IMATINIB MESYLATE POLYMORPHS GENERATED BY CRYSTALLIZATION IN AQUEOUS INORGANIC SALT SOLUTIONS

Abstract: The solution relates to a method of preparation of an imatinib mesylate polymorph as an API form suitable for dosage forms. Formation of new polymorphs of tyrrosine kinase inhibitors proceeds depending on the conditions, said method consisting of the following steps: a) preparation of imatinib mesylate by reaction of the imatinib base and methanesulfonic acid in aqueous environment or in a water-organic solvent mixture, with optional addition of an organic solvent; b) addition of an inorganic salt in an aqueous solution, controlling the pH and ionic strength of the solution; c) crystallization process at controlled temperature. The solution also relates to the crystalline form of imatinib mesylate polymorph and use thereof. Two new polymorphous forms of Imatinib mesylate are accessible through this method, these forms are named polymorph "Z1" and "Z2". "Z1" is characterized by peaks in the XRPD at 5.3; 7.5; 10.0; 10.6; 14.1; 15.0 and 16.6°. "Z2" is characterized by peaks in the XRPD at 5.5; 10.6; 10.9; 14.9; 17.0 and 21.9°.
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IMATINIB MESYLATE POLYMORPHS GENERATED BY CRYSTALLIZATION IN AQUEOUS INORGANIC SALT SOLUTIONS

Technical Field
The invention relates to a method of production of new polymorphs of imatinib mesylate and a method of applying them.

Background Art
Imatinib is an inhibitor of the family of tyrosine kinase proteins and it is used in treatment of various types of tumour diseases, usually in the form of the salt with methanesulfonic acid.

It is available in the market under trade name Glivec (Novartis) in the form of tablets for oral application.

Imatinib (contained in the product in the form of mesylate - IM) is a derivative of phenylaminopyrimidine. It works as a selective competitive inhibitor of tyrosine kinases ABL, BCR/ABL, c-Kit, PDGFR-a, PDGFR-b and Arg. Imatinib is indicated for treatment of patients with a Philadelphia chromosome - Ph (or bcr/abl) positive chronic myeloid leukaemia (CML) in the first line, with Ph+ acute lymphoblastic leukaemia (ALL), gastrointestinal stromal tumour, chronic eosinophilic leukaemia or hyper-eosinophilic syndrome and systemic mastocytosis with positivity FIP1LI/PDGFR-a or ETV6/PDGFR-b.

Pharmacological properties

When administered orally, IM is absorbed quickly and achieves the maximum plasmatic concentration in about 1 to 3 hours post application, independently of the simultaneous food intake. Bioavailability of the substance exceeds 97%. Biological half-time of imatinib elimination ranges between 15 and 20 hours, which enables administration in one dose daily. Pharmacokinetic parameters do not vary after repeated administration and a balanced state is achieved at plasmatic concentrations which are 1.5 to 3 times higher than those achieved at single administration. The balanced state is achieved after approximately one-month administration. EVI in plasma is bound almost completely to proteins, in particular albumin.

Imatinib is bio-transformed in liver by cytochrome system P-450, particularly the CYP3A4 isoenzyme. The degradation results in a whole range of substances eliminated from organism mainly through stools (in about 70%), a minor part is eliminated through urine (10%). About 20% of the administered dose is eliminated through stools in an unchanged form.
Approximately 80% of the drug is eliminated within a week, the terminal elimination half-time after a dose reaches three weeks.

Polymorphic forms of imatinib

So far, a number of polymorphs of imatinib has been described.

Overview and comparison with new polymorphs according to the submitted invention are summarized in Table 1.

WO07/023182 Novartis - Delta and epsilon crystal forms of imatinib mesylate

WO07/059963A1 Novartis - F, G, H, I and K crystal forms of imatinib mesylate

WO99/03854A1 Novartis - Crystalline form beta of imatinib mesylate

WO06/024863A1 Cipla - Imatinib mesylate: Preparation of form alpha, form alpha; Stable crystal form; Stable crystal form of needle crystals

WO06/048890A1 Sun - Alpha non needle shape form; Crystalline form of imatinib mesylate

WO05/077933A1 Natco - Form alpha2; Process for form beta imatinib mesylate

WO06/054314 Natco - Crystalline forms I and II; Composition containing I, II or mixture of imatinib mesylate

WO04/106326A1 HeteroDrugs - Crystalline form H1; Imatinib mesylate hydrate

WO05/095379B1 InstytutFarmPL - Preparation alpha form; "dimethanesulphonic" acid, crystalline form, form I, II, mixture

Description of API preparation and generation of solid dispersions of imatinib mesylate and using cellulose derivatives.


Imatinib and its salts as antitumor drugs - patent US 5 521 184.

Two crystalline forms (α-form and β-form) of imatinib mesylate - WO 99/03854.

WO 99/03854 - two amorphous forms of imatinib mesylate.

Other patents include:

Stabilized amorphous forms of imatinib mesylate

The invention relates to a stabilized amorphous form of the addition salt of imatinib and
methanesulfonic acid, to pharmaceutical preparations like capsules and tablets containing said form, use of said form in diagnostic methods or possibly for treatment of animals and particularly humans, and use of formulations stabilizing the amorphous form of imatinib mesylate.

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Stabilized amorphous forms of imatinib mesylate


10  

Stabilized amorphous forms of imatinib mesylate.


Procedures for preparation of a crystalline form of imatinib mesylate


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Crystalline imatinib mesylate, production thereof, production of amorphous imatinib mesylate and solid products containing crystalline or amorphous imatinib mesylate

The invention relates to solvates of imatinib mesylate with aliphatic alcohols, ethers, nitromethane or acetic acid, showing improved properties when handling them. Characterization of crystalline imatinib mesylate was also discovered by means of solid phase 13C NMR spectra and X-ray diffraction, a method of preparation of amorphous imatinib mesylate, of pharmaceutical compositions containing crystalline or amorphous imatinib mesylate and a method of preparation of those pharmaceuticals. For example, 3 g of imatinib base was mixed in 60 ml of ethanol at 10 °C, 0.375 ml of methanesulfonic acid was added and the dispersion mixture was crystallized at -5 °C for 3 days. 50 ml of tert-butyl methyl ether was added to the dispersion, the white solid substance was filtered, washed with petroleum ether and crystalline form IV of imatinib mesylate was obtained by drying.

Crystalline imatinib mesylate, manufacture thereof, manufacture of amorphous imatinib mesylate and solid compositions containing crystalline or amorphous imatinib mesylate. Jegorov, Alexandr; Veverka, Miroslav; Aronhime, Judith; Gavenda, Ales; Faustmann, Jiri.
Crystalline forms of imatinib mesylate and forms for therapeutic doses (containing these crystalline forms) for diagnostics and treatment of tumours

The invention relates to crystalline forms F-, G-, H-, I-, and K of the addition salt of methanesulfonic acid and 4-(4-methylpiperazine-1-yl-methyl)-N-[4-methyl-3-(4-(pyridine-3-yl)pyrimidine-2-yl-amino)phenyl]-benzamide (imatinib), specific procedures for preparing the same, pharmaceutical compositions containing these crystalline forms, use thereof in diagnostic methods or for treatment of warm-blooded animals, in particular humans.

Crystalline form F of imatinib mesylate was prepared using benzyl alcohol or a mixture of benzyl alcohol and ethyl acetate and formulated in tablets. Tablets containing 100 mg of crystalline form F of imatinib mesylate were prepared by direct compression of a mixture containing 100 mg of the active ingredient, 240 mg of crystalline lactose, 80 mg of Avicel, 20 mg of PVPPXL, 2 mg of Aerosil and 5 mg of magnesium stearate.


Preparation of α-form of imatinib mesylate

A procedure for preparation of crystalline imatinib mesylate, substantially in the pure α-form is mentioned, which involves particularly crystallizing of imatinib mesylate from an organic solvent containing imatinib, methanesulfonic acid and crystal nuclei of imatinib mesylate α-form, the crystal nuclei having been added before imatinib mesylate started to precipitate in the mixture. In addition, stable free-flowing crystals of imatinib mesylate in substantially pure α-form are mentioned and so are pharmaceutical products containing stable free-flowing crystals of imatinib mesylate.

Preparation of imatinib mesylate α-form.

Synthesis methods of imatinib mesylate and preparation of polymorphs
A review article relating to syntheses from 4-(methylpipperazine-1-ylmethyl)-N-[4-methyl-3-[4-(pyridine-3-yl)pyrimidyn-2-ylamino]phenyl]benzamide (imatinib) and its polymorphism, preparation of salt adducts and in particular a six-step synthesis of imatinib mesylate and its α polymorph as developed in the Institute of Pharmaceutical Research in Warsaw.

Imatinib mesylate - synthesis methods and preparation of polymorphs.

Polymorphic forms of imatinib mesylate
The invention relates to new crystalline polymorphous forms I and II of imatinib mesylate and methods to prepare them. Form I is prepared by mixing polymorphous form α2 or β of imatinib mesylate in chloroform and water in heat and distilling of water with following filtration. Form II is prepared by lyophilisation of an aqueous solution of polymorphs α2 or β. The invention also relates to pharmaceutical compositions containing the new forms useful in treatment of chromic myeloid leukaemia and accelerated challenge conditions.

Preparation procedure of crystalline form of imatinib mesylate
The method of preparation of polymorphic crystalline form of imatinib mesylate in a crystalline form not corresponding to needles is shown. This crystalline form is characterised by a difference in specific gravity <0.15 g/ml between the "tapped" and "untapped" density.

Process for the preparation of a polymorphic crystalline form of imatinib mesylate.

Oral matrix solid dosage form with controlled release in the stomach containing imatinib
A pharmaceutical solid dosage form with controlled release in the stomach, containing imatinib or its salts appropriate for pharmaceutical purposes and polymorphs of the salts such as β, α2, form 1 and form 2 for once daily use in the form of coated tablets, minitablets or pellets filled in hard gelatine capsule.
Controlled-release gastric floating matrix formulation containing Imatinib


5 Novel polymorphic form of imatinib mesylate and a process for its preparation

The invention mentions a new stable crystalline form of imatinib mesylate produced as a α2-form, which is stable at laboratory temperature and even at higher temperatures up to 120 °C and under accelerated challenge conditions and is well soluble in water. This invention also mentions pharmaceutical compositions containing a new stable α2-form of imatinib mesylate and other common excipients. The products are beneficial in treatment of chronic myeloid leukaemia. This new α2-form or imatinib mesylate is prepared by mixing imatinib base in isopropyl alcohol at laboratory temperature, followed by addition of methanesulfonic acid, heating to 50-60 °C and filtration. This invention also mentions another procedure of preparation of a new stable crystalline α2-form or imatinib mesylate by transformation of polymorphic modification β of imatinib mesylate after mixing in water and organic solvents, azeotropic distillation of water, cooling and filtration of crystals in α2-form.

Novel polymorphic form of imatinib mesylate and a process for its preparation.

Amala, Kompella; Srinivasa Rao, Thungathurthi; Adibhatla Kali Satya, Bhujanga Rao; Rachakonda, Sreenivas; Venkaiah Chowdary, Nannapaneni; Podili, Khadgaphathi. (Natco Pharma Limited, India). PCT Int. Appl. (2005), 38 pp. WO 2005/077933 A1 20050825

New polymorphs of imatinib mesylate

Polymorphs of imatinib mesylate, procedures to prepare them and pharmaceutical products containing those polymorphs are mentioned. Imatinib mesylate is prepared from imatinib free base by dissolving in chlorinated solvent and reaction with methanesulfonic acid. The crystalline form of imatinib mesylate was characterised by X-ray powder diffraction. Imatinib mesylate hydrate is prepared by dissolving imatinib mesylate in a mixture of an appropriate solvent and water and removing of solvents from the solution. For example, preparation of imatinib mesylate by dissolving of 5g of free base of imatinib in 50 ml of chloroform at laboratory temperature and adding of 0.75 ml of methanesulfonic acid is described. After 5-hour stirring at laboratory temperature the separated crystals were filtered and dried. 5 mg of imatinib mesylate in H1-form was obtained.
Novel polymorphs of imatinib mesylate.

Preparation of crystalline imatinib base

Imatinib crystalline base in form I and preparation procedures of form I of imatinib crystalline base, which is suitable for preparation of imatinib salts, e.g. mesylate, are mentioned. Production procedure of imatinib salt from the form I imatinib crystalline base is also mentioned. Imatinib was prepared in reaction of N-(5-amino-2-methylphenyl)-4-(3-pyridyl)-2-pyrimidine amine with 4-(4-methylpiperazinylmethyl)benzoylchloride in pyridine and repurification.

Preparation of crystalline imatinib base.


Preparation of crystalline methanesulfonic acid addition salts of imatinib

The invention relates to addition salts of methanesulfonic acid and imatinib and procedures of preparation. The invention mainly relates to a procedure of preparing crystalline form α of imatinib methanesulfonate. In addition, the invention relates to new acid addition salts of imatinib with 2 moles of methanesulfonic acid and their polymorphic forms and pharmaceutical compositions derived of them. Suspension of imatinib in anhydrous ethanol was heated to 75 °C and methanesulfonic acid was added slowly dropwise. Ethyl acetate was added and the mixture was cooled to 30 °C under stirring. Crystal nuclei of α-form were added and the mixture was cooled and stirred at 13-20 °C for 4 hours. Crystals were filtered and dried. Yield of imatinib mesylate crystalline form α was 65.0%.

Preparation of crystalline methanesulfonic acid addition salts of imatinib.
Szczepek, Wojciech; Samson-Lazinska, Dorota; Zagrodzki, Bogdan; Glice, Magdalena; Maruszak, Wioleta; Korczak, Kataryzna; Modzelewski, Ryszard; Lawecka, Marta; Kaczmarek, Lukasz; Szelejewski, Wieslaw; Fraczek, Urszula; Cmoch, Piotr. (Instytut Farmaceutyczny, Pol.). PCT Int. Appl. (2005), 68 pp. WO 2005/095379 A2 20051013
Significance of the present patent solution and the advantage against the current state:

API's are an extremely valuable "core" material for pharmaceutical industry. However, it is known that nowadays more than a half of newly developed API's is classified in BCS II and VI. i.e. newly developed molecules are hardly soluble under physiological conditions, or hardly absorbable, or show both these two fundamental problems for development of dosage forms. This problem is resolved usually by production both of salts and polymorphs, hydrates, solvates, or nanoparticles of API. Pharmaceutically useful crystals are profiled as one of modern approaches of how to achieve an API with required physicochemical parameters. In comparison to other groups of API solid forms, co-crystals offer a range of benefits both in terms of modulation of API characteristics (a unique structure and the corresponding profile of physicochemical characteristics) and in terms of IP.

Pharmaceutical co-crystals as crystalline molecular complexes provide an alternative solid API modification to salts and polymorphs even tough this field has not achieved their status yet. Definition of molecules an API may form co-crystal with is considerably wide in the point of view of registration authorities, e.g. according to an FDA's definition it is any component which can be a part of food in the USA. There are more than 3000 such molecules defined in the USA now.

Disclosure of Invention

The invention provides a method of production of new imatinib mesylate polymorphs and a method of their use.

The present patent application describes a rational design for new polymorphs of imatinib mesylate (and other salts, such as chloride).

The rational design for formation of polymorphs is based on an energetic change for non-covalent interactions of the molecules of the active pharmaceutical ingredient (API) depending on the solvent and ionic strength. While the prior patents describe the generation of imatinib mesylate polymorphs in organic solvents, the approach presented in the patent is based on the generation of new polymorphs in aqueous environment in which interaction of dissolved API molecules is determined by energetic dominance of energetic contributions in nucleation.
This results in another arrangement of molecules in initial nucleation, and thus in formation of new, so far not described, polymorphs. In regard to solubility of API in aqueous environment the ionic strength of the solution has to be adjusted, the pH being so controlled that no protonation change of API occurs. Concentration of organic modifier and crystallization temperature are other critical factors. Using these parameters the process can be set so that quantitative crystallization/precipitation (in the case of an amorphous API) of the required polymorph is reached.

This process then results in both highly stable polymorphs (demonstrated by stress tests), hydrates and also co-crystals of API with inorganic salts. They were used in the process of preparation of dosage forms with a range of excipients and the result of the formulation process is dosage forms which are satisfactory both in terms of stability and dissolution.

The method according to the invention surprisingly enables preparation of new API forms with improved properties (solubility, stability) compared to the previously described and prepared methods using only variations of used solvents and crystallization conditions. Generally, this approach resolves inappropriate properties of active ingredients (API), e.g. their poor solubility in aqueous environment which is based on their nature - mostly they are organic compounds.

**Detailed description of invention**

The invention relates to preparation of new imatinib mesylate polymorphs, particularly using rational design to control the polymorphism.

Constructing of organic materials, particularly API's of required properties, is in the centre of pharmaceutical industry interest.

The patent submits a protocol for rational design and preparation to control API polymorphism.

The main sphere is the control resulting in properties of the solid form based on control of topology of a crystalline or amorphous API.

Topology is controlled both by the solvent and the ionic strength and presence of an inorganic salt activating the initial nucleation and crystallization.
Two basic types of polymorphism are distinguished - packing and conformational - and their combinations. The essence of the invention lies in that a concept of solvent (environment-controlled self-structuring and conformation changes is submitted. The concept is based on variation of individual energetic contributions (such as H-bonding, hydrophobic interaction) owing to the environment chosen for crystallization. Formations: packing in water is other than in organic solvents. A rational approach to new polymorphs based on selection of aqueous or aqueous-organic environment, (also effect of the ionic strength), which will provide, due to modifications of non-covalent interactions, a way of packing other than in organic solvents.

Change from an organic solvent of the type of chlorinated carbohydrates or ethyl acetate to aqueous or water-alcohol mixed solvent weakens considerably intermolecular interactions based on H-bonds, while, on the contrary, the energetic contribution of van der Waals stacking interactions will be strengthened. This is the base of a rational approach to new polymorphs, moreover supported by the fact that aqueous or aqueous-alcoholic environment enables easy variation of ionic strength of the solution and thus additional strengthening of interactions of aromatics in this environment leading to new polymorphs.

In addition to the new polymorphs of imatinib mesylate, the method according to the present patent enables preparation of hydrates and solvates (with alcohols), co-crystals with inorganic salts, in particular NaCl and KCl.

The invention also includes methods of preparation of these polymorphs and use of them. The produced complexes and co-crystals were characterized using NIR, ssNMR, Raman, FTIR, XRPD, elementary analysis methods.

The present patent application describes a rational design of new polymorphs of imatinib mesylate (and other salts, e.g. chloride).

The rational design of polymorph production is based on energetic change for non-covalent interactions of API molecules depending on solvent and ionic strength. While the prior patents describe generation of imatinib mesylate polymorphs in organic solvents, the method presented in the present patent is based on a generation of new polymorphs in aqueous environment, in which interaction of dissolved API molecules is determined by energetic dominance of the following energetic contributions:

- $\pi-\pi$ stacking of aromatic parts of molecule;
- hydrophobic interactions (while H-bonds play a minor role in this competitive environment);
- effect of the concentration of the used salt.

This results in different packing of the molecules in the initial nucleation and thus in formation of new, so far not described polymorphs. Owing to API solubility in an aqueous environment the ionic strength of solution should be adjusted, the pH being controlled so that a protonation change of the API does not occur. Other critical factors include concentration of the organic modifier and crystallization temperature. Using these parameters the method can be set so that quantitative crystallization/precipitation of the desired polymorph occurs (in the case of an amorphous API).

This method results in considerably stable polymorphs (proved by stress tests) hydrates and co-crystals of API with inorganic salts. These were used for preparation process of dosage forms with various excipients, and the result of the formulation process gives dosage forms satisfactory in terms of both stability and dissolution, compared to the original dosage form (using polymorph beta, or alpha T).

Using this method, new polymorphs can be generated in various conditions, with the ionic strength value from 0.1 to 50 units.

Various temperatures and use of an organic modifier (organic solvent in an amount of 0 to 49 % v/v).

The new polymorphs are preferably prepared using salts with the same anion that the API has (of mesylates of alkali metals and alkaline earths), either separately or in combination with other inorganic salts, preferably chlorides and bromides, in which the cation is a salt of alkali metals and alkaline earths.

The new polymorph, hydrate or co-crystal, is then isolated by crystallization (crystallization temperature from 30 °C to 95 °C) or centrifugation.

The new polymorphs are evaluated using powder X-ray structural analysis, Raman spectroscopy, solid phase NMR, NIR-spectroscopy and elementary analysis (C,H,N,S).
The new polymorphs, hydrates and co-crystals with inorganic salts are used for preparation of dosage forms, by the method of direct compacting with selected excipients, extrusion or wet granulation (in an ethanol-water mixture containing up to 25% of water). Stability of the dosage form was determined using both HPLC (impurity profile) and spectroscopic methods, in particular NIR.

Variation of physicochemical properties of the particular API offers the desired differences in dissolution characteristics, stability and bioavailability. Stability relates to both chemical stability and, in particular, morphological stability as in technology of a dosage form production conversion of particular crystalline and amorphous forms is often seen, which leads to undesirable changes in dissolution and bioavailability characteristics.

An industrially feasible methodology of obtaining new polymorphs of tyrosine kinase inhibitors has been elaborated. The arrangement consists in adding an API solution in a selected protic solvent or in an aqueous solution to an aqueous solution of salt having the selected pH and ionic strength. This arrangement results in crystallization of new, so far not described polymorphs.

Preparation of the new polymorph either starts from imatinib base followed by conversion thereof to the mesylate by adding one equivalent of methanesulfonic acid, or the preparation starts with other polymorphs or an amorphous salt of imatinib mesylate, preferably the alpha or beta polymorph. An aqueous solution of imatinib mesylate is prepared and further processed via a method resulting in crystallization from aqueous or aqueous-organic environment. The prepared polymorph of imatinib mesylate, which is crystallized at -30 to 90°C, is then isolated by filtration or centrifugation. Crystallization at a temperature lower than 0°C is advantageously used for crystallization in aqueous-organic environment, or in a water-acetonitrile mixture. Appropriate alcohols to be used include methyl alcohol (MeOH), ethyl alcohol (EtOH), isopropyl alcohol, and other water-miscible organic solvents, acetonitrile, tetrahydrofuran (THF), dimethyl sulfoxide (DMSO), dimethylformamide (DMF), or their mixtures.

The ionic strength of the solution is controlled by adding salts, preferably sodium of potassium mesylate, NaCl and KCl, preferably in combination with sodium mesylate and potassium mesylate and other salts, in resulting concentration 0.01 M to 5 M, or a saturated solution of the given salt in the used solvent is used.

The ionic strength was maintained in the range between 0.001 and 50.
The prepared API polymer is isolated by filtration or centrifugation. The residual organic solvent is removed by drying in vacuo at 20 to 30 °C for 1 to 24 hours, with solvates drying is performed from the laboratory temperature to 50 °C. The formation of the polymorph results in modification of dissolution properties and increasing of chemical and morphological stability of API.

Satisfactory dissolution properties of API are, in addition to stability, the crucial properties for preparation of a pharmaceutical composition.

In addition to the active ingredient, the final dissolution profile is also substantially influenced by selection of appropriate excipients. When preparing a dosage form, use of excipients of the following range proved to be significantly beneficial: microcrystalline cellulose, lactose, crosspovidone, hypromellose, magnesium stearate, avicel, awerosil, anhydrous silicon dioxide. These excipients enable preparation of a medicinal product in tablets. Use of coated tablets, preferably those in which the coating layer consists of red iron(III) oxide (El 72), yellow iron(III) oxide (El 72), macrogol, talc and hypromellose proved suitable as it prevents irritation in the stomach area.

As a filling agent, fillers selected from soluble mono-, oligo- or polysaccharides, or insoluble polysaccharides can be used.

Thus prepared composition can be used for treatment of chronic myeloid leukaemia (CML), acute lymphoblastic leukaemia (ALL), gastrointestinal stromal tumour, chronic eosinophilic leukaemia or hypereosinophilic syndrome and systemic mastocytosis.

The new imatinib mesylate polymorphs prepared according to the invention are suitable for preparation of a targeted-release composition, in which the kinase inhibitor is released preferentially in leukaemic cells.

The results of analyses of kinase inhibitor polymorphs were performed by IR, Raman, NIR ssNMR, XRPD and elementary analysis methods; they are mentioned in a Table and in the attached figures (see the appendix).

Stability of the prepared polymorph and dosage forms prepared by direct compacting was studied using a recently developed HPTLC and HPLC methodology:

Stability-indicating **HPTLC determination of imatinib** mesylate in bulk drug and pharmaceutical dosage form. Vadera, N.; Subramanian, G.; Musmade, P.: Journal of
Validation of an HPLC Method for the Determination of Imatinib Mesylate in Pharmaceutical Dosage. Rosasco, Maria; Moyano, Maria; Pizzorno, Maria; Segall, Adriana.: Journal of Liquid Chromatography & Related Technologies (2005), 28(20), 3283-3292.

FT-Raman spectra were measured using the FT-Raman spectrometer RFS 100/S (Bruker, Germany) by accumulating of 256 scans with the spectral resolution 2 cm\(^{-1}\) and laser performance of 250 mW.

NMR spectra were measured in the NMR spectrometer Bruker AVANCE 500 MHz using a 4 mm CP/MAS probe, rotation speed 13 kHz, contact time 2 ms, number of scans 500.

X-ray powder diffraction: The reported records were measured using the diffractometer X’PERT PRO MPD PANalytical with a graphite monochromator, radiation used CuKa (\(\lambda=1.542\)A), excitation voltage: 45 kV, anodic current: 40 mA, measured range: 4 - 40° 2\(\Theta\) step size: 0.008° 2\(\Theta\) irradiated part of sample 10 mm, measurement was performed on an Si plate covered with a PE foil.

NiR spectroscopy: The reported records were obtained using the spectrometer Smart Near-IR UpDrift\textsuperscript{TM} Nicolet\textsuperscript{TM} 6700 FT-IR/NIR, Thermo Scientifics, U.S.A. By comparing with the spectra of the individual starting materials significant changes, or interactions, were seen in the spectra of all reported samples.

**Brief Description of Drawings:**

*Fig. 1:* NIR spectra of the imatinib base (in the top) with \(\alpha\)-polymorph of imatinib mesylate (in the middle) and in \(\beta\)-polymorph of imatinib mesylate (in the bottom).

*Fig. 2:* NIR spectra of \(\alpha\)-polymorph of imatinib mesylate (in the top) and \(\beta\)-polymorph of imatinib mesylate (top middle) and samples of imatinib mesylate crystallized from water with addition of NaCl (bottom middle) and imatinib mesylate crystallized from water with addition of KCl (bottom). In the spectra of samples crystallized from water differences against the starting materials can be clearly recognized. Differences in spectra of the two samples are not noticeable.

*Fig. 3:* NIR spectra of \(\alpha\)-polymorph of imatinib mesylate (in the top) and \(\beta\)-polymorph of imatinib mesylate (upper middle) and samples of imatinib mesylate crystallized from water.
with addition of KBr (middle bottom) and imatinib mesylate crystallized form methanol with addition of KBr (in the bottom). In the spectra of samples crystallized from water or methanol differences against the starting materials can be clearly recognized. Differences in spectra of the two samples are not noticeable.

Fig. 4: NIR spectra of imatinib mesylate crystallized from water with addition of NaCl (in the top), imatinib mesylate crystallized from water with addition of KCl (middle top), imatinib mesylate crystallized from water with addition of KBr (middle bottom) and imatinib mesylate crystallized from methanol with addition of KBr (in the bottom). Samples of imatinib crystallized from water in presence of NaCl or KCl in comparison to samples crystallized form water or methanol in presence of KBr differ in a small shift of the band and arm in the area of 6678 to 6609 cm⁻¹. Another difference of spectra of all four samples is not seen.

Fig. 5: NIR spectra of \( \alpha \)-polymorph of imatinib mesylate (in the top) and \( \beta \)-polymorph of imatinib mesylate (middle top) samples of imatinib mesylate crystallized from a mixture of water/methanol with addition of NaCl (middle bottom) imatinib mesylate crystallized from a mixture of water/methanol with addition of KCl (bottom). In the spectra of samples crystallized from a mixture of water/methanol differences from the starting materials can be clearly seen. Spectra of both samples differ in a small shift of the band and arm in the area of 6678 to 6609 cm⁻¹.

Fig. 6: NIR spectra of \( \alpha \)-polymorph of imatinib mesylate (in the top) and \( \beta \)-polymorph of imatinib mesylate (middle top) and samples of imatinib mesylate crystallized from water with addition of NaCl (middle bottom) and imatinib mesylate crystallized from a mixture of water/methanol with addition of NaCl (bottom). In spectra of samples crystallized from water and a mixture of water/methanol differences from the starting materials can be clearly seen. Spectra of the two samples crystallized from different medium differ in a small shift of the band and arm in the area of 6678 to 6609 cm⁻¹.

Fig. 7: NIR spectra \( \alpha \)-polymorph of imatinib mesylate (in the top) and \( \beta \)-polymorph of imatinib mesylate (middle top) and samples of imatinib mesylate crystallized from water with addition of KCl (middle bottom) and imatinib mesylate crystallized from a mixture of water/methanol with addition of KCl (in the bottom). In spectra of samples crystallized from water and a mixture of water/methanol differences from the starting materials can be clearly seen. Spectra of the two samples crystallized from different medium differ in a small shift of the band and arm in the area of 6678 to 6609 cm⁻¹.
Fig. 8: Comparison of $^{13}$C CP/MAS spectra of imatinib polymorphs (alpha - in the middle, beta - in the top) and their mixture 1:1 (in the bottom).

Fig. 9: Comparison of $^{13}$C CP/MAS spectra of imatinib polymorphs (alpha - in the bottom, beta - in the middle, base - in the top).

Fig. 10: Comparison of $^{13}$C CP/MAS spectra of imatinib polymorphs (alpha - in the bottom, beta - in the middle, imatinib NaCl - in the top)

Fig. U: Comparison of $^{13}$C CP/MAS spectra of imatinib polymorphs (alpha - in the bottom, beta - in the middle, imatinib KCl - in the top)

Fig. 12: Comparison of $^{13}$C CP/MAS spectra of imatinib polymorphs (alpha - in the bottom, beta - in the middle, imatinib KBr - $H_2O$ - in the top)

Fig. 13: Comparison of $^{13}$C CP/MAS spectra of imatinib polymorphs (alpha - in the bottom, beta - in the middle, imatinib KBr - MeOH - in the top)

Fig. 14: Comparison of $^{13}$C CP/MAS spectra of imatinib polymorphs (alpha - in the bottom, beta - in the middle, imatinib KCl - $H_2O$ - in the top)

Fig. 15: Comparison of $^{13}$C CP/MAS spectra of imatinib polymorphs (alpha - in the bottom, beta - in the middle, imatinib NaCl - $H_2O$ - in the top)

Fig. 16: Raman spectrum - Imatinib mesylate, new form Z1

Fig. 17: Raman spectrum - Imatinib mesylate, new form Z2

Fig. 18: Comparison of FT-Raman spectra of imatinib polymorphs (alpha - in the bottom, beta - in the middle, imatinib NaCl - in the top)

Fig. 19: Comparison of FT-Raman spectra of imatinib polymorphs (alpha - in the bottom, beta - in the middle, imatinib KCl - in the top)

Fig. 20: Comparison of FT-Raman spectra of Imatinib base, Imatinib mesylate forms $\alpha$, $\beta$ and the new polymorph.
Fig. 21: Comparison of FT-Raman imatinib polymorphs (alpha - in the bottom, beta - in the middle, imatinib KBr - H₂O - in the top)

Fig. 22: Comparison of FT-Raman imatinib polymorphs (alpha - in the bottom, beta - in the middle, imatinib KBr - MeOH - in the top)

Fig. 23: Comparison of FT-Raman imatinib polymorphs (alpha - in the bottom, beta - in the middle, imatinib KCl - H₂O - in the top)

Fig. 24: Comparison of FT-Raman spectra of imatinib polymorphs (alpha - in the bottom, beta - in the middle, imatinib NaCl - H₂O - in the top)

Fig. 25: Comparison of X-ray diffraction patterns of imatinib base, imatinib mesylate form α and form β.

Fig. 26: X-ray diffraction pattern of new imatinib mesylate polymorph - form Z1

Fig. 27: X-ray diffraction pattern of new imatinib mesylate polymorph - form Z2

Fig. 28: Comparison of X-ray diffraction patterns of imatinib base, imatinib mesylate form α, β and preparation of new imatinib mesylate polymorph / NaCl.

Fig. 29: Comparison of X-ray diffraction patterns of imatinib base, imatinib mesylate form α, β and preparation of new imatinib mesylate polymorph / KCl.

Fig. 30: Comparison of X-ray diffraction patterns of imatinib base, imatinib mesylate form α, β and preparation of new imatinib mesylate polymorph / NaCl-H₂O.

Fig. 31: Comparison of X-ray diffraction patterns of imatinib base, imatinib mesylate form α, β and preparation of new imatinib mesylate polymorph / KCl-H₂O.

Fig. 32: Summarized comparison of X-ray diffraction patterns of imatinib base, imatinib mesylate form α, β and preparation of a new polymorph.

Fig. 33: NIR spectrum of new imatinib mesylate polymorph - form Z1
Fig. 34. NIR spectrum of new imatinib mesylate polymorph - form Z2

Examples:

The method of preparation, characterization and use of imatinib mesylate polymorphs are described.

The preparation method and characterization are documented by the following examples, without being limited by them in any respect.

Example 1.

4.936 g of imatinib base was suspended in water (50 ml), then 0.75 ml of methanesulphonic acid was added at 50°C. To the thus formed aqueous solution (pH 5.2) 60 ml of 2M potassium mesylate was added, stirred for 24 hours at laboratory temperature and crystallized at 50°C for 1-24 hours. The product was sucked off and dried in vacuo at 20-25°C for 24 hours. A new polymorph Z1 of imatinib mesylate was obtained. The product was characterized using elementary analysis (C,H,N,S) and various spectroscopical and thermal methods; DSC, ssNMR, Raman, FTIR, NIR and X-ray structural analysis XRPD.

Elementary analysis of imatinib mesylate. Found: 60.83 % C, 6.11 % H, 16.47 % N, 5.32 % S; calculated: 61.10 % C; 5.98 % H; 16.63 % N; 5.44 % S.

XRPD: 53; 7.5, 10.0; 10.6; 14.1; 15.0 a 16.6° (2θ± 0.2° 2θ).

Solid phase 1H-NMR: 109.1, 115.4, 124.0, 128.5, 129.9, 132.8, 137.8, 139.1, 140.6, 147.3, 151.4, 156.9, 158.6, 165.4

FT-Raman 3062, 2952, 2920, 1663, 1612, 1596, 1314, 1273, 1252, 1041, 987 cm⁻¹.

NIR: Interval ≥ 9000 9838 0

Example 2.

1 mmole of imatinib base was suspended in water (8 ml), a solution of 1 molar equivalent of methanesulphonic acid (in 1-3 ml of water) was then added at 25°C, to this solution of imatinib mesylate 10 ml of EtOH and 5 ml of a saturated solution of sodium mesylate was added and
crystallized at 0-5 °C for 24 hours. The product was sucked off and dried at vacuum at a temperature of 20 - 30 °C. A new polymorph Z2 of imatinib mesylate-dihydrate was obtained. The product was characterised using elementary analysis (C,H,N,S) and various spectroscopical and thermal methods; ssNMR, Raman, FTIR, NIR and X-ray structural analysis XRPD.

New polymorph imatinib mesylate-dihydrate is characterised according to Fig. 1 and elementary analysis; found: 6.32 % H, 57.42 % C, 15.88 % N, 4.98 % S. Calculated: 5.47 % H, 52.81 % C, 14.37 % N, 4.70 % S.

XRPD: 5.5; 10.9; 10.6; 14.9; 17.0 and 21.9° (2Θ± 0.2° 2Θ).


FT-Raman: 3061, 2978, 2914, 1659, 1591, 1324, 1282, 1043 cm⁻¹.

NIR: Interval ≥ 9200: bands 11895.4; 11847.6; 11706.7; 9706.7.

Interval 9200-7000: bands 8773.1; 8581.3; 8475.5; 8125.3; 7880.6; 7737.2; 7327.6; 7230.6; 7121.3.

Interval 7000-5200: bands 6625.5; 6340.9; 6302.6; 6110.6; 5975.8; 5868.2; 5825.8; 5726.4; 5642.7; 5497.9; 5404.3; 5330.9.

Interval 5200-4000: differently cleft bands with arms 4960.0; 4893.8; 4876.6; 4813.9; 4778.0; 4655.1; 461 1.4; 4570.7; 4519.4; 4434.5; 4418.2; 4308.3; 4261.7; 4153.3; 4083.0; 4031.7.

Example 3.

5.897 g of imatinib mesylate, alpha polymorph, was dissolved in water (60-150 ml), then a solution of 10 molar equivalents of inorganic salt, preferably sodium mesylate and potassium mesylate (in 30-150 ml of water) was added at 25°C and the mixture was crystallized at 0-5 °C for 1-24 hours. The product, polymorph of imatinib mesylate, a co-crystal with KCl, was sucked off and dried in vacuo at 20-30 °C and characterised using elementary analysis (C, H, N, S) and various spectroscopical and thermal methods, DSC, ssNMR, Raman, FTIR, NIR and X-ray structural analysis XRPD.

A new polymorph of imatinib mesylate was obtained, KCl. 2H₂O.

Elementary analysis; found: 5.40 % H, 52.15 % C, 14.17 % N, 4.57 % S.; Calculated: 5.47 % H, 52.81 % C, 14.37 % N, 4.70 % S.
Example 4.

5.897 g of imatinib mesylate, beta polymorph, was dissolved in water (50-150 ml), pH 5.2, then a solution of 5-50 molar equivalents of sodium mesylate (in 30-150 ml of water), 50 ml of EtOH was added at 25°C, and the mixture was crystallized at a temperature of 0-5°C for 1 to 24 hours. After stirring for 24 h the crystallization mixture was evaporated in an evaporator to 150 ml. The product, 5.82 g of imatinib mesylate Z1 polymorph, was sucked off and dried in vacuo at 20-30 °C and characterised using elementary analysis (C, H, N, S) and various spectroscopical and thermal methods; ssNMR, Raman, FTIR, NIR and X-ray structural analysis XRPD.

Elementary analysis for imatinib mesylate. Found: 60.91 % C, 6.09 % H, 16.51 % N, 5.28 % S; calculated: 61.10 % C; 5.98 % H; 16.63 % N; 5.44 % S.

Example 5.

4.936 g of imatinib base was suspended in water (50 ml), then 0.75 ml of methanesulfonic acid was added at 5°C. To the thus produced aqueous solution (pH 5.2) 80 ml of acetonitrile was added and to this solution 30 ml of 2M solution of sodium mesylate was added and the mixture was crystallized at 0-5°C for 1-24 hours. The product, 5.99 g of imatinib mesylate-dihydrate.2H₂O was sucked off and dried in vacuo at 20 °C and characterised using elementary analysis (C, H, N, S) and a range of spectroscopical and thermal methods; DSC, ssNMR, Raman, FTIR, NIR and X-ray structural analysis XRPD.

New polymorph of imatinib mesylate is characterised according to Fig. 1 and by elementary analysis, found: 6.32 % H, 57.42 % C, 15.88 % N, 4.98 % S.

Calculated: 57.58 % C; 6.28 % H; 15.67 % N; 5.12 % S.

Example 6.

5 g of imatinib base was suspended in water (50 ml), then 0.75 ml of methanesulfonic acid was added at 5°C. To the thus produced aqueous solution 80 ml of methanol was added and to this solution 30 ml of a saturated solution of potassium mesylate was added; pH 7.0, the mixture was crystallized at pH 7.0 at -25 °C for 1-24 hours. The product, 5.85 g, mixed polymorph of imatinib mesylate (a mixture of beta and Z1) was sucked off and dried in vacuo at 20 °C and characterised using elementary analysis (C, H, N, S) and various spectroscopical and thermal methods; DSC, ssNMR, Raman, FTIR, NIR and X-ray structural analysis XRPD.
Example 7.
5 g of imatinib base was suspended in water (50 ml), then 0.75 ml of methanesulfonic acid was added at 5°C. To the thus produced aqueous solution 50 ml of methanol was added and to this solution 30 ml of a saturated solution of KCl and 30 ml of a saturated solution of potassium mesylate was added; the mixture was crystallized at -15 °C for 1-24 hours. The product, 5.85 g, imatinib chloride mesylate was sucked off and dried in vacuo at 20 °C and characterised using elementary analysis (C, H, N, S) and various spectroscopical and thermal methods; DSC, ssNMR, Raman, FTIR, NIR and X-ray structural analysis XRPD.

Example 8.
5.897 g of imatinib mesylate, beta polymorph, was dissolved in water (30 ml), then 30 ml of a 3M solution of NaCl, then 50 ml of EtOH was added at 25°C and the mixture was crystallized at 0-3 °C for 24-48 hours. The product, 5.82 g (polymorph of imatinib chloride, co-crystal with NaCl) was sucked off and dried in vacuo at 20-30 °C and characterised using elementary analysis (C, H, N, S) and various spectroscopical and thermal methods; DSC, ssNMR, Raman, FTIR, NIR and X-ray structural analysis XRPD.

Similarly, imatinib mesylate, crystal with NaCl was prepared using a mixture of solutions of sodium mesylate and sodium chloride (30 ml of 2M solutions)

Found for imatinib mesylate, NaCl dihydrate: 5.45% N, 53.88% C, 14.56% N, 4.65% S, 51.1

Example 9.
5.897 g of imatinib mesylate, beta polymorph, was dissolved in water (60 ml), then 30 ml of EtOH was added at 25°C, followed by addition of 30 ml of a saturated solution of KMes, pH 7, and the mixture was crystallized at a temperature of 0-10 °C for 1-24 hours. The product, 5.88 g of imatinib mesylate polymorph in a mixture with the imatinib base, was sucked off and dried in vacuo at 20-30 °C and characterised using elementary analysis (C, H, N, S) and various spectroscopical and thermal methods; DSC, ssNMR, Raman, FTIR, NIR and X-ray structural analysis XRPD.

Example 10.
5.897 g of imatinib mesylate, alpha polymorph, was dissolved in water (60 ml), followed by addition of 30 ml of a 3M solution of potassium mesylate, pH was adjusted at 5.5 and then 95
ml of acetonitrile was added at 20 °C, the mixture was crystallized at 0-3 °C for 1-24 hours. The product, 5.80 g imatinib mesylate polymorph (polymorph Zl) was sucked off and dried in vacuo at 20-30 °C and characterised using elementary analysis (C, H, N, S) and various spectroscopical and thermal methods; DSC, ssNMR, Raman, FTIR, NIR and X-ray structural analysis XRPD.

Example 11.
5.897 g of imatinib mesylate, alpha polymorph, was dissolved in water (70 ml), followed by gradual addition of 30 ml of a 3M solution of KCl and 20 ml of 2M potassium mesylate, then 55 ml of acetone was added at 15 °C, the mixture was crystallized at 4 °C for 24 hours. The product, 5.81 g of a polymorph of imatinib mesylate. chloride, was sucked off and dried in vacuo at 20-30 °C and characterised using elementary analysis (C, H, N, S) and various spectroscopical and thermal methods; DSC, ssNMR, Raman, FTIR, NIR and X-ray structural analysis XRPD.

Particle size of API produced using this method was within 110-850 nm.

Example 12.
5.897 g of imatinib mesylate, beta polymorph, was dissolved in water (30 ml), then 25 ml of isopropyl alcohol and 20 ml of acetonitrile was added at 25 °C, followed by addition of 30 ml of a 2M solution of KMes, and the mixture was crystallized at -5 °C for 1-24 hours. The product, 5.90 g of imatinib mesylate polymorph Z2, was sucked off and dried in vacuo at a temperature of 20-30 °C and characterised using elementary analysis (C, H, N, S) and various spectroscopical and thermal methods; DSC, ssNMR, Raman, FTIR, NIR, and X-ray structural analysis XRPD.

Example 13.
5.897 g of imatinib mesylate, beta polymorph, was dissolved in water (30 ml), then 15 ml of isopropyl alcohol and 15 ml of THF was added at 25 °C, followed by addition of 30 ml of a 2M solution of NaCl, and the mixture was crystallized at -5 °C for 24 hours. The product, 5.90 g of polymorph of imatinib chloride, was obtained via centrifugation and dried in vacuo at a temperature of 30 °C and characterised using elementary analysis (C, H, N, S) and various
spectroscopical and thermal methods; DSC, ssNMR, Raman, FTIR, NIR and X-ray structural analysis XRPD.

Example 14.

5.897 g of imatinib mesylate, amorphous, was dissolved in water (30 ml), then 15 ml of isopropyl alcohol and 15 ml of THF was added at 25°C, followed by addition of 25 ml of a 1M solution of NaCl and 10 ml of a 2M solution of sodium mesylate, and the mixture was crystallized at -10°C for 24 hours. The product, 5.90 g polymorph of imatinib mesylate co-crystal with NaCl, was obtained via centrifugation and dried in vacuo at a temperature of 30°C and characterised using elementary analysis (C, H, N, S) and various spectroscopical and thermal methods; DSC, ssNMR, Raman, FTIR, NIR and X-ray structural analysis XRPD.

Example 15.

5.897 g of imatinib mesylate, amorphous, was dissolved in water (30 ml), then a 2M solution of KMes was added at laboratory temperature and the mixture was crystallized at 10°C for 24 hours. The product, 5.90 g polymorph of imatinib mesylate Z2 hydrate, was obtained via centrifugation and dried in vacuo at a temperature of 20°C and characterised using elementary analysis (C, H, N, S) and various spectroscopical and thermal methods; DSC, ssNMR, Raman, FTIR, NIR and X-ray structural analysis XRPD.

Example 16.

Stability studies of the new polymorph were conducted according to

**Stability-indicating HPTLC determination of imatinib mesylate in bulk drug and pharmaceutical dosage form.** Vadera, N.; Subramanian, G.; Musmade, P.: Journal of Pharmaceutical and Biomedical Analysis (2007), 43(2), 722-726

**Validation of an HPLC Method for the Determination of Imatinib Mesylate in Pharmaceutical Dosage.** Rosasco, Maria; Moyano, Maria; Pizzorno, Maria; Segall, Adriana.: Journal of Liquid Chromatography & Related Technologies (2005), 28(20), 3283-3292.

Example 17.

A dosage form using the new polymorph was prepared by direct compacting, in which the excipients used included lactose, avicel, PVP, aerosil, magnesium stearate,
Klucel EF Ethocel-VlOO, Lauroglycol FCC and sodium stearyl fumarate, the content of API being within 20-60%.

Compatibility of the new polymorph of imatinib mesylate was tested with the following excipients: magnesium stearate, polyvinyl pyrrolidone, microcrystalline cellulose. Binary mixtures were analysed using NIR spectroscopy, both at laboratory temperature and a temperature of 40 °C. Challenge tests revealed formation of impurities in the presence of magnesium stearate.

Stability of the formulation with a high content of API, from 50 to 90 wt per cent, was tested. Comparing of beta and the new polymorph, hydrate, showed comparable utility and stability. A stable formulation is based on the following composition of excipients: Povidone, Hypromellose, Hydroxypropylcellulose) in an amount of 3% to 10% of the tablet weight,
The stable formulation further contains crosspovidone (2 t-10%), a lubricant (e.g. magnesium stearate (0.2 to 1.5 %) and colloidal silicon dioxide (colloidal 0.1 - 1.0 %).

Example 18.
As per example 17 with the API content within 20-65%.

Example 19.
As per example 17 with the API particle size within 1-1000 µm.

Example 20
As per example 17 with the API particle size within 100 nm - 1 µm.
Table 1 - Comparison of imatinib mesylate polymorphs (Z1 and Z2 forms) with the results cited in literature

<table>
<thead>
<tr>
<th>WP</th>
<th>polymorphs</th>
<th>XRPD</th>
<th>ssNMR Solid state $^{13}$CNMR</th>
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<th>Elementary analysis</th>
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<td>α</td>
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<td>112.2, 117.3, 122.3, 126.2, 129.7, 130.1, 134.7, 135.7, 137.9, 142.0, 148.3, 151.5, 158.0, 163.9, 164.7, 165.9</td>
<td>3059, 2969, 2934, 1665, 1609, 1590, 1305, 1291, 1038, 979 cm$^{-1}$</td>
<td>Interval 9000-8200 bands 8760 7, 8673 5, 8584 6, 8420 3 Interval 8200-6600 bands 7923 0, 7403 9, 7351 3, 7331 9 (arm), 7257 4, 7253 3, 6963 9, 6839 9, 6797 8, 6753 0 Interval 6600-5250 bands 6405 0, 6245 5, 6227 1, 6038 3 (arm), 5979 2, 5961 3, 5917 9, 5790 0, 5745 4, 5658 7, 5619 3, 5513 15422 9, 5402 5, 5360 2, 5295 7 Interval 5250-4000 bands 5144 8, 4834 3, 4794 8, 4704 6 (arm), 4635 3, 4614 1 (arm), 4548 8, 4418 8, 4359 8, 4319 3, 4219 2, 4155 7, 4067 9</td>
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| Present application | Z 1               | 5.3; 7.5; 10.0; 10.6; 14.1; 15.0 and 16.6° (2θ ± 0.2° 2θ). | 109.1, 115.4, 124.0, 128.5, 129.9, 132.8, 137.8, 139.1, 140.6, 147.3, 151.4, 156.9, 158.6, 165.4 | 3062, 2952, 2920, 1663, 1612, 1596, 1314, 1273, 1252, 1041, 987 cm⁻¹ | Interval ≥ 9000 9838 0  
Interval 9000-7600 bands  
8793 6, 8474 3, 8353 1, 8276 1, 8213 6, 8086 9, 7936 8  
Interval 7600-6200 cleft band  
6691 1, 6627 1 with arms  
7327 7, 7119 2, 6415 4  
Interval 6200-5400 bands  
6120 8, 5977 6 (arms 5936 8, 5913 5, 5866 2, 5835 0), bands  
5788 5, 5713 7, 5638 8, 5477 9  
Interval 5400-4500 bands  
5327 1, 5288 2, 5104 4, 5109 3, 5002 3, 4977 0, 4937 0, 4904 5, 4819 7, 4778 3, 4718 3, 4690 0, 4655 2, 4613 1, 4562 3, 4546 6  
Interval 4500-4000 bands  
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<td>Present application differently cleft bands with arms 4960 0, 4893 8, 4876 6, 48 13 9, 4778 0, 4655 1, 461 1 4, 4570 7, 45 19 4, 4434 5, 4418 2, 4308 3, 426 1 7, 4 153 3, 4083 0, 403 1 7</td>
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Claims

1. A method of producing an imatinib mesylate polymorph, said method consisting of the following steps:
   a) preparation of imatinib mesylate by reaction of the imatinib base and methanesulfonic acid in an aqueous environment or in a water-organic solvent mixture, with optional addition of an organic solvent;
   b) addition of an inorganic salt in an aqueous solution, controlling the pH and ionic strength of the solution;
   c) crystallization process at controlled temperature.

2. The method according to claim 1, characterized in that the water-miscible organic solvent is selected from the group consisting of C1 to C5 alcohols, C3 to C9 ketones, dimethylformamide (DMF), dimethylsulfoxide (DMSO), tetrahydrofuran (THF), ethylene glycol, and ethylene glycol dimethylether.

3. The method according to claims 1-2, characterized in that the water-miscible organic solvent is:
   a) a protic polar solvent: methyl alcohol, ethyl alcohol, 2-propanol, or ethylene glycol.
   b) an aprotic polar solvent: acetone, methylethyl ketone, DMF, DMSO, THF, ethylene glycol dimethylether, or tetrahydrofuran.

4. The method according to claims 1-3, characterized in that the water-miscible organic solvent is: methyl alcohol, ethyl alcohol or acetone.

5. The method according to claims 1-4, characterized in that the solvent is either water alone or a mixture of water-organic solvent with a content of the solvent up to 99% v/v.

6. The method according to claims 1-5, characterized in that the solvent is a mixture of water-organic solvent with a content of water 50-80% v/v.

7. The method according to claims 1-6, characterized in that the inorganic salt is a salt of a strong acid and a strong base.
8. The method according to claims 1-7, \textbf{characterized in that} the inorganic salt is a salt of a strong monobasic, dibasic and tribasic, or multibasic, acid and a base.

9. The method according to claims 1-8, \textbf{characterized in that} the inorganic salt is a halide or mesylate.

10. The method according to claims 1-9, \textbf{characterized in that} the inorganic salt is sodium chloride, potassium chloride, potassium bromide, sodium mesylate, or potassium mesylate.

11. The method according to claims 1-10, \textbf{characterized in that} the inorganic salt is a mixture of at least two salts selected from the group consisting of sodium chloride, potassium chloride, potassium bromide, sodium mesylate, or potassium mesylate, in a ratio of 1 - 100 to 100 - 1.

12. The method according to claims 1-11, \textbf{characterized in that} the ionic strength of the solution in crystallization ranges between 0.0001 and 50.

13. The method according to claims 1-12, \textbf{characterized in that} in crystallization a solution with the inorganic salt concentration ranging between 1 mM and 5 M, or a saturated solution of the salt in the given environment, is used.

14. The method according to claims 1-13, \textbf{characterized in that} in crystallization a solution with the inorganic salt concentration ranging between 0.1 M and 2 M, or a saturated solution of the salt in the given environment, is used.

15. The method according to claims 1-14, \textbf{characterized in that} the crystallization temperature is in the range of -50 to 100 °C.

16. The method according to claims 1-15, \textbf{characterized in that} the crystallization temperature is in the range of -20 to 50 °C.

17. The method according to claims 1-16, \textbf{characterized in that} the crystallization temperature is in the range of -10 to 30 °C.
18. The method according to any one of the preceding claims, **characterized in that** the product results in the form of a solvate or hydrate.

19. The method according to any one of the preceding claims, **characterized in that** the product results in the form of a solvate or hydrate with ethanol, methanol or isopropanol.

20. The method according to any one of the preceding claims, **characterized in that** the product is isolated by centrifugation or sucking-off.

21. The method according to any one of the preceding claims, **characterized in that** the concentration of imatinib mesylate in the crystallization environment is from 0.1 to 25 wt %.

22. The method according to any one of the preceding claims, **characterized in that** the concentration of imatinib mesylate in the crystallization environment is from 1 to 15 wt %.

23. The method according to any one of the preceding claims, **characterized in that** the specific gravity of the crystallization solution is from 0.2 g/ml to 5 g/ml.

24. The method according to any one of the preceding claims, **characterized in that** the specific gravity of the crystallization solution is from 0.5 g/ml to 2.5 g/ml.

25. Crystalline polymorph Z1 of imatinib mesylate, characterized by an X-ray diffraction analysis, wherein the characteristic peaks are as follows: 5.3; 7.5; 10.0; 10.6; 14.1; 15.0 and 16.6° (2Θ± 0.2° 2Θ).

26. Crystalline polymorph Z1 of imatinib mesylate, characterized by the following solid phase 13C -NMR shifts: 165.3; 158.8; 152.1; 147.6; 139.0; 132.6; 128.9; 123.9; 115.3; 109.2; 59.7; 54.5; 50.2; 44.2; 16.8 ppm.

27. Crystalline polymorph Z1 of imatinib, showing the following characteristic bands of FT-Raman spectrum with spectral resolution 4 cm⁻¹: 3061, 2918, 1660, 1611, 1592, 1323, 1281 cm⁻¹.
28. Crystalline polymorph $Z_2$ of imatinib mesylate, characterized by an X-ray diffraction analysis, wherein the characteristic peaks are as follows: 5.5; 10.9; 10.6; 14.9; 17.0 and 21.9° ($2\Theta \pm 0.2° 2\Theta$).

29. Crystalline polymorph $Z_2$ of imatinib mesylate, characterized by the following solid phase $^{13}C$-NMR shifts: 107.6; 113.5; 116.3; 122.3; 125.5; 126.8; 129.3; 130.0; 133.6; 136.2; 140.3; 148.5; 156.2; 157.1; 161.1; 165.2 ppm.

30. Crystalline polymorph $Z_2$ of imatinib, showing the following characteristic bands of FT-Raman spectrum with spectral resolution $4\text{ cm}^{-1}$: 3061, 2978, 2914, 1659, 1611, 1591, 1324, 1282, 1043 $\text{cm}^{-1}$.

31. A polymorph of imatinib mesylate, obtained by a method according to any one of claims 1-24, characterized in that it is in the form of a co-crystal or solid solution with at least one inorganic salt.

32. Imatinib mesylate polymorph according to claim 31, characterized in that it is in the form of a co-crystal or solid solution with at least one inorganic salt selected from halides or salts with methanesulfonic acid.

33. Imatinib mesylate polymorph according to claims 31-32, characterized in that it is in the form of a co-crystal or solid solution with at least one inorganic salt selected from the group consisting of sodium chloride, potassium chloride, potassium bromide, sodium mesylate, and potassium mesylate.

34. Imatinib mesylate polymorph according to claims 31-33, characterized in that it is in the form of a co-crystal or solid solution with potassium chloride.

35. Crystalline polymorph of imatinib mesylate according to claims 25-34, characterized in that the particle size is in the range of 1 $\mu$m to 100 $\mu$m.

36. Crystalline polymorph of imatinib mesylate according to claims 25-34, characterized in that the particle size is in the range of 10 nm to 1 $\mu$m.
37. Crystalline polymorph of imatinib mesylate according to claims 25-34, characterized in that it has a purity (HPLC) higher than 99%.

38. Crystalline polymorph of imatinib mesylate according to claims 25-34, characterized in that it has a purity (HPLC) higher than 99.5%.

39. A pharmaceutical composition containing a polymorph of imatinib mesylate as defined in claims 25-34.

40. The pharmaceutical composition according to claim 39, characterized in that the content of the active ingredient is from 10 to 40%.

41. The pharmaceutical composition according to claim 39, characterized in that the high content of the active ingredient is from 40 to 70%.

42. The pharmaceutical composition containing a polymorph of imatinib mesylate according to claims 31-34 in the form of a co-crystal with potassium chloride or sodium chloride, characterized in that the content of the active ingredient is from 4 to 70%.

43. A pharmaceutical composition with controlled release, containing a polymorph of imatinib mesylate as defined in claims 25-34.

44. The pharmaceutical composition according to claim 43, characterized in that it is in the form of a coated tablet.

45. The coated tablet according to claim 44, characterized in that the excipients are microcrystalline cellulose, lactose, crosspovidone, hypromellose, magnesium stearate, avicel, awerosil, anhydrous silicon dioxide, and the coating layer consists of red iron(III) oxide (E172), yellow iron(III) oxide (E172), macrogol, talc and hypromellose.
46. A dosage form of imatinib mesylate according to claims 39-45, characterized in that it contains fillers selected from soluble mono-, oligo- or polysaccharides, or insoluble polysaccharides.

47. Use of the pharmaceutical composition containing an imatinib mesylate polymorph according to claims 39-46 for the treatment of chronic myeloid leukaemia (CML), acute lymphoblastic leukaemia (ALL), gastrointestinal stromal tumour, chronic eosinophilic leukaemia, or hypereosinophilic syndrome and systemic mastocytosis.

48. A pharmaceutical composition with directed release, containing an imatinib mesylate polymorph according to claims 25-34, characterized in that the kinase inhibitor is released preferentially in leukaemic cells.
A.

NIR spectroscopy: The records were obtained using spectrometer Smart Near-IR UpDrift™ Nicolet™ 6700 FT-IR/NIR, Thermo Scientific, U.S.A.

Fig. 1
NMR spectra were measured in NMR spectrometer Bruker AVANCE 500 MHz using a 4mm CP/MAS probe, rotation speed 13 kHz, contact time 2 ms, number of scans 500.

Fig. 8
Fig. 12
FT-Daman spektra were measured in FT-Raman spectrometer RFS 100/S (Bruker, Germany) by accumulating 256 scans with spectral resolution 2 cm\(^{-1}\) and laser performance 250 mW.
Fig. 19

Fig. 20
Fig. 23

Fig. 24
X-ray diffraction analysis: The diffraction pattern was obtained in diffractometer XPERT PRO MPD PANalytical with graphite monochromator, radiation used: CuKα (λ = 1.542 Å), excitation voltage: 45 kV, anode current: 40 mA, measured range: 4 - 40° 2θ, step size: 0.008° 2θ, measurement performed in an Si holder with PE foil.

Characteristic peaks: 5.3; 7.5; 10.0; 10.6; 14.1; 15.0 and 16.6° 2θ ± 0.2° 2θ.

Fig. 25
**A. CLASSIFICATION OF SUBJECT MATTER**

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

**INV.** C07D401/04 A61P35/00 A61K31/506

**ADD.**

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)

- C07D
- A61P
- A61K

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

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

<table>
<thead>
<tr>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No</th>
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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

Date of the actual completion of the international search

28 December 2010

Date of mailing of the international search report

12/01/2011

Name and mailing address of the ISA/

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NL- 2280 HV Rijswijk
Tel (+31-70) 340-2040,
Fax (+31-70) 340-3016

Authorized officer

Lange, Tim
<table>
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<tr>
<th>Category</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
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<tr>
<td></td>
<td>Use of Imatinib mesylate for the treatment of cancer;</td>
<td>1-48</td>
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<td></td>
<td>Example for isolation of polymorphous form of Imatinib mesylate from aqueous organic solution see:</td>
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<tr>
<td></td>
<td>page 52; example 19</td>
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<td>WO 2010/081443 A2 (ZENTIVA K S [CZ]; KRAL VLADIMIR [CZ]; JAMPILEK JOSEF [CZ]; HAVLICEK JA) 22 July 2010 (2010-07-22) co-crystals of Imatinib mesylate with guanidine HCl salt in ratios of 1:1, 1:2, 1:3, 1:5; page 37; table 1 Method of producing Imatinib mesylate co-crystals by adding an inorganic salt (KCl) to an aqueous solution in order to increase ionic strength. claim 36; example 9 Pharmaceutical compositions with Imatinib Mesylate and their use in treatment of leukemia. (&quot;Imatinib&quot; in this document actually represents &quot;Imatinib mesylate, see structure on page 9) (see page 9 claims 4,21,22</td>
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<td>B.S. Furniss, A.J. Jannaford, P.W.G. Smith, A.R. Tatchell: &quot;Vogel's Textbook of Practical Organic Chemistry&quot;, 1989, Longman Scientific &amp; Technical, New York, XP007916555, ISBN: 0-582-46236-3 vol. 5th edit, page 158, &quot;In the isolation of organic compounds from aqueous solutions, use is frequently made of the fact that the solubility of many organic compounds in water is considerably decreased by the presence of dissolved inorganic salts (NaCl, CaCl2, (NH4)2SO4 etc.). This is the so called &quot;salting-out effect&quot;.; page 158, line 21 - line 25</td>
<td>1-24</td>
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| WO 2010081443 A2                       | 22-07-2010      | NONE                     |                 |

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