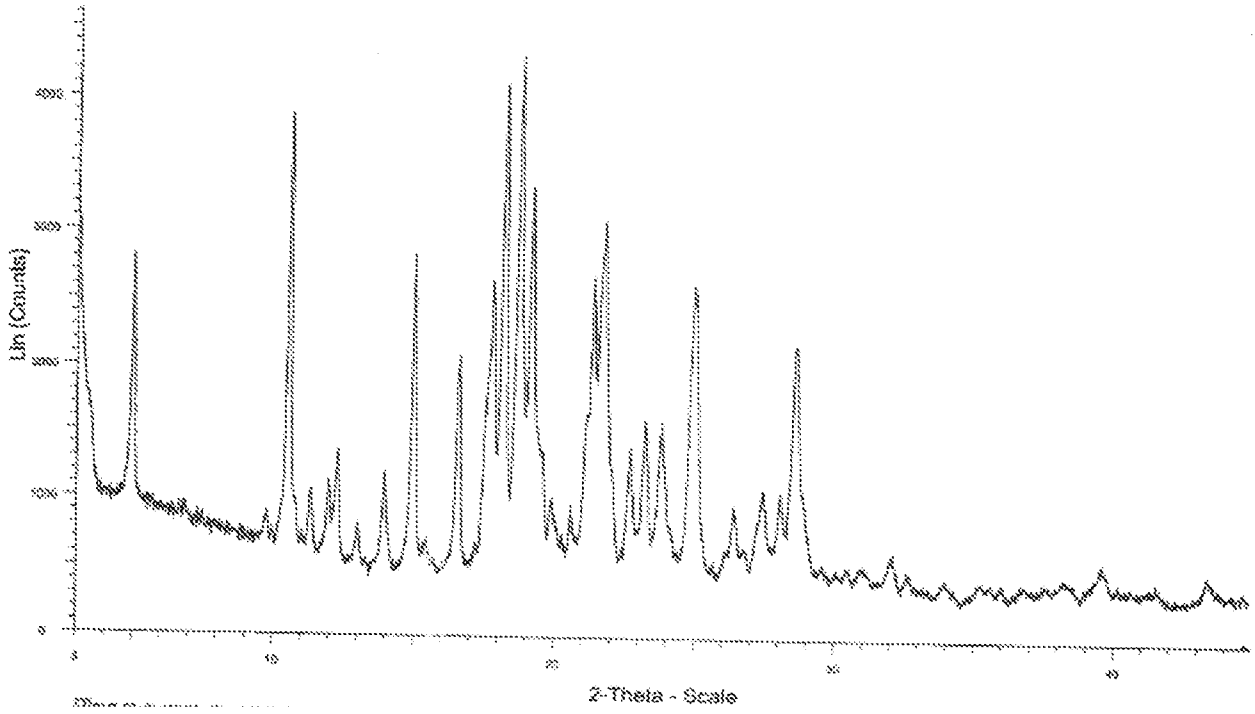


Figure 9: Powder X-ray diffraction (XRD) pattern of α-form of imatinib mesylate prepared according to the process disclosed in Example 19

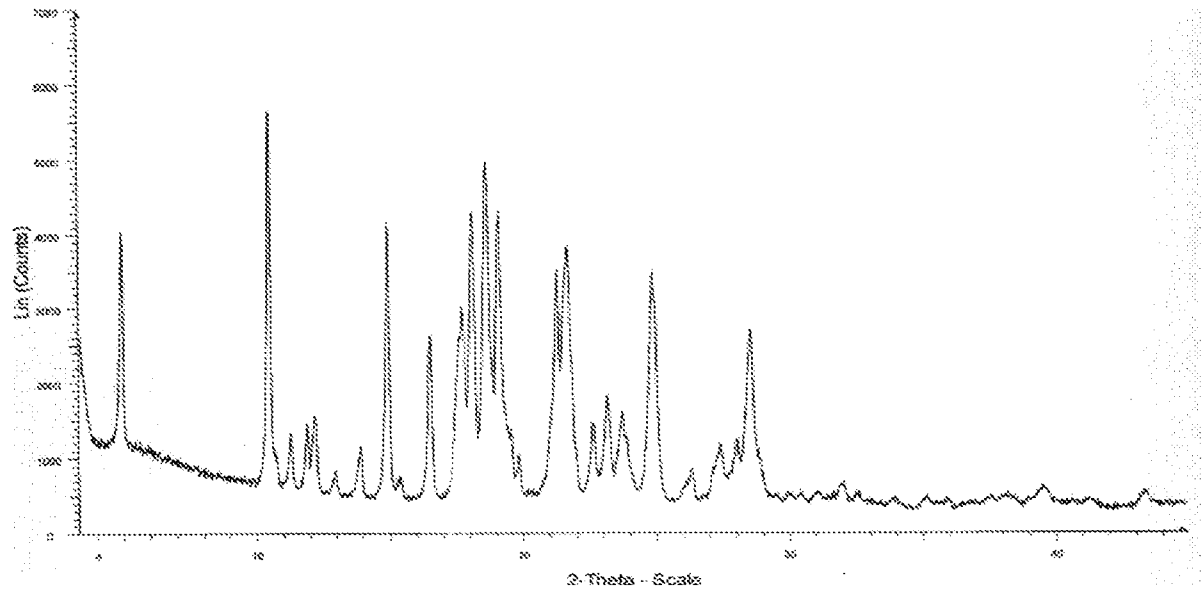


Figure 10: Powder X-ray diffraction (XRD) pattern of α-form of imatinib mesylate prepared according to the process disclosed in Example 20

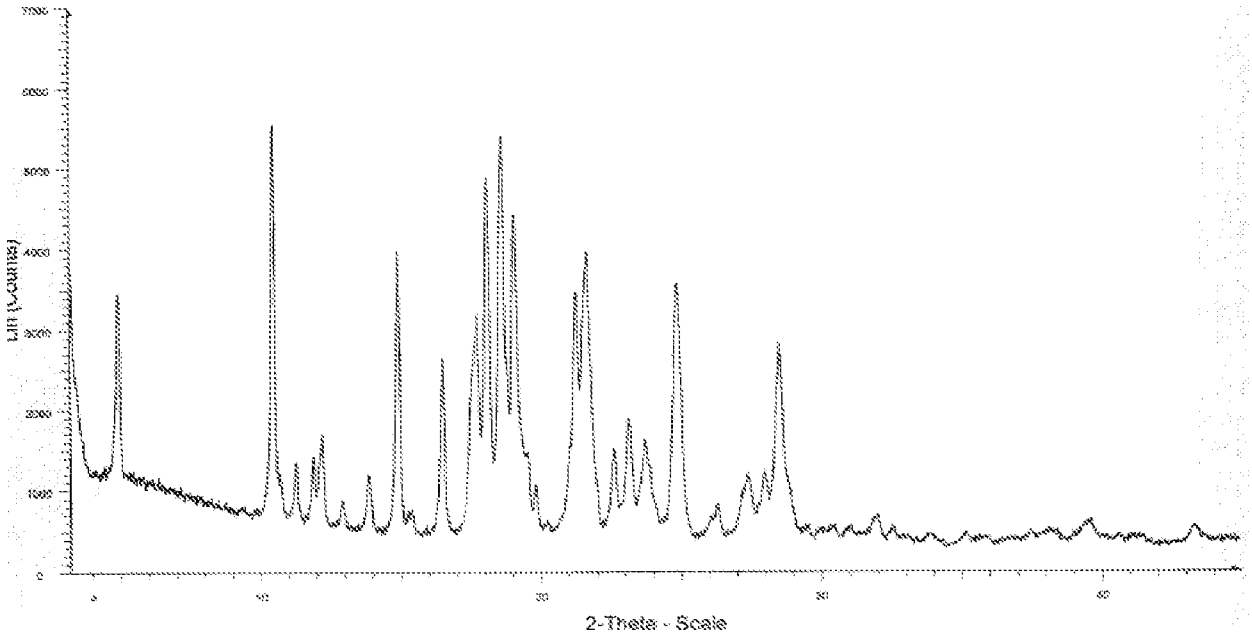


Figure 11: Powder X-ray diffraction (XRD) pattern of α-form of imatinib mesylate prepared according to the process disclosed in Example 21

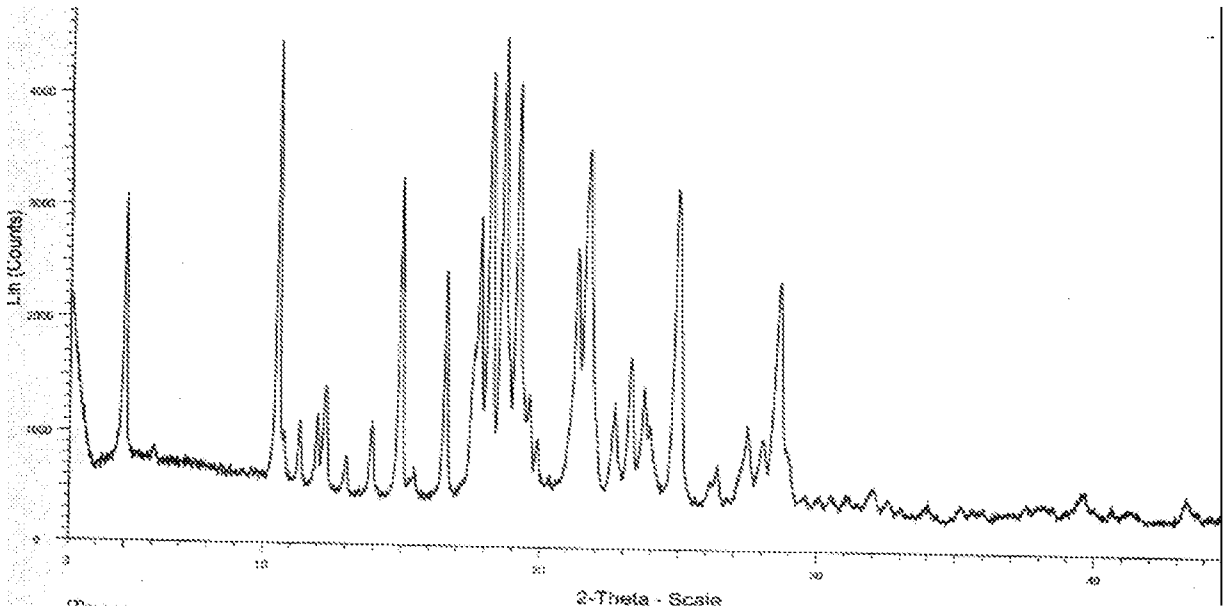


Figure 12: Powder X-ray diffraction (XRD) pattern of α-form of imatinib mesylate prepared according to the process disclosed in Example 22

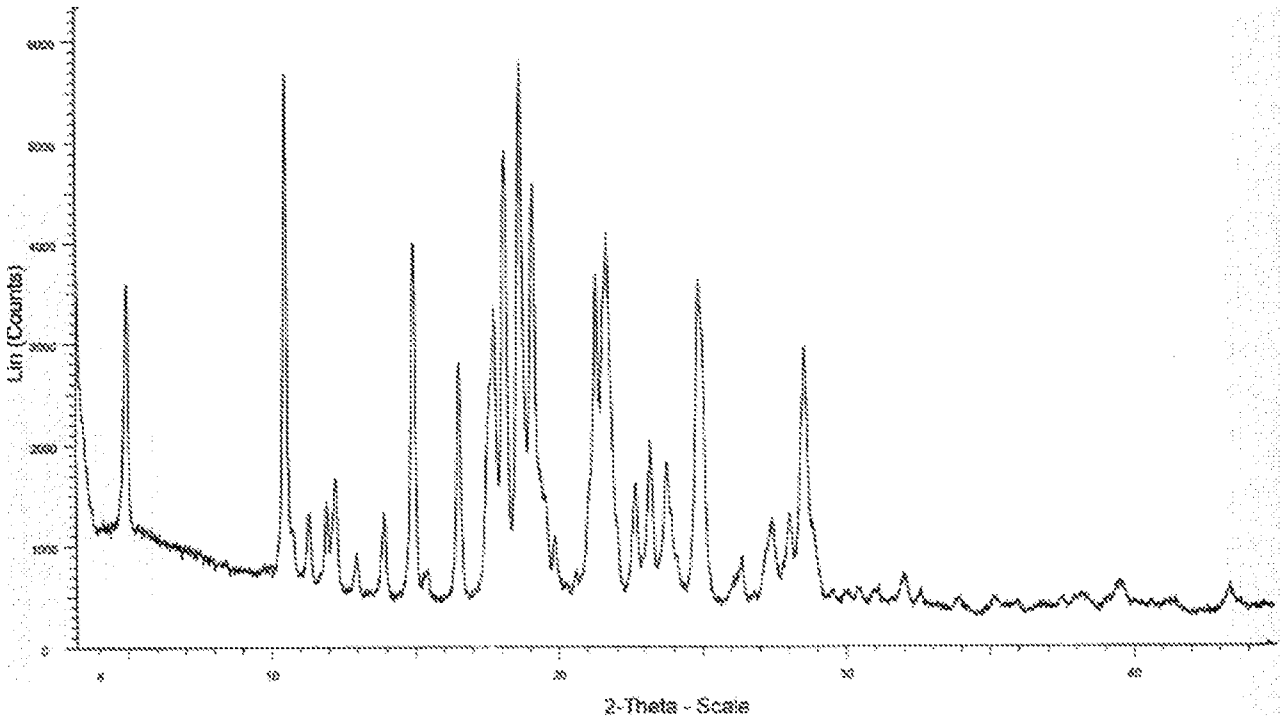


Figure 13: Powder X-ray diffraction (XRD) pattern of α-form of imatinib mesylate prepared according to the process disclosed in Example 23

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2010/003418

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D401/04 A61K31/506 A61P35/02
ADD.

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D

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

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2006/021458 A2 (GPC BIOTECH A.-G., GERMANY) 2 March 2006 (2006-03-02) page 57, line 15 - page 59, line 2; claim 1	1-10, 32-35
X	WO 2004/108699 A1 (NATCO PHARMA LIMITED, INDIA) 16 December 2004 (2004-12-16) page 21, line 11 - page 22, line 24	1-10, 32-35
X	WO 2006/071130 A2 (INSTYTUT FARMACEUTYCZNY, POL.) 6 July 2006 (2006-07-06) page 20, line 3 - page 21, line 16; claims	1-10, 32-35

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[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
7 April 2011	10/06/2011

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Gavriliu, Daniela

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Form PCT/ISA/210 (second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2010/003418

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DATABASE CAPLUS [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; KOMPELLA, AMALA ET AL: "A process for the preparation of highly pure imatinib base", XP002631808, retrieved from STN Database accession no. 2008:1466023 abstract -----	1-10
X	WO 2008/135980 A1 (CHEMAGIS LTD [IL]; XING LIU [CN]; XUNGUI HE [CN]; WANG YUAN [CN]; BEKH) 13 November 2008 (2008-11-13) claims; examples -----	1-10, 32-35
X	EP 1 988 089 A1 (SICOR INC [US]) 5 November 2008 (2008-11-05) claims; example 5 -----	1-10, 32-35

1

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB2010/003418

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

1-10, 32-35

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1-10, 32-35

   Imatinib or its salts and their pharmaceutical compositions and uses

   ---

2. claims: 11-21

   A process for purification of imatinib

   ---

3. claims: 22-24

   A process for preparing crystalline form-alpha of imatinib mesylate, using a imatinib free base as raw material

   ---

4. claims: 25-27

   A process for preparig crystalline form-alpha of imatinib mesylate, using a imatinib mesylate as raw material

   ---

5. claim: 28

   N-acetylpiperazine derivative of formula A

   ---

6. claim: 29

   N-acetylamino derivative of formula B

   ---

7. claim: 30

   N-chloromethylamino derivative of formula C

   ---

8. claim: 31

   Imatinib impurity of formula E

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/IB2010/003418

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2006021458 A2	02-03-2006	CA 2578122 A1	02-03-2006
		EP 1786781 A2	23-05-2007
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		US 2008187575 A1	07-08-2008
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WO 2006071130 A2	06-07-2006	AT 481398 T	15-10-2010
		EP 1833815 A2	19-09-2007
		SI 1833815 T1	31-01-2011
		US 2008194819 A1	14-08-2008
WO 2008135980 A1	13-11-2008	EP 2146978 A1	27-01-2010
		JP 2010526056 T	29-07-2010
		US 2008275055 A1	06-11-2008
EP 1988089 A1	05-11-2008	EP 2009008 A1	31-12-2008