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Quantitative determination of two polymorphic forms of imatinib mesylate in a drug substance and tablet formulation by X-ray powder diffraction, differential scanning calorimetry and attenuated total reflectance Fourier transform infrared spectroscopy

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ABSTRACT

Imatinib has been identified as a tyrosine kinase inhibitor that selectively inhibits the Abl tyrosine kinases, including Bcr-Abl. The active substance used in drug product is the mesylate salt form of imatinib, a phenylaminopyrimidine derivative and chemically named as *N*-(3-(4-(pyridin-3-yl) pyrimidin-2-ylamino)-4-methylphenyl)-4-((4-methylpiperazin-1-yl) methyl)-benzamide methanesulfonic acid salt. It exhibits many polymorphic forms and most stable and commercialized polymorphs are known as α and β forms. Molecules in α and β polymorphic forms exhibit significant conformational differences due to their different intra- and intermolecular interactions, which stabilize their molecular conformations and affect their physicochemical properties such as bulk density, melting point, solubility, stability, and processability. The manufacturing process of a drug tablet included granulation, compression, coating, and drying may cause polymorphic conversions. Therefore, polymorphic content of the drug substance should be controlled during quality control and stability testing. Attenuated total reflectance Fourier transform infrared (ATR-FTIR) spectroscopy, differential scanning calorimetry (DSC), and powder X-ray diffraction (PXRD) methods were evaluated for determination of the polymorphic content of the drug substance and drug product; and PXRD was the most accurate technique and selected as preferred method and validated. Prior to development of a quantification method, pure α and β polymorphs were characterized and used throughout the method development and validation studies. Mixtures with different ratios of α and β forms were scanned using X-ray diffractometer with a scan rate of 0.250°/min over an angular range of 19.5–21.0° 2θ and the peak heights for characteristic peak of β form at 20.5 ± 0.2° 2θ diffraction angle were used to generate a calibration curve. The detection limit of β polymorph in α form imatinib mesylate tablets was found as 4% and the linear regression analysis data for the calibration plots showed good linear relationship with correlation coefficient of 0.992 with respect to relative peak height in the concentration range of 12–75 wt% β form containing tablet mixtures. The obtained results at each stage of the validation study proved that the method is specific, repeatable, precise and accurate, and could be used for determination of β polymorph content in tablets produced by using α polymorph of imatinib mesylate. The developed PXRD quantification method was used to monitor the polymorphic purity of α form drug substance and corresponding drug products during the quality control analyses and stability studies, and the results indicated that α form was stable and not converted to β form during the manufacturing process and stability period.

1. Introduction

Polymorphism is defined in a different way depending on the scientific field of use, such as computer science, biology, and chemistry or material science. For the latter, polymorphism is the ability of a solid material to exist in more than one form or crystal structure. A recent study estimated that 80–90% of organic compounds can exist in multiple crystalline forms (polymorphs, hydrates, solvates), and more than half of the pharmaceutical drug compounds exhibit solid-state polymorphism [1]. Crystalline forms have different arrangements and/or conformations of the molecules in the crystal lattice. Amorphous forms consist of disordered arrangements of molecules that do not possess a distinguishable crystal

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lattice. Solvates are crystal forms containing either stoichiometric or nonstoichiometric amounts of a solvent [2–4].

Due to the differences in their intra- and intermolecular solid–state structures, polymorphic forms of a drug substance can have different chemical and physical properties, including melting point, solubility, mechanical properties, and bulk density. These properties can have a direct effect on the ability to process and/or manufacture the drug substance and the drug product, as well as on drug product stability, dissolution, and bioavailability. Thus, polymorphism can affect the quality, safety, and efficacy of the drug product [5]. Therefore, the investigation of polymorphism in raw materials and also in solid dosage forms is becoming a common practice in industrial quality control routines. A range of analytical techniques, such as PXRD, DSC, ATR-FTIR, near-infrared spectroscopy (NIR), diffuse reflectance infrared spectroscopy (DRIFTS), Raman spectroscopy, solid state ^{13}C NMR spectroscopy, and terahertz (THz) spectroscopy, have proven suitable for the analysis and quantification of polymorphic mixtures [6–14].

Imatinib is a drug used to treat certain types of cancer and marketed as its mesylate salt (Scheme 1). It is a tyrosine kinase inhibitor and one of the first molecularly targeted therapies used in the clinic. Its efficacy was proven in the treatment of chronic myeloid leukemia (CML), gastrointestinal stromal tumors, and also in other malignancies that involve expression of a tyrosine kinase [15]. Imatinib mesylate is prepared using a fully synthetic process and shows polymorphism. Due to its novel structure and potent biological activity, several synthetic methods were developed by organic and pharmaceutical chemists for imatinib, its salts, adsorbates, and polymorphs including amorphous form [16–21]. Among these crystalline forms α and β polymorphs were commercialized and used as a drug substance in pharmaceutical industry. Complete solid-state characterization of these two common forms was studied together with their thermal behavior and grinding effects on their crystalline form by PXRD and DSC techniques [22]. Also, a detailed vibrational spectroscopic investigation of β form was done by using FTIR and FT-Raman spectra supported by quantum mechanical calculations [23]. In particular, α form was described as metastable at room temperature and was then initially indicated as not useful for the preparation of pharmaceutical preparations [24]. Depending on the applied process and modification of thermodynamic variables like pressure or temperature, either a polymorphic conversion or formation of an amorphous substance may occur during production of solid dosage drug products [25]. The aim of the present work is to provide a quantification method for β form content in α form of imatinib mesylate in a tablet formulation. This method allows us to test the polymorphic purity of the drug substance in tablet and used for quality control and stability testing of the drug product. In spite of many studies reported, there is no report about polymorphic quantification of imatinib mesylate polymorphs. At first, we focused our work on the study of quantification of β form in α form of active pharmaceutical ingredient (API) by using PXRD, DSC, and ATR-FTIR. Subsequently, we have applied the corresponding methods to tablet formulations, and finally the selected quantification method (PXRD) was validated for determination of β form content in tablets produced by using α form of imatinib mesylate. The validated PXRD method was used for stability testing of tablets and results showed that α form of imatinib mesylate is stable in tablet formulation used during these studies and no conversion was observed to β crystalline form.

2. Materials and methods

2.1. Materials and preparation of polymorphs

Imatinib mesylate samples were taken from commercial batches produced by Deva Holding A.Ş. (Tekirdağ, Turkey). Imatinib mesylate standards were supplied by a specialized team on standardization of reference standards for analytical use in Deva. Imatinib base used for synthesis of imatinib mesylate was supplied from Cdymax Pharma (India). Synthetic and analytical reagents and solvents were supplied from different commercial chemical sources such as; Merck KGaA (Darmstadt, Germany), J.T. Baker (Phillipsburg, USA), Sigma–Aldrich (St. Louis, MO, USA), Lab-Scan (Gliwice, Poland), and Acros Organics (Geel, Belgium). Deionized water was prepared using MilliQ plus purification system (Millipore, USA). Deuterated solvents (dimethylsulfoxide-d6 and D_2O) were purchased from Merck (Darmstadt, Germany). Evidence of the chemical structures has been provided by an examination of ^1H NMR, ^{13}C NMR, and mass spectral data, and of polymorphic forms by PXRD, DSC and ATR-FTIR spectroscopy. Purity of each polymorph was tested by validated HPLC and GC methods and determined to contain <0.5% of other process related impurities. Both polymorphs were anhydrous and their water content was found below 0.5%. The analysis was carried out by Karl–Fischer (KF) titration of 1.0 g sample using pyridine-free iodosulphurous reagent (CombiTitrant 5 one-component reagent for volumetric KF titration 1 mL equal to ca. 5 mg H_2O, Merck, Germany) on Metrohm 795 KFT Titrino instrument (Switzerland). Tablet formulations were containing the following excipients besides the active drug substance: microcrystalline cellulose (Type 302) (JRS Pharma, Germany), hydroxypropylmethyl cellulose (HPMC E3) (Dow, USA), crospovidone (BASF, Germany), colloidal silicon dioxide (Evonik Industries, Germany), and magnesium stearate (Peter Greven GmbH, Germany).

2.1.1. Synthesis of imatinib mesylate β form

A solution of methanesulfonic acid in methanol was added slowly (in ca. 10 min) into a suspension of imatinib base in methanol at room temperature. After complete dissolution active carbon was added and the mixture was heated and stirred at reflux temperature (65–70 °C) for 30 min. Then, it was filtered through celite and the filtrate was concentrated to dryness. The foamy residue was dissolved in methanol and allowed to crystallize at ambient temperature. After crystallization, the mixture is stirred for 2 h at room temperature and the crystals were collected by filtration, and dried for 3–5 h at 60 °C in vacuo to afford off-white crystalline product (β form).

2.1.2. Synthesis of imatinib mesylate α form

Half amount of methanesulfonic acid solution in diisopropyl ether was added slowly (in ca. 30 min) into a suspension of imatinib base in isopropyl alcohol at reflux temperature (80–85 °C). After addition of hot isopropyl alcohol, second half of the methanesulfonic acid solution in diisopropyl ether was added slowly (in ca. 30 min) and the mixture was stirred at reflux temperature for 30 min. Then, it was cooled to 30–35 °C, filtered, and the crystals were dried for 6–8 h at 90–95 °C in vacuo to afford off-white crystalline product (α form).

2.2. Preparation of samples

Samples were prepared in fine powder form and sieved for uniformity of the particles. Sample preparation and measurements were carried out under controlled relative humidity (60 ± 5%) and temperature (25 ± 2 °C) conditions. Samples/standards were prepared by mixing them in a mortar and sieving to get homogeneous mixtures. Tablet samples were prepared by peeling the coating material and then the seed tablet was grinded in a mortar with a pestle and sieved to obtain a homogeneous powder. Standard α-β polymorphic API mixtures were prepared at different ratios