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Molecular salts and co-crystals of mirtazapine with promising physicochemical properties

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ABSTRACT

Pharmaceutically suitable non-sublimating salts and molecular salts of anti-depressant drug R/S-mirtazapine with one of several dicarboxilic acids were studied. The salts/salt molecules were characterized by powder X-ray diffraction, differential scanning calorimetry and thermogravimetric analysis and crystal structure of tartarate and oxalate molecular salt were determined by single crystal X-ray diffraction. The salts/salt molecules of mirtazapine do not show any sublimation at elevated temperature whereas sublimation of mirtazapine has been observed at ambient temperature. The aqueous solubility of the mirtazapine molecular salts was significantly improved with a maximum of citrate salt which was about 180 times more than the solubility of the parent mirtazapine at 35 °C.

1. Introduction

Mirtazapine((±)-2-methyl-1,2,3,4,10,14b-hexahydropyrazino [2,1-a]pyrido[2,3-c][2]benzazepine, hereinafter abbreviated as MITZ, shown in Fig. 1 is a noradrenergic and specific serotonergic antidepressant (NaSSA) [1], that is used primarily in the treatment of depression. It is also commonly used as an anxiolytic, hypnotic, antiemetic and appetite stimulant. MITZ has been marketed under several brand names such as Avanza, Axit, Mirtaz, Mirtazon, Remeron, Zispin. In terms of structure, mirtazapine can also be classified as a tetracyclic antidepressant (TeCA) and is the 6-aza analog of mianserin [2]. It is racemic and comes as a combination of both R and S-stereoisomers.

It was found that formulations containing MITZ suffer from problems caused by the sublimation of MITZ which is having a half-life of 20–40 h. S- and R-mirtazapine pure bases are slowly sublimating compounds at ambient temperature, but the salts of mirtazapine viz. maleate, fumarate, malonate, adipate, salicylate, sachharinate, hydrobromide reported to be non-sublimating [3–7]. Thus, pharmaceutical composition comprising an enantiomer of MITZ can be improved by selecting a pharmaceutically acceptable non-sublimating salt of an enantiomer of MITZ.

There are only two published papers of MITZ salts reported by Bhatt et al. [3] and Sarma et al. [4]. We found contradictory report on solubility of MITZ, as authors of the first paper mentioned MITZ as practically insoluble drug in water (<0.05 mg mL^{-1}), while the latter claimed MITZ as highly soluble drug (1 mg mL^{-1}). The aim of this study, therefore, was to rationally design and prepare a series of pharmaceutically acceptable MITZ salts, evaluate their sublimation rate and also to make a comparative study of the solubility and dissolution rate of MITZ salts with that of MITZ free base.

In recent years, a high-throughput approach has become standard when a salt screening is adopted with due attention to its pKa values. Conventional strategies dictate that in order to form a stable salt, at least a three-unit difference in pKa between the salt and the free base is required. The N-methyl basic site of the piperazine group has a *p*Ka of 7.1. Therefore, according to the Δ*p*Ka rule, it should form salts with acids of *p*Ka < 4.

In the previously reported structure [3,4] of mitrazapium salts by Sarma et al. and Bhat et al., the supramolecular interaction was ionic two-point synthon between the carboxylate anion which acts as an acceptor and the protonated N^+—H-site and the C—H of the asymmetric carbon atom. Our goal was to observe whether the same supramolecular two point synthon formation is universal in all the salt formation of MITZ, even when hydroxyl group is present along with dicarboxilic acid in a molecule. Based on the supramolecular strategy of crystal engineering and the pKa rule, the following MITZ salts were attempted in this study: MITZ-oxalate, MITZ-tartrate and MITZ-citrate. With the aim of formation of salt

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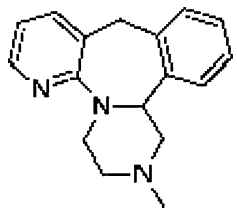

Fig. 1. Chemical structure of mirtazapine.

of oxalic acid of mirtazapine, molecular salt which is quite unusual was observed in the crystal structure of MITZ with oxalic acid.

The chemical structures of successful conformers which formed salts with MITZ are presented in Fig. 2. Solution evaporation techniques were used to prepare the salts. Physical states of MITZ were characterized by powder X-ray diffraction (PXRD), differential scanning calorimetry (DSC) and thermogravimetric analysis (TGA). We also determined the single crystal structure of the tartrate and oxalate molecular salts to understand the salt crystal structures for their enhanced stabilities and also to verify the ionic two point synthon formation.

The non-sublimating nature of the MITZ salts was measured and less than 1% of the MITZ salts were found to be sublimating from the sample.

2. Experimental

2.1. Materials

Mirtazapine was a gift sample from ApotexPharmaChem Inc. (Canada). Other chemicals were purchased from Sigma Aldrich and were used as received.

2.2. Mirtazapine citrate salts (1:1 MITZ/citric acid)

This material was prepared by solvent evaporation. Mirtazapine (265 mg, 1 mmol) and citric acid (192 mg, 1 mmol) were dissolved in 10 mL of methanol and heated at 100 °C with constant stirring in a sealed tube for 2 h. The solution was then filtered through 5 μm filter paper (VWR brand, 5.5 cm) to remove insolubles. The filtered solution was then allowed to evaporate slowly at room temperature.

2.3. Mirtazapine tartrate salts (1:1 MITZ/tartaric acid)

This material was prepared by solvent evaporation. Mirtazapine (265 mg, 1 mmol) and DL-tartaric acid (150 mg, 1 mmol) were dissolved in 10 mL of methanol and heated at 100 °C in a sealed tube with constant stirring for 2 h. The filtered solution was then allowed to evaporate slowly at room temperature. Single crystals suitable for single crystal X-ray diffraction analysis were obtained after 7 days.

2.4. Mirtazapine oxalic acid salt co-crystal (1:1 MITZ/oxalic acid)

This material was prepared by solvent evaporation. Mirtazapine (265 mg, 1 mmol) and oxalic acid (102 mg, 1 mmol) were dissolved in 10 mL of methanol and heated at 100 °C with constant stirring in a sealed tube for 2 h. The filtered solution was then allowed to evaporate slowly at room temperature. Single crystals of MITZ oxalic molecular salt were obtained after 2 days and were analyzed by single crystal X-ray diffraction.

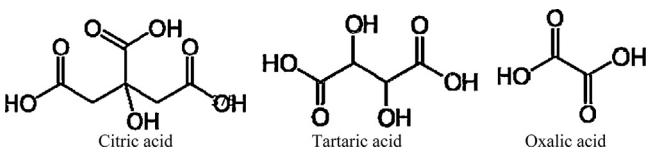

Fig. 2. Dicarboxilic acids that successfully formed salts with mirtazapine.

2.5. Powder X-ray diffraction (PXRD)

The PXRD spectra were collected on a Rigaku-Miniflexbenchtop X-ray powder diffractometer (Carlsbad, CA) using CuKα (λ = 1.54059 Å) radiation obtained at 30 kV and 15 mA. The scans were run from 5.0° to 30.0° 2θ, increasing at a step size of 0.05° 2θ with a counting time of 2 s for each step. The diffractograms were processed using JADE 7.0 software. Calibration was performed using a silicon standard.

2.6. Differential scanning calorimetry (DSC)

The melting points were measured with a Mettler Toledo DSC 822e differential scanning calorimeter (Greifensee, Switzerland). Accurately weighed samples (~3 mg) were prepared in a covered aluminum crucible having pierced lids to allow escape of volatiles. The sensors and samples were under nitrogen purge during the experiments. The temperature calibration was carried out using the melting point of highly pure indium in the medium temperature range. Heating rate of 5 °C/min was selected.

2.7. Thermogravimetric analysis (TGA)

TGA was performed on a Mettler-Toledo TGA/SDTA 851e instrument. Approximately 2 mg sample was heated from 25 to 300 °C at 10 °C/min under nitrogen purge.

2.8. Single crystal X-ray diffraction

Single crystals of MITZ salts were grown from methanol solution at room temperature. The single crystal sample was mounted on a Mitegen polyimide micromount with a small amount of Paratone N oil. X-ray measurements were made on a Bruker Kappa Axis Apex2 diffractometer at a temperature of 110 K. The unit cell dimensions were determined from a symmetry constrained fit of 8574 reflections with 4.9° < 2θ < 58.56°. The frame integration was performed using SAINT [8]. The resulting raw data were scaled and absorption corrected, using a multi-scan averaging of symmetry equivalent data using SADABS [9].

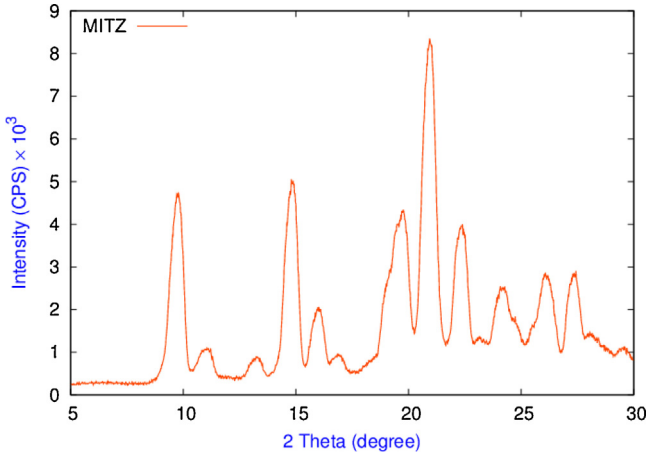

Fig. 3. PXRD pattern of mirtazapinefree base.