Short communication

Stability studies and structural characterization of pramipexole

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ABSTRACT

Stability studies of pramipexole dihydrochloride performed under following conditions of temperature and relative humidity (RH): 25 °C 60% RH and 40 °C 75% RH revealed its tendency to the water sorption and the monohydrate formation. The structural changes occurring during storage were studied by infrared spectroscopy and X-ray powder diffraction methods. The thermogravimetry technique was used to control the water sorption by the substance. Pramipexole dihydrochloride monohydrate was characterized by nuclear magnetic resonance and X-ray single crystal diffraction methods. The monohydrate crystallizes in the orthorhombic crystal system in the space group P212121.

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1. Introduction

Pramipexole ((S)-2-amino-4,5,6,7-tetrahydro-6-propylamine-benzothiazole dihydrochloride) is a synthetic aminobenzothiazole derivative. The addition of the N-propylamino group makes pramipexole a potent dopamine receptor antagonist [1]. It is used to treat symptoms of Parkinson's disease.

Nowadays there is growing interest in hydrates of an active pharmaceutical ingredient. Apart from polymorphs they are highly desirable in the pharmaceutical industry. European pharmacopeia specifies in monographs anhydrate and hydrate forms as well [2].

The small water molecule can fill structural voids as well as by acting as a hydrogen donor and/or acceptor may link a crystal majority into stable crystal structures. The water molecule forms bonds with the other water molecule and also with functional groups like carbonyls, amines, and alcohols [3].

Due to high solubility and biocompatibility amine hydrochlorides are often chosen as drug products. They can easily form hydrates because charged ammonium and chloride ions are in a proximity and hydrogen bonded to water molecules [3,4].

Hydrates are easily generated by suspending the substance in water or by wetting. Also a water sorption is commonly used to obtain hydrates [3,5]. Therefore short and long term stability tests are the easiest way to check a tendency of a substance to a hydrate formation.

Thermoanalytical techniques as well as X-ray powder diffraction and infrared spectroscopy are successfully applied for studies of hydrates formation [6–8].

The aim of this paper is the investigation of influence of temperature, relative humidity (RH) and time on physicochemical properties of pramipexole dihydrochloride.

2. Experimental

2.1. Materials

The commercial sample of pramipexole dihydrochloride, Batch no. 20050203, Changzhou Huaren Chemical Co., LTD, (Changzhou, Jiangsu, China) was taken to stability studies. For the article clarity the sample was marked as PX. The sample was stored under following conditions: 6 months at 25 °C in 60% RH (sample PXa) and at 40 °C in 75% RH (sample PXb) as well as 9 months at 25 °C in 60% RH (sample PXc).

2.2. Infrared spectroscopy (IR)

The IR spectra were recorded on the Perkin-Elmer FT-IR BX spectrometer (Waltham, Massachusetts, USA) in the range from 4000 to 400 cm^{-1}. A spectral resolution of 4 cm^{-1} was used. Solid samples were measured in KBr (Merck KGaA, Darmstadt, Germany) pellets.

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2.3. X-ray powder diffraction (XRPD)

XRPD studies were performed by means of the MiniFlex diffractometer (Rigaku Corporation, Tokyo, Japan) using CuK$_{\alpha 1}$ radiation. Samples were pressed on a glass plate. The instrument was operated in the range from 3° to 40° with the scan rate of 0.03°/min.

2.4. Thermal analysis (DSC and TGA)

Thermal analyses were carried out by means of the differential scanning calorimeter DSC 822 with IntraCooler and the thermogravimether TGA/SDTA 851 cells (Mettler Toledo GmbH, Schwerzenbach, Switzerland) in the nitrogen atmosphere. Accurately weighed samples (4–7 mg) were packed in aluminium pans with pierced lids. In DSC experiments samples were heated from 25 to 300 °C, with the scanning rate of 10 °C/min, whereas in TGA experiments samples were heated from 25 to 180 °C, with scanning rate of 5 °C/min. TGA measurements were blank curve corrected.

2.5. Nuclear magnetic resonance (NMR)

The ^{1}H NMR spectrum of pramipexole dihydrochloride monohydrate was performed on the Varian INOVA-500 spectrometer (Palo Alto, California, USA) and the ^{13}C NMR spectrum was performed on the Varian Gemini-2000 spectrometer (Palo Alto, California, USA) at ~500 and ~50 MHz transmitter frequency for ^{1}H and ^{13}C, respectively. Spectra were measured in DMSO-d$_6$ solution (Armar AG, Döttingen, Switzerland) at the room temperature relatively to DMSO signal (2.49 ppm for ^{1}H and 39.5 ppm for ^{13}C) as a chemical shift standard.

2.6. X-ray single crystal diffraction

The measurement of crystal was performed on a KM4CCD κ-axis diffractometer (Bruker AXS GmbH, Karlsruhe, Germany) with graphite-monochromated MoK$_\alpha$ radiation. The data were corrected for Lorentz and polarization effects. Multi-scan absorption correction has been applied. Data reduction and analysis were carried out with the Oxford Diffraction programs [9]. The structure
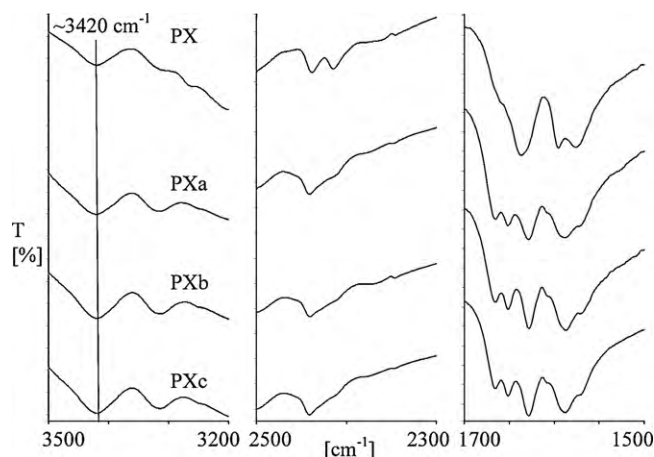

Fig. 1. The comparison of IR spectra of the initial sample (PX), samples stored 6 months: at 25 °C in 60% RH (PXa), at 40 °C in 75% RH (PXb) and the sample stored 9 months at 25 °C in 60% RH (PXc) in three distinctive bands ranges.

was solved by direct methods [10] and refined using SHELXL [11] and WinGX Program System [12].

3. Results and discussion

3.1. Stability studies

Fig. 1 shows the comparison of IR spectra of the initial PX sample and stored 6 months at 25 °C (PXa), 40 °C (PXb) and 9 months at 25 °C (PXc) in three distinctive bands ranges: form 3500 to 3200 cm^{-1}, from 2500 to 2300 cm^{-1} and from 1700 to 1500 cm^{-1}. The band coming from water, 3420 cm^{-1}, is visible in all the studied spectra. Apart from this band it is visible that spectra of stored samples are substantially different from the initial one. In the initial sample the band 3420 cm^{-1} indicates the presence of adsorbed water. The spectrum of initial sample can be further characterized by following bands [cm^{-1}]: 3157, 2968, 2767, 2678, 2517, 2438, 2414, 1637, 1595, 1576, 1458, 1356, 801, 713. After 6 months of storage at 25 and 40 °C water molecules incorporate into the crystal

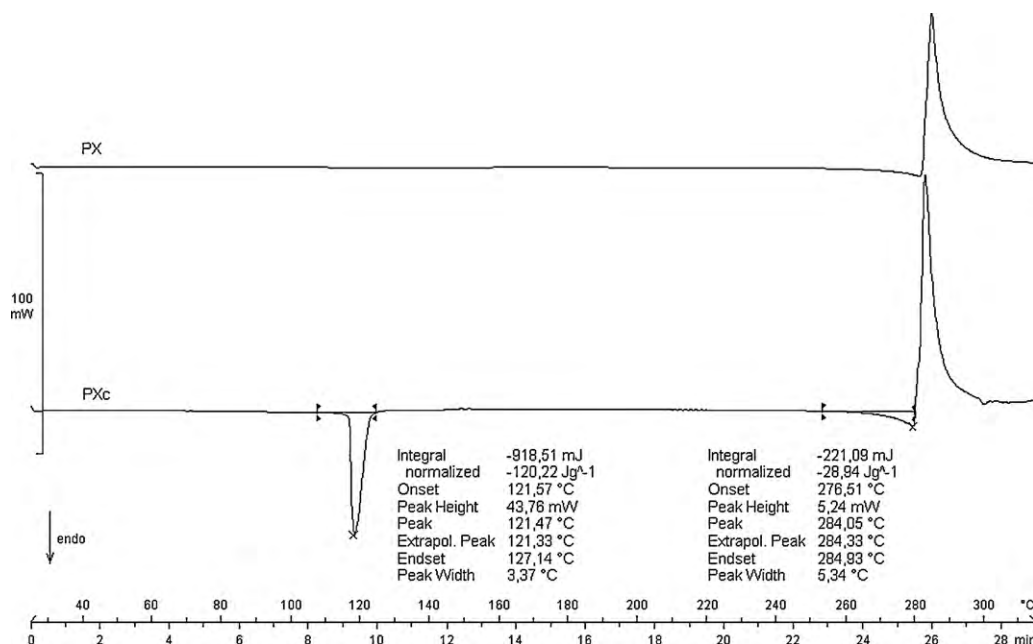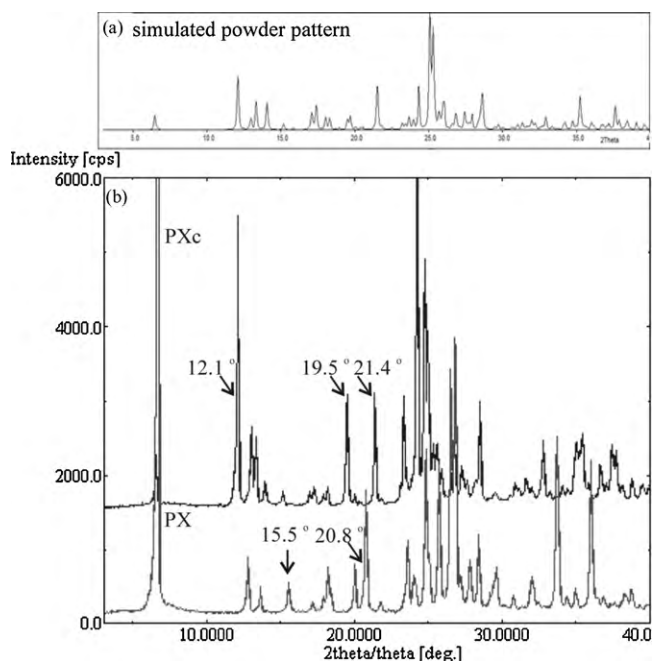**Fig. 2.** DSC curves of the initial sample (PX) and the sample stored 9 months at 25 °C in 60% RH (PXc).

Fig. 3. (a) The simulated powder pattern of pramipexole monohydrate. (b) The comparison of powder patterns of pramipexole monohydrate (PXc) and anhydrous pramipexole (PX) with marked distinguishable peaks.

Table 1
^{1}H and ^{13}C NMR signals prescribed to atoms in the pramipexole dihydrochloride monohydrate molecule.

Position	Proton – ^{1}H	Carbon – ^{13}C
2		~168.75 ppm
4	Multiplet, 1p, ~2.53 ppm	~20.86 ppm
	Multiplet, 1p, ~2.65 ppm	
5	Multiplet, 1p, ~1.96 ppm	~23.40 ppm
	Multiplet, 1p, ~2.26 ppm	
6	Broad signal, 1p, ~3.47 ppm	~52.25 ppm
7	Multiplet, 1p, ~2.80 ppm	~24.75 ppm
	Doublet of doublets ($J_1 \approx 16.0$ Hz, $J_2 \approx 4.7$ Hz), 1p, ~3.03 ppm	
8		~110.90 ppm
9		~132.92 ppm
11	Multiplet, 2p, ~2.84 ppm	~45.95 ppm
12	Multiplet, 2p, ~1.70 ppm	~19.05 ppm
13	Triplet ($J \approx 7.5$ Hz), 3p, ~0.90 ppm	~11.16 ppm
NH + NH$_2$ + 2HCl + H$_2$O	Signals at ~9.51 ppm, ~9.61 ppm and very broad signal at ~3.75 ppm	

ascribed to the proper position number of the atom. Assignments of the ^{1}H and ^{13}C NMR signals of pramipexole dihydrochloride monohydrate were made by using the results of two-dimensional NMR spectroscopy: gradient selected HSQC (directly bounded hydrogen and carbon nuclei) and HMBC (long-range correlation hydrogen–carbon) experiments.

The structure of pramipexole dihydrochloride monohydrate was solved by X-ray single crystal diffraction. Characteristic crystallographic parameters of the monohydrate are following: unit cell parameters: $a = 7.0939(2)$ Å, $b = 15.1763(3)$ Å, $c = 27.2761(6)$ Å, $\alpha = \beta = \gamma = 90°$, space group P2$_1$2$_1$2$_1$, $V = 2936.52(12)$ Å^3, $Z = 8$.
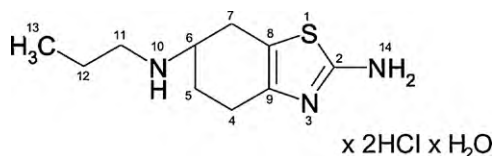
structure of pramipexole. Further studies carried out after 9 months proved the stability of the formed hydrate. The hydrate is characterized by following bands [cm^{-1}]: 3313, 3168, 2964, 2744, 2622, 2440, 1665, 1651, 1608, 1587, 1465, 1432, 1362, 761, 715.

The significant increase in a water content after 9 months of storage in a comparison with an initial water content is proved by a thermogravimetric analysis. The mass loss changes from 0.6% to 6.0% for the initial sample and stored 9 months at 25 °C, respectively. The value of 6.0% agrees with the theoretical water content in pramipexole dihydrochloride monohydrate. Visible changes are demonstrated also in DSC curves (Fig. 2). The DSC curve of the initial sample PX shows only the small endotherm at about 277 °C coming from the substance melting with the simultaneous decomposition effect whereas the DSC trace of PXc shows the additional endotherm at 122 °C coming from the water evaporation.

X-ray powder diffraction proved structural changes occurring during stability studies. The powder diffraction pattern of the initial sample PX of pramipexole dihydrochloride substantially differs from pramipexole dihydrochloride monohydrate PXc (Fig. 3b), especially in following peak positions: 15.5°; 20.8° for PX and 12.1°; 19.5°; 21.4° for PXc.

3.2. Structural characterization of pramipexole dihydrochloride monohydrate

The identification of pramipexole dihydrochloride monohydrate was proved by NMR studies. Fig. 4 shows the molecule of pramipexole dihydrochloride monohydrate with the position number of each atom. In Table 1 ^{1}H and ^{13}C NMR signals are

Fig. 4. The molecule of pramipexole dihydrochloride monohydrate with position numbers of each atom.

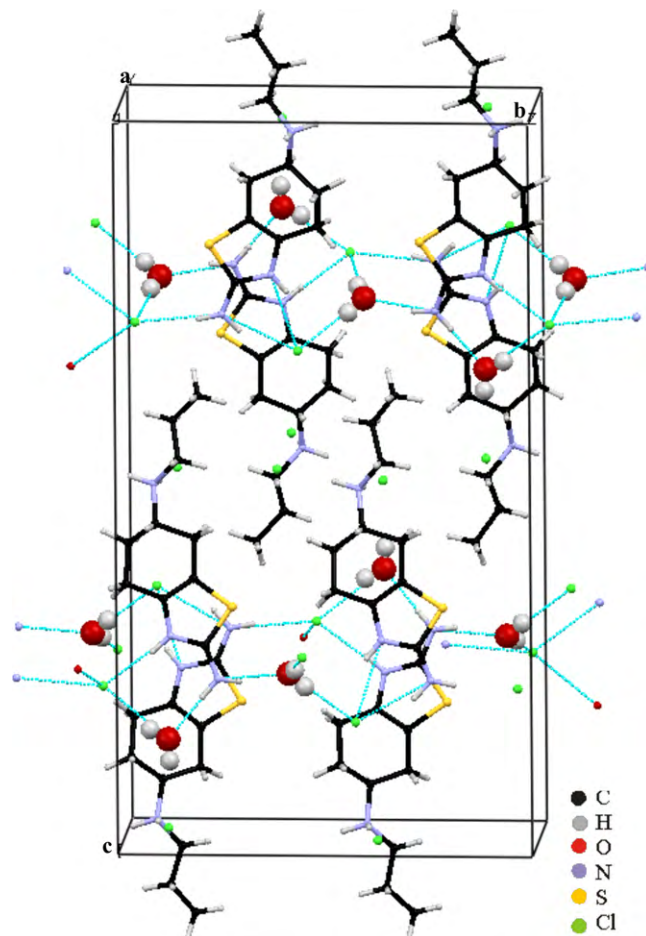**Fig. 5.** Hydrogen bonding in pramipexole dihydrochloride monohydrate molecule.

The crystal structure of the studied molecules has straight tunnels running along the *b*-axis of the lattice. In the atomic arrangement of pramipexole the helical chain is built up by chloride and water molecules which are spreading along the *b*-axis. The water molecule is located between two chloride atoms of pramipexole molecules via hydrogen bonds. The single water molecule appears to participate in three H-bonding interactions. It serves as the donor for two atoms of chloride and as the acceptor for the primary amine (Fig. 5).

In Fig. 3a the simulated powder pattern of the hydrate is generated. All the peaks' positions of the simulated pattern agree well with the experimental one (PXc).

4. Conclusions

By means of IR and XRPD techniques it has been shown that water sorption by pramipexole leads to the hydrate formation. This was a quite fast process because it happened after 6 months of storage at 25 °C in 60% RH and at 40 °C in 75% RH as well. The X-ray single crystal measurement proved that the water absorption into the crystal lattice is highly privileged by the presence of both the primary amine and the chloride atom which take part in the hydrogen bonds geometry.

Acknowledgements

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