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NEW SOLID FORM OF PROMETHAZINE HYDROCHLORIDE

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ABSTRACT. The main objective of the present paper was to obtain new solid forms of Promethazine Hydrochloride (PTZ). The preparation was performed by grinding in a ball mill equipment Promethazine Hydrochloride and acetic acid (1:1). To evidence this new solid form of Promethazine Hydrochloride, different investigation techniques have been used: X-ray diffraction (XRD), Fourier transformed infrared (FTIR) spectroscopy, and Differential Thermal Analysis (DTA). XRPD data allowed the determination of the crystallographic system and lattice parameters. The new solid form crystallizes in a monoclinic system having the following unit cell parameters: a=14.52Å, b=9.33Å, c=14.21Å, α=90°, β=110.59°, γ=90°. In the FTIR spectra of PTZ and PTZ-acetic acid the displacement of the bands, indicating the formation of a new compound, appears in the 1500-4000 cm^{-1} spectral range. In the DTA thermograms, the difference between the onset temperatures suggests that these two samples represent different solid forms.

Keywords: *Promethazine Hydrochloride, solid form.*

INTRODUCTION

The new solid forms of API-active pharmaceutical ingredient are important in the field of pharmaceuticals because of their potential to modify the physico-chemical properties of the drug for a desired therapeutic use. Significant improvements of the API properties can often be achieved by the development of new solid forms [1].

PTZ, (RS)-dimethyl [1-methyl-2-(phenothiazone-10-yl) ethyl] amine hydrochloride is a phenothiazine derivate, a first-generation antihistamine of the phenothiazine family [2]. It is used for the amelioration of the allergic

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reactions, the treatment of motion sickness and the prevention and control of nausea and vomiting, associated with certain types of anesthesia and surgery [3].

Recently, two crystalline structures of PTZ were determined by single crystal XRD and revealed a case of intergrowth of polymorphic domains. The two crystal structures of PTZ have been characterized and the conformation and crystal packing have been determined [4]. It was established that due to disorder, one form is less stable and it transforms into the more stable, but still disordered polymorph. In order to improve the stability of PTZ we investigated the possibility of obtaining new solid forms.

This study is focused on the preparation and characterization of a new solid form of PTZ. The preparation method consists in grinding the mixture PTZ - acetic acid (1:1) in a vibratory ball mill apparatus. For such a preparation method, it is not easy to describe the process leading to the formation of a new compound; an evaluation of the potential interaction between molecules is necessary. In our case, the most probable interaction is that of the carbonyl from acetic acid which may form hydrogen bonds with the nitrogen from the aliphatic part of PTZ. The component mixture is mechanically activated in the vibratory ball mill [5].

The resulted compound was investigated by X-ray powder diffraction (XRPD), infrared (FTIR) spectroscopy and differential thermal analysis (DTA).

RESULTS AND DISCUSSIONS

Figure 1 presents the X-Ray diffraction pattern of Promethazine Hydrochloride (PTZ) and of the PTZ - acetic acid form obtained as a result of the grinding preparation. The XRPD pattern for acetic acid is not necessary to be shown in the figure because of its liquid nature. Figure 1 indicates that the XRPD pattern of PTZ - acetic acid form is different from the XRPD pattern of PTZ, indicating that a new solid form was obtained. Indexing of the X-ray powder diffraction pattern was carried out using X-Cell indexing algorithm [6]. From the powder diffraction indexing it was obtained that the new solid form crystallizes in a monoclinic system having the following unit cell parameters: a=14.52Å, b=9.33Å, c=14.21Å, α=90°, β=110.59°, γ=90°.

In order to characterize the new solid form, the first technique was the FTIR spectroscopy. The FTIR spectra of PTZ and of the PTZ- acetic acid are presented in Figure 2.

The characteristic vibrational frequencies corresponding to the PTZ and PTZ-acetic acid are presented. The spectra of the PTZ contain the characteristic absorption bands due to CH stretching (2800-3000 cm^{-1}), NH^{+} stretching (2200-2480 cm^{-1}), aromatic C=C stretching (1591 cm^{-1}), CH_3 and CH_2 bending (1430-1470 cm^{-1}), C-N stretching of tertiary amine (1334 cm^{-1}), out plane CH bending of distributed aromatic (1378 cm^{-1}), according to literature [7].

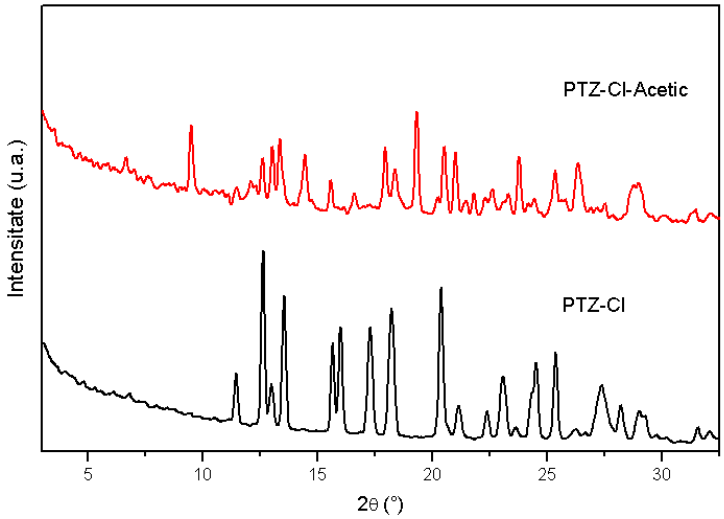

Figure 1. X-ray powder diffraction for PTZ and PTZ-acetic acid.

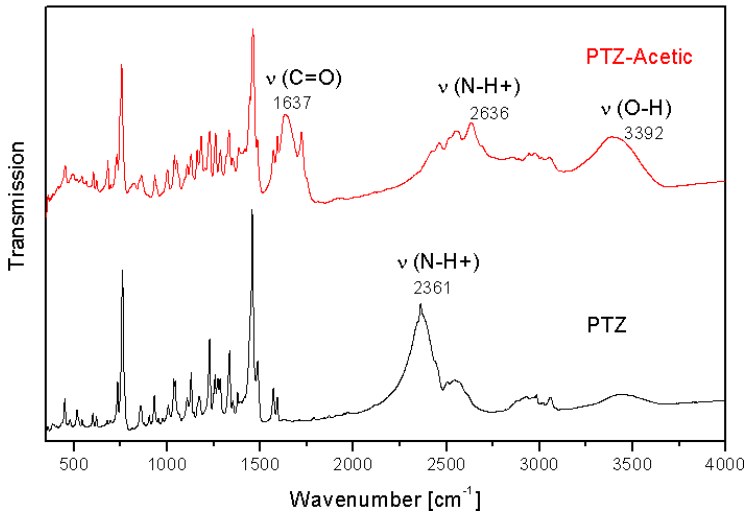

Figure 2. FTIR spectra of Promethazin Hydrochloride and its new solid form with acetic acid in the 350-4000 cm^{-1} spectral range.

It is to notice that the FTIR spectra of PTZ and PTZ-acetic acid are quite similar in the spectral region 350-1500 cm^{-1} and that displacement of the bands is appearing in the 1500-4000 cm^{-1} spectral range. The carbonyl stretch of acetic acid appears as an absorption band at 1637cm^{-1}. Concerning the O-H stretch, it is present in the spectrum as a wide band at 3392 cm^{-1} [8], [9].

The PTZ crystal structure was solved by Borodi et al. [4]. The molecular configuration of the PTZ molecule and the intermolecular hydrogen bond with the Cl atom are shown in Figure 3. The organic cation interact with Cl^- anion via N-H^+··· Cl hydrogen bond.

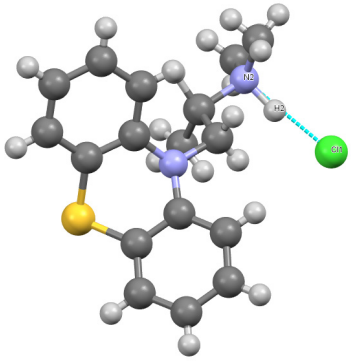

Figure 3. Model of molecular structure of PTZ

Based on the as determined crystal structure of PTZ, the IR spectrum was simulated and assignments were made. For the N-H^+ bond a vibration feature at 2361cm^{-1} is observed. In the FTIR spectrum of the PTZ-acetic acid form a significant reduction in the band intensity was found. In the meantime, a considerable band shift from 2361 cm^{-1} to a higher wave number (2636 cm^{-1}) is taking place. This is due to structural changes in the vicinity of the nitrogen ion, most likely generated by its interaction with the acetic acid.

Another way to characterize the new solid form is Differential Thermal Analysis. The DTA thermogram of PTZ (see Figure 4) shows a sharp endothermic peak at 230 °C, corresponding to the melting point.

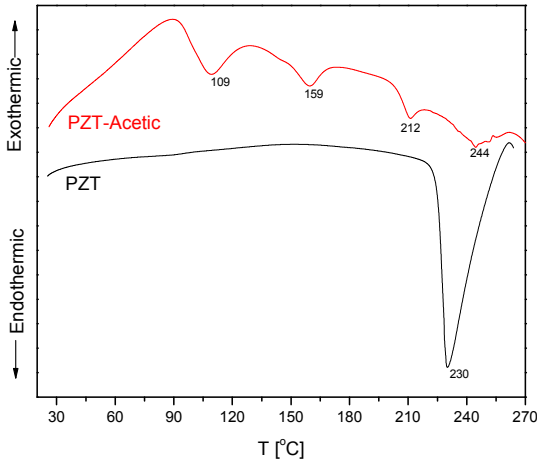

Figure 4. DTA curves of PTZ and PTZ-acetic acid.

The new form with acetic acid presents a different DTA thermogram as compared to that of PTZ. This thermogram shows a broad endothermic peak below 109°C due to acetic acid and water elimination by evaporation, and another broad endothermic peak at 159°C probably corresponding to a hydrochloride acid elimination [10]. The next thermal event, occurring at 212°C, corresponds to the melting of the sample, followed by another sharp endothermic peak with maximum around 244°C which corresponds to the decomposition of the compound. The difference between the onset temperatures and the heat of fusions suggests that these two samples represent different solid forms.

CONCLUSIONS

A new solid form Promethazin–Acetic acid was prepared by a grinding procedure. XRD analysis, FTIR spectroscopy and DTA indicate the formation of new solid form. Based on the X-ray powder diffraction the lattice parameters for the new compound were determined.

EXPERIMENTAL SECTION

Pure acetic acid was purchased from *Sigma Aldrich* and started material Promethazine Hydrocloride by Microsin. Both compounds were used without further purification. Based on grinding in a ball mill procedure [7], the new solid form was prepared by milling a mixture of 1:1 Promethazine Hydrochloride and acetic acid. Vibratory ball mill was used to prevent evaporation of acetic acid. Milling occurs for 90 minutes at a frequency of 27.5 Hz. The solid mixture it was maintained at room temperature until the next day to dry.

X-Ray powder pattern was obtained using D8 Advanced diffractometer equipped with Ge (111) monochromator in the incident beam and EyeLynx position detector using Cu tube (Cu $K\alpha_1$ radiation; λ=1.54056 Å).

The FTIR absorption spectra of the studied samples were obtained with a JASCO FTIR 6200 spectrometer in the 4000 - 400 cm^{-1} spectral range with a resolution of 4 cm^{-1}. The IR absorption measurements were performed using the KBr pellet technique.

The thermal behaviour of studied samples was carried out using a Perkin Elmer TG/DTA 6300 thermal analyzer under Ar gas atmosphere. About 25 mg of sample was heated in Pt-holder with another Pt-holder containing α-alumina as a reference material. A uniform heating rate of 10 °C/ min. was adopted.

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