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Short Communication

Thermal stability study of crystalline and novel spray-dried amorphous nilotinib hydrochloride

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ABSTRACT

The thermal characteristics and the thermal degradation of crystalline and amorphous nilotinib hydrochloride (NH) were studied. The spray drying technique was successfully utilized for the amorphization of NH and was evaluated by spectroscopic techniques and differential scanning calorimetry (DSC). The ethanolic spray drying process yielded amorphous NH with a glass transition temperature (T_g) of 147 °C.

Thermal characterization of the amorphous phase was performed by heat capacity measurements using modulated DSC (mDSC). Thermal degradation was studied by thermogravimetric analysis (TGA).

The derived thermodynamic properties of the amorphous NH indicate fragile behaviour and a low crystallization tendency.

NH was found to be molecularly stable up to 193 °C. After which, the thermal degradation displayed two phases. The values of the thermal degradation parameters were estimated using the Ozawa-Flynn-Wall and Friedman non-isothermal, model-free, isoconversional methods The results indicate the two phases to be single-step reactions.

The examination of the physical stability of amorphous NH during storage and at elevated temperatures showed stability at 180 °C for at least 5 h and at 20–25 °C/60% RH for at least 6 months. During these periods, no crystallization was observed.

This study is the first to report the thermal characteristics of NH. Additionally, it is also the first to describe the full thermal analysis of a spray-dried amorphous drug. The thermal data may be used in the projection of future production processes and storage conditions of amorphous NH.

1. Introduction

The tyrosine kinase inhibitor nilotinib hydrochloride (NH) (see Supplementary Fig. S1 in the online version at DOI: 10.1016/j.jpba.2017.10.001) is registered for the treatment of newly diagnosed adults with Philadelphia chromosome positive myeloid leukemia (Ph+ CML) in the chronic phase. It is also indicated for the treatment of chronic and accelerated phase Ph+ CML in adult patients that are resistant or intolerant to prior therapy that included imatinib [1].

The oral dosage form of NH (Tasigna®) contains the crystalline polymorph B and is associated with poor solubility and permeability that hinders its bioavailability [2]. Solubility and bioavailability improvement of drugs may be achieved by formulating the amorphous form. Although the amorphous form is often less stable than the crystalline polymorphs, it tends to exhibit improved dissolution characteristics [3].

A nanoparticle formulation containing amorphous NH have been shown to markedly increase the solubility of the drug [4]. Furthermore, another study with this formulation demonstrated an increase in the human bioavailability and shows the advantages of utilizing the amorphous form [5].

Amorphous drug can be manufactured from crystalline material by usage of a large variety of techniques. The spray drying tech-

Abbreviations: NH, nilotinib hydrochloride; OFW, ozawa-flynn-wall; F, Friedman.

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nique was chosen for this study because it enables relatively short production times, large- and small-scale productions and due to its setting flexibility [6]. Additionally, spray drying has successfully been applied in the development and production of various formulations that contain amorphous drugs [7]. The use of the spray-drying technique for the production of amorphous NH has not been reported previously in literature.

The application of thermal analysis methods is important in the pharmaceutical industry, especially in cases where amorphous forms are involved [8]. The methods can be used in studies of polymorph stability, crystallization, stability, compatibility and kinetic parameters. The thermal properties may determine the choice of production methods, storage conditions, bioavailability and by extension, therapeutic efficiency [9]. Additionally, formulation development that follows Quality by Design (QbD) principles should include a full assessment of drug characteristics [10]. This approach will allow for critical drug properties to be identified timely.

For these reasons, it is of importance to study the thermal characteristics and thermal stability of the amorphous form and the crystalline polymorph from which it is produced. No information is available in literature about the thermal behavior of either crystalline or amorphous NH. Furthermore, a full thermal and thermodynamic analysis of a spray-dried amorphous drug has also not been reported before. This study is the first to perform these analyses and establish these characteristics.

The spray-drying process was evaluated by ^{1}H- and ^{13}C-Nuclear Magnetic Resonance spectroscopy (NMR), Fourier transform infrared spectroscopy (FTIR), powder X-ray diffraction (XRD) and differential scanning calorimetry (DSC). The thermal characteristics of the amorphous state of NH were assessed using modulated temperature DSC (MTDSC). The thermal stability and degradation of NH were studied with thermogravimetric analysis and were evaluated by the non-isothermal, isoconversional Ozawa-Flynn-Wall (OFW) and Friedman (F) methods as is recommended by the International Confederation for Thermal Analysis and Calorimetry [11].

The results from this study may be used in the quality control of both crystalline and amorphous and may play a role in the design of production processes and the choice of storage conditions.

2. Materials and methods

2.1. Materials

NH monohydrate was purchased from Avachem Scientific (San Antonio, TX, USA) and was supplied with a certificate of analysis. All analyses were compared to a reference standard to exclude any batch-to-batch differences. The reference standard of NH (monohydrate) was acquired from AlsaChim (Illkirch, France). All other chemicals were of analytical grade. Residual solvents (<0.5%) were detected by gas chromatography. Moisture content was determined by Karl Fisher titration.

2.2. Amorphous phase preparation

The amorphous phase of the compound was prepared by the spray drying technique using a Büchi MiniSpray Dryer B-290, Inert Loop B-295, High performance cyclone, 1.5 mm nozzle cap and 0.7 mm nozzle tip (Büchi). Spray dry system settings were: Spray feed 20%; N_2 atomization flow 40 mm; aspirator flow 100%; inlet temperature 120 °C; outlet temperature 75 °C; inert loop temperature −20 °C. NH monohydrate (10 g/L) was dissolved in 100% ethanol and the solution was stirred using a magnetic stirrer at 20–25 °C.

2.3. ^{1}H-, ^{13}C-Nuclear magnetic resonance spectroscopy (NMR)

NMR spectra were recorded with an Avance Ultrashield instrument (Bruker Corporation, Billerica, MA, USA). The ^{1}H NMR and ^{13}C NMR spectra were recorded at 300 MHz and 75 MHZ, respectively. The samples were dissolved in DMSO (highest peak in multiplet at 2.50 ppm). In the ^{13}C-spectrum, the center peak of the DMSO signal was at 38.5 ppm.

2.4. Fourier transform infrared spectroscopy (FTIR)

FT-IR spectra were recorded from 650 to 4000 cm^{-1} with a resolution of 2 cm^{-1} with a FT-IR 8400S Spectrophotometer equipped with a golden gate® (Shimadzu, 's-Hertogenbosch, the Netherlands). A total of 64 scans were averaged into one spectrum. Data analysis was performed with IR Solution software V1.4 (Shimadzu).

2.5. Powder X-ray diffraction (XRD)

X-ray diffraction of powder samples was performed with an X'pert pro diffractometer equipped with an X-celerator (PANanalytical, Almelo, The Netherlands). Samples were placed in a 0.5 mm deep metal sample holder. Samples were scanned at a current of 30 mA and a tension of 40 kV. The scanning grange was 10–60° 2-θ, with a step size of 0.020° 2-θ and a scanning speed of 0.002° 2-θ per second. The spectra were processed using HighScore software v4.5.

2.6. (modulated) differential scanning calorimetry ((m)DSC)

mDSC and DSC measurements were performed with a Discovery DSC (TA Instruments) equipped with a refrigerating device and suitable for direct heat capacity measurements. Temperature scale and heat flow were calibrated with indium reference disks. Drug samples of approximately 3–5 mg were weighed in Tzero aluminium pans (TA Instruments), compacted, sealed and placed in the autosampler. Each sample was equilibrated at 20 °C, after which the samples were heated with a speed of 10 °C/min to the previous with TGA determined safe temperature. An empty sample pan was weighed and used as reference to the heat capacity of the pans.

The mDSC instrument settings for the heat capacity measurements were as follows: a modulation period of 100 s, a modulation amplitude of +/− 0.5 °K and an underlying heat rate of 1 °K/min. The heat capacity constant (KC_p) was calibrated using a sapphire disc weighing approximately 25 mg. Heat capacity measurements for the crystalline and amorphous compound were performed over a temperature range of 25 °C (absolute) to 20 °C above the melting point of NH. Analysis of the (m)DSC results was carried out with the Trios discovery evaluation software version v4.0.2.30774 (TA instruments).

2.7. Thermogravimetric analysis

Thermogravimetric analysis (TGA) was performed on a Q50 thermogravimetric analyzer (TA Instruments, New Castle, DE, USA). The weight change is measured as a function of time and/or temperature. A typical sample (+/− 10 mg) was placed on a platina sample holder and heated from room temperature to 1000 °C at heating rates of 2.5, 5, 10, 20 and 40 °K/min. Advantage software (TA Instruments) v5.5.22 was used for the analysis of the TGA data.