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Synthesis, characterization and solubility of a new anthelmintic salt: Mebendazole nitrate

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ABSTRACT

Salt formation approach was taken to improve Mebendazole (MBZ) solubility. MBZ polymorph A was easily recrystallized as a 1:1 nitrate salt (MBZ N) in methanol. Single crystal X-ray diffraction data show that MBZ N crystallizes in the $P\bar{1}$ space group. By strong intermolecular *H*-bonding interactions, MBZ is associated with a nitrate anion forming a supramolecular $R_2^2(8)$ synthon. Crystal packing is stabilized by these *H*-bonds, through which each nitrate connects two molecules of MBZ forming chains along the *b* axis. The vibrational behavior studied by micro FT-Raman and FT-IR spectroscopy is consistent with the crystal structure. Thermal analysis of the salt indicates that the compound is stable up to 150 °C, when an almost simultaneous elimination of HNO_3 and CO_2 occurs. MBZ N equilibrium solubility was evaluated in hydrochloric acid 0.1 M solution and compared with those of MBZ A and C. An improvement in a factor of 5 and 1.22 was found respectively.

1. Introduction

Mebendazole (MBZ), IUPAC name: ((5-benzoyl-1H-benzimidazole-2-yl)-carbamic acid methyl ester), is a synthetic anthelmintic drug included in the World Health Organization's Model List of Essential Medicines [1]. It was first synthesized and developed by *Janssen Pharmaceutica* and introduced in Belgium in 1972 [2]. Since then, its importance in the health systems of both developed and developing countries was quickly increased due to its broad-spectrum activity against single or mixed infections caused by several parasitic worm species (helmianthiasis). Mebendazole is a white to slightly yellowish crystalline solid, and exists in three polymorphic forms, called A, B and C [3], which show differences in their properties, mainly in their solubility [4,5]. This drug can be included in Class II of the Biopharmaceutics Classification Systems (BCS) (low solubility and high permeability) [6,7]. MBZ is administrated orally as a tablet formulation or suspension, and commercially available pharmaceutical products are often a mixture of polymorphs A and C of variable proportions [8–10].

Biodisponibility of MBZ is limited by its very low water solubility [11]. Even though some discrepancies are reported in the literature about the relative solubility of forms B and C [3–5], all the authors agree that polymorphic form C is the most efficacious one, and it is pharmaceutically preferred since its solubility is enough to ensure an acceptable bioavailability. Polymorph A is the least soluble form and therapeutic assays suggests it has similar efficacy than a placebo in controlling worm infections [12–14]. Since form A is the most stable form [15], it is of interest to find a way to obtain a new MBZ solid form, from pure polymorph A (or from a mixture of polymorphs), with greater solubility, which could provide a therapeutic activity level at least similar to polymorph C.

Since 1980, several MBZ multicomponent structures have been reported, including three salts from strong acids (Mebendazole hydrobromide – MBZ·HBr – [16], Mebendazole hydrochloride – MBZ·HCl – [17] and Mebendazole mesylate monohydrate – MBZ M – [18]) and a series of solvates and salts from carboxylic acids [19–21]. All these new MBZ solid forms were obtained by different synthesis approaches such as salt formation with solvent evaporation (SES) or liquid assisted grinding (LAG). The most common and simple approach to obtain a multicomponent crystalline system is to form a salt by proton transfer from an acid to a basic site of the API, forming two ionic components, with opposite charges, that could eventually crystallize together [22].

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Here we report the synthesis, isolation and characterization of a new MBZ multicomponent Active Pharmaceutical Ingredient (API): Mebendazole nitrate salt (MBZ N). The crystalline structure of this new stable salt was solved by single-crystal X-ray diffraction while a complete physical–chemical characterization of the compound, by solid-state techniques (powder X-ray diffraction, thermogravimetric analysis, differential scanning calorimetry, hot-stage microscopy, Raman and infrared spectroscopies), was also carried out. The characterization also includes solubility studies in hydrochloric acid solution 0.1 M media and comparison with solubility of MBZ A and C.

2. Experimental details

MBZ A was purchased from Sigma-Aldrich Brazil® and used without any further purification. Nitric acid and the solvents methanol and ethanol were obtained from commercial sources and also used directly. Solubility of MBZ C was determined for a sample of a pharmaceutical product supplying by the Laboratorio de Control de Calidad de Medicamentos (UNSL, San Luis, Argentina).

2.1. Supramolecular synthesis

25 mg of MBZ A were suspended in 10 mL of methanol. At room temperature and with constant magnetic stirring (500 rpm), a white suspension was formed, and then 100 μL of concentrated nitric acid were added to achieve almost complete dissolution of the solid. The stirring was stopped after 10 min, and the suspension was filtered. Finally, the solution was brought to 5 °C to achieve slow evaporation of the solvent. After approx. five days, the formation of small, colorless prismatic crystals was observed on the walls of the beaker and in the liquid. These crystals were separated by filtration and washed several times with Milli-Q© water. Powder X-ray diffraction was used to check the purity of the solid form reported here (see Fig. 1).

2.2. Single crystal structure determination

A suitable-sized clear crystal was selected for the single crystal X-ray diffraction experiment. The crystallographic data for the crystal were collected at room temperature (293 K) on a Bruker APEX-II diffractometer with CCD detector system equipped with a Mo source (λ = 0.71073 Å). Data integration, cell determination and final parameters were obtained using the software Bruker SAINT [23] included in APEX2 software suite. Using Olex2 [24], the structure was solved by direct methods and the model obtained was refined by full–matrix least squares on F^2 (SHELXL-97) [25]. All the hydrogen atoms were placed in calculated positions and refined with fixed individual displacement parameters [$U_{iso}(H) = 1.2U_{eq}$ or $1.5U_{eq}$] according to the riding model. Molecular representations, tables and pictures were generated by MERCURY 3.8 [26] and Olex2 [24]. The CIF was deposited in the Cambridge Structural Data Base [27] under the code CCDC 1585622. Copies of the data can be obtained, free of charge, via www.ccdc.cam.ac.uk.

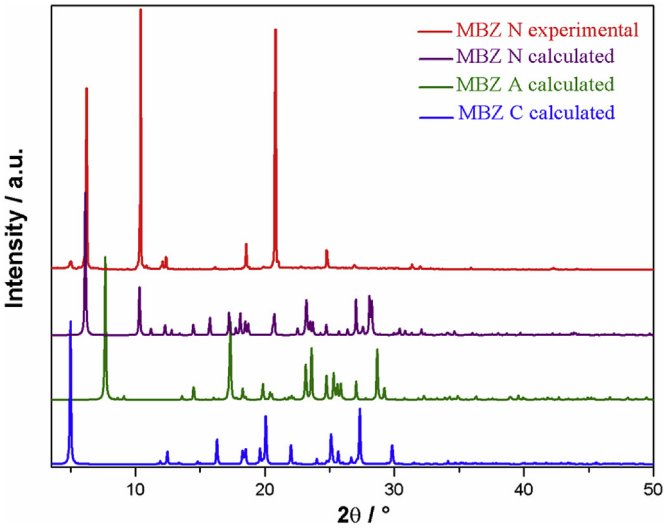

Fig. 1. Experimental PXRD pattern of MBZ N (red) compared with calculated patterns of MBZ N (violet), MBZ A (green) and MBZ C (blue). (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

2.3. Powder X-ray diffraction (PXRD)

Powder X-ray diffraction patterns were obtained with a Rigaku Ru200B Rotaflex diffractometer (Rigaku Company, Tokyo, Japan) in Bragg-Brentano reflective geometry, with CuKα radiation (λ = 1.5406 Å) at 40 kV-60 mA and Ni filter. The diffractograms were acquired in the 5–50° 2θ range with a step width of 0.02° and a constant counting time of 3 s per step.

2.4. Hot-stage polarized optical microscopy (HSM)

A Leica DM2500P microscope (Leica Microsystems AG, Wetzlar, Germany) coupled to a Linkam T95-PE hot-stage equipment (Linkam Scientific Instruments, London, UK) was used for hot-stage microscopy, with air atmosphere, temperature rate of 10 °C min^{-1} and temperature range from RT to 400 °C. Data were visualized with the Linksys 32 software for hot-stage control.

2.5. Thermal analysis

Thermogravimetric analysis curve was obtained with a Shimadzu TGA-60 thermogravimetric analyzer (Shimadzu Inc. Kyoto, Japan), using alumina pan, flowing nitrogen at 50 mL min^{-1}, and a heating rate of 10 °C min^{-1} from RT to 600 °C. Measures were collected and processed with «TA60» software, associated to the analyzer.

Differential scanning calorimetry curve was obtained with a Shimadzu DSC-60 differential scanning calorimeter (Shimadzu Inc. Kyoto, Japan), using aluminum pan, flowing air at 50 mL min^{-1}, and a heating rate of 10 °C min^{-1} from RT to 600 °C. Measures were collected and processed with «TA60» software, associated to the calorimeter.

2.6. Electronic and vibrational spectra

UV–visible absorbance measures were carried out in an Agilent 8454 UV–vis spectrophotometer (Agilent Technologies, Santa Clara, CA, USA), and processed with «8453 UV Visible Chem station Rev.A.10.01» software associated to the instrument.

Fourier transformed infrared spectrum was recorded on a Nicolet *Protégé 460* spectrophotometer (Nicolet Instrument Corporation, Madison, Wisconsin, USA) provided with a CsI beamsplitter, in the 4000–400 cm^{-1} range with 64 scans and spectral resolution of 4 cm^{-1}, using the KBr pellet technique. Measures were collected and processed with «Omnic » software, associated to the spectrometer.

LabRAM HR Evolution Raman spectrometer (Horiba Scientific, Kyoto, Japan) was used for micro Raman spectroscopy. Measures were collected and processed with «LabSpec 6 Spectroscopy Suite » software, associated to the spectrometer. Parameters used