

Modelling and investigation of amoxicillin chemical interaction with mineral waters containing a significant amount of calcium and magnesium salts

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Abstract

In recent years, the interaction of drugs with the components of food and drinks has been actively researched to ensure rational therapy. It is particularly important for amoxicillin as an antibiotic group of drugs, considering the issue of resistance. A study of the interaction of amoxicillin with mineral waters, which in significant quantities may contain cations and anions and enter complexation reactions, has not been conducted before. For the study, various chemical and physicochemical methods were used. Also in vitro dissolution test with conditions of simultaneous administration of amoxicillin with mineral waters in a 0.1M HCl was modelled. Results showed that amoxicillin could form multiple complex compounds with magnesium cations in the 0.1 M HCl with different stoichiometry. The study showed that from several investigated mineral waters, presented on the Ukrainian market, the “Karpatska dzherelna” could interact with amoxicillin in the medium of a 0.1 M HCl.

Keywords

amoxicillin tablets, dissolution test, drug interaction, metal complexes

Introduction

Amoxicillin is a semi-synthetic antibiotic of a wide spectrum of activity, effective against many gram-positive and gram-negative microorganisms (Fig. 1) (White et al. 2004). According to the World Health Organization (WHO) Essential Medicines List (2019) amoxicillin is recommended as a first-choice medicine for treatment upper and lower respiratory tract diseases such as community-acquired pneumonia, complicated intra-abdominal infections, exacerbations of Chronic obstructive pulmonary disease (COPD), hospital-acquired pneumonia,

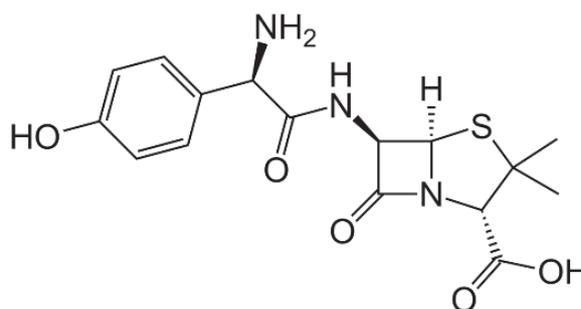


Figure 1. Structural formula of amoxicillin.

lower urinary tract infections, skin and soft tissue infections, Helicobacter associated gastritis and many other types of diseases caused by major pathogens. Regarding WHO Model List of Essential Medicines, amoxicillin is included in the Access group of antibiotics showing lower resistance potential than antibiotics in Watch and Reserve groups. Considering the relative safety of taking amoxicillin, it is often prescribed for outpatient treatment. In this case, compliance with the regimen is very important.

Therefore, it is necessary to provide patients with high-quality and relevant information about the rules of rational administration of the drug. This includes possible drug interactions with other drugs, foods, and drinks. To date, the package leaflet contains information that amoxicillin is independent of food intake, but recent studies have shown the opposite. For instance, the results of the study, conducted on healthy volunteers, showed that oral absorption of amoxicillin is reduced when administered immediately following a meal. In that very same study, the influence of water intake was determining (Welling et al. 1977). It also happens frequently that patients are simultaneously taking several drugs (Mozayani and Raymon 2012; Yeh et al. 2009). In this case, the possibility of drug interactions should be considered. Various studies of drug interactions have also been conducted. There are some dangerous drug-drug amoxicillin interactions, such as with a probenecid (Shanson et al. 1984), phenylbutazone, acetylsalicylic acid (Carbon 1990), warfarin (Zhang et al. 2011). Although, data regarding the latter are controversial. Recent results of the randomized controlled trial showed that amoxicillin + clavulanic acid did not influence the international normalized ratio (INR) in patients treated with stable warfarin therapy, suggesting that the previously observed INR increase in these patients may not be attributable to a drug-drug interaction (Zayed and Abdallah 2005).

As for the reception of a joint intake of amoxicillin with drinks and water, then recommendations for rational rules are not listed in the leaflet.

However, mineral waters contain cations of alkali-earth metals they can possibly interact with a molecule of amoxicillin and this problem is not well understood. Some sources of literature claim that this process can negatively affect the ability of an antibiotic to be absorbed, while others (Imran et al. 2006) note an increase in antimicrobial activity when the association with metal ions occurs. Existing studies (Cardiano et al. 2017; De Arruda et al. 2019; Zayed and Abdallah 2005) report about the potential formation of complexes between the carboxyl and β -lactamase groups, and cations such as Ca^{2+} , Cu^{2+} , Al^{3+} , Zn^{2+} , Fe^{3+} and others, which are part of other drugs, food products, mineral waters, and beverages. But since most of these amoxicillin metal complexes were obtained by directed organic synthesis, the main goal of our research was to study if this interaction is possible to happen spontaneously in the conditions of the human body. To achieve that aim, we performed a preliminary study that consisted of qualitative chemical reactions and UV spectrophotometry study. After that, we designed an in vitro model by

using the “Dissolution” test to find out if the presence of metal ions in mineral waters can have an impact on the bioavailability of amoxicillin.

Materials and methods

For a preliminary study of complexation, simple chemical methods can be used. Since the essence of the experiment was to find out the possible interaction of amoxicillin with metal salts in a medium close to the stomach one, for further researches as a solvent a 0.1 M solution of hydrochloric acid was used. During the experiment, quality reactions with salts of Ca^{2+} and Mg^{2+} in a medium of 0.1 M dilute hydrochloric acid were firstly performed to detect possible interaction with the test substance amoxicillin.

Chemical interactions between molecules of the compounds do not always appear by visible changes. Proceeding from this, absorption spectrophotometry in the ultraviolet region of the spectrum was chosen to detect possible interaction of amoxicillin with metal salts.

UV-spectrophotometric study of amoxicillin in various solvent media

Solutions for studying the character of the amoxicillin UV spectra in different solvent media were prepared: control sample – 0.001% solution of amoxicillin in 0.1 M HCl; test samples – 0.001% solution of amoxicillin with addition of Ca^{2+} and Mg^{2+} salts aliquot. Weights of salts were taken in the stoichiometric ratio of salt to antibiotic 1: 2. The analysis was carried out on spectrophotometer “Evolution 60S” (Thermo Scientific, USA) at a wavelength of 200–400 nm.

For analysis of possible complex formation, Job’s method of continuous variations was used (Job 1928). For that purpose initial solutions of amoxicillin and salts with equal molar ratios ($1 \cdot 10^{-3}$ M/l) were prepared and further diluted with 0.1 M HCl to get final ratios of the antibiotic and salt 1:9, 2:8, 3:7, 4:6, 5:5, 6:4, 7:3, 8:2, 9:1. The absorbance of obtained solutions was measured in maxima 203 nm, 230 nm and 272 nm.

To determine the possible interaction of amoxicillin with calcium and magnesium salts, an effect on the release of amoxicillin from tablets in a medium of 0.1 M hydrochloric acid solution with the addition of a mineral waters portion was conducted and “Dissolution” test was performed (United States Pharmacopeia 2017; State Pharmacopoeia of Ukraine 2014a, 2014b, 2015).

The subjects of the study were amoxicillin tablets AMOXIL 500 mg, No. 20, Corporation Arterium, Ukraine.

An analysis of the mineral water market was conducted, as well as an analysis of their composition. To study the interaction, the following trademarks of mineral water, containing the largest number of cations, were selected:

- “Borjomi”, manufacturer: IDS Borjomi, Georgia.
- “Karpatska dzherelna”, manufacturer: “The Carpathian mineral waters”, Ukraine.

- “Yessentuki №17”, manufacturer: “Essentuki Mineral Water Factory”, Russian Federation.
- “Truskavetska”, manufacturer: “Akva-EKO”, Ukraine.

Despite the benefits of mineral water, patients do not always take them with medicines. Therefore, for research, it was also taken tap urban water. Also, mineral waters from local Kharkiv sources often used by citizens were selected for research: “Kharkiv city spring water #1” and “Kharkiv city spring water #2”.

Defining the quantitative content of calcium and magnesium cations in waters

Since the content of mineral substances is regulated in a certain range of permissible concentrations, the quantitative content of calcium and magnesium cations in the selected samples of mineral waters was determined by complexometric titration: *Calcium cation*. 25 ml of pre-degassed mineral water are placed in a conical flask for titration, 5 ml of a solution of sodium hydroxide diluted, and 25 mg of the indicator mixture of murexide are added. Titrate with 0.01 M disodium edetate solution until the color changes from pink to violet (Lytvynenko YeYu 2017; Georgiyants VA et al. 2018).

The sum of cations of calcium and magnesium

25 ml of pre-degassed mineral water are placed in a conical flask, 5 ml of ammonia buffer solution is added, 25 mg of the eriochrome black T indicator mixture is added and titrated with 0.01 M disodium edetate solution until the color of the solution changes from violet to blue.

To calculate the content of magnesium cation, we use the difference in the volume of titrant titrated by the number of cations of metals, and the volume of titrant spent on titration of calcium cation.

Modeling of amoxicillin in vitro dissolution test with mineral waters

To simulate the interaction of amoxicillin with cations of metals, the “Dissolution” test was carried out in a medium of 0.1 M hydrochloric acid solution, which pH is closest to the pH of the stomach, in a volume of 700 ml with the addition of 100 ml of the test mineral water degassed on ultrasound bath.

For a control experiment as a dissolution medium, a 0.1 M solution of hydrochloric acid in a volume of 800 ml was used.

An analytical balance Mettler Toledo AB-204 / A and grade A volumetric flasks were used during the study. All reagents and test specimens meet the pharmacopoeia requirements. PharmaTest PT-DT70 (Germany) is used as test equipment for dissolution test, apparatus 2 (baskets). The rotation speed of the baskets was 150 rpm. Test time – 45 min. The samples were taken after 5, 10, 15, 30, 45

minutes from the beginning of the study. The number of repetitions for each of the studies was six.

Samples were taken at specified intervals of time, using a 10 ml pipette, from the middle region between the surface of the dissolving medium and the top of the rotating basket. The aliquot for analysis was filtered through a laboratory “blue ribbon” paper filter and not compensated for an equal volume of dissolution medium, but was taken into account in the final formula for calculating the amount of released amoxicillin.

After finishing the test, preparation of the test solutions was performed: 5 ml of the test solution filtrate was placed in a 20 ml volumetric flask and the volume of the solution was completed to the mark with a 0.1 M solution of hydrochloric acid and mixed.

Preparation of the comparison solution: 62 mg of amoxicillin was placed in a 100 ml volumetric flask, dissolved in a small amount of a 0.1 M solution of hydrochloric acid, and the volume of the solution was completed to the mark with the same solvent. After this, 5 ml of the resulting solution was placed in a 20 ml volumetric flask; the volume of the solution was brought to the mark with the same solvent and mixed.

The quantitative content of the active substance was determined by spectrophotometry in the ultraviolet region of the spectrum. Measurement of the test solution and the comparison solution absorbance was carried out on a spectrophotometer “Evolution 60S” at a wavelength of 250–300 nm. As a blank solution, a 0.1 M solution of hydrochloric acid was used.

A similarity factor was calculated to determine the similarity of the dissolution profiles (European Medicines Agency: Guideline on the investigation of bioequivalence 2010):

$$f_2 = 50 \cdot \log \left[\frac{100}{\sqrt{1 + \frac{1}{n} \sum_{i=1}^n (R_{(i)} - T_{(i)})^2}} \right]$$

where:

n – number of time points;

$R_{(i)}$ – the mean percent reference sample dissolved at time t after initiation of the study (sample without adding mineral water), %;

$T(t)$ – is the mean percent test sample dissolved at time t after initiation of the study (samples with mineral water), %.

Results and discussion

Visible changes (qualitative analysis)

When added Ca^{2+} , Mg^{2+} to the solution of amoxicillin in the medium of 0.1 M solution of HCl, visible changes were not observed.

UV-spectrophotometry method

Results of UV-spectrophotometry study of the simultaneous presence of amoxicillin and chosen metal salts in a

medium of 0.1 M HCl are shown in Figure 2. We observe an increase in the absorbance of amoxicillin with the addition of Ca^{2+} as well as Mg^{2+} salts in a medium of 0.1 M hydrochloric acid at a maximum wavelength 230 ± 1 , in comparison with the control sample.

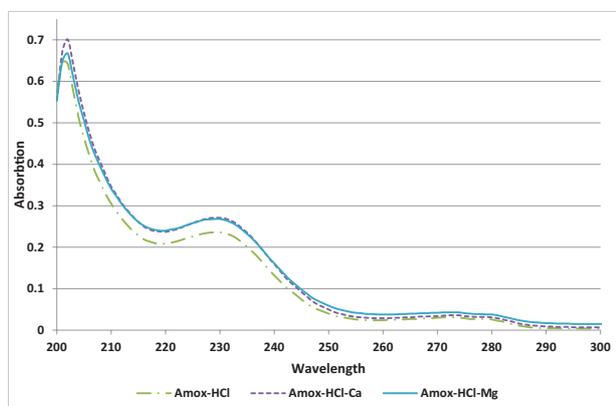


Figure 2. UV spectra of amoxicillin with the addition of Ca^{2+} , Mg^{2+} in a medium of 0.1 M hydrochloric acid.

Job's method

The UV-spectrum of amoxicillin in 0.1M hydrochloric acid has three maxima at wavelengths 203nm, 230 ± 1 nm and 272 ± 1 nm. Herewith, first maxima fluctuate while adding different salts from 202 to 208 nm. To control, we took into account changes in absorbance at all maxima. In the experiment with salts of calcium, proportional increase in the absorbance in all three maxima was observed, respectively as the concentration of the antibiotic increased. This could mean that no interaction occurs with calcium salts (Fig. 3).

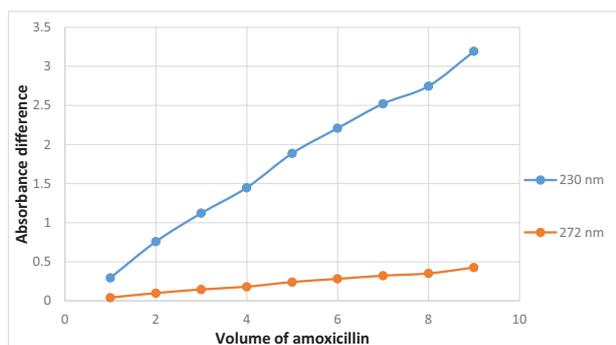


Figure 3. Job's plot for amoxicillin and Ca in 0.1 M HCl at wavelength 230 nm, 272 nm.

While adding magnesium salts maxima in absorbance at 273 nm was observed on Job's plot for the solution with ratio 5:5. Absorbance reached the peak at this point and then remain steady – next solutions with ratios 6:4 and subsequent show approximately the same absorbance as 5:5 solution (Figs 4, 5). This may possibly indicate the formation of several complex compounds.

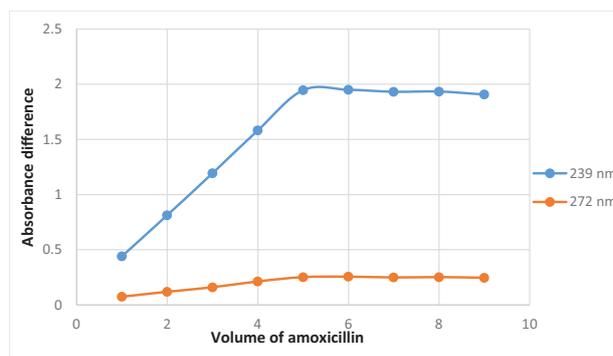


Figure 4. Job's plot for amoxicillin and Mg in 0.1 M HCl at wavelength 239 nm, 272 nm.

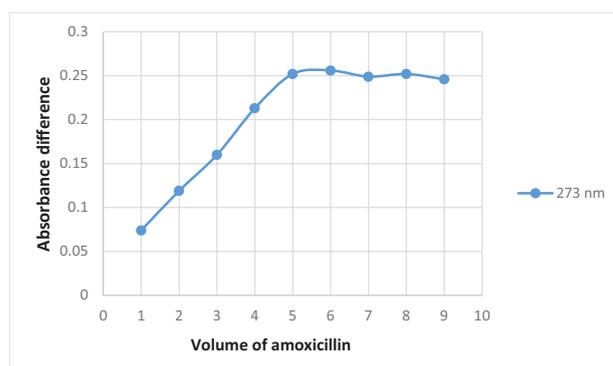


Figure 5. Job's plot for amoxicillin and Mg in 0.1 M HCl at 273 nm.

Determination of the content of calcium and magnesium cations in mineral waters

The results showed that the content of calcium cations in the investigated mineral waters “Borjomi”, “Truskavetska” was in the average range of the concentrations specified by the manufacturer, but concentration value for “Yessentuki №17” and “Karpatska dzherelna” dropped out of the interval (Table 1). Concentration of Ca^{2+} in mineral waters varied through a range from 43.65 mg/l (“Truskavetska”) to 48.41 mg/l (“Karpatska dzherelna”). The concentration of Mg^{2+} varied through a wider range and was minimum in “Karpatska dzherelna” (7.86 mg/l) and maximum in “Truskavetska” (28.26 mg/l).

For city spring waters the sum content of calcium was higher and fluctuated in a range of 47.09 mg/l (tap water) and 64.02 mg/l (Kharkiv city spring water #1). Thus the content of calcium in city spring water #1 is in 1.3 times more than in “Karpatska dzherelna” (Table 2). The concentration of Mg^{2+} remained steady near 11 mg/l for all researched city waters.

“Dissolution” test for amoxicillin tablets in simulated medium

The results of determining the dissolution of amoxicillin from tablets in a 0.1 M HCl medium with addition of mineral waters are given in Table 3 and Figure 6.

Table 1. Results of quantitative determination of calcium and magnesium cations content in mineral waters by complexometric titration.

№	Volume of a standard solution, ml			Quantitative content, x, mg					
	For titration of Ca ²⁺	For total titration of cations	Volumes difference (Volume for titration of Mg ²⁺)	Defined practically	Average	Specified by the manu-facturer, mg/l	Defined practically	Average	Specified by the manu-facturer, mg/l
"Karpatska dzherelna"									
1	6.1	7.5	1.4	48.41	48.41	50–200	6.74	7.86	<50
2	6.5	8.5	2	51.58			9.63		
3	6.2	7.7	1.5	49.20			7.22		
"Borjomi"									
1	5.6	10.4	4.8	44.44	44.44	20–150	23.10	24.55	<150
2	5.2	10.2	5	41.27			24.07		
3	5.1	10.6	5.5	40.47			26.47		
"Truskavetska"									
1	5.5	11.9	6.4	43.65	43.65	10–180	30.81	28.26	<100
2	5.6	12	6.4	44.44			31.12		
3	7	11.7	4.7	55.55			22.85		
"Yessentuki №17"									
1	6	11.7	5.7	47.62	47.09	50–200	27.44	26.79	<150
2	5.6	11.5	5.9	44.44			28.40		
3	6.2	11.3	5.1	49.20			24.55		

Table 2. Results of quantitative determination of calcium and magnesium cations content in local Kharkiv spring waters and tap water by complexometric titration.

№	Volume of a standard solution, ml			Quantitative content, x, mg			
	For titration of Ca ²⁺	For total titration of cations	Volumes difference (Volume for titration of Mg ²⁺)	Defined practically	Average	Defined practically	Average
Kharkiv city spring water #1							
1	8.9	10.4	1.5	70.63	64.02	7.22	11.23
2	7.2	10.7	3.5	57.14		16.85	
3	8.1	10.1	2	64.28		9.63	
Kharkiv city spring water #2							
1	7.7	9.4	1.7	61.11	56.61	8.18	10.91
2	6.7	9.8	3.1	53.17		14.92	
3	7	9	2	55.55		9.63	
City tap water							
1	6	8	2	47.62	47.09	9.63	11.71
2	6.1	8.9	2.8	48.41		13.48	
3	5.7	8.2	2.5	45.23		12.03	

Table 3. Results of amoxicillin release from tablets in 0.1M HCl with added portion of mineral waters.

Time Min	Medium															
	0.1 M HCl		0.1 M HCl with added "Borjomi"		0.1 M HCl with added "Essentuki 17"		0.1 M HCl with added "Truskavetska"		0.1 M HCl with added "Karpatska dzherelna"		0.1 M HCl with added "Kharkiv spring water #1"		0.1 M HCl with added "Kharkiv spring water#2"		0.1 M HCl with added tap water	
	Content, %	RSDx _r , %	Content, %	RSDx _r , %	Content, %	RSDx _r , %	Content, %	RSDx _r , %	Content, %	RSDx _r , %	Content, %	RSDx _r , %	Content, %	RSDx _r , %	Content, %	RSDx _r , %
0	0.00		0.00		0.00		0.00		0.00		0.00		0.00		0.00	
5	68.45	11.40	66.11	7.30	62.15	8.37	66.70	6.56	56.18	7.90	63.05	8.47	58.65	5.59	61.33	7.04
10	98.90	2.87	82.42	0.80	81.41	1.22	88.69	1.78	77.97	1.14	79.77	1.64	77.14	1.65	78.44	1.23
15	100.91	0.96	82.66	0.80	81.18	1.06	87.33	1.49	79.63	1.19	81.68	1.31	79.03	1.56	78.32	0.61
30	101.63	0.25	83.05	0.78	80.74	1.11	89.11	1.31	79.68	1.41	80.79	1.33	77.63	1.05	80.05	1.23
45	101.68	1.31	83.34	0.27	79.37	0.82	96.77	1.13	80.46	1.33	80.88	0.77	80.21	0.82	81.31	2.76

As it can be seen in Fig. 6 there is a significant increase in the concentration of amoxicillin in a medium of 0.1 M HCl solution with addition of mineral water "Truskavetska" in comparison with the control sample. Concentration also increased slightly in samples with the addition of Kharkiv city spring water #1, "Yessentuki-17" and "Borjomi". The increase in concentration can be explained by an increase in absorbance during the interaction of amoxicillin with metal salts.

For each control point, the relative standard deviation of the average result (RSD_x) was calculated, which should be less than 20% for the first control point, and less than 10% for the remaining points (European Medicines Agency (2010) Guideline on the investigation of bioequivalence). All values meet the requirements (Table 3).

Similarity factors calculated for study samples are shown in Table 4.

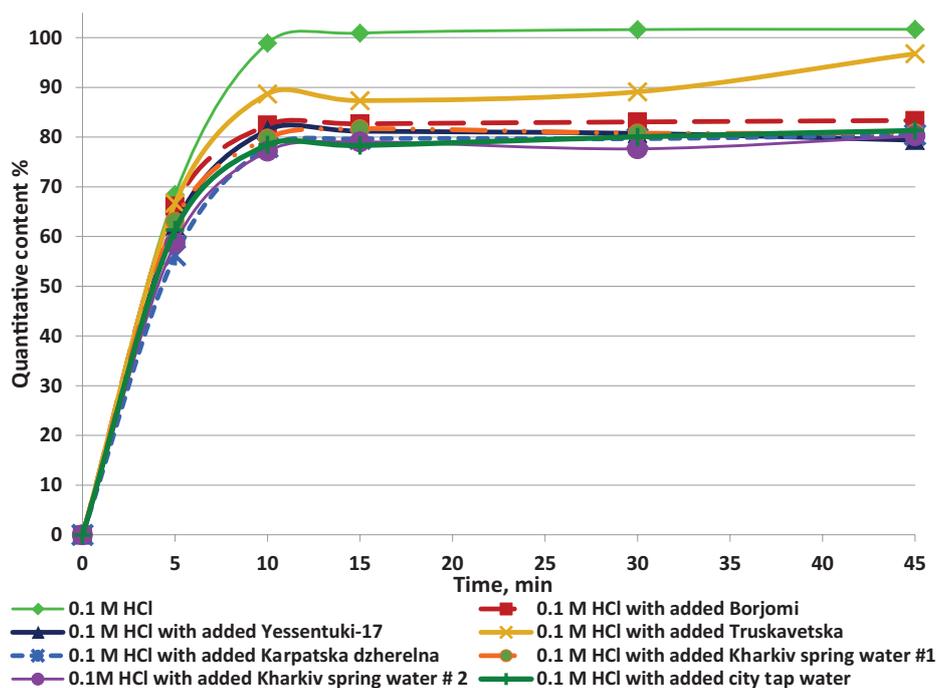


Figure 6. Amoxicillin tablets dissolution profile in a 0.1M HCl medium with added mineral waters.

Table 4. Similarity factors of amoxicillin tablets in a medium of 0.1 M HCl with the presence of mineral waters.

Sample	0.1 M HCl with added "Borjomi"	0.1 M HCl with added "Yessentuki-17"	0.1 M HCl with added "Truskavetska"	0.1 M HCl with added "Karpatska dzherelna"	0.1M HCl with added Kharkiv city spring water #1	0.1M HCl with added Kharkiv city spring water #2	0.1M HCl with added city tap water
f_2 , %	57.09	51.65	68.32	47.77	96.91	92.52	92.26

Two dissolution profiles are considered to be similar if the similarity factor (f_2) is in the range of 50% to 100%. This indicates that the bioavailabilities of the test sample and the comparison sample are considered to be equivalent.

The similarity factors determined show that the dissolution profiles of amoxicillin tablets in a medium of 0.1 M HCl with the addition of almost all, except one, mineral waters are similar. Similarity factor of "Karpatska dzherelna" mineral water is 47.77, which doesn't correspond to the acceptance criteria.

Conclusions

The UV-spectrophotometry study showed that the most likely formation of the amoxicillin complexes with magnesi-

um cations in the 0.1 M HCl medium. Using Job's method, we found that amoxicillin is most likely to form several complexes with magnesium with stoichiometry 5:5, 6:4, 3:7, 8:2 and 9:1. Conducted modelling of simultaneous administration of amoxicillin and mineral waters by in vitro dissolution test showed an interaction of researched antibiotic with mineral water "Karpatska dzherelna" in the medium of a 0.1 M HCl solution. As evidenced by the dissolution profile and low similarity factor in comparison with the control. Thus, the simultaneous administration of this mineral water and amoxicillin can affect the bioavailability of the drug. This issue requires further in-depth study using modern analysis methods. Afterwards, it may be considered to make changes in the recommendations of admission, and accordingly in the leaflet to improve the quality of pharmaceutical care and the effectiveness of therapy.

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