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INTERACTION OF METRONIDAZOLE WITH APPLE PECTIN

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Abstract

In this work, a study was carried out by the interaction of metronidazole with apple pectin by IR Fourier of Spectroscopy. It is shown that the presence of a complexation ability of pectin allows the immobilization of metronidazole due to weak hydrogen and coordination bonds. Owing that it was possible to obtain highly effective therapeutic systems, reduce antibiotic resistance to pathogens, which is confirmed by clinical studies.

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Introduction. Traditional routes of administration of the drug reduce its local effectiveness and cause side effects. Metronidazole is soluble in acidic pH of the stomach, so we suggested using its administration with a pectin solution to prolong its effect in the intestinal space, avoiding its loss in the stomach.

We conducted a clinical study in the period from 1988 to 2018, at the Dushanbe City Clinical Infectious Diseases Hospital, where the effectiveness of pectin in the complex treatment of acute intestinal infections with antibacterial agents – tetracycline, metronidazole and ciprofloxacin was demonstrated.

The study was conducted in the period from 2011 to 2020, at the City Clinical Infectious Diseases Hospital in Dushanbe. The main results of the conducted clinical trials were presented in the work [Muhidinov et al., 2024], which demonstrated the effectiveness of pectin in the complex treatment of acute intestinal infections with antibacterial agents – tetracycline, metronidazole and ciprofloxacin. A total of 53 patients with intestinal amoebiasis and 52 patients with acute dysentery aged 21-60 years participated in the studies. The use of pectin in the complex therapy of patients was carried out in accordance with the pharmacopoeia article of the Ministry of Health of the Republic of Tajikistan (VFS- 230021-14) and with their voluntary consent. It was shown that in patients diagnosed with intestinal amoebiasis, the plasma concentration of metronidazole reached its maximum value (42±2.3 mg/l) 2 hours after administration and assumed almost constant values in the range of 32-34±3.5 mg/l during the day, while in patients taking traditional forms of the drug, its the concentration decreased markedly (5.0±1.2 mg/l).

In this work, we conducted a study on the interaction of metronidazole with apple pectin, since the interaction between metronidazole and pectin, leading to a change in its activity, has not been studied.

There are 9 known drugs that interact with pectins: atorvastatin; cerivastatin; digitoxin; digoxin; fluvastatin; lovastatin; pravastatin; red yeast rice; simvastatin.

Pectin polysaccharides (PP) consist of homo- and rhamnogalacturonans containing, along with hydroxyl groups, carboxylic functional groups in the main chain of the polymer [Muhidinov et al., 2021]. The presence of these reactive functional groups is associated with the prospects of using PP-based complexes [Khairullina et al. 2017]. Pectin polysaccharides are able to absorb and firmly retain the active components of medicinal substances, this may serve as the basis for the use of pectin as the basis for dosage forms with prolonged action, since the introduction of pectin can enhance the therapeutic effect or reduce the side effects of drugs [Mukhidinov et al. 2019, Rakhmonov et al. 2015].

Obtained results and their analysis. To study the interaction of pectin with metronidazole, we used the IR-Fourier spectroscopy method on a Spectrum 65 FT-IR instrument (Perkin Elmer, Switzerland). The IR-Fourier spectra were analyzed using the KnownitAll and IRPal 2.0 application software package.

The IR-Fourier spectra of the standard drug metronidazole (Gedeon Richter standard) are shown in the figure.

The standard metronidazole sample showed characteristic absorption peaks at 3210 cm^{-1}, 3098 cm^{-1},1570 cm^{-1}, 1471 cm^{-1}, 1426 cm^{-1}, 1369 cm^{-1}, 1266 cm^{-1}, 1189 cm^{-1}, 907 cm^{-1}, 824 cm^{-1} and 744 cm^{-1}. A characteristic vibrational peak for valence vibrations of hydroxyl groups was observed at 3210 cm^{-1} and C-H bonds at 3098 cm^{-1}. The IR peaks at 1600 and 1523 cm^{-1} were attributed to the valence vibrations C=C and C=N, respectively. The asymmetric oscillation of N=O was attributed to the peak at 1471 cm^{-1}, the deformation vibrations of the CH_2 groups to the peak at 1426 cm^{-1}, and the C-C valence vibrations, respectively, to the peak at 1425-1426 cm^{-1}. The FT-IR data of the control metronidazole are well supported by literature data [Trivedi et al., 2015].

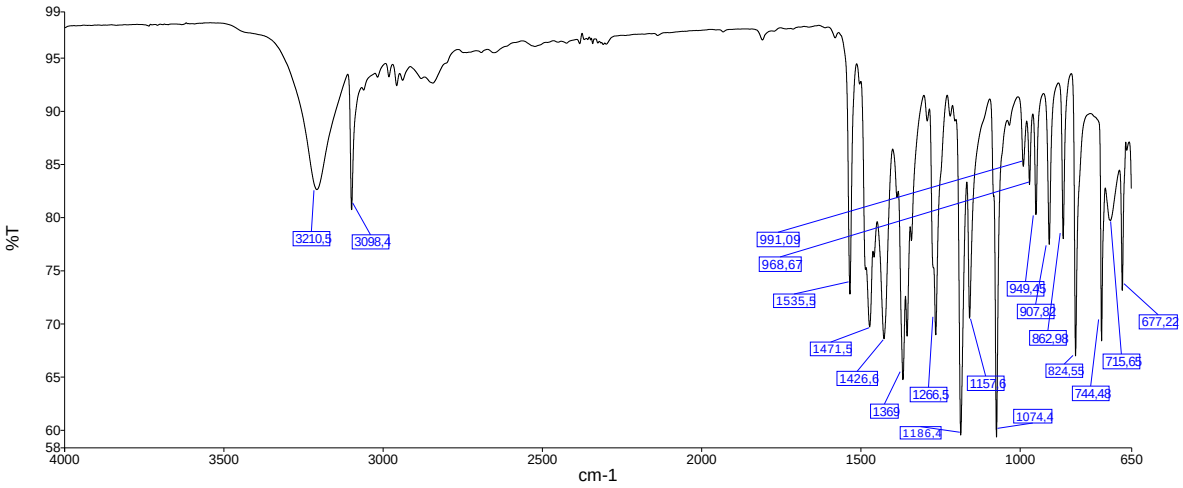


Figure 1. IR-Fourier spectra of the standard drug metronidazole (Gedeon Richter standard)

Characteristic peaks were found in the IR-Fourier spectra of apple pectin (PPYAM) at 3336 cm^{-1}, 2943 cm^{-1}, 1733 cm^{-1}, 1633 cm^{-1}, 1331 cm^{-1}, 1224 cm^{-1}, 1143 cm^{-1}, 1075 cm^{-1}, 831 cm^{-1} (the table).

An intense wide band with a maximum in the region of 3336 cm^{-1} corresponds to fluctuations in the hydroxyl groups of pectin. The observed absorption band with a maximum of 2943 cm^{-1} is characteristic of the valence oscillation of the C-H group. The IR spectrum of the sample shows an absorption band with a maximum of 1733 cm^{-1}, corresponding to valence vibrations of the ester ν (C=O) carboxyl groups of galacturonic residues in the PP molecule.

Samples	areas of IR absorption, cm^{-1}								
ПВ ЯВ(М) 120-10-2.0-д1	3336	1733	1633	1331	1224	1143	1075	1016	831
Apple pectin Metronidazole 10_5.0	3326	1737	1613	1360		1143	1075	1013	
Apple pectin Metronidazole 10_7.5	3330	1740	1607	1367		1146	1075	1013	831
Apple pectin Metronidazole 10_10	3323	1737	1610	1370		1143	1075	1013	831
Apple pectin Metronidazole 10_12	3310	1733	1610	1370		1146	1075	1010	831
Apple pectin Metronidazole 10_14	3323	1740	1607	1370		1143	1075	1013	831
Metronidazole	3210			1369	1266	1189			824

A study of the complexing properties of pectin in a mixture with various ratios with metronidazole has shown that pectin does not destroy the drug molecules. It forms stable complex

compounds with them due to hydrogen bonds (displacement in the range of 3336-3310 cm^{-1}) and weak intermolecular coordination bonds (displacement of absorption at 2934-2944 cm^{-1}), leading to deaggregation of PP macromolecules, as evidenced by the indicated displacement and amplification of peaks for pectin carboxyl groups at 1610 cm^{-1}.

Conclusions: Thus, the presence of the complexing ability of pectin suggests that when it interacts with metronidazole, they are immobilized (fixed) on the basis of a biopolymer due to weak hydrogen and coordination bonds. Due to this, it is possible to obtain highly effective therapeutic systems and reduce the resistance of antibiotics to infectious agents, which is confirmed by clinical studies [Kimatov R.S., 2024].

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