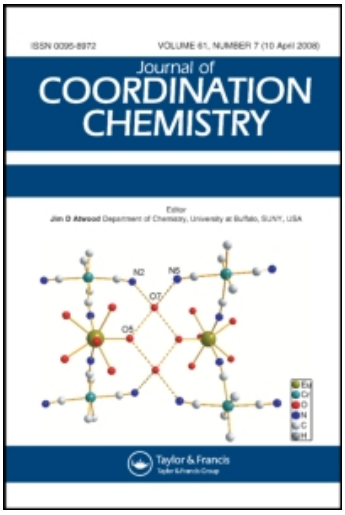

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Complex formation of the anti-inflammatory drugs tenoxicam and piroxicam with Fe(III) in methanol and acetone

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A spectrophotometric study of the chemical coordination of two nonsteroidal anti-inflammatory drugs (tenoxicam and piroxicam) with Fe(III) has been undertaken in methanol in order to determine the stoichiometry and formation constants of the formed complexes, 1 : 1 and 1 : 2 stoichiometric ratios [Fe(III) : oxicam]. The formation constants determined with the aid of the program SQUAD, at 293 K in methanol, are: Fe(tenox), $\log \beta_{11} = 4.71 \pm 0.03$; Fe(tenox)$_2$, $\log \beta_{12} = 8.57 \pm 0.04$; Fe(pirox), $\log \beta_{11} = 5.54 \pm 0.09$; Fe(pirox)$_2$, $\log \beta_{12} = 9.75 \pm 0.08$. However, the study in acetone gave rise to complexes with completely different stoichiometric ratios with polynuclear species [dimers of Fe(III)]. The formation constants determined with the aid of program SQUAD, at 293 K in acetone, are: Fe$_2$(tenox), $\log \beta_{21} = 9.04 \pm 0.03$; Fe$_2$(tenox)$_2$, $\log \beta_{22} = 14.75 \pm 0.06$; Fe$_2$(tenox)$_3$, $\log \beta_{23} = 18.45 \pm 0.07$; Fe$_2$(pirox), $\log \beta_{21} = 9.06 \pm 0.30$; Fe$_2$(pirox)$_2$, $\log \beta_{22} = 14.77 \pm 0.09$; Fe$_2$(tenox)$_3$, $\log \beta_{23} = 18.48 \pm 0.40$. Besides the well-known effect of the solvent on thermodynamic constants, the stoichiometry seems to be strongly driven by the nature of the solvent.

Keywords: Fe(III)–oxicam complexes; Formation constants; Program SQUAD; Nonaqueous solvents; Spectrophotometric study

1. Introduction

Metal ions play a primary role in biological systems. The presence of drugs that interact competitively with natural ligands for metal ions changes metal distribution in blood plasma and other biological fluids, and *vice versa* [1–3].

Therefore, knowledge of the distribution of chemical species at equilibrium, formed during interaction of drugs with metal ions, may be useful to propose mechanisms for the drug action against a particular disease. This information is also useful for

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diminution or potentiation of the drug effects derived from the formation of these complexes [3].

Rheumatoid arthritis causes inflammation in muscles and articulations [1–4]. Members of the oxicam family, mainly piroxicam and tenoxicam (figure 1) [5], have been employed against this disease due to their analgesic and antipyretic effects, which are improved by complexation with metal ions.

Notwithstanding the well-known role of Fe(III) in chronic diseases, its interaction with drugs has not been clearly established. On the other hand, iron is an essential element for life, i.e. a constituent of transport proteins and enzymes [6–8].

One solid complex of Fe(III) with isoxicam, which shows a 1 : 3 Fe(III) : isoxicam stoichiometry, has been reported in [9]; in this paper isoxicam acts as a monoanionic chelate with coordination that involves the oxygen belonging to the enolate and the oxygen of amide. Later, Bury and Underhill [10] reported a solid complex of Fe(III) with tenoxicam with the same kind of coordination, 1 : 3 Fe(III) : tenoxicam. Pipe *et al.* [11] have also found the same stoichiometry for the solid complex formed between Fe(III) and piroxicam. Unfortunately, none of these established the formation constants of these complexes.

In contrast, García *et al.* [12] have proposed a flow injection analysis–spectrophotometric method to determine tenoxicam in methanol solutions. By the method of continuous variations and molar ratio, they found the formation of a complex, in solution, with 1 : 2 Fe(III) : tenoxicam stoichiometry with a $\log \beta_{12} = 8.21 \pm 0.08$ and a molar absorptivity coefficient $\varepsilon^{(540)} = 1.04 \times 10^3\,\mathrm{M}^{-1}\,\mathrm{cm}^{-1}$.

To determine the stoichiometry of the Fe(III)–tenoxicam complexes in solution, a spectrophotometric study has been undertaken using methanol and acetone as solvents (because of the low solubility of oxicams in water). The formed complexes and their equilibrium constants were determined using the computational programs TRIANG [13] and SQUAD [14], respectively; the study was also extended to include the Fe(III)–piroxicam system with the same solvents.

2. Experimental

2.1. *Reagents and equipment*

Tenoxicam and piroxicam drugs, of analytical grade, were obtained from Sigma and anhydrous $FeCl_3$ from Merck. Spectroscopic grade methanol and acetone from Baker were employed.

Spectrophotometric data were obtained with a Perkin–Elmer Lambda 18 spectrophotometer using quartz cells of 1 cm optical path length. Volumes were added by means of a digital burette II of Merck.

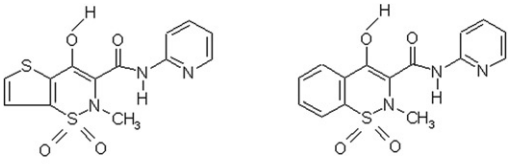

Figure 1. Chemical structures of some members of the oxicam family.

2.2. *Procedures for the speciation studies in methanol and acetone*

In order to determine the stoichiometric Fe(III) : oxicam ratios of the complexes in methanol, the molar ratio and continuous variations methods were employed. Fe(III) and oxicam solutions, 5×10^{-4} M, each were prepared and mixed, as usual, in the continuous variations method. For the molar ratio method the [Fe(III)] was maintained to 1×10^{-4} M while the oxicam concentration was varied from 0 to 4×10^{-4} M. In both methods, spectra were recorded in the 500–700 nm range. Each experiment was repeated at least three times. Temperature was maintained to (293 ± 1) K. For the studies in acetone, the concentrations were 10 times higher than in methanol.

3. Results and discussion

Molecular tenoxicam and piroxicam are not significatively dissociated or protonated when dissolved in water, and it is expected that in solvents with lower dielectric constant they are neutral species. Therefore, it is very likely that in the complexes reported the ligand remains neutral. For simplicity, the total complex charges are omitted.

3.1. *Speciation studies of Fe(III)–tenoxicam and Fe(III)–piroxicam systems in methanol*

3.1.1. Molar ratio method. Figure 2 shows the typical absorption spectra for the Fe(III)–tenoxicam system in the molar ratio method. It is important to remark that the slightly yellow initial solution of anhydrous $FeCl_3$ becomes red and the color intensifies as the tenoxicam concentration increases in the system. At the same time, a hypsochromic shift is observed in the maximum of the spectra. The behavior for methanolic solutions of Fe(III) and piroxicam is similar to the Fe(III) and tenoxicam solutions, which is in agreement with the work of García *et al*. [12].

Figure 3 presents a typical molar ratio curve for methanol solutions of Fe(III)–tenoxicam at 540 nm. The maximum change of slope for this system is observed for the molar ratio of 2 tenoxicam ligands for each Fe(III) ion, corresponding to a 1 : 2 Fe(III) : tenoxicam.

Results from TRIANG indicate that two species need to be considered in order to explain the spectroscopic information, no matter the absolute uncertainty of transmittance input to TRIANG in the range from 0.001 to 0.01. Thus, it is very likely that two complexes are formed in these systems, and not only one, as concluded by García *et al*. [12]. It is important to analyze the results obtained by the method of continuous variations.

3.1.2. Continuous variations method. Figure 4 displays the absorption spectra for Fe(III)–tenoxicam in methanol for these experiments corresponding to the continuous variations method, and figure 5 presents the typical continuous variation curve at 540 nm.

Figure 5 exhibits a maximum absorbance value at a tenoxicam molar fraction close to 2/3. According to continuous variation method, for simple systems the maximum of

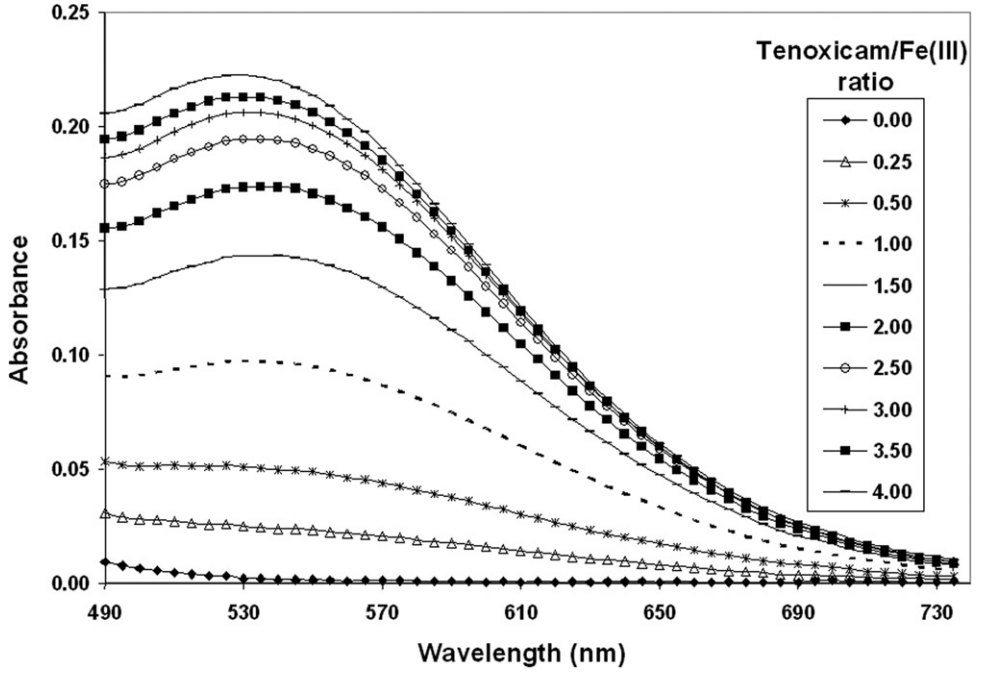

Figure 2. Absorption spectra of the Fe(III)–tenoxicam system in methanol obtained during the molar ratio method. $[Fe(III)] = 1 \times 10^{-4}$ M.

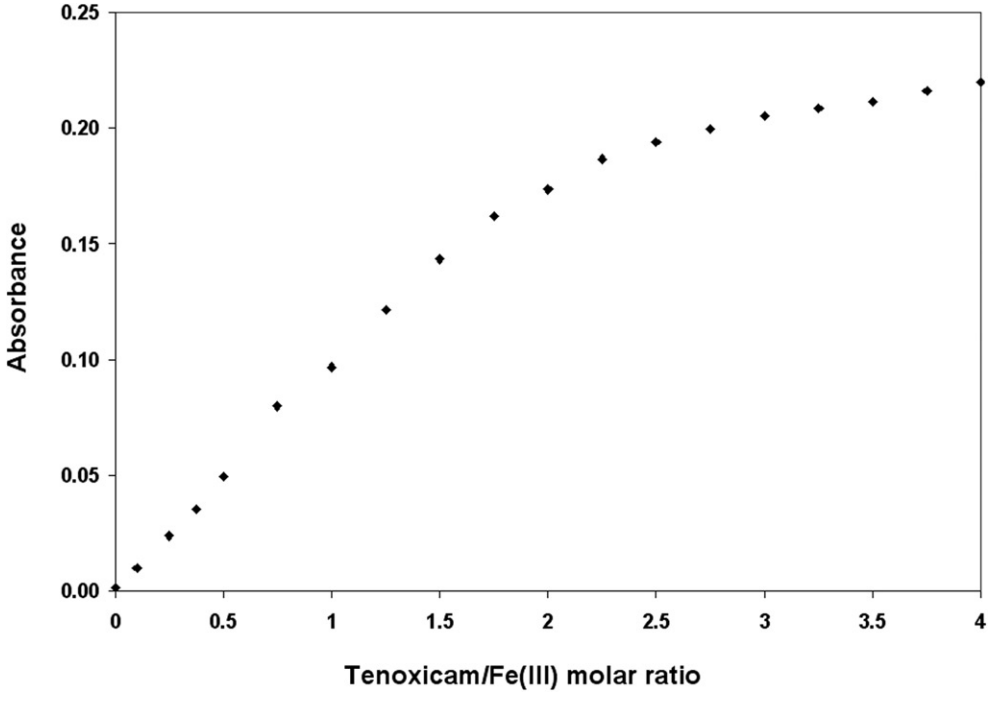

Figure 3. Typical molar ratio curve obtained in methanol for the Fe(III)–tenoxicam system at a wavelength of 540 nm. $[Fe(III)] = 1 \times 10^{-4}$ M.

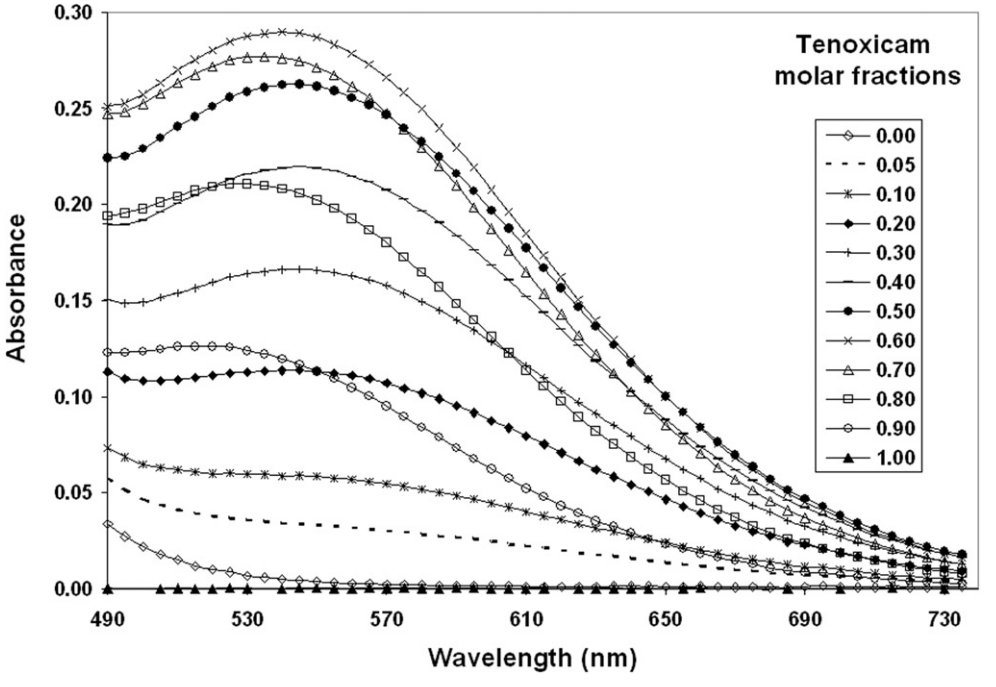

Figure 4. Absorption spectra of the Fe(III)–tenoxicam system in methanol obtained during the continuous variations method. $[Fe(III)] + [tenox] = 5 \times 10^{-4}$ M.

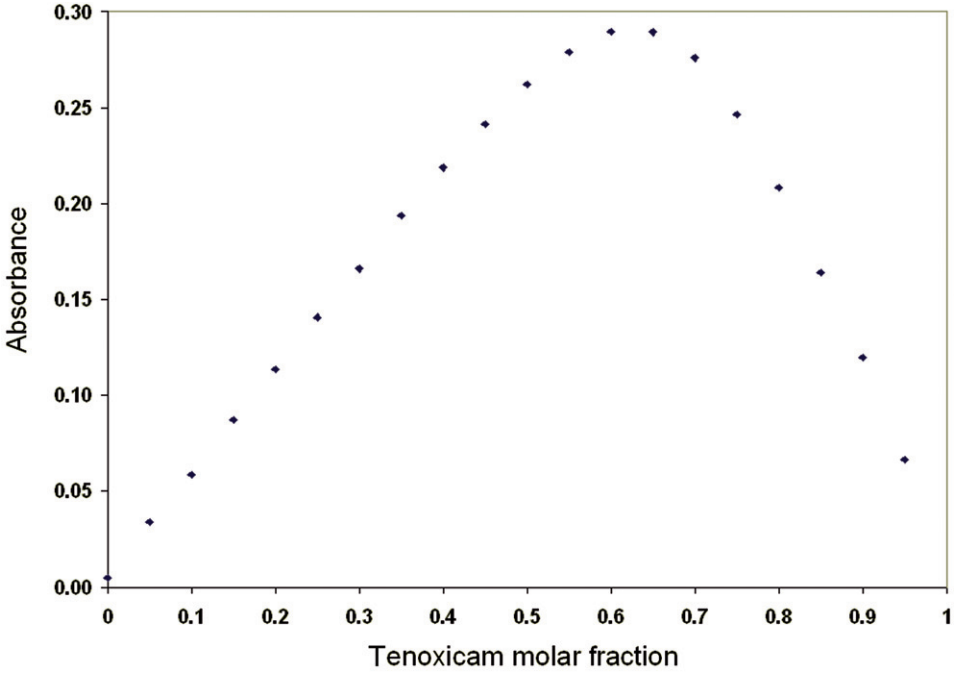

Figure 5. Typical continuous variations curve obtained in methanol for the Fe(III)–tenoxicam system at a wavelength of 540 nm. $[Fe(III)] + [tenox] = 5 \times 10^{-4}$ M.

the curve occurs for a ligand molar fraction value of $n/(n+1)$, n being the stoichiometric coefficient of the ligand with respect to the metal ion. Thus, we have at least the formation of a 1 : 2 Fe(III) : tenoxicam complex. Again, the continuous variations experiments for the Fe(III)–piroxicam methanolic solutions give very similar responses to those observed in figures 3 and 4. In both cases, TRIANG estimates that two absorbing species are needed to best fit the experimental spectra.

The program SQUAD was employed to refine the formation constant values for the Fe(III)–tenoxicam and Fe(III)–piroxicam systems in methanol. Results of the molar ratio and continuous variations method were combined and 50 absorbance data for each one of the 24 spectra were input to SQUAD. Table 1 shows the better refinement parameters obtained for these systems.

The results shown in table 1 for the $Fe(tenox)_2$ are in good agreement with that reported by García *et al*. [12]. However, an additional Fe(tenox) complex was found. For the Fe(III)–piroxicam system, the two corresponding species are also present.

In figure 6, the Fe(III)–tenoxicam molar absorptivity coefficients obtained from SQUAD in methanol are displayed. The values obtained for the Fe(III)–piroxicam system in methanol are practically the same. The value reported by García *et al*. [12] at a wavelength of 540 nm ($1.04 \times 10^3\,M^{-1}\,cm^{-1}$) seems to correspond to a weighed mean to value of those shown in figure 6.

3.2. *Speciation studies of Fe(III)–tenoxicam and Fe(III)–piroxicam systems in acetone*

3.2.1. Molar ratio method. A spectrophotometric study for these systems in acetone was undertaken. In this solvent it is possible to have oxicam concentrations higher than in methanol. Molar ratio and continuous variation methods were also applied in order to determine the stoichiometric coefficients and formation constants of Fe(III) with both ligands.

Figure 7 shows the absorption spectra of the Fe(III)–piroxicam system obtained by the molar ratio method. One isosbestic point at a wavelength of 565 nm for the systems with piroxicam molar ratios ranging from 1 to 4 implies the presence of one chemical equilibrium that involves exchange of piroxicam for systems with piroxicam molar ratios higher than 1. The behavior of Fe(III)–tenoxicam system is similar.

Results from TRIANG indicate that three species need to be considered to explain the spectroscopic information of both Fe(III)–oxicam systems, no matter the absolute uncertainty of transmittance introduced to TRIANG.

Table 1. Species and formation constants ($\log\beta$) corresponding to the better refining obtained with SQUAD for the Fe(III)–tenoxicam and Fe(III)–piroxicam systems in methanol.

Species	$\log\beta$	σ_A[a]	U[b]
Fe(tenox) (1 : 1)	4.71 (0.03)	4.17×10^{-3}	1.65×10^{-2}
$Fe(tenox)_2$ (1 : 2)	8.57 (0.04)		
Fe(pirox) (1 : 1)	5.54 (0.09)	1.71×10^{-3}	1.20×10^{-2}
$Fe(pirox)_2$ (1 : 2)	9.75 (0.08)		

Notes: [a]Total SD of the absorbance data.
[b]Sum of square residuals of absorbance data.

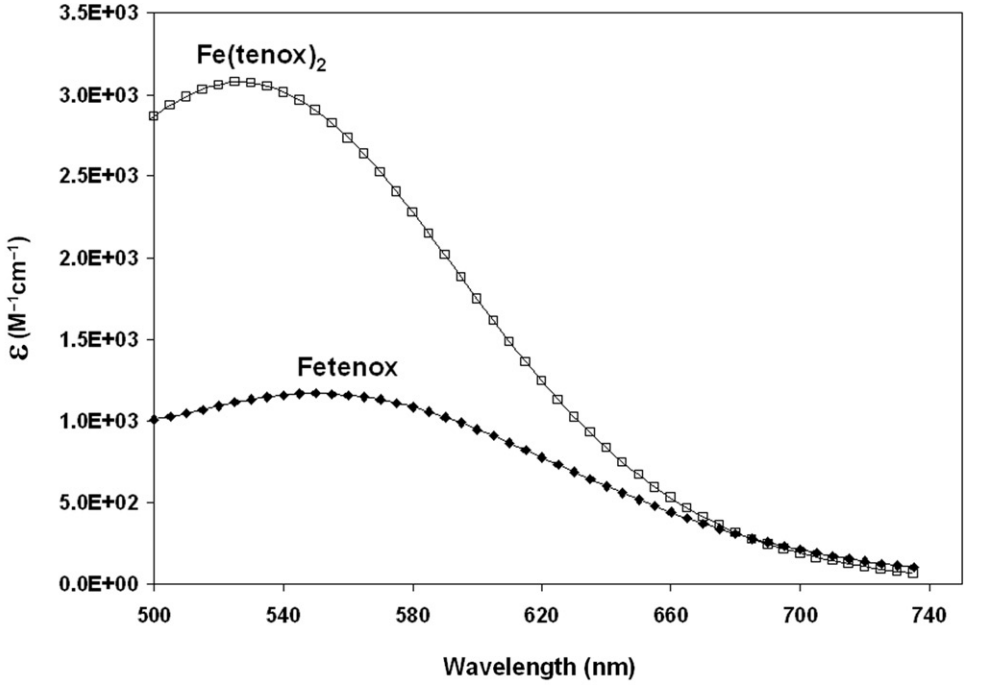

Figure 6. Molar absorptivity coefficients of the species calculated by the program SQUAD for the Fe(III)–tenoxicam system in methanol.

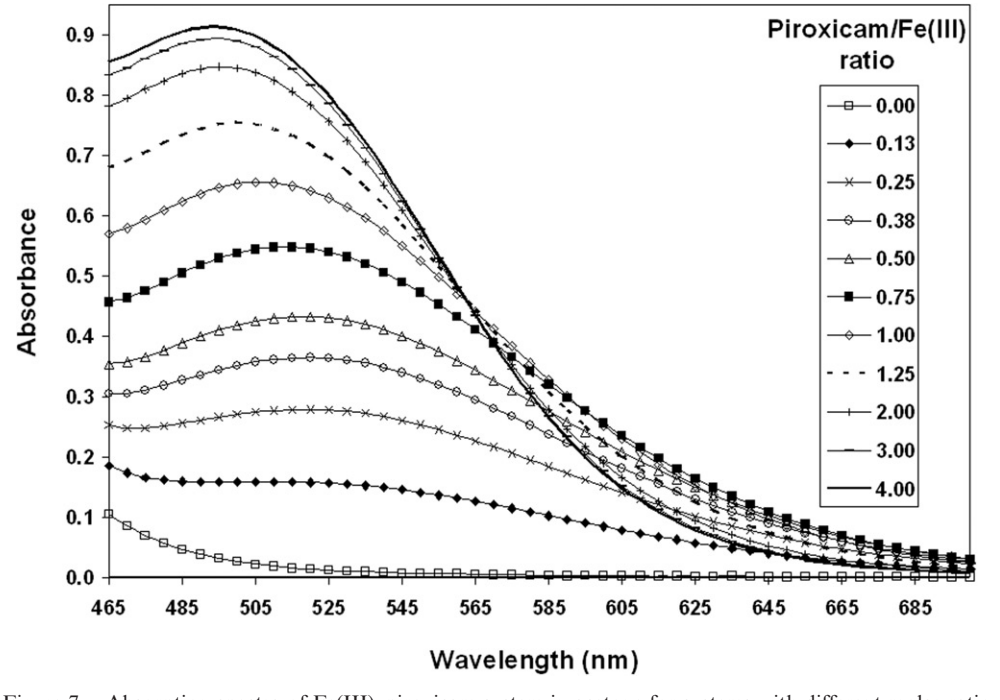

Figure 7. Absorption spectra of Fe(III)–piroxicam system in acetone for systems with different molar ratio of piroxicam/Fe(III). $[Fe(III)] = 1 \times 10^{-3}$ M.

Figure 8 presents the typical molar ratio curve for the Fe(III)–piroxicam system in acetone at a wavelength of 520 nm. If one and only one complex was formed in this system, and its chemical behavior were simple, the stoichiometric ratio of the formed species would correspond to 1 : 1 Fe(III) : piroxicam. Nevertheless, deviation from the expected linear response is shown for molar ratio lower than 1. This behavior and the results obtained with TRIANG indicate formation of polynuclear Fe(III) complexes.

3.2.2. Continuous variations method. In order to confirm the formation of polynuclear Fe(III) species in the Fe(III)–oxicam systems, continuous variation methods were followed. The absorption spectra for the continuous variation method of the Fe(III)–piroxicam system in acetone are shown in figure 9 and the typical curve obtained for this method, at a wavelength of 520 nm, is presented in figure 10.

Figure 10 shows deviation from linear behavior at molar fractions lower than 0.5, which may be interpreted as indication of polynuclear species formation with stoichiometric ratios $m:n$ of Fe(III) : piroxicam – with $m>n$ – in addition to a $m:m$ Fe(III)/piroxicam complex.

The behavior of the system observed with the continuous variations method for the Fe(III)–tenoxicam is similar to those previously described for the Fe(III)–piroxicam system.

The results for the absorbance data corresponding to the continuous variation method, processed with the program TRIANG, also indicate that three species should be considered to explain the spectroscopic information of both Fe(III)–oxicam systems, no matter the absolute uncertainty of transmittance introduced to TRIANG.

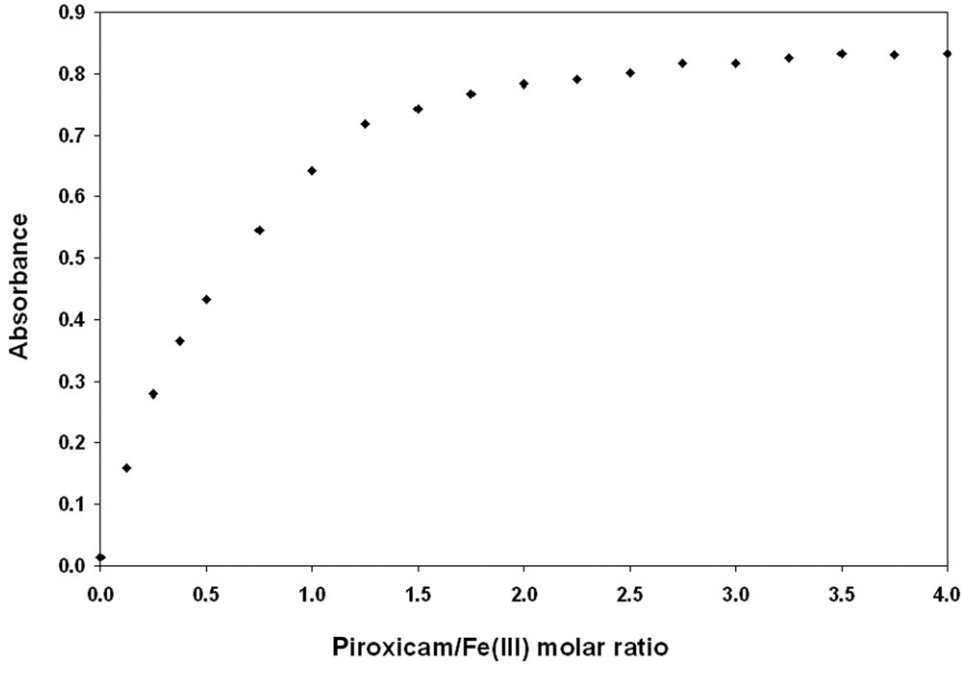

Figure 8. Typical molar ratio curve for the Fe(III)–piroxicam system in acetone at a wavelength of 520 nm. $[Fe(III)] = 1 \times 10^{-3}$ M.

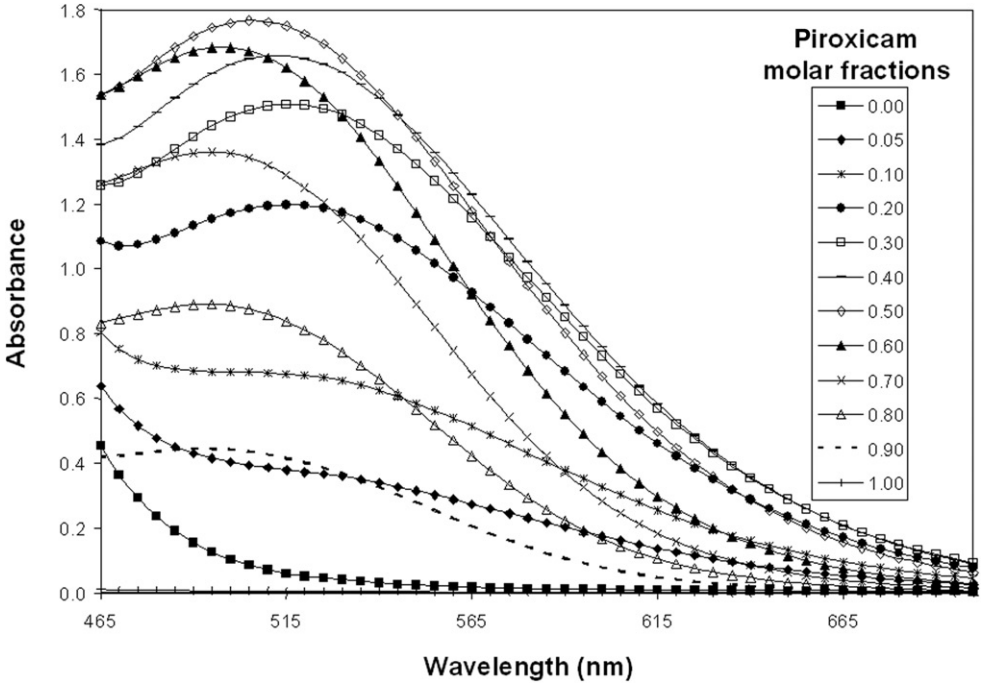

Figure 9. Absorption spectra of the Fe(III)–piroxicam system for continuous variations method in acetone. $[Fe(III)] + [pirox] = 5 \times 10^{-3}$ M.

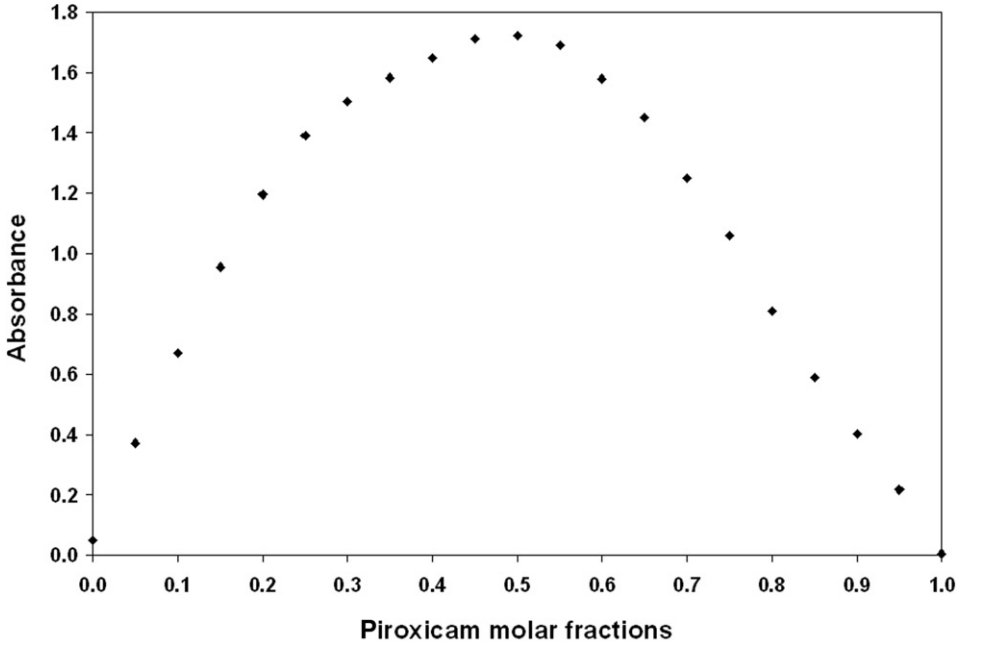

Figure 10. Typical continuous variations curve obtained for the Fe(III)–piroxicam system in acetone at a wavelength of 520 nm. $[Fe(III)] + [pirox] = 5 \times 10^{-3}$ M.

The program SQUAD was employed to refine the formation constant values for the Fe(III)–piroxicam and Fe(III)–tenoxicam systems in acetone. Results of the molar ratio and continuous variation method were combined and a set of 50 absorbance data for each one of the 24 spectra input to SQUAD. Several chemical models were considered, but always the formation of at least one or two polynuclear Fe(III) species was necessary to achieve some convergence of the program. Results reported in table 2 show that the best refinement is obtained for these systems when the formation of dimers of Fe(III) is considered.

The differences in stoichiometry of the complexes reported in tables 1 and 2 may be explained due to dielectric constants of the solvents (33 for methanol and 21 for acetone

Table 2. Species and formation constants ($\log \beta$) corresponding to the better refining obtained with SQUAD for the Fe(III)–tenoxicam and Fe(III)–piroxicam systems in acetone.

Species	Log β	σ_A[a]	U[b]
Fe_2(tenox) (2 : 1)	9.04 (0.03)	6.07×10^{-3}	2.58×10^{-2}
Fe_2(tenox)$_2$ (2 : 2)	14.75 (0.06)		
Fe_2(tenox)$_3$ (2 : 3)	18.45 (0.07)		
Fe_2(pirox) (2 : 1)	9.06 (0.3)	8.80×10^{-3}	4.39×10^{-2}
Fe_2(pirox)$_2$ (2 : 2)	14.77 (0.09)		
Fe_2(pirox)$_3$ (2 : 3)	18.48 (0.4)		

Notes: [a]Total SD of the absorbance data.
[b]Sum of square residuals of absorbance data.

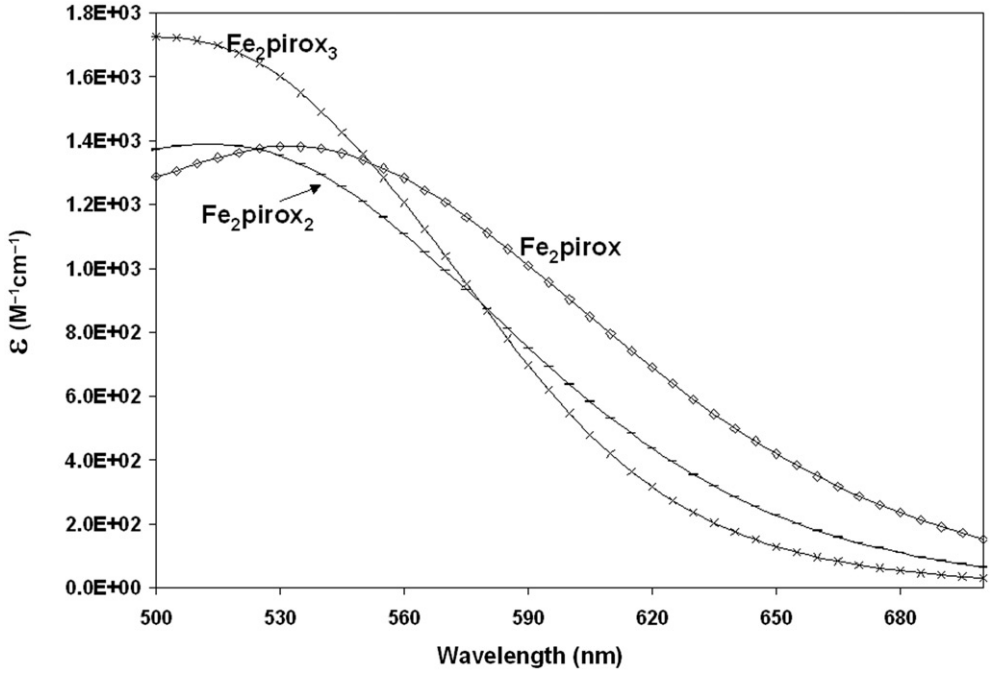

Figure 11. Molar absorptivity coefficients of the species calculated by the program SQUAD in the Fe(III)–piroxicam system in acetone.

at 25°C), their relative basicities (higher for methanol than acetone) and the difference in the solute concentrations (10 times greater in acetone than in methanol).

Figure 11 shows the Fe(III)–piroxicam molar absorptivity coefficients obtained from SQUAD in methanol. A comparison of figure 6 and figure 11 shows that the shapes of the molar absorptivity coefficients for Fe(III)–oxicam in both solvents are similar, reflecting that the same *d* electronic transitions may be involved.

4. Conclusions

In this work the formation of the red species $Fe(tenox)_2$ was confirmed by spectrophotometry, as previously reported by García *et al.* [12] for the Fe(III)–tenoxicam system in methanol. Moreover, the formation of a second complex Fe(tenox) was also demonstrated in the present study. The formation constants and molar absorptivity coefficients of both species were determined with the aid of SQUAD, as well as the same kind of species for Fe(III)–piroxicam system; the corresponding formation constants and molar absorptivity coefficients were also determined.

The Fe(III)–tenoxicam and Fe(III)–piroxicam systems in acetone give formation of three red dimers: $Fe_2(oxicam)$, $Fe_2(oxicam)_2$ and $Fe_2(oxicam)_3$. The formation constants and molar absorptivity coefficients of these species were also determined with SQUAD.

The lower value of the dielectric constant of acetone with respect to methanol and the higher concentration of Fe(III) and oxicam achieved in acetone seems to be determinant, not only for the stability of the formed species, but for the structure of the coordination compounds. In none of the conditions studied in the present work was the formation of $Fe(oxicam)_3$ complexes found.

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