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THERMAL CHARACTERIZATION OF INDINAVIR SULFATE USING TG, DSC AND DSC-PHOTOVISUAL

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The object of the present work is to study the thermal characteristics of indinavir sulfate and to evaluate the quality of the raw materials. Indinavir A, B, C and reference samples were obtained from different suppliers and submitted to TG, DSC and DSC-photovisual analyses. TG/DTG curves indicated a desolvation and dehydration processes and were confirmed by DSC. According to the DSC curves the fusion took place at about 141–142°C for indinavir C and Reference sample B and about 146–149°C for the others. DSC-photovisual showed insoluble raw materials for indinavir C at 160°C. Indinavir sulfate is highly hygroscopic drug which requires attention during storage and manufacture by pharmaceutical industry.

Keywords: *DSC-photovisual, indinavir sulfate, pseudo-polymorphism, quality control, TG*

Introduction

Indinavir sulfate (IS) is used as a HIV protease inhibitor and combined with other drugs such as lamivudine and zidovudine in anti-AIDS cocktails. This therapy is often monitored to evaluate the possibility of toxicological risks to patients, adverse reaction and interactions with foodstuffs products [1]. The quality of indinavir raw material and its related compounds must be monitored by pharmaceuticals industries to minimize these adverse effects.

Thermal analysis has been used in the development of solid pharmaceutical forms [2–8], for purity determination of raw materials [9–12], for characterization of phytopharmaceuticals [13–15] and to investigate the polymorph and pseudo-polymorph phenomena of pharmaceuticals [16, 17].

The polymorph, pseudo-polymorph and amorphous forms of pharmaceuticals are common, which can affect the melting point, heat capacity, volume, density, solubility, dissolution rate and the bioavailability of drugs [18].

Particularly, pseudo-polymorphic forms can develop in pharmaceuticals after long storage times, grinding, milling and tablet making [19]. Accurate quality control of raw materials is necessary to ensure the batch-to-batch quality of pharmaceutical products, and among other techniques DSC and TG have been used for this purpose [20, 21]. The aim of this work was to identify and characterize the quality of indinavir sulfate in commercial samples according to their thermoanalytical properties, mainly TG and DSC-photovisual.

Experimental

Indinavir samples

Indinavir sulfate as active compounds were provided by LAFEPE from three different suppliers and submitted to thermal analysis studies as received. Indinavir A (Lot. IS1871201), reference sample A; indinavir B (Lot. IDV011108), reference sample B and indinavir C (Lot. IS-054022002) were donated by A (Hetero drugs®), B (Xiamen Mchem®) and C (Aurobindo Pharma®) suppliers, respectively.

Methods

Karl Fisher method

For water content determination of indinavir A and B anhydrous methanol and Karl Fisher solutions, both from Merck® and Karl Fisher apparatus from Quimis® were used. The specification of maximum percentage (≤1.50%) of water content in raw materials is described in Drug Master File from suppliers.

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Thermogravimetric analysis

The TG curves were performed in a Shimadzu model TGA-50H thermobalance at a heating rate of 10°C min^{-1}, in synthetic air (flow rate: 20 mL min^{-1}) in the temperature range of 25–900°C. The sample (5.00 mg±10%) was placed to an α-alumina crucible. The TG instrument was calibrated using calcium oxalate monohydrate.

Differential scanning calorimetry coupled to photovisual system

The DSC curves of IS were recorded in a Shimadzu model DSC-50 calorimeter coupled to a photovisual system (an Olympus microscopy connected to a Sanyo camera, model VCC-D520) at a heating rates of 5, 10, 15 and 20°C min^{-1}, in nitrogen in the temperature range of 25–400°C. The samples (2.00 mg±10%) were put into an aluminum sample holder then the cell was sealed hermetically. The temperature and heat flow of the DSC instrument were calibrated by the melting point and enthalpy of indium and zinc standards.

Results and discussion

Karl Fisher method

The results of the water content determination revealed 1.73% of water content for indinavir A and 2.00% for sample B, respectively. These values were higher compared to the suppliers' specifications (1.50%). The Karl Fisher test did not result insufficient amount water for indinavir C.

Thermogravimetry

The TG profiles of indinavir sulfate were similar for all samples. The samples presented three mass loss steps (Fig. 1). The only difference found between samples was the TG profile in the 25–166°C temperature range. Table 1 shows the mass losses for indinavir sulfate raw materials and reference samples. The desolvation and dehydration of the raw materials A, B, C and reference samples A and B exhibited 4.10, 3.23 4.54, 4.29 and 4.25% of mass losses, respectively. Presence of synthetic air in the TG system shifted the mass loss of volatilization to higher temperature due the higher concentration of gases in vapor phase resulting in change of the chemical equilibrium between the solvent in liquid and solvent in vapor phases, but it was favorable to liquid phase up to 166°C. TG curve presented formation of residue at superior temperature of 720°C causing 2.07, 2.03, 2,65, 1.80 and 3.01 of mass losses for indinavir sulfate A, B, C, reference sample A and B, respectively.

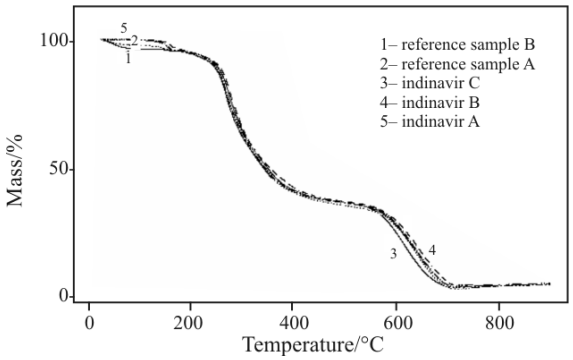

Fig. 1 TG curves of indinavir sulfate at 10°C min^{-1}

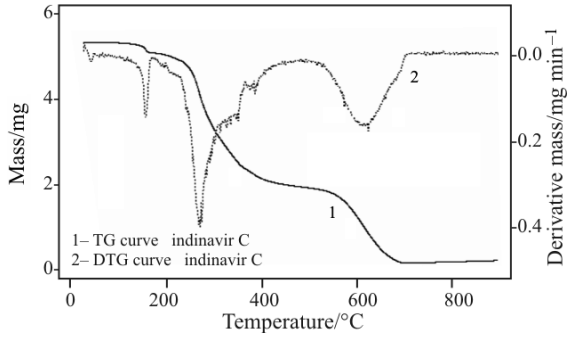

Fig. 2 TG/DTG curves of indinavir sulfate C at 10°C min^{-1}

Table 1 Mass losses for indinavir sulfate raw materials (heating rate: 10°C min^{-1})

Samples	Temperature range/°C mass loss/%		
Raw materials	25–166	166–356	356–720
A	4.10	49.76	44.07
B	3.23	49.22	45.72
C	4.54	47.89	43.04
Reference samples			
A	4.29	49.17	42.70
B	4.25	47.12	44.65

In the DTG curves between 25–252°C one can observe a shoulder before the second DTG peak. In the same temperature range the TG curves show 12.02, 11.88, 10.85, 11.90 and 10.72% for indinavir sulfate A, B, C, reference sample A and B of mass losses, respectively. The sulfurous odor what could be felt during the thermal runs might one of the sign of sulfate liberation (Fig. 2).

Stoichiometrically, one mol of sulfate corresponds to 12.66% of mass loss per one molecule of indinavir sulfate ethanolate. According to Peterson *et al*. [22] indinavir occurs in the form of indinavir sulfate ethanolate (solvate). In agreement with [23, 24] from the TG data non stoichiometric composition for the investigated sample was calculated. Other techniques as infrared spectroscopy, X-ray powder diffraction, ^{13}C-NMR

Table 2 Calorimetric data for indinavir sulfate raw materials (heating rate: 10°C min^{-1})

Raw materials	Peak of desolvation	Peak of fusion
A	71.4°C (–8.1 J g^{-1})	147.2°C (–62.0 J g^{-1})
B	76.5°C (–8.2 J g^{-1})	149.3°C (–63.7 J g^{-1})
C	73.7°C (–24.6 J g^{-1})	141.3°C (–54.4 J g^{-1})
Reference samples		
A	82.1°C (–41.7 J g^{-1})	146.2°C (–35.8 J g^{-1})
B	95.8°C (–61.8 J g^{-1})	142.0°C (–21.3 J g^{-1})

spectroscopy, TG-FTIR and TG-MS should be used to provide additional evidences on this subject.

Differential scanning calorimetry

Indinavir sulfate was characterized using DSC as well. In the calorimetric curves in the 70–95, 141–149 and 180–320°C temperature ranges three main peaks can be observed (Fig. 3). The temperature and endothermic peaks of dessolvation besides peaks of fusion and heats of fusion for indinavir A, B, C and reference sample A and B are showed in the Table 2. These endothermic peaks correspond to ethanol desolvation (boiling point of ethanol: 78°C) [25] in raw materials and reference sample A, except to the reference sample B (95.8°C) which exhibited an endothermic peak for desolvation of water.

Probably this water in reference samples accumulated because of the bad storage conditions or the long term of storage of reference samples. The DSC and TG data demonstrated the importance to determine the amount of solvents in different samples and suggest two solvate forms of indinavir sulfate (Fig. 3). These initial DSC and TG data are important in the aspect of the chemical stability of indinavir sulfate during the long term exposition and established the better storage and processing conditions of dosage forms of indinavir sulfate. The DSC curves of indinavir sulfate indicate different melting temperatures for the samples (Table 2).

The vertical dotted and solid lines in Fig. 3 suggest two temperature ranges of fusion for the two possible

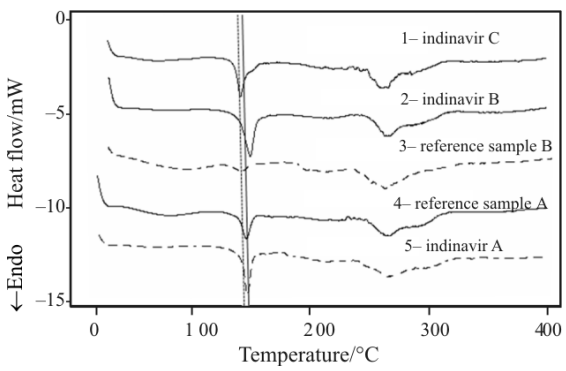

Fig. 3 DSC curves of reference samples and raw materials of indinavir sulfate

pseudo-polymorphic forms of indinavir sulfate. The reference sample B and indinavir C show different fusion peaks [141–142°C] compared to reference sample A and raw materials A and B [146–149°C] (Fig. 3). Indinavir sulfate presented a melting point at 150–153°C in agreement with the literature [25].

According to Grant presence of additional bonds between the host molecules and water molecules and changes in the bonding between host molecules they alter the cooperativity of the molecules in the crystal lattice and hence the melting point. Changes in intermolecular interactions within solid and hence modifies the internal energy and therefore the change in the enthalpy and entropy of the solid. These changes result in change in the free energy and chemical potential and hence in the thermodynamic activity. Finally, changes in thermodynamic activity due hydration or solvation alter the pharmaceutical properties such as solubility and chemical stability [26].

A correlation was found between the mass losses calculated from the TG curves and the decomposition ranges in the DSC curves at 252°C for the different indinavir samples. The thermogravimetry data (Fig. 2) were coherent with DSC data (Fig. 3). Indinavir presented endothermic peaks at 252°C in the DSC curves which appears as a shoulder in the DTG curves. The corresponding mass losses for the volatilization of the sulfate are between 10.72–12.02% according to the TG curves.

DSC coupled to a photovisual system

The DSC – photovisual analysis confirmed the volatilization process which can be seen by bubbling (Fig. 4 – photos B3 and C3). The DSC photovisual evidenced differences in the thermal behavior of indinavir samples. In spite of the analyses has been performed in open cell some differences were detected between raw materials. Indinavir A and B presented total fusion at 160°C which is different from indinavir C (Fig. 4 – photos B3, C3 and A3, respectively). Indinavir C presented characteristics of insoluble material in open cell conditions and very different from closed cell conditions. Similar process was observed in the reference sample B (Fig. 4 – photo E_2). These samples

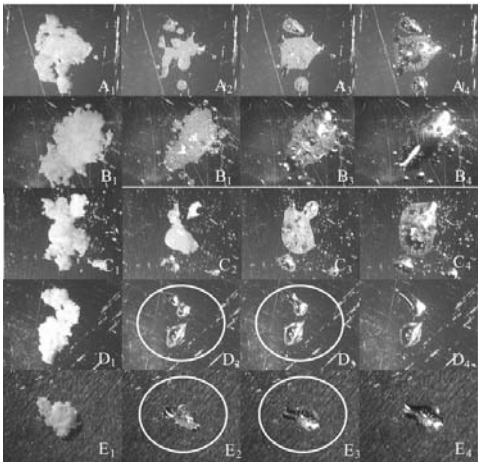

Fig. 4 DSC photovisual: (room temperature) – photos A1, B1, C1, D1 and E1; (151°C) – A2, B2, C2, D2 and E2 ; (160°C) – A3, B3, C3, D3 and E3; (165°C) – A4, B4, C4, D4 and E4 for indinavir C, B, A, reference sample A and reference sample B, respectively

exhibited incomplete fusion process at 150°C which were different from reference sample A.

The DSC-photovisual demonstrated the formation of two kinds of solvates with changes in the peak of fusion and melting point of indinavir sulfate. The presence of different amounts of water in indinavir molecule can alter the thermal and physicochemical properties (e.g. solubility and bioavailability) of the drug.

Conclusions

TG/DTG data demonstrated presence of volatile solvents in raw materials of indinavir sulfate and volatilization of sulfate in indinavir molecule.

DSC data have suggested the presence of two types of solvates in indinavir sulfate drug substance. Indinavir C and reference sample B may represent a solvation form which differs from indinavir A, B and reference sample A. DSC-photovisual has demonstrated differences in the melting point for indinavir C which can cause differences in solubility of indinavir drug. Thermal analysis data have proven to be a versatile tool to differentiate the indinavir sulfate through their physicochemical properties, especially pseudo-polymorphism but it requires other additional experiments using other analytical techniques.

The thermal data demonstrated that indinavir sulfate is a highly hygroscopic drug, which requires attention during the storage and manufacture by pharmaceutical industry.

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