Complexes of the Anti-inflamatory Non-steroidal Drugs from Oxicam Family

1. Synthesis and characterization of the Zn(II) complex with Piroxicam

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Zinc(II) complex of piroxicam with interesting anti-inflammatory profile has been prepared and characterized by elemental analysis, FT-IR spectroscopy, X-ray diffractometry and thermal analysis. The empirical formulae of the complex, $[Zn(PX)_2(H_2O)_2]$ x $2H_2O$ was determined by the mentioned methods, but especially by elemental analysis and the thermoanalytical methods. From the FT-IR spectrum and X-ray diffractogram was established that the piroxicam, as ligand, binds to the Zn(II) ion monodentaly through their enolic oxygen and pyridinc nitrogen atom, respectively. The thermal behaviour of the complex was studied by simultaneous TG-DTG-DTA methods, under non-isothermal conditions and in a dynamic air atmosphere. According to the thermal curves, especially TG curve, the complex contain two molecules of co-ordination water and two molecules of crystallization water, respectively. On further heating of the anhydrous compound up to 807 °C the thermal degradation of the piroxicam and the intermediate formed took place. Zinc oxide was found as the final product of the thermal decomposition.

Keywords: piroxicam, zinc(II) complex, elemental analysis, thermogravimetry, thermal decomposition

Non-steroidal anti-inflammatory drugs (NSAIDs), are a well-known class of drugs that are antipyretic, analgesic and anti-inflammatory agents. They are used in clinical practice for the treatement of inflammatory disorders including arthritis and cancer as well as for prevention of myocardial infarction and Alzheimer's disease [1]. NSAIDs have been shown to be potent inhibitors of prostaglandin synthesis through inhibition of one of the obligatory enzyme, in the inflammatory cascade viz. cyclo-oxygenase (Cox), which exists in two isoforms reffered as Cox-1 and Cox-2, respectively [2]. Compounds inhibiting Cox-1 enzymes have been shown to cause gastrointestinal irritations and kidney damages since the enzyme is involved in the physiological function of protecting gastric mucosa [3]. Consequently, research efforts have been directed towards evolving compounds which are specific Cox-2 inhibitors, especially metal complexes of NSAIDs, which can minimize their deleterious effects.

Piroxicam (PX) 4-hydroxy-2-methyl-N-2-pyridyl-2H-1,2-benzthiazine-3-carboxamide-1,1-dioxide (fig. 1) is a non-steroidal anti-inflammatory drug, from the oxicam family, which shows chemopreventive and chemosuppressive effects in different cancer cell lines and animal models. Even though the molecular mechanism behind their principal function, i.e. as analgesic and anti-inflammatory agents is quite well understood, it is not clear exactly how they exert their anticancer effects. Anticancer effects of these drugs have been implicated to occur both by the cyclo-oxygenase (Cox)-dependent and Cox-independent pathway [4,5].

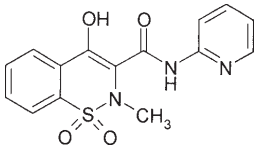

Fig. 1. The chemical structure of piroxicam

It is well established that metal ions play a wide range of important roles in biological systems. The presence of drugs that can compete with other biological molecules for the metal ions, changes the distribution of these ions in blood plasma and other fluids. On the other hand, presence of these metal ions can affect the bio-availability of these drugs. Knowledge of the species formed by combining a metal ion with a drug provides useful information to approach the mechanisms of action of the drug for a disease under treatment and ultimately this can also diminish collateral effects and enhance the efficacy of the parent drug [6-10].

For the characterization of the new compounds with possible pharmacological properties, beside the classical methods such as UV-VIS and FT-IR spectroscopy, respectively X-ray diffraction, the thermal methods are used in an increased proportion.

Thermal analysis is one of the most widely used methods for studying the solid state of pharmaceutical substances. The thermoanalytical curves provide important information regarding the physico-chemical properties of the pharmaceuticals compounds (stability, polymorphism, phase transition, kinetic analysis, compatibility etc [11-16].

In our previous articles [17-29] we provided the importance of the thermal and kinetic analysis in estimation on the thermal behaviour of different pharmaceuticals, respectively their compatibility.

In the present paper, we report the synthesis of a mixed-ligand complex of Zn(II) and piroxicam, which was investigated by elemental analysis, infrared spectroscopy, single-crystal-X-ray diffraction and thermal analysis techniques.

Experimental part

Materials

All chemicals used were analytical reagent products.

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The PX drug was supplied by China. $Zn(CH_3COO)_2$ x $2H_2O$ and KOH were obtained from Romania.

Synthesis of complex

To 2.0 mmoles (0.3314 g) of piroxicam, dissolved in 25 mL ethanol by heating, was added 1.0 mmole (0.2195 g) $Zn(CH_3COO)_2 . 2H_2O$ (aqueous solution) by stirring. The yellow precipitate formed was filtered, washed several times with ethanol, and dried in vacuum.

Methods

Elemental analyse of C and H was carried out on a Vario El elemental analizer. The Zn(II) content was determined by complexonometric titration with EDTA, in buffer solution (NH_3-NH_4Cl) and *p*H = 10, using Eriochrome black T as indicator.

Infrared spectra (400-4000 cm^{-1}) for piroxicam and its complex with Zn(II) were recorded on a Perkin-Elmer FT-IR 1600 spectrometer. The samples for the FT-IR spectra measurements were prepared as KBr discs.

X-ray diffraction patterns (XRPD) were obtained with a Brucker D8 Advance X-ray diffractometer using MoKα radiation (Zr filter on the diffracted beam, 50 kW and 40 mA) in a Bragg-Brentano θ:2θ configuration, with soller and fixed slits and a NaI (Tl) scintillation detector. The measurements of 2θ ranged between 0° and 30°. Data analysis and acquisition were performed using DIFRACT ^{plus} software from Bruker AXS.

Thermal stability and decomposition of the complex was determined by Netzch-STA 449 TG/DTA instrument, recording TG, DTG and DTA curves. The determination was made at heating rate (β) of 10°C . min^{-1} with full scale. The sample (≈20 mg) was heated in platinum crucible, under a dynamic atmosphere of air (20 mL . min^{-1}) until 1200 °C.

Results and discussions

Synthesis

The mixed-ligand complex was prepared according to the following equation:

$$2HPX + Zn(CH_3COO)_2 \xrightarrow{\text{in } C_2H_5OH;H_2O} Zn(PX)_2 + 2CH_3COOH$$

We have studied the system Zn(II)-PX for the combination ratio M:L 1:1 ; 1:2 and respectively 1:3. From these systems, we were able to isolate and characterize the following type of mononuclear complex: $[Zn(PX)_2(H_2O)_2] . 2H_2O$. Figure 2 presents the chemical structure of the complex obtained.

The formulae proposed for this compound was established on the basis of elemental chemical analysis, correlated with physico-chemical investigations (FT-IR spectroscopy and X-ray diffraction) and thermal analysis, especially for the determination of the co-ordination and crystallization water, as well the molecular formulae.

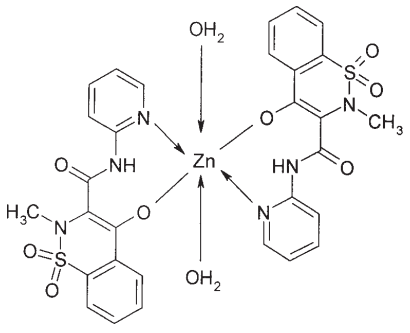

Fig. 2. The chemical structure of Zn-Piroxicam complex

The results of the elemental analysis for the complex with the formulae: $C_{30}H_{32}N_6O_{12}S_2Zn$ (M = 798.2) are the following: Anal. Calcd. C 45.10 ; H 4.01 ; N 10.52 ; S 8.02 ; Zn 8.19. Found: C 45.25 ; H 3.87 ; N 10.37 ; S 8.13 ; Zn 8.02.

Infrared spectroscopy

The FT-IR spectroscopy is the most suitable technique of the non-destructive spectroscopic methods and has become an attractive method in the analysis of pharmaceutical solids, since the materials are not subject to thermal or mechanical energy during sample preparation, therefore preventing solid-state transformation. The appearance, respectively disappearance of new absorption bands, broadening of bands, and alteration in intensity are the main characteristics to evidence the difference between substances (samples) [30-32].

Characteristic FT-IR peaks of the piroxicam and the corresponding complex with zinc are given in table 1 and Figure 3.

The infrared spectrum of complex presents a broad absorption band in the water stretching region (3600-3300 cm^{-1}) and the strong shoulder of band in water bending region (1630-1608 cm^{-1}).

The IR spectrum of complex exhibit absorption bands of ligand (piroxicam). The absence of large systematic shifts of ν(NH) and δ(NH) bands (3350-3130 cm^{-1} region) in the spectrum of the complex compared with that of the ligand indicates that there is no interaction between the NH group and the metal ion.

The associated N-H bands are weaker than the corresponding O-H bands. N-H bending vibrations appear approximately in 1588 cm^{-1}.

The PX complex give rise to a strong band responsible for the C=O stretching. Conjugation between the carbonyl group and the amide, nitrogen causes small frequency shifts. The strong band observed at 1588 cm^{-1} is assigned to this mode. This band remained almost in the same range as the amide group of the free PX ligand (1630-1577 cm^{-1}), indicating that the PX ligand does not coordinate through amide group.

The bands of pyridine ring vibrations in the FT-IR spectrum of the free ligand occur in the ranges of 1576-1436, 1351-1149 and 1039-938 cm^{-1}, while those in the spectrum of complex are in the ranges of 1634-1486, 1402-1160 and 1065-1012 cm^{-1}. Their shifts to higher frequencies in the FT-IR spectrum of Zn(II) complex suggest the co-ordination of piroxicam through the pyridine ring nitrogen atom [33,34].

X-ray diffraction

To investigate the configuration of the complex obtained, besides the FT-IR spectroscopy which is a qualitative analysis technique, the X-ray powder diffraction (XRPD) has been used for qualitative and quantitative identification of crystallinity. The number of the speciality papers which uses XRPD is growing [35-37].

The appearance of new lines and disappearance of some of the lines present in the ligand, respectively the shifting of some of the diffraction lines of higher moderate and lower intensities in the complex, which are originally present in the X-ray diffraction patterns of the ligand indicats the presence of a new compound.

The X-ray diffraction patterns of the piroxicam and of its complex with Zn(II) are shown in figure 4.

For complete the general image, in table 2 are presented the main X-ray diffraction data for ligand and complex.

From figure 4 and table 2 it can be remarked a great difference between the diffractograms of the ligand,

Table 1
MAIN FT-IR ABSORPTIONS BANDS (CM^{-1}) FOR PX AND ITS COMPLEX WITH Zn(II)

Ligand	Complex	Assignement
-	3600-3300m	$\nu OH(H_2O)$
3338m	-	νOH(enol); νNH
1631m	1588sh,vs	$\nu C=O$(amid)
1576m	-	νNH; ring str. (py)
1531vs	1517vs	νNH; ring str. (py)
1467w	1485s	ring str. (py)
1435vs	1402vs	ring str. (py); νC-N str.(amid)
1351vs	1324vs	vasym. SO_2
1300s	1303w-m	C-N str.(am)
1182s	1198m-s	vsym. SO_2; CC str. (py)
1149s	1160w-m	NH rock
1092w	1065m	i.p. C-H (py)
1039m	1047w-m	i.p. C-H (py)
875w	880vw	o.p. C-H (py)
830m	832vw	o.p. C-H (py)
773s	766s	o.p. C-II (py)
731m	-	o.p. C-H (py)
691w	675w	o.p. ring def.
625w	-	i.p. ring def o.p. O-II bend
582w	570m	$\nu O=CN$
563m	-	
	552w-m	νZn-N
	524w-m	
	418w-m	νZn-O
	404w-m	

where: vs-very strong, s-strong, m-medium, w-weak, vw-very weak, sh-shoulder, py-pyridine, amid-amide, am-amine, str-streching, def-deformation, rock-rocking, asym-asymetric, sym-symetric, i.p.-in plane, o.p.-out of plane

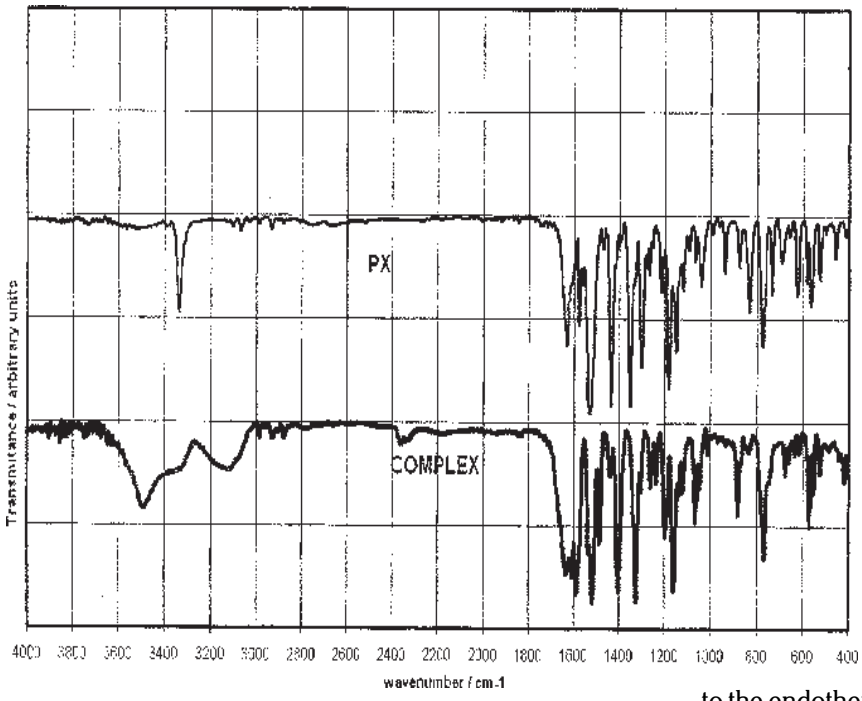

Fig. 3. FT-IR spectra of 1-piroxicam and 2-Zn(II) complex

respectively complex, by the disappearance, respectively the appearance of some meaningful lines.

Thermal analysis

Simultaneous thermogravimetry/derivative thermogravimetry (TG/DTG) and differential thermal analysis (DTA) were used to characterise the thermal stability of Zn(II) complex with piroxicam. The thermal correspondent curves, registered in air, are shown in figure 5.

The first and the second mass losses only at the stage between 48 and 86 °C and 86 to 136 °C (TG), corresponding to the endothermic peaks (81 and 110 °C) in the DTA curve, are due to the dehydratation stages with losses of 2.25% and 2.30%, respectively, which corresponds to two crystallization water molecules. In the next stage, two molecules of co-ordination water are eliminated in the temperature range of 136-223 °C, with a mass loss of 4.65%. Related endothermic DTA peak is at 210°C.

After dehydration, between 223 and 807°C the mass loss occurs in three stages with a loss of 80.2%. The first decomposition stage, from 223 to 500°C, (52.2%), is attributed to the partially decomposition of organic ligand

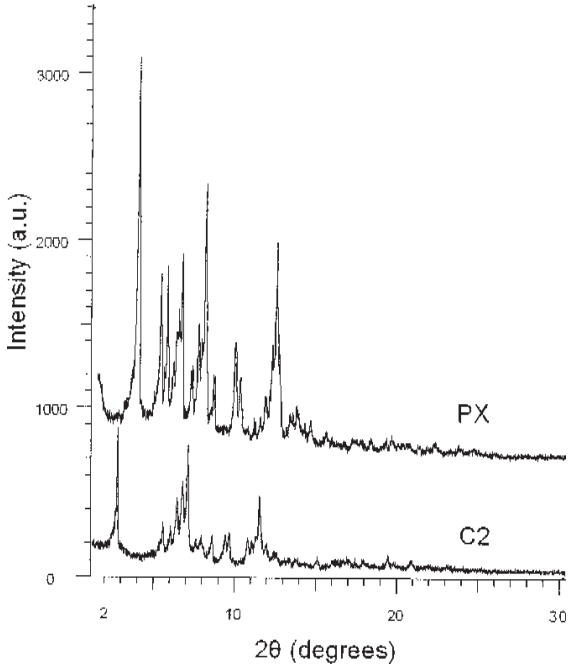

Fig. 4. X-ray diffractogram of piroxicam, respectively of its complex with Zn(II)

Piroxicam		Complex	
2θ	I%	2θ	I%
		2.678	97.6
3.972	100		
4.918	16.6		
5.349	45.9		
		5.506	36
5.573	22.7		
5.753	46		
		5.962	35.4
6.119	25		
6.347	31.4	6.384	58.5
6.454	36.1		
6.66	52.3	6.717	70.2
		7.037	100
7.284	23.4		
		7.531	26.9
7.667	34.1		
7.9	29.4	7.868	30.1
8.123	70.5		
		8.534	29.3
8.639	22		
		9.364	31.4
		9.605	33.8
9.962	31.8		
10.261	21.3		
10.705	8.2	10.754	28.7
		11.008	26.9
11.148	10.8		
		11.257	30.7
11.506	10.7	11.505	65.7
11.81	16.1		
		11.915	24.7
12.074	19		
12.232	30.6		
12.516	55.3	12.555	16.8
12.7	27.3		

Table 2
X-RAY DIFFRACTION DATA FOR PIROXICAM AND ITS COMPLEX WITH Zn(II)

(piroxicam). This process is one complex, with two different kinetics of decomposition, which correspond to the exothermic peaks (246 and 455 °C) in the DTA curve.

The last two mass losses between 500-723°C (25%) and 723-807°C (2%) are due to the oxidation and the thermal decomposition of the intermediate, leading to the zinc oxide. The oxidation process is accompanied by a very short exothermic effect (DTA_{peak} = 591°C), while the thermal decomposition is characterised by a small endothermic peak (DTA_{peak} = 782 °C) in the DTA curve. The final decomposition product is ZnO (exp. 10.6%; calc. 10.2%).

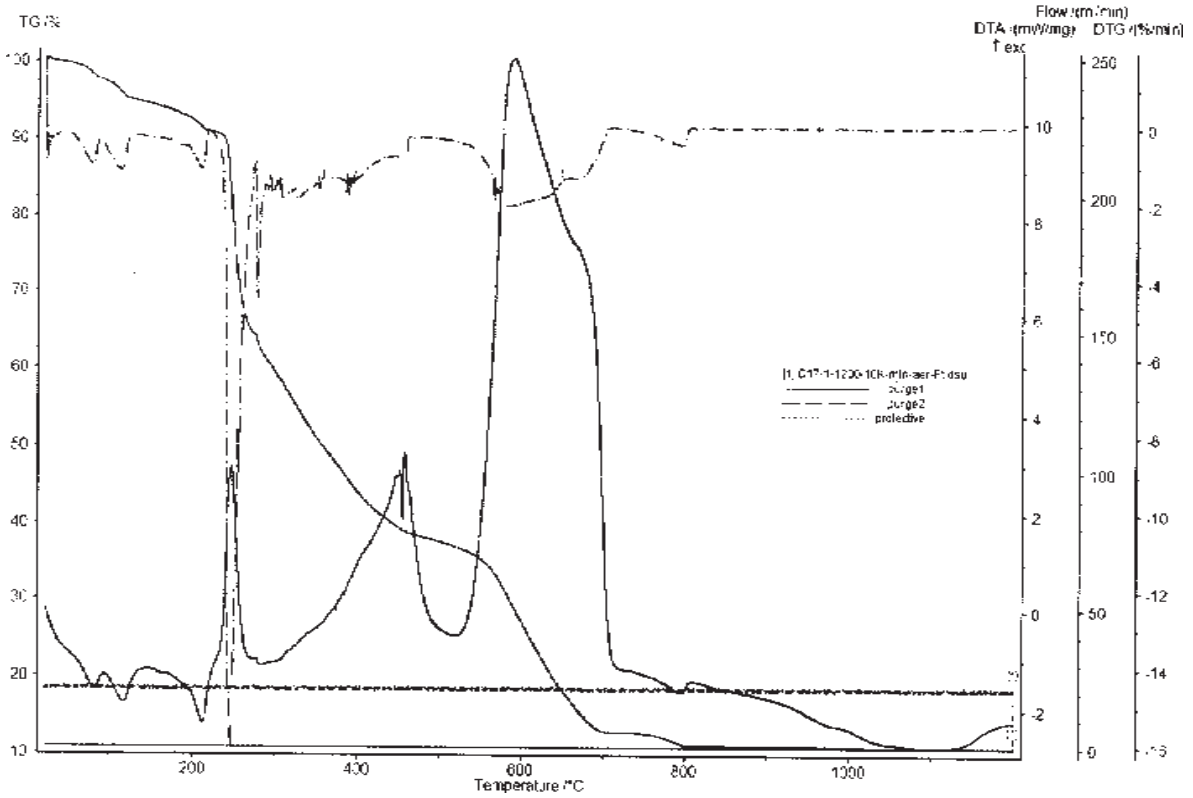

Fig.5. TG, DTG and DTA curves of the $[Zn(PX)_2(H_2O)_2]$. $2H_2O$

Conclusions

The piroxicam, an anti-inflammatory non-steroidal drug, from the oxicam family, present a big interest for the preparation of some pharmaceutical co-ordination compounds with pharmacological activity. This paper describes the synthesis and characterization of complex $[Zn(PX)_2(H_2O)_2]$. $2H_2O$, formed as a crystalline compound, in the reaction of Zn(II) with PX, used as ligand.

For the determination of the empirical formulae, respectively for the characterization of the new complex, we have used the elemental analysis, FT-IR spectroscopy, X-ray diffraction and thermal analysis.

The FT-IR spectrum and X-ray analysis of the complex demonstrated that Zn(II) ion is co-ordinated by the nitrogen atom of pyridine ring and the acidic oxygen of the enol group.

The FT-IR spectrum confirmed the presence of water, but without to differentiate between the water molecules located inside and outside of complex co-ordination sphere. The adequate differentiation was made by thermal analysis (studied by TG, DTG and DTA techniques), which determines the steps of dehydration, and the quantity of water eliminated. According to the TG and DTG curves, the complex prepared has two molecules of co-ordination water, respectively two molecules of crystallization water.

After dehydration, the anhydrous compound decomposes progressively, with the formation of ZnO as final product. The percentage of this compound corresponds to the empirical formulae of the complex synthesised.

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