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IR-spectroscopy research into the structure of products of interaction between metronidazole and metal salts

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ABSTRACT

The studying of the drugs interaction is a pressing problem in practical medicine and pharmacy that requires additional investigation of the nature of its influence on the biological activity of pharmacological substances and on the organism of a patient. To study the nature of the interaction we have synthesized compounds that are products of interactions of metronidazole with metal salts, which are components of drugs. Investigation of structures of the obtained compounds was carried out by IR spectrometry using infrared spectrometer with Fourier transformation Tensor 27 «Bruker» (Germany). The changes in the infrared absorption spectra indicate changes in the structure of metronidazole in the cases of interaction of metal cations. It confirms obtaining of new compounds. During the research it was established that metronidazole behaves like a bidentate ligand. Specifically, for the samples of Metronidazole-Mg, Metronidazole-Al, Metronidazole-Fe^{2+} and Metronidazole-Bi it was established that the metronidazole is associated with metal cation via the nitrogen atom, which is located in the third position of the imidazole cycle, and through the oxygen atom of the hydroxy group. The results, obtained in the study of the Metronidazole-Ca and Metronidazole-Fe^{3+} samples, indicates a slightly different nature of the interaction that needs further study.

Key words: drug interaction, metronidazole, metal salts, IR-spectrometry.

INTRODUCTION

Drugs interaction not only with each other, but also with food, drinks and more has been an urgent problem for the last decades. After analyzing the literature and international database of medications, we are faced with the fact that the effects of interaction could have both negative and positive impact on the pharmacological activity of drugs. During the process of interaction different phenomena could be observed as the effect on the drugs absorption, biotransformation disorders, synergism, antagonism or summation of action, its potentiating, increase or decrease of the toxic effects of biologically active substances and their metabolites on the organism etc. [3, 8].

Metronidazole is one of the drugs, which for various reasons is often used together with antacids, medicines of iron and bismuth, food and drinks rich in multivalent cations.

Previously, using UV-spectrophotometry [2] we have confirmed the interaction of metronidazole with Ca^{2+}, Mg^{2+}, Al^{3+}, Fe^{2+}, Fe^{3+}, Bi^{3+} salts in solutions at various pH levels, and subsequently the products of their interaction were isolated. Further physical and physicochemical studies (UV-spectrophotometry, the melting point determination, the

elemental composition) [5] confirmed the preparation of compounds that differ from the properties of pure metronidazole.

As these methods do not allow us to determine the way of the interaction of metronidazole with these cations, the aim of our further study was to investigate structural bonds in the obtained compounds using IR-spectroscopy to determine the nature of interaction between metronidazole and metal cations.

MATERIALS AND METHODS

The objects of our study were complex compounds of metronidazole, as a ligand, with the metal cations: calcium, magnesium, aluminum, iron (II), iron (III), bismuth, which were synthesized by us earlier [5]. Substance of metronidazole (b.20130541, manufacturer: Hubei Hongyuan Pharmaceutical Co., Ltd, China) were parent compound of synthesized complexes and it were used as a reference sample.

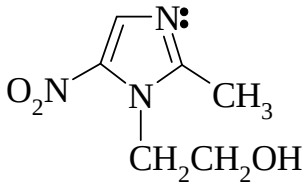
The research was carried out in the State scientific-research laboratory for medicinal substances quality control, National University of Pharmacy, Kharkiv, Ukraine.

The infrared spectrometer with Fourier transformation Tensor 27 «Bruker» (Germany) was used for the measurement of infrared spectra of the samples and reference compounds. The METTLER TOLEDO AB204-S (UK) analytical balance as well as the manual hydraulic press PGR-10 (Ukraine) was used during the experiment. Potassium bromide, previously dried to constant weight, was used for the manufacture of discs with the test and reference samples. The equipment and the reagents were used in the experiment meet the requirements of the State Pharmacopoeia of Ukraine, which is harmonized with the European Pharmacopoeia.

The discs of potassium bromide with the researching compounds were prepared with a 0.5% concentration of synthesized compounds. The disc of potassium bromide with metronidazole substance with the same concentration was used as a reference sample.

Measurements of IR-spectrums of the test and the reference samples were carried out in the frequency range from 4000 cm^{-1} up to 400 cm^{-1}. The absorption of the carrier was compensated by carrying out of research against disk with potassium bromide without the test substances addition.

RESULTS AND DISCUSSION



Metronidazole
2-(2-methyl-5-nitro-1*H*-imidazol-1-yl)ethanol

Considering the peculiarity of the chemical structure of metronidazole we can suggest with high probability that the most reactionary active centers are alcoholic hydroxyl, due to the possibility to separate of hydrogen proton, and the tertiary nitrogen atom, which is located in the third position of the imidazole cycle by having undivided pair of electrons in the outer orbital [1, 4, 6, 7].

Therefore, when studying IR-spectra of the analyzed compounds and the metronidazole we paid close attention to fluctuations of these functional groups. In the infrared spectrum of metronidazole (Fig. 1, Table 1) stretching vibrations of –OH-associated group were indicated by two absorption bands at 3220.85 cm^{-1} and 3100.79 cm^{-1}. Bonds –C=C– and –C=N– of imidazole cycle are characterized by fluctuations in the frequency range from 1700 cm^{-1} up to 1500 cm^{-1}, but in the spectrum of pure metronidazole they are pronounced not strongly.

Table 1. Characteristic absorption bands in the infrared spectra of metronidazole and its complexes

	MTZ	MTZ-Ca	MTZ-Mg	MTZ-Al	MTZ-Fe^{2+}	MTZ-Fe^{3+}	MTZ-Bi
ν (O-H bound)	3710.70	-	3385.30	3723.05	3382.72	3752.33	3749.48
ν(O-H associated)	3220.85 3100.79	3220.52 3100.88	3244.44	3218.30 3100.93	-	3220.69 3100.96	3446.70
ν(C=O)	2342.02	-	2342.99	2521.35	2337.47	-	2426.41
ν(C=C) **ν(C=N)**	-	-	1661.52	1635.76	1647.39	-	1635.12
ν(N=O)	1535.59 1368.90	1535.71 1368.91	1537.62 1370.84	1535.90 1369.70	1549.39 1374.59	1535.71 1368.93	1539.70 1384.25
ν(C=C)	1265.53	1265.55	1267.25	1265.69	-	1265.59	1268.98
ν (C-N)	1187.45	1187.51	1188.70	1187.68	1190.89	1187.57	1188.02
ν(C-O)	1074.51	1074.47	1087.96	1075.03	1090.08	1074.52	-
σ (C-H)	825.72	825.72	827.39	825.88	829.45	825.83	835.29
M-OH	-	-	626.59	606.78	624.73	-	524.61

MTZ – Metronidazole

The characteristic absorption bands at 1535.59 cm^{-1} and 1368.90 cm^{-1} characterize stretching vibrations of nitro-group, however, as is evidenced by the data in comparative Table 1, the changes in significant fluctuations do not occur, so we can conclude that it is not involved in the formation of the bonds with the metal cations. The characteristic absorption bands at 1265.53 cm^{-1} at 1187.45 cm^{-1}, which correspond to –C=C– and –C=N– bonds in the structure of metronidazole, based on the data in Table 1, are stored in the test samples, so they also not involved in the formation of new bonds.

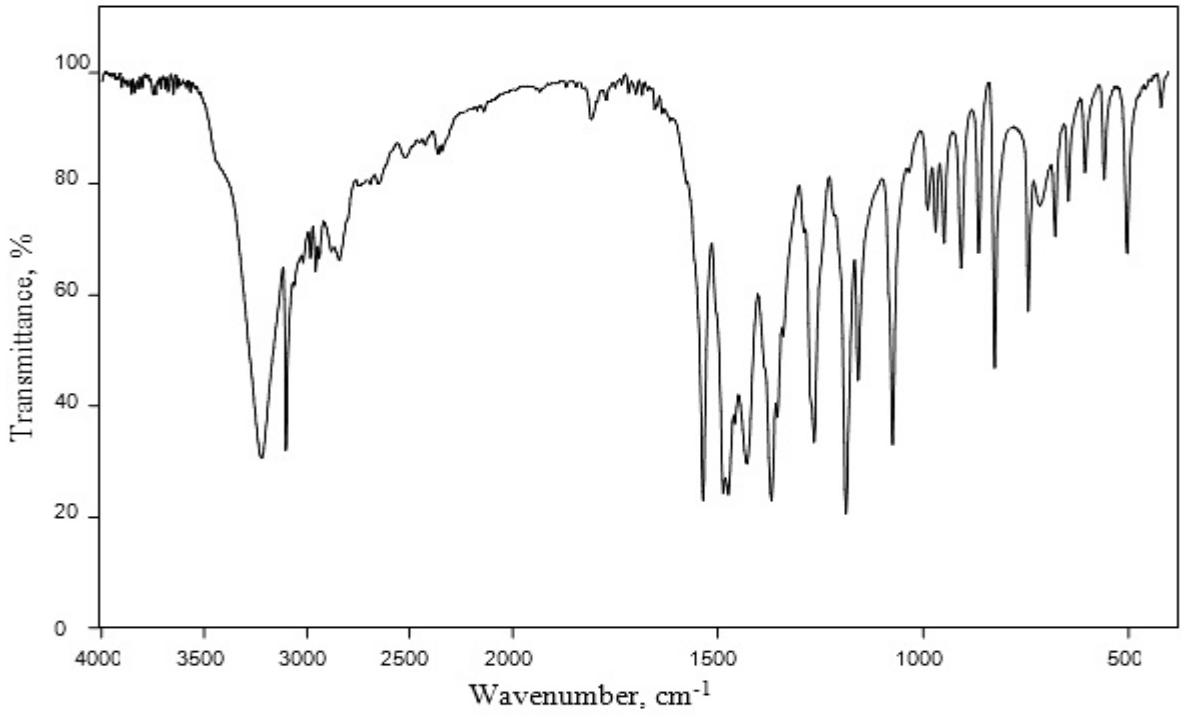


Fig. 1. IR-spectrum of metronidazole

The IR-spectra of comparison of interaction products with the spectrum of the pure compound are shown in Fig. 2-7. The comparative spectra of samples of metronidazole-Ca (MTZ-Ca) and metronidazole-Fe^{3+} (MTZ-Fe^{3+}) with metronidazole are shown in fig. 2-3. The IR-spectra of ligand and obtained compounds with the cations of calcium and iron (III) are similar, and they are compared with the original compound. However it should be noted that the disappearance of the absorption band, which is present in metronidazole at 2342.04 cm^{-1} and corresponds to a carbonyl group, is observed in both cases. Also, there is a smoothing of the absorption bands in areas at 4000-3500 cm^{-1} and 1700-1500 cm^{-1}, which indicate the presence of changes in the imidazole ring, but, unfortunately, these differences do not allow us to unambiguously determine the structure of formed compounds, therefore it requires a more detailed study of the structure with additional methods.

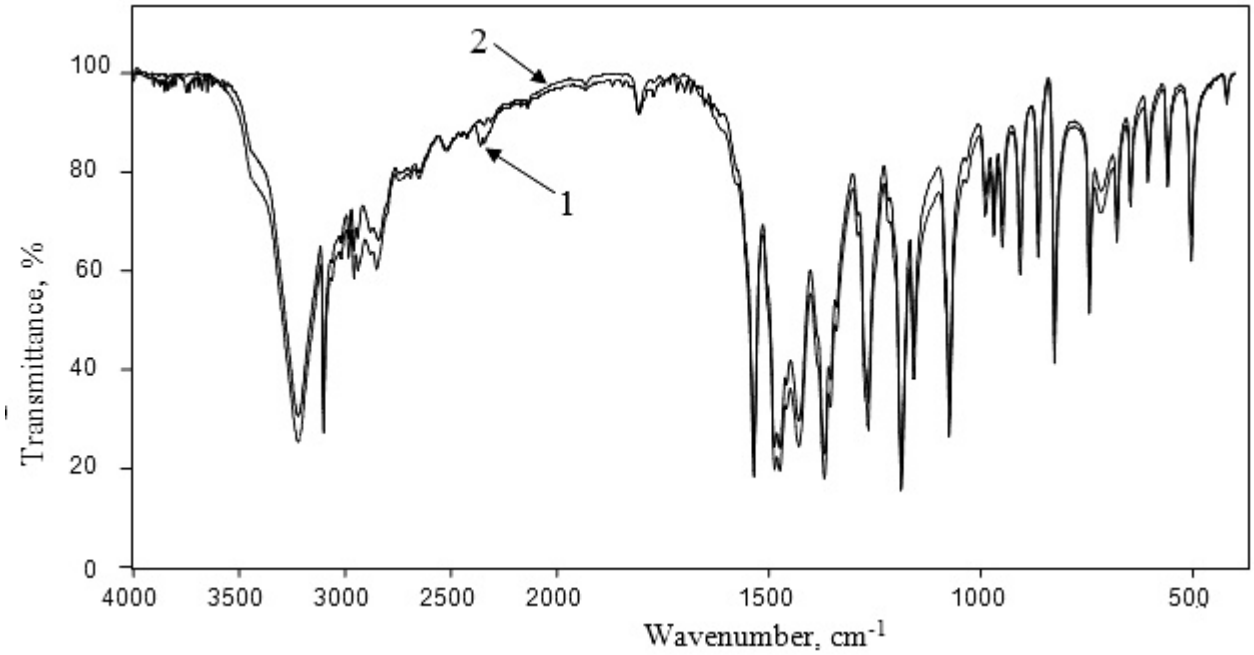


Fig. 2. IR-spectrum of metronidazole (1) and of its complex with Ca (2)

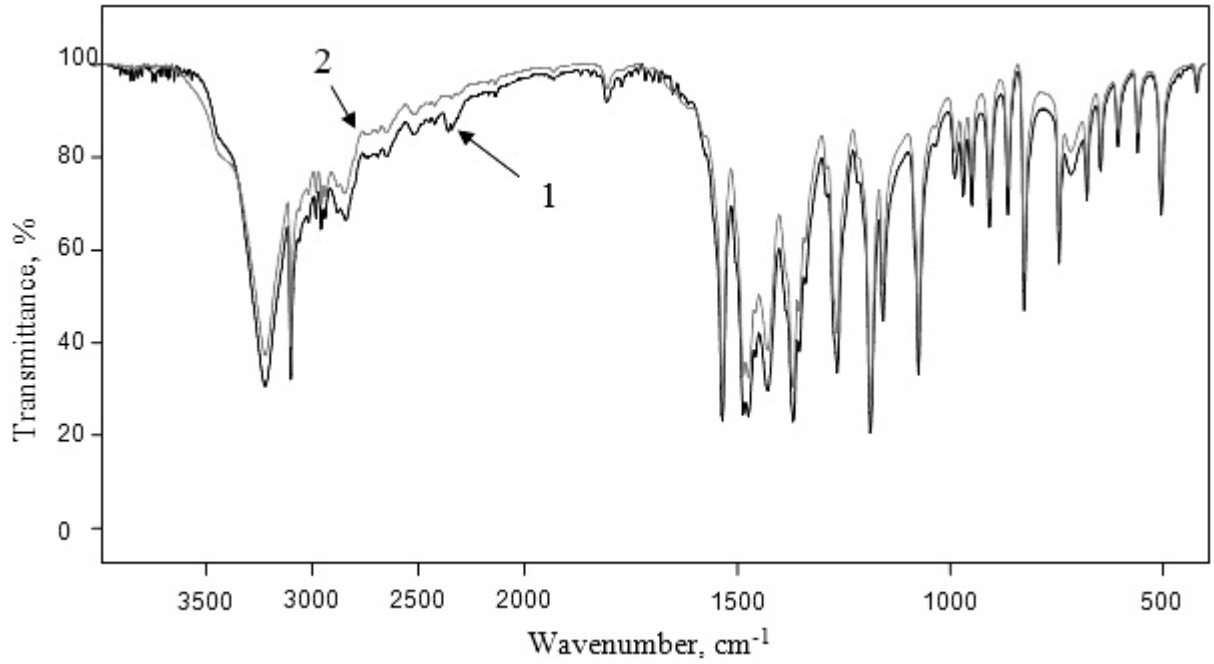


Fig.3. IR-spectrum of metronidazole (1) and of its complex with Fe^{3+} (2)

Analyzing the infrared spectra of metronidazole-Mg (MTZ-Mg) (Fig. 4), we see that in contrast to the original metronidazole, a shift of characteristic absorption band is observed at a frequency of 3385.30 cm^{-1}, which corresponds to a bound alcoholic –OH-group, so we can assume that coordination bond is formed by an alcoholic hydroxy group. A change of valence oscillations, which observed in the frequency range of 1700-1500 cm^{-1}, indicates the changes in the structure of the imidazole cycle, so it evidenes chelation also through the nitrogen atom in the third position and characterizes inclusion in the coordination sphere water molecules [4, 6, 7]. In the specified frequency range the absorption band is observed at 1661.52 cm^{-1}, what indicates the changes in bond –C=N–. The allotment of characteristic absorption band at 626.59 cm^{-1} is not marked in the metronidazole that is why, basing our own judgments on literature data [4, 6, 7], we can approximately attribute the specified band to the M-OH-bond of complexes.

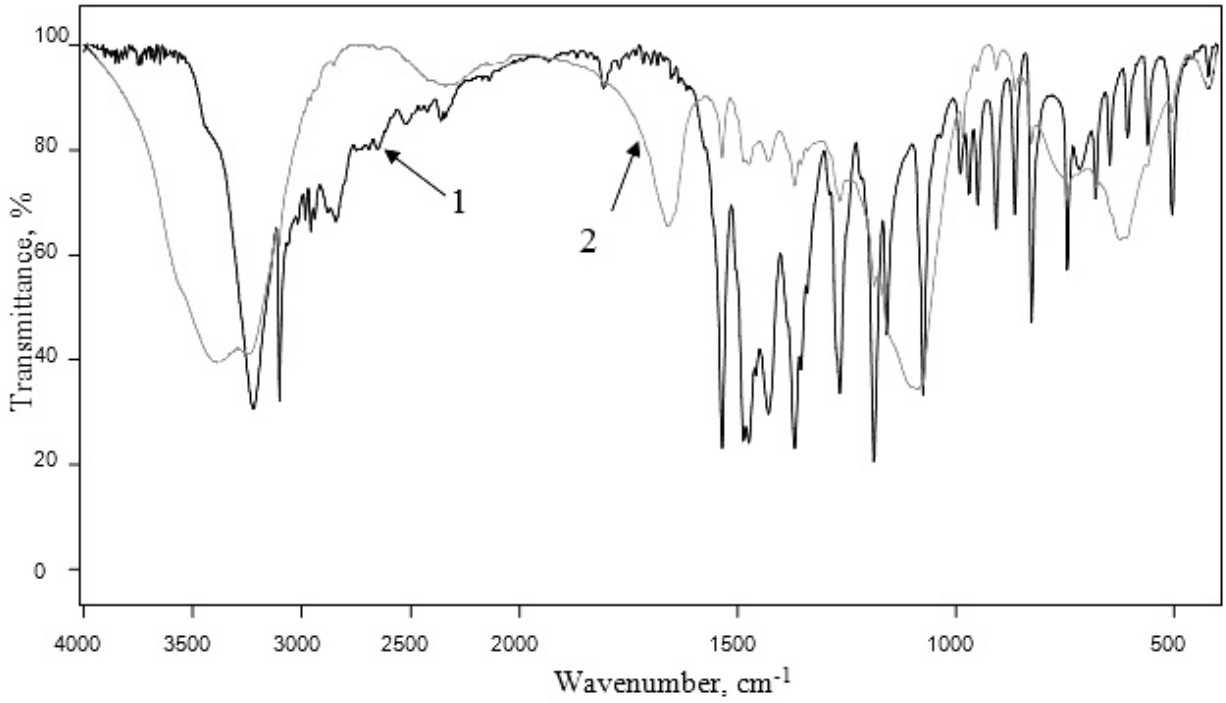


Fig.4. IR-spectrum of metronidazole (1) and of its complex with Mg (2)

The samples of metronidazole-Al (MTZ-Al), metronidazole-Fe^{2+} (MTZ-Fe^{2+}) and metronidazole-Bi (MTZ-Bi), as demonstrated in Table 1 and the comparative IR-spectra, which are shown in Fig. 5-7, have similar characteristic absorption bands with the sample of MTZ-Mg.

For the MTZ-Al sample, which is presented in Fig. 5, the shift of characteristic absorption bands at 3723.05 cm^{-1} indicates the involvement of –OH-groups in the process of complex formation. Moreover, the changes of characteristic absorption bands which are observed in the frequency range of 1700-1500 cm^{-1} confirms the complex formation through the N-3 atom of the imidazole cycle. The absorption band at 606.78 cm^{-1}, as in the sample of MTZ-Mg, was attributed by us to the M-OH-bond of metal complexes.

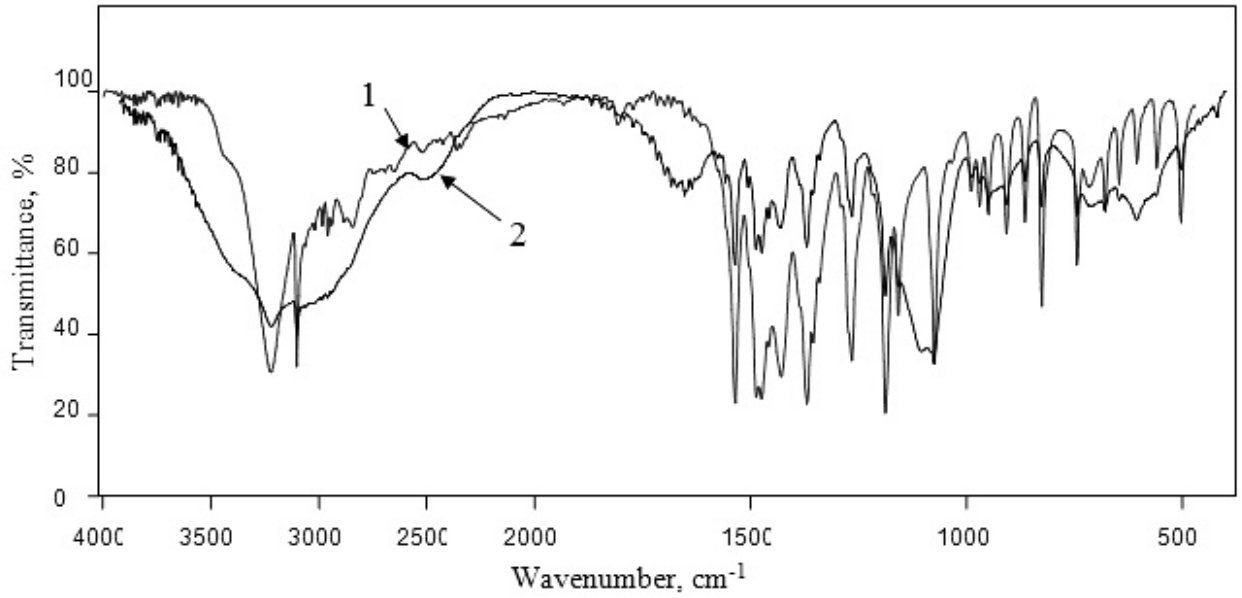


Fig.5. IR-spectrum of metronidazole (1) and of its complex with Al (2)

For the sample of MTZ-Fe^{2+} (Fig. 6) the involvement of alcoholic –OH-group in the complexation is confirmed by the absorption band at 3382.72 cm^{-1}. The oscillation changes in the absorption range of 1700-1500 cm^{-1} and the presence of absorption bands at 1647.39 cm^{-1} indicated the changes in the structure of the imidazole cycle of

metronidazole and the probability of complex formation through the N-3 atom. And the appearance of the absorption band at 624.73 cm^{-1} can be attributed to M-OH-bond between the metronidazole and the metal-complexing agent.

The MTZ-Bi (Fig. 7) also has the changes of characteristic absorption bands. The changing of absorption nature in the frequency range of 1700-1500 cm^{-1} and the appearance of absorption at 1635.12 cm^{-1} indicates the participation of the imidazole cycle of metronidazole in complexation through the nitrogen atom in N-3 location. The shift of the absorption band at 3749.48 cm^{-1} may indicate the involvement of alcoholic hydroxyl groups in complexation and the additional band at 524.61 cm^{-1} can be attributed to the bond between the hydroxyl group and metal cations. It should be mentioned that in the MTZ-Bi sample a significant distinction of the characteristic absorption band is observed at 1384.25 cm^{-1}. This absorption band characterizes NO_2-group, where its possible presence in the coordination sphere of the complex may be assumed.

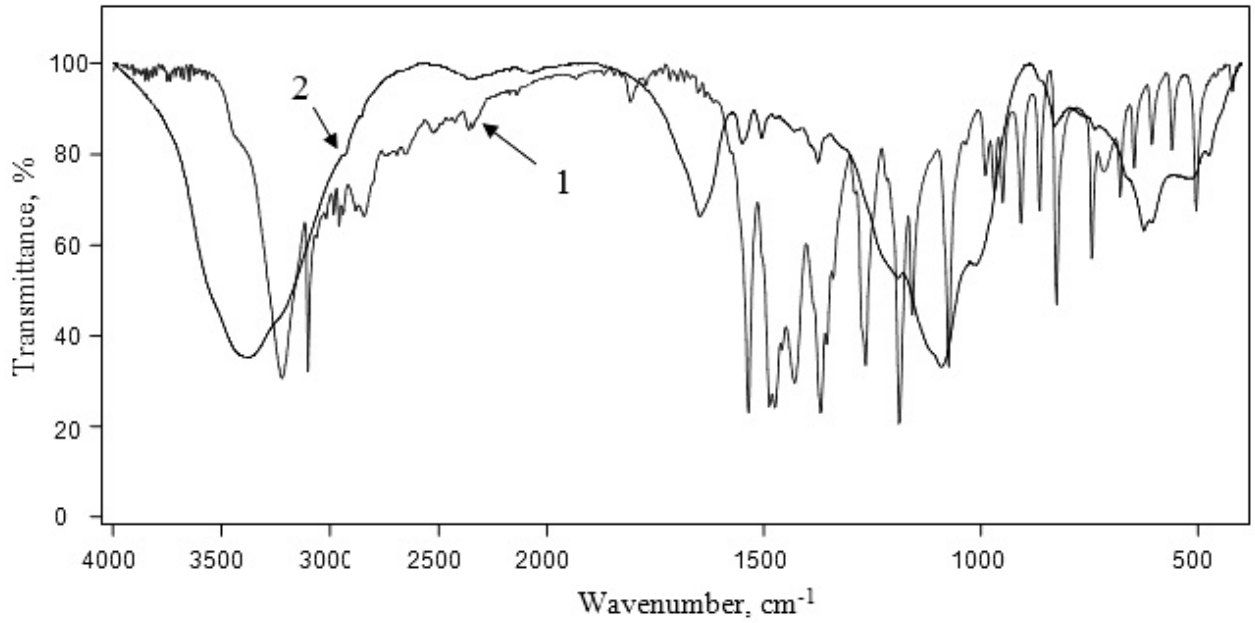


Fig.6. IR-spectrum of metronidazole (1) and of its complex with Fe^{2+} (2)

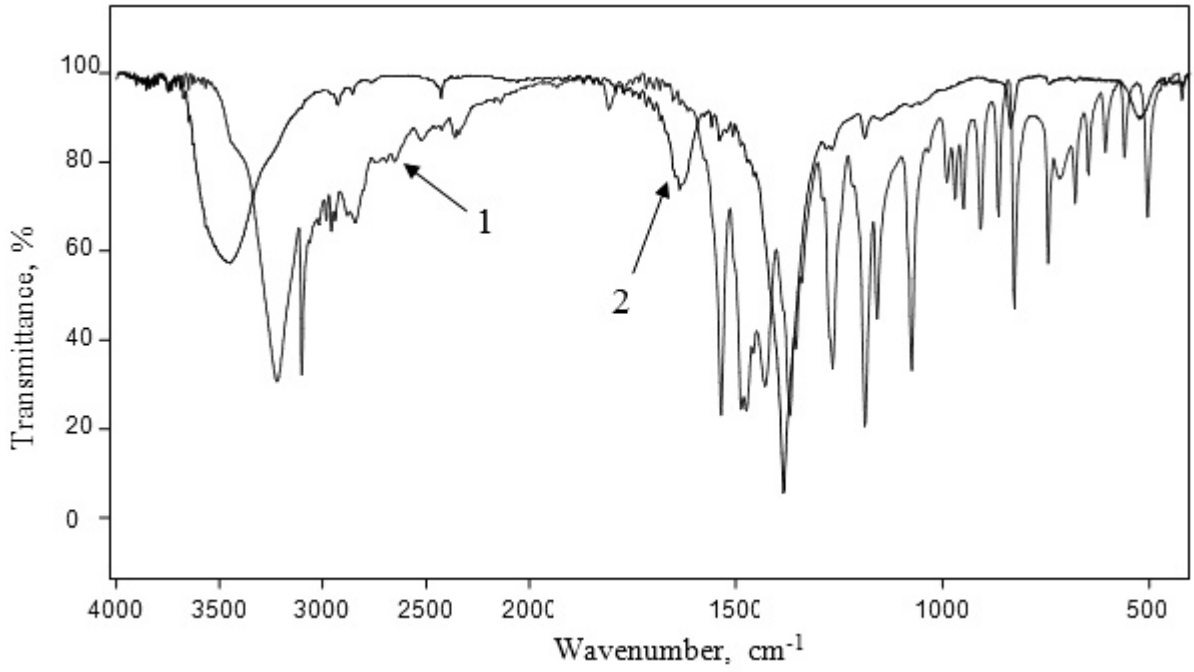


Fig. 7. IR-spectrum of metronidazole (1) and of its complex with Bi (2)

So the results of infrared spectral studies of synthesized compounds enable us to conclude about the formation of metal complexes for the MTZ-Mg, MTZ-Al, MTZ-Fe^{2+} and MTZ-Bi samples. Moreover, in these cases metronidazole behaves like a bidentate ligand, forming bonds via the hydroxyl group and N-3 nitrogen atom of the imidazole ring. The results, obtained in the study of the Metronidazole-Ca and Metronidazole-Fe^{3+} samples, indicate a slightly different nature of bonds between the metal cations and the metronidazole, and it requires further study of the structure.

CONCLUSION

1. The infrared spectrometric research of the metronidazole and the products of its interaction with metal salts confirms the creation of new compounds due to the formation of the bonds between metal cations and of the original substance via the tertiary nitrogen atom in the third position of the imidazole cycle and via the oxygen of the ethanolic group.
2. The comparative analysis of the MTZ-Ca and MTZ-Fe^{3+} samples with the pure metronidazole indicates that the test samples have a slightly different nature of the bonds of the ligand with the metals, in contrast to the MTZ-Mg, MTZ-Al, MTZ-Fe2+ and MTZ-Bi samples and it requires an additional study of the structure.
3. The changes of characteristic absorption bands are observed for the spectra of the MTZ-Mg, MTZ-Al and MTZ-Fe^{2+} samples compared to the parent compound. The results indicate that metronidazole behaves like a bidentate ligand with the indicated metals, and complexing bonds are observed via the N-3 nitrogen atom in the imidazole cycle and via the alcoholic OH-group.
4. The transmission spectra of metronidazole with Bi complexes, which have the absorption bands similar in its characteristic to the absorption bands in the MTZ-Mg, MTZ-Al and MTZ-Fe^{2+} samples, also confirms the process of chelation. However, in contrast to these samples, in the MTZ-Bi in the graph of infrared absorption spectrum, the greatest intensity is observed in the absorption band corresponding to NO_2-group, which may indicate its participation in the complex compound formation.

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