Anti-inflammatory Drugs Interacting with Cu(II) Metal Ion
Synthesis, characterization and thermal behaviour of the complex with ketoprofen

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New metal (II) complex with empirical formula $[Cu(KET)_2]_2 \cdot 0.5H_2O$ (where KET = $C_6H_5COC_6H_4CH(CH_3)COO^-$) was isolated and investigated. The elemental analysis, Fourier transformed infrared spectroscopy (FT-IR), X-ray diffraction powder (XRPD) and thermal analysis were used to study solid Ketoprofen (KET) of Cu(II) metal ion. The thermal behavior was studied by thermogravimetry (TG), derivative thermogravimetry (DTG) and differential scaning calorimetry (DSC) methods under non-isothermal conditions in a dynamic air atmosphere. The results provided informations of the composition, structure, thermal behavior and thermal decomposition. The FT-IR spectra of studied complex revealed also absorption of the carboxylate group, for which is important the position of asymmetric, symmetric frequencies. The value of their separation allow to deduce about type of coordination these groups.

Keywords: anti-inflammatory drug, ketoprofen, FT-IR spectroscopy, X-ray analysis, thermal analysis

Non-steroidal anti-inflammatory drugs (NSAIDs) are frequently used for treatment of inflammatory conditions and the mechanism of the action is mainly related to the inhibition of the cyclooxygenase-2 enzyme (Cox-2). The experimental and epidemiological studies have demonstrated that NSAIDs also display promising chemopreventive activities, especially for colorectal cancer with high Cox-2 expression [1,2]. It is possibly that the pharmacological basis for their anti-cancer or cancers preventive activities may involve Cox-2 inhibition, because prostaglandins generated by Cox-2 could promote tumor invasiveness, angiogenesis, and progression in cancers [3,4]. Inhibition of Cox-2 would arrest carcinogenesis and thus prevent cancer development and regress cancer once developed. There is a lack of correlation between Cox-2 inhibitory potency and anti-cancer activity of these NSAIDs. Some non-Cox-2 inhibitory analogs derivatized from Cox-2 inhibitors still exhibit potent anti-cancer activities.

Although it is debatable about the mechanism for anti-cancer effects of Cox-2 inhibitors, some NSAIDs have been evaluated as anti-cancer agents either alone or in combination with other chemotherapeutic agents in the preclinical and clinical studies [5]. However, using Cox-2 inhibitors may be associated with cardiovascular side effects, which limit the application of Cox-2 inhibitors in cancer chemotherapy [6]. Development of non-Cox-2 active analogs based on known Cox-2 inhibitors is an important strategy for the discovery of new anti-cancer drugs with high efficiency and less toxicity.

The Ketoprofen (KET), 2-(3-benzoylphenyl)-propionic acid, which structural formula is shown in figure 1, is a non-steroidal anti-inflammatory agent that belongs to the class of 2-arylpropionic acids, which constitute a considerable group of pharmaceutical and commercial interest. From the pharmacological stand point, the 2-arylpropionic acids act by blocking the conversion of arachidonic acid into prostaglandins and tromboxane A2,

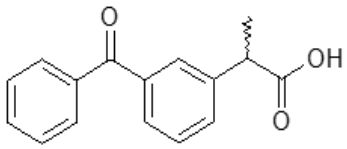

Fig. 1. The chemical structure of ketoprofen

responsible for the inflammatory mechanism through inhibition of cyclooxygenase. It is effective in the long-term management of rheumatoid arthritis, ankylosing spondilistis, osteoarthritis and acute out, as well as mild to moderate pain and dysmenorrheal [7, 8], and has been used as model drug for such investigation.

Synthesis of metal complexes containing active drugs as ligands is a research area of increasing interest for bioinorganic, pharmaceutical and medicinal chemistry, the main goal being to develop new anti-inflammatory drugs, with a high rate of efficacy and less side effects [9].

The study of these metal complexes is important because of the synergistic action of the beneficial effects of the ligand and the activity of the metal, different active functions combining in the same molecule.

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.

Copper, Cu(II), an essential element, has received considerable attention with regard to its presence in normal blood plasma and serum components. It has been established that cooper-dependent enzymes are required for hemoglobin synthesis, growth, bone formation, reproduction, fertility, development and function of the central and peripheral nervous systems, cardiac and nerve function, cellular respiration, mental and behavioral development etc. Copper-dependent processes appear to be required for modulation of prostaglandin synthesis, lysosomal membrane stabilization, and modulation of histaminic activity.

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It was suggested that the mode of action of many anti-inflammatory drugs may involve the chelation with some bioactive metals such as Cu(II), Zn(II), Cd(III) and it facilitates the transfer of the metal to and from a site of inflammation or pain.

Reports abound in the literature concerning the active role of copper complexes in the control of inflammatory diseases. Other pharmacological activities of copper complexes and their potential as antiarthritic, antiulcer, anticancer, antidiabetic and antiepileptic drugs have been reported [10,11].

For proper investigation of substances and medicinal products it is necessary to use appropriate techniques of instrumental analysis. Recent literature screening shows the high interest in the use of thermoanalytical techniques, thermogravimetry (TG), derivative thermogravimetry (DTG), differential thermal analysis (DTA) and differential scanning calorimetry (DSC) for this purpose, as well as of classical methods such as UV-Vis and FT-IR spectroscopy, respectively X-ray diffraction [12,13].

Thermal analysis is among the most widely used techniques for analyzing substances of pharmaceutical interest and resolving and/or identifying problems in the field of pharmaceutical technology. They reveal valuable information about the physical properties of materials such as stability, compatibility, polymorphism, decomposition kinetics, phase transition, purity etc. [14,15] These techniques allow a rapid acquisition of results and require relatively simple experimental conditions; however it is advisable to use other analytical techniques to assist in the interpretation of thermal analytical results.

In some of our previous papers [16-22], we have presented the importance and the utility of thermo-analytical methods in the estimation of thermal stability of some pharmaceuticals, by thermal behavior and kinetic analysis, respectively their compatibility.

As a part of our continuing work on the synthesis, characterization and applications of metal complexes with non-steroidal anti-inflammatory drugs [23-27], herein, we report the synthesis and characterization of Cu(II) complex with anti-inflammatory drug, 2-(3-benzoylphenyl)-propionic acid. The coordination manner of the ligand to the metal centre was investigated by means of elemental analysis, FT-IR spectroscopy, X-ray diffraction paterns and thermal analysis.

Experimental part

Materials, method and equipment

All chemical used were analytical reagent products.

The KET drug was obtained from S.I.M.S., Italy, lot: 138315.

$Cu(CH_3COO)_2 \cdot 2H_2O$ and KOH were obtained from Merck, Germany.

Aqueous solution of ketoprofen potassium salt (0.1 mol L^{-1}) was prepared by neutralization aqueous ketoprofen suspension with 0.1 mol L^{-1} potasium hydroxide solution and the pH was adjusted to 8.0.

Cu (II) was used as its acetate and cca. 0.1 mol L^{-1} aqueous solution of this ion were prepared by direct weighing and dissolution of the salt.

Solid state compound was prepared by adding slowly with continuos stiring, solution of copper acetate (1.0 mmoles = 0.1996 g) to the respective solution of ketoprofen potassium salt (2.0 mmoles = 0.5846 g) until precipitation of metal ion. The green precipitate washed with distilled water in order to elimination of acetate ions, filtered through and dried on Whatman no. 42 filter paper, and kept in a desicator over anhydrous calcium chloride.

Elemental analyse of C and H was carried out on a Vario El elemental analyzer. The Cu (II) content was determined by complexonometric titration with EDTA, in buffer solution ($NH_3 - NH_4Cl$) an *p*H = 8, using Murexid as indicator.

The FT-IR of spectra of ketoprofen (ligand) and its coordinative compound with Cu(II) were recorded on a Perkin-Elmer FT-IR 1600 spectrometer in the spectral range of 400 – 4000 cm^{-1}. 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 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 DSC curves. The determinations were made at heating rate (β) of 10 °Cmin^{-1} with full scale. The sample (≈20 mg) was heated in platinum crucible, under a dynamic atmosphere of air (20 mL·min^{-1}) up to 1200°C.

Results and discussions

Synthesis

The complex with Cu(II) metal ion have been prepared by simple reaction which involves deprotonation of the ligand by KOH in aqueous solution, followed by complexation with a metal salt.

$$\text{I}\quad 2HKET + 2KOH \rightarrow 2KKET + 2H_2O$$
$$\text{II}\quad 4KKET + 2Cu(CH_3COO)_2 \rightarrow [Cu(KET)_2]_2 + 4CH_3COOK$$

The X-ray powder patterns showed that the green compound was obtained with low crystallinity degree.

To establish the combination ratio we have studied the systems Cu(II)-KKET in ratios 1:1; 1:2 and respectively 1:3. From these systems, we were able to isolate and characterize the following type of mononuclear complex: $[Cu(KET)_2]_2 \cdot 0.5H_2O$. Figure 2 presents the chemical structure of the complex obtained.

The formula proposed for this compound was established on the bases 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 formula, on the base of final residue of the decomposition termique.

The results of the elemental analysis for the complex with the formula $[Cu(KET)_2]_2 \cdot 0.5H_2O \equiv [C_{64}H_{52}O_{12}] \cdot 0.5H_2O$ Cu_2 (M = 1149) are the following: Anal. (%) Calcd. C 66.84 ; H 4.61 ; Cu 11.06. Found: C 66.91 ; H 4.52 ; Zn 11.12.

Infrared spectroscopy

The FT-IR spectroscopy is the most suitable technique of the non-destructive spectroscopic methods and has became 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 FT-IR spectroscopy has many advantages as a chemical analysis technique. First, it is a universal technique. Solids, liquids, gases, semi-solids, powders and polymers are all routinely analyzed. Second, FT-IR spectra are information rich; the peak positions, intensities, widths and shapes, in a spectrum all provide useful information.

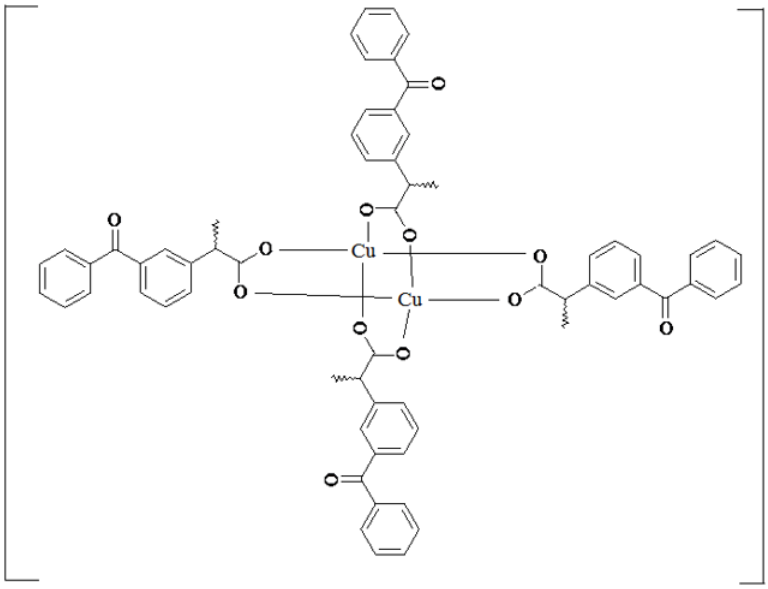

Fig. 2 The proposed chemical structure of Cu-Ketoprofen complex

Table 1

FT-IR SPECTROSCOPIC DATA FOR POTASSIUM KETOPROFEN AND FOR ITS COMPLEX DATA WITH COPPER (II)

Compound	$\nu_{C=O}$ / cm^{-1}	$\nu_{asym(COO^-)}$ / cm^{-1}	$\nu_{sym(COO^-)}$ / cm^{-1}	$\Delta\nu$ / cm^{-1}
KKET	1698 ; 1656	1577	1420 ; 1370	181
$[Cu(KET)_2]_2 \cdot 0.5H_2O$	1678 ; 1647	1552	1448 ; 1409	123

Third, FT-IR spectroscopy is a relatively fast and easy technique. The majority of samples can be prepared, scanned and the results plotted in less than five minutes. FT-IR spectroscopy is also a sensitive technique. Finally, FT-IR instruments are relative inexpensive [28].

The appearance, respectively disappearance of new absorption bands, broadening of bands, and alteration in intensity are the main characteristics to evidence the differences between substances (samples) [29,30].

The assignments of FT-IR bands were made by comparing the spectra of the complex with that of the free ligand.

The IR spectrum of complex exhibits absorption bands of ketoprofen ligand.

The principal infrared spectroscopic data on ketoprofen (potassium salt) and its compound with Cu(II) are shown in table 1.

The infrared spectra of complex display a broad absorption band in the water stretching region (3700 – 3300 cm^{-1} range), with the value of maximum absorption at 3481 cm^{-1}, characteristic for ν_{O-H} vibrations from water molecules.

The bands found for ketoprofen (potassium salt) are centered at 1698 and 1656 cm^{-1} (ketonic carbonyl stretches), 1577 cm^{-1} (asymmetrical carboxylate vibration), respectively 1420 and 1370 cm^{-1} (symmetrical carboxylate vibration).

The ketonic carbonyl stretches vibrations frequency is unchanged in the complex in comparison with potassium salt (1678 ; 1647 cm^{-1}). These data suggest the ketonic carbonyl does not participate in coordination with the metal center.

The principal characteristic of the FT-IR spectrum of complex is the frequency of the $\nu_{asym(COO^-)}$ and $\nu_{sym(COO^-)}$ stretching vibrations. The frequency of these bands depends upon the coordination mode of the carboxylate ligand. For the – COO^- – group, unidentate or bidentate modes of coordination have been observed. The unidentate mode of binding shows two very strong broad ν_{asym} and ν_{ym} stretching bands in the region 1560 – 1620 and 1370 – 1425 cm^{-1} respectively, with an average $\Delta\nu$ value 180 cm^{-1} (150 – 210 cm^{-1}). For the bidentate chelate co-ordination mode the $\nu_{asym(COO^-)}$ band occurs at a lower frequency, at 1520 – 1570 cm^{-1}, while the $\nu_{sym(COO^-)}$ stretching frequency increases by about 30 cm^{-1} (1410 – 1450 cm^{-1}) giving an average $\Delta\nu$ value of 115 cm^{-1} (70 – 130 cm^{-1}). No distinguished differences between bidentate double bound and bidentate triple bound co-ordination mode could be extracted from $\nu_{asym(COO^-)}$ and $\nu_{sym(COO^-)}$ stretching frequencies or to $\Delta\nu$ values.

For the complex with ketoprofen the $\nu_{asym(COO^-)}$ occurs at 1552 cm^{-1} and $\nu_{sym(COO^-)}$ at 1448, respectively 1409 cm^{-1}, while the calculated value of (delta) (asymmetrical-symmetrical carboxylate vibrations) shows smaller value (123 cm^{-1}) in comparison of that value calculated for the potassium salt (181 cm^{-1}, table 1). This result suggests the bidentate chelate coordination mode, with one oxygen atom of carboxylate group to one metallic ion [29,31].

The formation of the metal complex is also sustained by the apparition of one new sharp absorption band at the 417 cm^{-1} in the spectrum of the Cu(II) complex, without having a correspondence in the spectrum of free ligand. This new band can be attributed to vibration of copper-ligand bands, namely ν_{Cu-O}.

X-ray diffraction patterns

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 [32,33].

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 indicates the presence of a new compound.

The X-ray diffraction patterns of ketoprofen and of its complex with Zn(II) are shown in figure 3.

From figure 3 it can be remarked a great difference between the difragtograms of the ligand, respectively complex, by the disappearance of majority of the diffraction

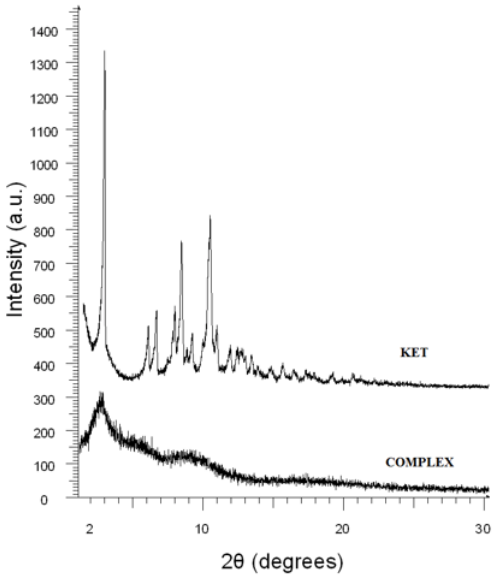

Fig. 3. X-ray diffractogram of ketoprofen, respectively of its complex with Cu(II)

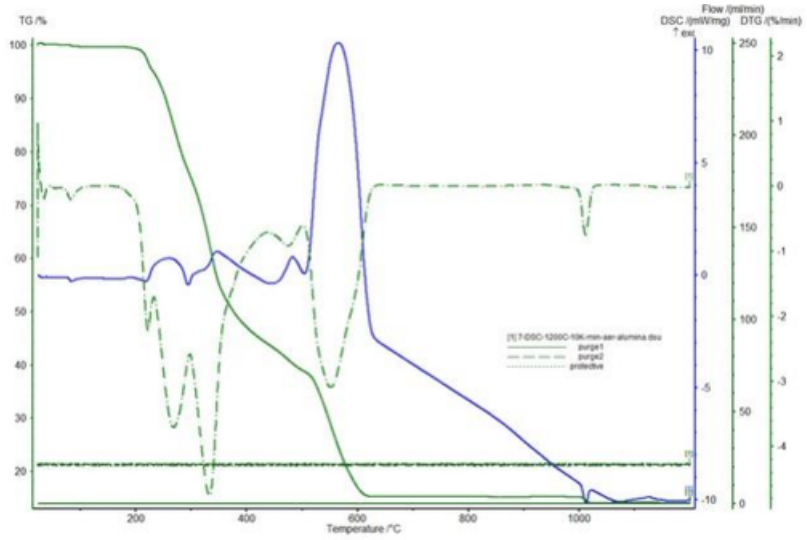

Fig. 4 Thermoanalytical curves of the compound $[Cu(KET)_2]_2 \cdot 0.5H_2O$

Steps	Temperature ranges of decomposition/°C	DTG peaks/°C	DSC peaks/°C	Mass loss/% (Δm/%)
I	63.6 – 100.0	88.2	88.2 endo	0.78
II	200.0 – 522.7	218.2	218.2 endo	61.36
		272.7	254.5 exo	
			300.0 endo	
		336.4	350.0 exo	
			481.8 exo	
III	522.7 – 630.5	554.5	568.2 exo strong	24.40
IV	1000.0 – 1200.0	1022.4	1022.4 endo	2.33

Table 2
TERMOANALYTICAL DATA OF THE COMPOUND ANALYZED: $[Cu(KET)_2]_2 \cdot 0.5H_2O$

lines in ligand, respectively the appearance of some meaningful lines. These differences indicate the formation of a new compound.

Thermal analysis

The simultaneous TG, DTG and DSC curves of the complex are shown in figure 4. The thermoanalytical curves mentioned are been registered during heating in air atmosphere, in the temperature range 25.0 – 1200.0 °C. The data obtained from these curves, supporded by chemical and X-ray diffraction pattern investigations are given in the table 2.

The thermal decomposition of the complex $[Cu(KET)_2]_2 \cdot 0.5H_2O$ unfolds practically in four steps, without being able to afford to delimit the second and third steps. It is very difficult to specify the nature of the intermediate compounds because of the complexity of decomposition process with simultaneous and/or competitive reactions.

The first mass loss (0.78%) from 63.6 to 100.0 °C is attributed to dehydration, which occurs in a single step and TG curve shows that the anhydrous compound is stable up to 200.0 °C. The process is characterized by an endothermic peak on the DSC curve and occurs at a low temperature, suggesting a weak bonding of water in the complex structure. Practically, this water loss can be associated to the lattice water (water of crystallization).

After dehydration, the mass losses observed are due to the thermal decomposition of organic ligand. These take place in consecutive and/or overlapping steps with partial losses.

For the anhydrous copper compound, the thermal decomposition occurs in three steps. The first step (between 200.0 – 522.7 °C) is characterised by large mass loss (61.36%) and is attributed to the decomposition of organic ligand. The TG curve, especially DTG and DSC show the complexity of the process through the related DTG peaks (three), respectively DSC peaks (five). Small exothermic peaks corresponding to this loss are observed in DSC curve, probably due to endothermic and exothermic reactions that take place simultaneously such as breaking and rearrangement of the bands. The second step is attributed to the oxidation of the organic matter and it is accompanied by a very strong exothermic event in the DSC curve. The last mass loss (the third step), between 1000.0 – 1200.0 °C (Δm = 2.33%), accompanied by a small endothermic peak corresponds to the reduction of copper oxide (CuO) to metallic copper (Cu). The temperature of Cu formation (1022.4°C) from CuO is similar to that reported in the literature. Calculation based on the mass loss up to 1200.0°C are in good agreement with the formation of Cu as final residue (exp. 11.13% ; calc. 11.06%).

Conclusions

Our study shows that Cu(II) can form complex with ketoprofen, the one drug of the carboxylate NSAIDs group that show anticancer effects. Synthesis and properties of this type of compound was investigated by means of elemental analysis, FT-IR spectroscopy, X-ray diffraction pattern and thermal analysis.

Based on the results of elemental analysis and the TG curve, a general formula could be established for the synthesized compound, namely: $[Cu(KET)_2]_2 \cdot 0.5H_2O$. The spectroscopic infrared experimental data suggests that the carboxylate of ketoprofen is coordinate to metal as bidentate bond, namely four carboxylate groups from four ligand molecules are in a bidentate briding mode.

The crystallization water, evidenced by FT-IR spectroscopy, was confirmed and determined by thermal analysis, in the TG curve.

A four stages decomposition process is shown in the thermal analysis. The thermal investigation (studied by TG, DTG and DSC techniques) show that obtained complex decomposes progressively, and the first step of thermolysis is dehydratation. In the same time, the thermal decomposition process is one complex with simultaneous and/or consecutive reactions. The final product of the thermal decomposition is Cu, which through its percentage confirms the empirical formula of the new complex prepared.

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