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Line broadening in the 77 K ^{57}Fe-Mössbauer spectra of some ferrous iron-containing medicines

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Abstract We report line broadening in the 77 K ^{57}Fe Mössbauer spectra of some commercially available medicines based on ferrous sulfates and on ferrous fumarates. While introducing only a single ferrous doublet is required to fit the RT spectra of all samples, on the contrary the line shapes of the 77 K spectra are properly described with two ferrous doublets. We discuss eight different static and dynamic hypotheses as possible physical origins for these two doublets, but finally we propose that the reasons are similar for the ferrous sulfates and for the ferrous fumarates containing medicines, and it can be due to the presence of easily dehydrated and hydrated ferrous compounds. The presence of several hydrated sulfates was confirmed by RT Raman spectroscopy. Possible implications of these results related with the hydrated character by which the active parts of the medicines are fabricated by the pharmaceutical companies are also discussed.

Keywords ^{57}Fe Mössbauer spectroscopy · Raman spectroscopy · Medicines · Ferrous sulfates · Ferrous fumarates

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Highlights

- 77 K Mössbauer and RT Raman spectroscopies were used to study six commercial ferrous containing medicines.
- Line broadening in the 77 K Mössbauer spectra was observed and accounted for by introducing two doublets.
- The physical origin of the two doublets in the two types of medicines are probably associated to differently hydrated iron sites.

1 Introduction

Room temperature (RT) ^{57}Fe Mössbauer spectrometry (MS) has been used for some time in the study of Ferrous-containing medicines [1–9]. The technique has proven to be very valuable because of the following facts: (i) by locating the pair of quadrupole splitting (Δ) and isomer shift (δ) values in the Δ vs. δ diagram [10], it is possible to determine the coordination oxidation and electronic spin states of each Fe species in the medicaments; (ii) by comparing the quadrupole splitting (Δ) values, it is possible to distinguish ferrous gluconate, ferrous fumarate and ferrous sulfate [1–15]; (iii) it should be possible to distinguish the hydrated character, n, of the ferrous sulfates ($FeSO_4 \cdot nH_2O$, with $n = 0,\ 1,\ 4,\ 5,\ 6,\ 7$), because the ferrous sulfates with high n values exhibit the larger values of quadrupole splitting [11, 12]; (iv) the technique has helped to reveal the presence of contaminant iron phases in different medicaments [2–9]. Here, it is worth mentioning, that ^{57}Fe MS is not sensitive to the chemical constituents of the excipients in the medicines, because, in principle they do not contain Fe. Indeed, iron is only present in the active part of the medicine. Therefore, MS is a simple and powerful technique for studying these types of samples. This is in contrast with other techniques like XRD, Raman or infrared spectroscopies which detect all phases including the ones composing the excipients, therefore making the analysis of the data a difficult task.

We have noticed that most Mössbauer studies on ferrous containing medicines have been performed at RT [1–4, 6–10]. In fact, we have not found reports on Fe^{2+} based medicines at lower temperature, to the best of our knowledge. On the contrary, there are some variable temperature Mössbauer studies for Fe^{2+} minerals and synthetic samples. Rothstein et al. [12] have experimentally studied several ferrous minerals (szomolnoquite, rozenite, melanterite, etc.) from 12 K till 295 K. Ingalls [16] have theoretically investigated the temperature dependence of $FeSO_4 \cdot 7H_2O$ and $FeSO_4$ among other ferrous compounds. Pápai and Vankó [17] have theoretically predicted the 5 K hyperfine parameters of $[Fe(H_2O)6]SO_4$. Van Alboom et al. [18] studied the variable temperature Mössbauer spectra of synthetic szomolnokite (FeSO4.H2O). Below 30 K, the authors observed a magnetic transition, and on passing through this temperature the spectra changed from only doublets to mixtures of sextets plus doublets. They did not report a change in the linewidth with decreasing temperature from 450 K till about 30 K. Garg et al. [15] have experimentally studied synthetic ferrous fumarates from 80 K to 300 K. In these experimental and theoretical works only one quadrupolar component was used to describe the spectra of these compounds, i.e. these spectra did not require the presence of two or more doublet components.

The main purpose of this paper is to investigate in detail the 77 K Mösbauer spectra of six commercially available ferrous containing medicines and to compare the results with the RT spectra, which were reported earlier [9]. By doing this work, we found an unexpected line

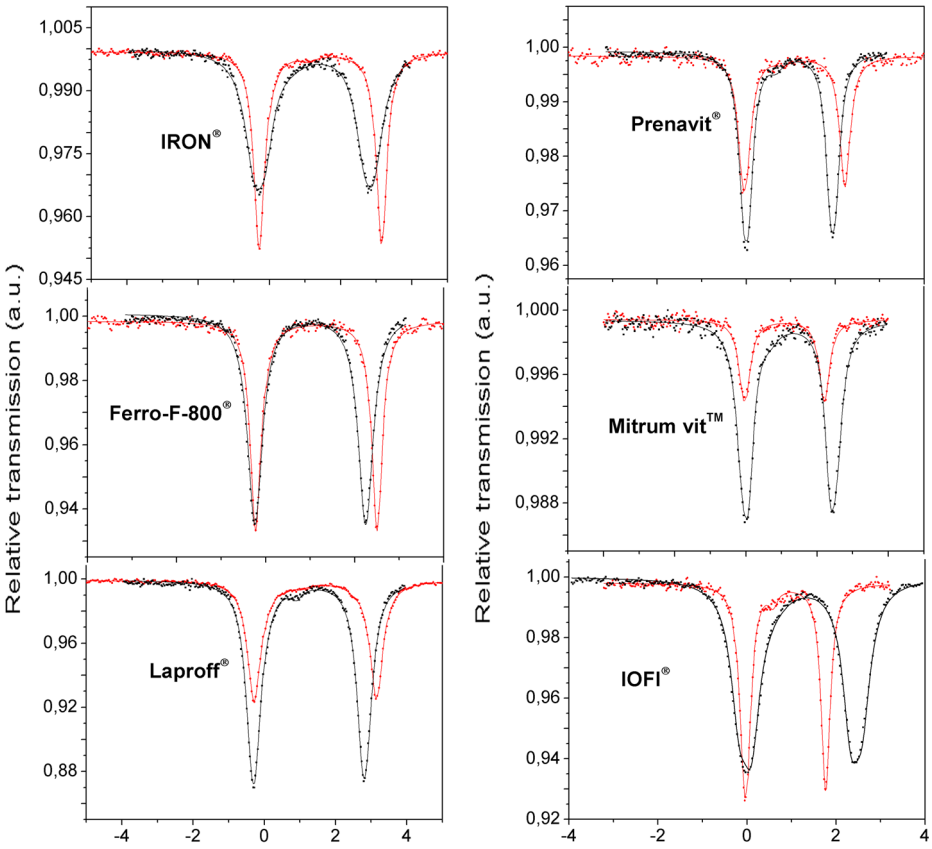

Fig. 1 Comparison of RT (*red lines*) and 77 K (*black lines*) Mössbauer spectra for the ferrous containing medicines

broadening in the low temperature spectra (see Fig. 1) and we offer a possible explanation for this observation and discuss some possible implications on the way by which the active parts of the medicaments are fabricated.

2 Experimental

We studied the physical properties of iron in six different commercially available medicines: Ferro-F-800®, Laproff®, IRON®, Mitrum vit™, Prenavit® and IOFI®. More information regarding these medicaments can be found elsewhere [9]. According to the information provided by the manufacturers, Ferro-F-800®, Laproff® and IRON® medicines contain ferrous sulfates, whereas IOFI® is based on ferrous fumarate. On the one hand, the types of ferrous materials for Mitrum vit™ and Prenavit® were not given by the manufacturers, but from their RT Mössbauer parameters, it was possible to conclude that they were based on ferrous fumarates [9]. Generally, ferrous sulfate medicines are dry, but the fumarate sample, Prenavit®, comes wet within the capsule. This sample was dried in a paper bag at room temperature for 3 days before taking Mössbauer measurements. To prepare the samples for

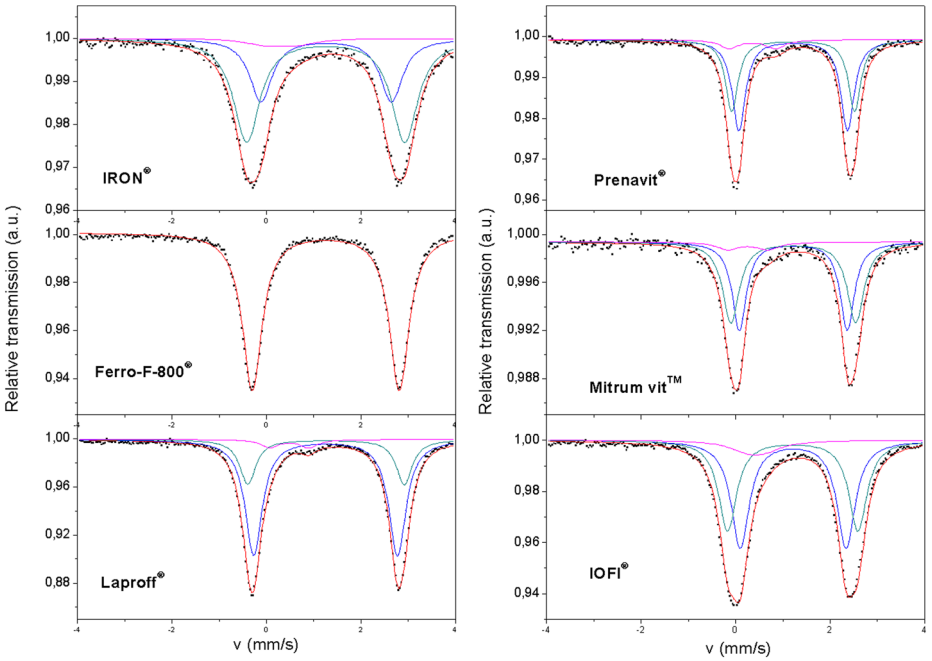

Fig. 2 77 K Mössbauer spectra for the ferrous containing medicines

MS measurements, firstly for some tablets the outer covers were removed. Afterwards, all tablets were crushed with a pestle, to obtain them in a powdered form. Finally, the powdered tablets were homogeneously distributed in the sample holder. The 77 K Mössbauer spectra for each absorber were collected in a time mode spectrometer working in the transmission geometry. Some experiments were at least duplicated to confirm the physical existence of the broadening of lines when cooling the samples from 300 K down to 77 K, preventing thus any instrumental and/or experimental artefacts. The spectra were analysed with the RECOIL program [19] assuming lorentzian lines. The values of isomer shift are quoted relative to that of α-Fe at RT. Mössbauer measurements were performed before the expiration dates of the tablets. In order to obtain further information on the hydrated character exhibited by the ferrous phases in the medicines, micro-Raman measurements at RT were performed on a Horiba Jobin-YvonLabRam HR system. Raman scattering was excited with the 633 nm line of a He-Ne laser source. A CCD camera was used as a detector and for collecting the laser light with a spatial resolution of 2–4 μm. Data were taken over sample areas with respective shades of colors, which were called red zone (RZ) and white zone (WZ).

3 Results

Before presenting the results obtained at 77 K, it is important to briefly summarize the main results obtained at RT, which were previously reported [9]. The RT Mössbauer spectra of the six medicines were dominated by a strong doublet with symmetrical Lorentzian lines.

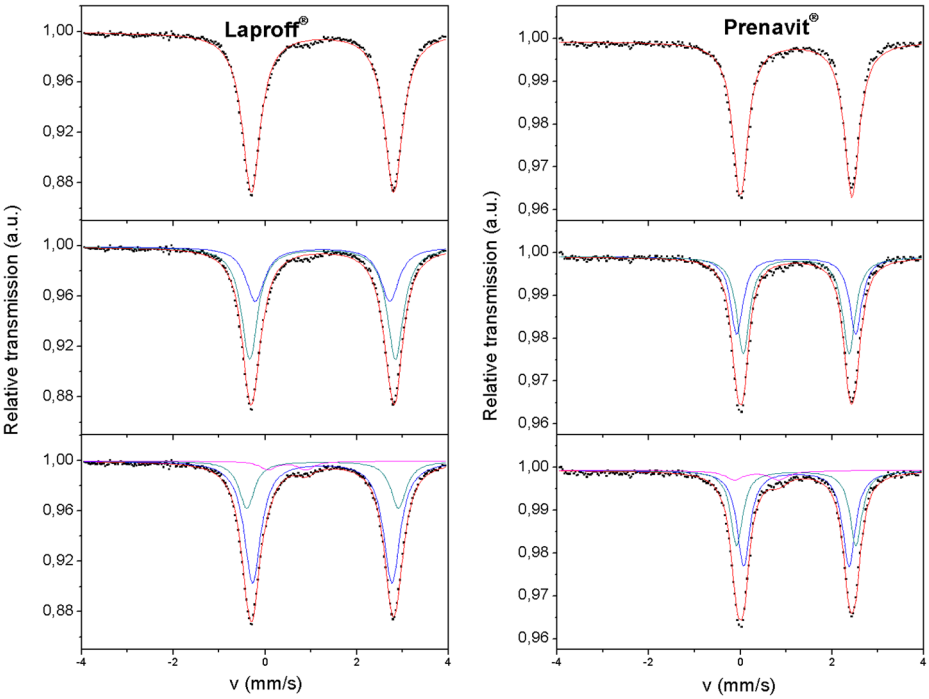

Fig. 3 77 K Mössbauer spectra for Laproff® (*left side*) and Prenavit® (*right side*) medicines. The spectra for each sample were fitted by introducing one (*upper part*), two (*middle part*) and three (*lower part*) doublets

The hyperfine parameters derived from the fittings were ascribed to the expected ferrous compounds. The hydrated character of the ferrous sulfates, i.e. the n value in the chemical formula $FeSO_4 \cdot nH_2O$ ($n = 0, 1, 4, 5, 6, 7$), could not be easily determined in these medicines, because their quadrupole splittings were very similar. Additionally, the RT spectra of the samples exhibited weak doublets with spectral areas ranging between 3 to 7% and assigned to the presence of iron impurity compounds.

Figure 2 shows the 77 K Mössbauer spectra of the six medicines. In comparison to the RT Mössbauer spectra (see Figure 1 of Reference [9]) we can notice that the low temperature spectra for all samples consist of doublets with broadened lines. The best fit for each sample is presented in Fig. 2. It is noted that the spectral shape for IRON®, and Laproff® are properly accounted for by introducing two strong doublets with symmetrical Lorentzian lines and a third weak doublet ascribed to the HS Fe^{3+}-based contaminant iron phase. The spectrum for Ferro-F-800® was fitted with a single doublet. On the other hand, the 77 K Mössbauer spectra of Mitrum vit™, Prenavit®and IOFI® are properly described by using two strong doublets with symmetrical Lorentzian lines and a third weak doublet due to an impurity phase. Due to the importance of these results, we want to demonstrate that the fitting showed for the spectra were the proper ones. Figure 3 illustrates three different fit trials of the 77 K Mössbauer spectra for Laproff® (left side) and for Prenavit® (right side). They were successively described by means of one, two and three quadrupolar components: it is clear that the later model allows a perfect description of the hyperfine structure, associated

Table 1 Hyperfine parameters derived from the fit of 77 K Mössbauer spectra for all medicines

Sample	Sites #	δ (mm/s)	Δ (mm/s)	$\Gamma/2$ (mm/s)	A_{Fe} (%)	χ^2
Ferro-F-800®	1	1.26	3.11	0.25	100	2.83
Laproff®	3	1.20	3.08	0.22	48	0.18
		1.32	3.07	0.22	48	
		0.27	1.19	0.25	4	
IRON®	3	1.11	3.12	0.30	41	0.18
		1.38	3.11	0.34	56	
		0.30	0.38	0.24	3	
Mitrum vit™	3	1.21	2.27	0.20	48	0.58
		1.22	2.59	0.20	48	
		0.25	1.09	0.17	4	
Prenavit®	3	1.21	2.28	0.15	46	0.68
		1.21	2.56	0.16	48	
		0.25	0.98	0.25	6	
IOFI®	3	1.20	2.71	0.23	47	0.1
		1.20	2.21	0.23	47	
		0.40	0.36	0.29	6	

Estimated errors are of about ± 0.01 mm/s for the isomer shift, δ, the quadrupole splitting, Δ, and the line width, Γ, and of about $\pm 2\%$ for the relative area, A

with the lowest value of the goodness χ^2 factor. The derived hyperfine parameters for the best fits are listed in Table 1.

In order to investigate in more detail the hydrated character of the ferrous sulfates and ferrous fumarates, we also collected RT Raman spectra for all medicines. The ferrous sulphate color may vary between yellowish white to greenish-blue (or blue) (http://www.mindat.org/min-2633.html). The ferrous fumarate color is reddish-brown. The physical aspect of ferrous sulfate and ferrous fumarate with the excipients, can be seen in the optical micrograph of Fig. 4. The Raman spectra taken on the WZ and RZ areas of ferrous sulfate did not differ. On the other hand the spectra of RZ for IOFI®, Prenavit® and Mitrumvit™ exhibit vibrational bands that can be assigned to ferrous fumarates. The Raman spectra for the samples are shown in Figs. 5 and 6. According to Chio and co-workers [20, 21] it is possible to unambiguously distinguish the hydrated character of the ferrous sulfates by using Raman spectroscopy. The authors reported that the wave numbers associated to the symmetric stretching vibrational (ν_1) modes can be used as a fingerprint for identifying the hydrated number n of $FeSO_4 \cdot nH_2O$, in such a way that the ν_1 increases with lowering n. Chio et al. [20, 21] worked with synthetic isolated ferrous sulfates. However, our samples are much more complex because of the intimate mixture of the ferrous phases with the excipients, whose phase composition is unknown to us. In spite of this difficulty we have tried to assign most of the bands observed in the Raman spectra of the medicines. The results of this careful analysis and comparison with other reports are presented in Tables 2 and 3 for ferrous sulfates and ferrous fumarates containing medicines, respectively. Additionally, the band positions are also presented in Fig. 7. According to the data there are several values of n for IRON®, Laproff®, and Ferro-F-800®. For example the bands at 1015 cm^{-1}

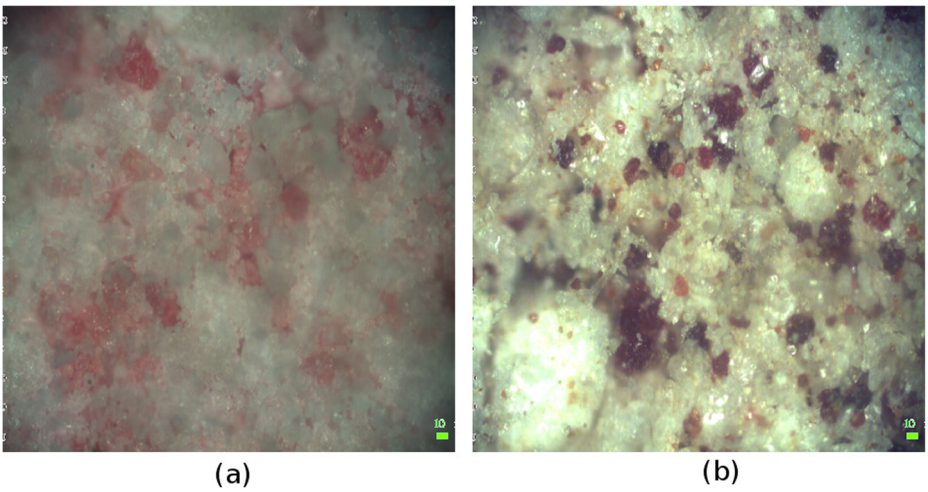

Fig. 4 Appearance of ferrous fumarate, ferrous sulfate and their excipients, in the medicines. **a** ferrous sulfate (Ferro-F-800®). **b** ferrous fumarate (IOFI®). Magnification × 10

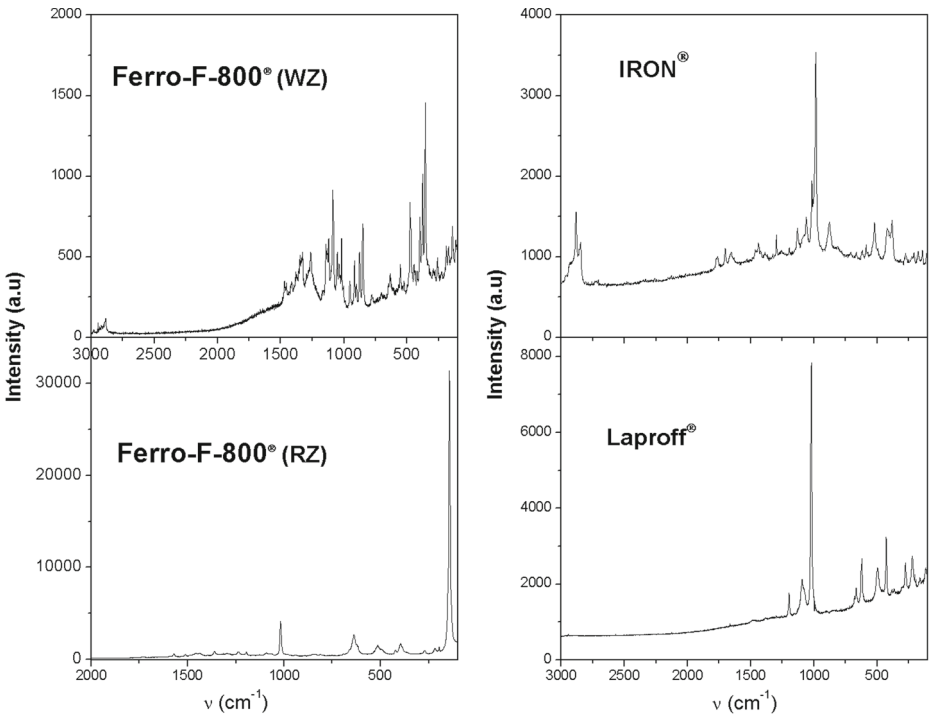

Fig. 5 Room temperature Raman spectra for the ferrous sulfate containing medicines

and 999 cm^{-1} can be ascribed to n equal to 1 and 4, respectively. The values of the vibrational bands found ferrous fumarate are reported by Gelder and coworkers [22], and Rane et al. [23], and Sobron and Alpers [24], whose data are shown in the last column of Table 3.

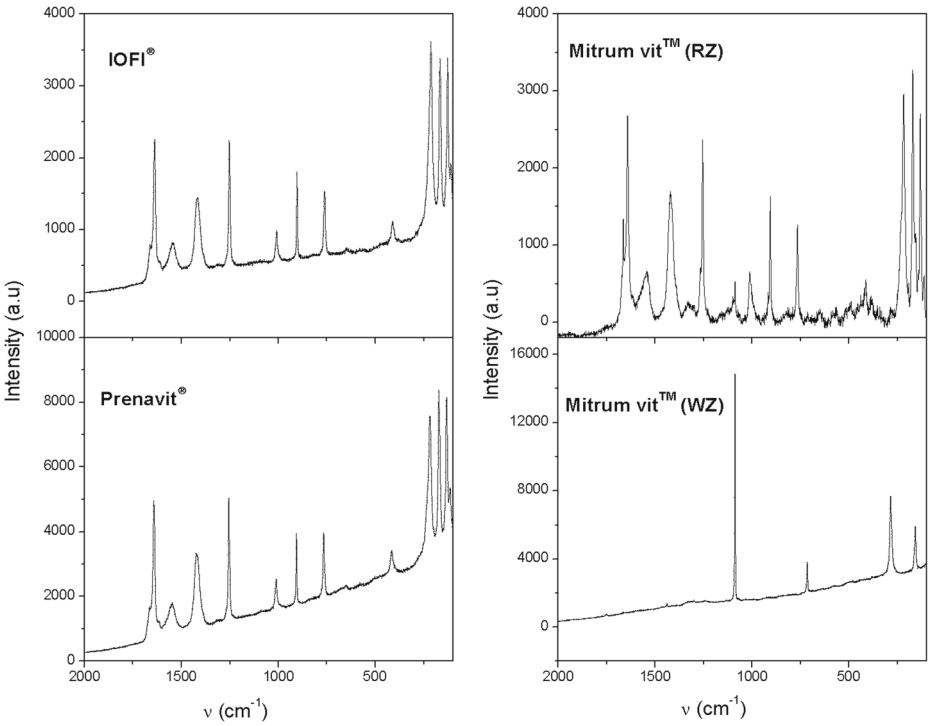

Fig. 6 Room temperature Raman spectra for for the ferrous fumarates containing medicines

Gelder et al. [22] reported 10 Raman bands of Merk brand fumarate; however, we must clarify that it is sodium salt, in which the cation is sodium instead iron. Moreover, Rane et al. [23] have reported IR bands found for ferrous fumarate-hydrazinate, i.e. hydrazine linked to the ferrous fumarate molecule.

4 Discussion

The absorption lines of the 77 K Mössbauer spectra are more broadened than the absorption lines of the RT spectra for all medicines. In fact, the RT Mössbuer spectra for these samples were fitted with a single doublet component, whereas the 77 K spectra were fitted with two doublets for the ferrous component. This is contrary to what has been usually reported for natural and synthetic isolated ferrous sulfates and ferrous fumarates. The Mössbauer spectra of melanterite, anhydrous ferrous sulfate, and ferrous fumarate collected at different temperatures have been fitted only with a single doublet [1–17]. We will show that the physical origin of these two doublets in the 77 K Mössbauer spectra of our medicines is a very complex issue that requires careful consideration of different possibilities.

Several hypothesis for explaining this phenomenon can be put forward, such as: (i) the divalent iron ions in the ferrous phases are occupying two different crystallographic sites

Table 2 Positions (in cm^{-1}) of the room temperature Raman bands for the ferrous sulfates bearing medicines

Ferro-F-800®	Laproff®	IRON®	Band Assignment
		3536	**ML**: H_2O & OH {3241.7, 3436.6, 3344.9 } [24].
		3471	ν_1 (H_2O), ν_3(H_2O) [20]. **ML**: {3371, 3436, 3506};
		3262	**Rz**: {3334, 3376, 3438, 3533, 3593};
		3161	**Sz**: $H_2O\{\nu_1, \nu_3\}$. {3246, 3333, 3410}
		2930	$2\nu_2(H_2O)$. [20] **ML**: 3227; **Rz**: 3272; **Sz**: 3137
2890		2884	
		2845	
		1767	
		1701	
		1657	$\nu_2(H_2O)$ [20]. **ML**: {1625, 1648} ; **Rz**: {1629, 1679}; **Sz**: {1630, 1735}
1471			**Sz**: ν_2H_2O. 1478
		1463	
1451			
		1435	
1415		1420	
1383		1388	
1347			
1326			
		1297	
1262			
	1198		
1145			
1130		1130	$\nu_3(SO_4)$ **ML**. 1102.8 [24], {1075, 1102,1138} [20];
1121			**Rz**. {1071, 1096, 1146, 1176};
	1094	1093	**Sz**. {1073, 1092, 1194};
1086		1083	
		1060	
1052			
1038			
1015	1020	1016	ν_1SO_4 **ML**. 978.0 [24]; 976 [20]. **Rz**. 990 [20]; **Sz**. 1018
999			
	979	986	
914			
899			
	788		
875		877	$\nu_{lib}(H_2O)$ [20] **ML**. 747; **Rz**. 784; **Sz**. 850
855			
778			
		708	
	666		

Table 2 (continued)

Ferro-F-800®	Laproff®	IRON®	Band assignment
634			$\underline{\nu_4(SO_4)}$ **ML**. { 558.8, 610.6, 633.3 } [24]; {565, 619} [20]
	622	617	**Rz**. {607, 622, 659} [20]; **Sz**. {615, 623, 661} [20];
		580	$\underline{\nu_{lib}(H_2O)}$ **Rz**. 586 [20]
553			
		520	
514			
	494		
477			
445			**ML**. $\underline{\nu_2(SO_4)}$ {380.6, 395.1, 410.5, 450.9 } [24]; **ML**. {446, 465} [20]
423	427	423	**Rz**. {456, 480} [20]; **Sz**. {423, 492} [20].
394			
376		378	
358	367		
289			$\underline{\nu_{trans}\ (Fe^{2+}, H_2O)}$
	275	274	**ML**. {206, 241, 264, 376} [20]
266			**Rz**. {211, 240, 286, 346, 382} [20]; **Sz**. { 158, 218, 271, 298} [20]
257			**ML**. Fe-OH. {177.0, 192.6, 213.3, 231.6, 249.0, 263.5} [24]
		223	
219	221		
		210	
197			*Lattice vibrations.* **ML**. {138, 185} [20];
172	161	173	**Rz**. {94, 106, 148, 168} [20];
144	140	143	**Sz**. 112 [20]
	114	108	

ν_{trans} (Fe^{2+}, H_2O): translational mode for the water molecule bound to iron. **ML**: melanterite, **Sz**: Szomolnokite,

Rz: Rozenite; ν_1: symmetric stretching; ν_2: symmetric bending; ν_3: anti-symmetric stretching;

ν_4, anti-symmetric bending; ν_{lib}: librational

underlined terms indicate the corresponding modes of vibration of molecules

and these sites are better resolved at low temperatures; (ii) there is a change in the electron population of the energy levels of ferrous ions by varying the temperature of the sample; (iii) there are dynamic effects that affect the line widths; (iv) there is a coupling between asymmetric vibrational modes and an electronic state having orbital degeneracy; (v) the ferrous compounds experience a phase transition; (vi) there is contribution coming from iron contamination probably in the excipients; (vii) there is an important variation in the recoilless f-factors of the spurious and possibly the hydrated phases, in such a way that at RT they have small f values and are not detected, but at low temperatures f increases and then become observable; and finally (viii) there is a presence of mixtures of several readily dehydrated ferrous phases in the medicines, in such a way these phases are undistinguishable at room temperature, but they become distinguishable at 77 K. Now, we will discuss one by one each of the mentioned hypothesis.

Table 3 Positions (in cm^{-1}) of the room temperature Raman bands for the ferrous fumarates bearing medicines

Mitrum vit™	IOFI®	Prenavit®	Band assignment
1665	1660	1663	{1529, 1640, ν(C=C) 1657 } [22]
1642	1638	1641	ν_{asy}(O-C-O) [23] 1650
1615	1613	1614	{1563, 1593} [22]
1545	1545	1549	
1422	1417	1411	$\nu(CO_2^-)$ 1430 [22]
1329			
1266			1293 [22]
1255	1252	1255	
1090 (WZ,RZ)*			1086 RSJYH
1012	1008	1012	
919			
906	904	906	913 [22]
	857		δ(O-C-O) [23] 800
766 (WZ)	762	765	768 [22]
717 (WZ)			
651 (WZ)	647	651	
575			
495			
416	410	415	
287 (WZ)*			285,2 RSJYH
219	218	218	
172	167	171	
158 (WZ,RZ)*			183.8 RSJYH
133	128	131	
114	110	113	

(WZ,RZ): data observed in both regions, white and red. (WZ): data on the white region

(*) data match with the database of Raman Spectrometer Jobin Yvon Horiba brand (RSJYH) for the iron carbonate $FeCO_3$

Regarding the first possible hypothesis, which is related with the presence of two distinct crystallographic sites that can be discerned at low temperatures, we will review the crystallographic structures of melanterite ($FeSO_4{\cdot}7H_2O$), anhydrous ferrous sulfate ($FeSO_4$), and ferrous fumarate ($C_4H_2FeO_4$), which are the active components of the medicines. Anderson et al. [25] have investigated the crystallographic and atomic structures of synthetic melanterite and proposed the existence of two different octahedral Fe^{2+} sites. On the other hand, $FeSO_4$ has an orthorhombic crystal structure with four $FeSO_4^{2-}$ per unit cell, and there is only one octahedral iron site. The structure consists of Fe^{2+} ions coordinated to six O^{2-} ions forming distorted FeO_6 octahedra. Each FeO_6 group has the same geometry and one axis running nearly parallel to the crystal *b* axis [14]. Now, the ferrous fumarate is the iron (II) salt of fumaric acid. The crystallographic structure of this compound is still an unsolved issue, but there are two models proposed. For Prabhakaran and Patel [26] the six oxygen atoms are bound to the iron atom belong to the fumaric acid salt molecule, whereas

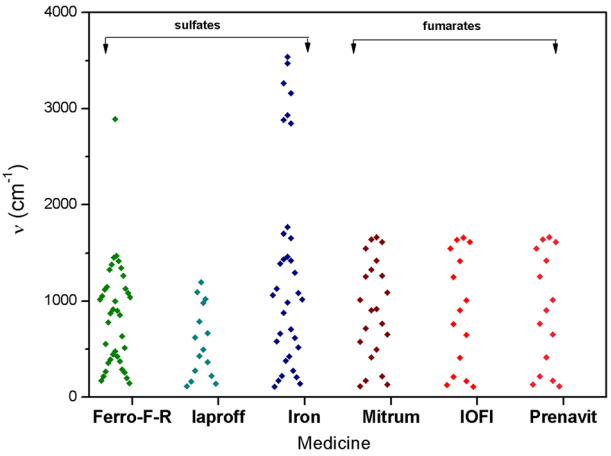

Fig. 7 Positions of the Raman peaks detected for the iron bearing medicines. For a given medicine, each point represent the position of a band

for Skuban et al. [27] two of the six oxygen atoms bonded to the iron atoms belong to water molecules, so that a hydrated ferrous sulfate results. In summary, there are two Fe crystallographic sites in $FeSO_4 \cdot 7H_2O$, but the 77 K spectrum for Ferro-F-800® medicine, which contains this iron phase, was fitted with only one doublet. And there is only one Fe^{2+} crystallographic in both $FeSO_4$ and ferrous fumarate, but the low temperature spectra of IRON®, Mitrumvit™, Prenavit® and IOFI® medicines were fitted with two doublets. Therefore, from the previous analysis, we could say that the hypothesis of the resolution of two distinct crystallographic sites at low temperatures cannot explain the observed line broadening at low temperatures, neither for the ferrous sulfates nor for the ferrous fumarates.

Next, let us discuss the second hypothesis related with a change in the electronic population by lowering the temperature. Ingalls [16] has calculated the energy separation, Δ_1 and Δ_2, between the ground electronic level and the next higher level for $FeSO_4 \cdot 7H_2O$ and $FeSO_4$ and found to be of $\Delta_1 = 480\ cm^{-1}$ and $\Delta_2 = 1300\ cm^{-1}$ for the former and of $\Delta_1 = 360\ cm^{-1}$ and $\Delta_2 = 1680\ cm^{-1}$, for the latter. Now, to the best of our knowledge, these values have not been calculated for the ferrous fumarates. However, according to Garg et al. [15], the values for other similar octahedral compounds, such as $FeC_2O_4 \cdot 2H_2O$ and $FeCl_2 \cdot 4H_2O$, can be used for comparison purposes. The corresponding values are of$\Delta_1 = 100\ cm^{-1}$ and $\Delta_2 = 960\ cm^{-1}$ for the former and of $\Delta_1 = 750\ cm^{-1}$ and $\Delta_2 = 2900\ cm^{-1}$, for the latter [16]. On the other hand, the thermal energy at RT is of the order of $200\ cm^{-1}$, and at 77 K is of course smaller ($\approx 52\ cm^{-1}$). Therefore, the thermal energy available at low temperature is not sufficient to overcome the energy barriers, Δ_1 and Δ_2. Therefore, this hypothesis cannot be used to explain the line broadening.

Regarding the third hypothesis which is related with dynamic effects, we can discuss two possible models: first, the thermal transitions times between the orbital states of the ferrous ions can be of the order of or larger than the quadrupole precession times, and second the hydration shell dynamics can affect the movement of the iron ions, and finally possible superparamagnetic effects. In relation to the first model, it has been long reported that the thermal transitions times between the orbital states of the ferrous ions (10^{-9}–10^{-11} s) are much shorter than the quadrupole precession times, which is of the order of 10^{-8} s [16]. Therefore, this first of the dynamic effects cannot be affecting the spectral line broadening

in the medicines. Now, regarding the second possible dynamic effect, it is worth mentioning that it has been demonstrated that in proteins the internal motion of the iron ions are directly affected by the dynamics of hydration shells [28, 29]. The question here is if this idea can also be used to understand the line broadening observed in the medicines. Of course the hydration shell is very different in proteins [28] in comparison to that in ferrous sulfates or ferrous fumarates in medicines. Whereas in proteins there can be of the order of 2000 water molecules per protein, which accounts for a hydrated shell thickness of about 0.5 nm [29], this number (of water molecules per chemical formula) is very much smaller in ferrous sulfates and ferrous fumatares, as it will be shown below. Therefore it is very hard to believe that the dynamics of water molecules could affect the iron motion in medicines and then could explain the observed line broadening.

Finally regarding the third dynamic effect, it is known that superparamagnetic behavior appears in sufficiently small ferromagnetic or ferrimagnetic particles. In small nanoparticles, the magnetization direction can randomly flip under the influence of temperature. Then, one compares the superparamagnetic relaxation time, τ, and the characteristic time of the measurement, which for Mössbauer spectrometry is related to the Larmor precession time of the nuclear magnetic moment, and is called τ_m [30–33]. If $\tau \ll \tau_m$, the particle behaves like a superparamagnet and a doublet (or a singlet) is observed in the Mössbauer spectrum. If $\tau \gg \tau_m$, the particle behaves like a magnetically ordered bulk material, and the spectrum consists of sextet with narrow lines. If τ is near to τ_m, the spectrum can consist of a combination of broad doublets and collapsed sextets with asymmetrically broadened lines. The temperature at which $\tau = \tau_m$ is called the blocking temperature. We have not found reports of Curie, Neel or even blocking temperatures near 77 K in either natural or synthetic ferrous fumarates or ferrous sulphates. In synthetic szomolnokite, Alboom et al. [34] reported a magnetic order-disorder transition at 29.6 ± 0.5 K. For the other ferrous samples, the spectra has been reported to consist of doublets down to even 5 K [12, 15–17]. Therefore, it is hard to believe that the broadening can be due to superparamagnetic effects.

The fourth hypothesis can also be discarded too. The dynamic and static Jahn-Teller effects have been reported in several compounds containing Fe^{2+} ions in octahedral environments [35]. However, these effects have not been used to explain the RT and the low temperature Mössbauer spectra of synthetic and natural ferrous sulfates and ferrous fumarates, which have been fitted by introducing only a single doublet [1–12, 15–17]. Moreover, the theoretical studies by Ingalls [16] and more recently by Pápai and Vankó [17], also reported the necessity of a single doublet to accurately describe the Mössbauer spectra at different temperatures for these compounds. Therefore the coupling between asymmetric vibrational modes and an electronic state having orbital degeneracy cannot explain the low temperature line broadening in the medicines.

There are no reports related with phase transitions neither in heptahydrate ferrous sulphates nor in ferrous fumarates, in fact as explained earlier, all theoretical and experimental Mössbauer studies only reported a single component in the Mössbauer spectra and a smooth temperature variation in their hyperfine parameters, i.e. there is no an abrupt change in these values. Therefore, the fifth hypothesis related with the possible existence of a phase transition in these ferrous compounds cannot be taken into account. Here it is worth mentioning that possible phase transitions, associated with water molecules ordering, were only observed in the low temperature Raman spectra for tetrahydrated ferrous sulphates, but this was not detected for monohydrated or for heptahydrated ferrous sulphate [20, 21].

Let us discuss the sixth hypothesis related with a possible contribution coming from iron contamination probably in the excipients. We found that both the RT and 77 K MS of

Ferro-F-800® exhibited a single doublet component, ruling out the presence of ferric iron contamination. On the contrary, the rest of medicines exhibit a weak ferric impurity phase whose relative spectral area does not change with varying the temperature change from RT to 77 K. On the other hand, from the previous results related with the determination of the iron content by using the relative recoilless f-factor for the Laproff® medicine, we ascribed the area of the RT ferrous doublet only to the active iron and not to the contamination. As a result, we found reasonable good agreement between the iron content determined by both Mössbauer spectrometry and chemical method. Therefore, these three experimental results rejected the possible contribution coming from iron contamination. In fact, it would be hardly difficult to believe that there is a transformation from Fe^{3+} to Fe^{2+} accompanied with a high increase in the spectral area just by lowering the temperature of these samples. Perhaps, here it is worth mentioning that there is a recent patent related with the preparation of medicines for the treatment of iron deficiency comprising ionic iron and haem iron [36]. This new medicine has in its composition two types of iron: ionic iron derived from synthetic salts and haem iron of natural origin. Therefore, one wonders if the medicines investigated in the present work have also similar properties. However, by checking the information available on the medicines, there is no information regarding the presence of two ironatoms coming from two different origins, i.e. the active parts are only ferrous sulfates or ferrous fumarates of unique origin.

Now, let us concentrate into the seventh hypothesis related with the possible strong difference between the RT and 77 K recoilless f-factors for the impurity iron phases. In this respect, we again can use the fact that the RT f-factor for Laproff® was used to determine the amount of iron in the medicament [9]. The value so obtained was in reasonable good agreement with the chemical method. This finding supports the idea that the second ferrous doublet for this medicament cannot be ascribed to iron impurities, but should come from the active part of the medicament itself, i.e. from the ferrous sulfate. The previously mentioned results clearly ruled out the seventh hypothesis.

Finally, we will discuss, the eight and last proposed hypothesis, which is related with the presence of mixtures of several readily dehydrated ferrous phases in the medicines, in such a way these phases are undistinguishable at room temperature, but they become distinguishable at 77 K. For the sake of clarity we will present the idea first for the ferrous sulfates and then for the ferrous fumarates containing medicines. At RT some loosely bound anions may vibrate (rotate or oscillate) at their lattice sites more easily, then reducing or disrupting the hydrogen bonding in some molecules [37]. However, at 77 K the anions are frozen or locked into a fixed position and form hydrogen bonds to the coordinated water and two doublets are observed in the spectra. Let discuss this fact in more detail. The strength of the hydrogen bonds can vary from very weak (1–2 kJ mol^{-1}) to extremely strong (161.5 kJ mol^{-1}) [38]. In the medicines, it is probable that the chemical method by which the ferrous phases were fabricated as well as the presence of the excipients can affect the bond strength in the samples. In fact, this strength depends on several factors such as temperature, pressure, bond angle, and environment. Now, on the other hand, the thermal energy per mole available at 300 K is of the order of 2.5 kJ mol^{-1}. Therefore we may assume that the water molecules are loosely bound to the structure of ferrous phases in the medicines. It can be thus expected that at RT the ferrous phases can be partly or completely dehydrated, but at 77 K these phases become distinguishable. Here it is worth mentioning that Anderson et al. [25] have reported that melanterite is easily dehydrated or hydrated during small changes in temperature and relative humidity. On the other hand, Matsuo et al. [39] have reported that partial dehydration of melanterite ($FeSO_4 \cdot 7H_2O$) to Szomolnokite ($FeSO_4 \cdot 4H_2O$) took place on exposure to dry flow of He/CH_4 gas inside the conversion-electron Mössbauer

chamber when the spectrum was collected at RT. On the contrary, this transformation was inhibited at 195 K. This result clearly means that $FeSO_4 \cdot 7H_2O$ can be readily dehydrated at RT but not at lower temperatures. All these findings support our interpretation. In fact, if we had assumed just the contrary, i.e. that the hydrated character of the ferrous phases do not change with temperature, but remains the same, then it is expected that the Mössbauer spectra should be fitted with same number of components at all temperatures. Therefore, we should expect the same number of components at RT and at 77 K. However, for the medicines investigated in the present work, this behavior was not observed. In this way, the doublets with the highest quadrupole splitting values can be associated with the iron atoms surrounded by oxygen atoms most of them belonging to water molecules, whereas the doublet with the lowest quadrupole splitting values can be ascribed to those iron atoms bonded to oxygen atoms few of them belonging to water molecules. In fact, Ingalls [23] reported that the theoretical Δ value for $FeSO_4 \cdot 7H_2O$ is greater than that for $FeSO_4$, which is in good agreement with the experimental work by Dyar et al. [11] for whom the higher quadrupole splitting values can be associated to the more hydrated ferrous sulfates. It is worth mentioning that the Raman spectroscopy analysis demonstrated the presence of not a single but several hydrated sulfates. Regarding the ferrous fumarates containing medicines, we will recall the two crystallographic models proposed for ferrous fumarate. In one model [26] the iron ions are coordinated to six oxygen atoms that belong to fumaric acid salt molecules, but in the other one the iron atoms are bonded to six oxygen atoms [27], two of them belong to water molecules and the other four to fumaric acid molecules. We suggest that the latter structural model could explain better our results. Now, we could use the same reasoning presented above. As mentioned, at RT the anions may vibrate up to reducing or disrupting some of the hydrogen bonds. However, at 77 K the anions are frozen or locked into a fixed position and form hydrogen bonds to the coordinated molecules. Therefore the two doublets observed at 77 K for the ferrous fumarate containing medicines can be ascribed to the presence of two types of iron sites, corresponding to different hydrated character. The more hydrated iron site is more symmetric than the less hydrated site; and therefore it is expected that the quadrupole splitting values be lower and higher, respectively.

In summary, the most reasonable interpretation for the observed line broadening and the origin of the two doublets observed at low temperatures is similar for both ferrous sulfates and for ferrous fumarates containing medicines, and could be ascribed to the presence of easily dehydrated and hydrated ferrous compounds in the medicines. An interesting implication of the present results could be related with the fact the fabrication process of the medicines affects the final physical properties exhibited of the active components. It is suggested that for the medicines a mixture of several n-hydrated ferrous phases were produced, in such a way that they were relatively easy to dehydrate, perhaps helped with aid of the excipients.

5 Conclusions

We have investigated the 77 K ^{57}Fe Mössbauer spectra of six commercially available iron-bearing medicines. In comparison to the RT spectra of all medicines, which were fitted with a single doublet, the 77 K spectra for medicines were reasonably fitted with two doublets. We discussed several different possible explanations for this observation, but finally it is suggested that the most probable origin is due to the presence of several easy dehydrated and hydrated ferrous compounds. These results suggest that the active parts of the medicines may consist of a mixture of several n-hydrated ferrous phases.

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