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Interaction studies between drugs and a purified natural clinoptilolite

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Abstract

Taking into account the biological properties of the purified natural clinoptilolite, NZ, some studies were conducted to evaluate the physicochemical interaction between this zeolite and two drugs, metronidazole and sulfamethoxazole, which cause considerable gastric side effects. Two modified forms of NZ were also considered. We have studied the drug solutions before and after the contact with the zeolitic materials in a wide range of pH values by UV spectroscopy. The structure of the two drugs remains unaltered after interaction with the zeolitic products. It is demonstrated that metronidazole adsorption by the different materials is small in acidic pH, and that the zeolitic materials studied do not adsorb sulfamethoxazole at the considered pH values. The overall study suggests the possibility of parallel administration of these products. These results are coherent with a complementary investigation by transmission IR spectroscopy about the possible incorporation of drug on NZ and its modified forms.
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Keywords: Natural zeolites; Clinoptilolite; Drugs interaction

1. Introduction

Natural zeolites are microporous aluminosilicates that have been extensively used in a wide range of industrial, agricultural and waste treatment applications [1]. It is well established that the multiple uses of these materials are based on their exceptional physicochemical properties [2]. Thus, obtaining new materials with great variety of physicochemical properties, resulting from modifications of the bare materials, has been a topic of considerable interest during the last years [3–5].

The use of the natural zeolites in animal health and nutrition, and also their long-term chemical and biological stability has been studied in the literature [1,6–10]. In particular, several works on biomedical applications of natural clinoptilolite have been published during the last five years [11–14]. For example, in recent papers Pavelic et al. reported a novel use of clinoptilolite as a potential adjuvant in anticancer treatment [13,14]. Considering that many biochemical processes are closely related to ion exchange, adsorption and catalysis, it is expected that natural zeolites could make a significant contribution to the pharmaceutical industry and medicine in the near future.

Purified natural clinoptilolite, NZ, from Tasajeras deposit (Cuba), has demonstrated good

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stability in its passage through the stomach, and the pharmacological and clinical studies have permitted to establish that this zeolite does not produce biological damage to humans [15,16]. Based on such properties, NZ and their modified forms have been evaluated as a gastric antacid, anti-diarrheic, antihyperglicemyc, hipocholesterolemic and as a matrix for the release of ions and organic molecules [4,15,17–20]. These products are considered as active principles, therefore, it is important from the pharmaceutical point of view, to determine if the co-administration with conventional drugs is possible. In this respect, recently Rivera et al. [21] studied the possible interactions between NZ and aspirin, and the results suggested that both products could be simultaneously administered.

Metronidazole is an antiparasitary drug very effective for the treatment of intestinal and intraabdominal infections [22]. Sulfamethoxazole is an antibiotic drug frequently employed in the treatment of respiratory infections and in the prophylaxis of immune-depressed patients [22]. However, the oral administration of these drugs may cause a group of side effects mainly associated with gastrointestinal disturbances [22]. Taking into account these facts, the aim of the present work is to carry out some studies on the interaction between the natural clinoptilolite (NZ) and these drugs, in order to evaluate the chemical behavior of both organic molecules in the presence of NZ, which is used itself as an antacid. The study was also conducted using two enriched forms of NZ, sodium and calcium. The experiments were carried out in aqueous medium simulating the pH and temperature conditions of the gastrointestinal tract. A further motivation of this study is that the physicochemical properties of NZ, in particular its bufferant character, could attenuate the gastrointestinal side effects associated to the above mentioned drugs in a parallel administration.

2. Experimental

2.1. Preparation of the zeolitic materials

The zeolitic mineral was ground, and then purified by washing with distilled water using a fluidized bed process. The resulting material was called NZ, which fulfils the requirements for the Cuban pharmaceutical industry use [16]. NZ is a powder of 37–90 μm particle size that consists of a mixture of about 70% clinoptilolite–heulandite, 5% mordenite, 15% anortite and 10% quartz.

The sodium- and calcium-enriched forms of NZ were obtained with 1 M NaCl and 1 M $CaCl_2$ solutions, respectively. The first step was a hydrothermal transformation that was carried out for 2 h at 100 °C, with constant stirring at atmospheric pressure and using a solid–liquid relation of 1:2. It was followed by centrifugation, and fresh solution was added to the solid with the same solid–liquid ratio. The system was then stirred for 18 h at room temperature. After this time, the last process was repeated for six extra hours. Finally, to remove the salt excess, the solid was washed with distilled water until the addition of silver nitrate to the supernatants gave a negative chloride test. The sodium- and calcium-enriched NZ were labeled Na-NZ and Ca-NZ, respectively.

Since NZ is of sedimentary origin, most of the grains have attached on the surface small amounts of non-zeolitic phases that still remain after the purification of the raw material. These phases might modify the interaction between the drugs and the zeolitic surface, so it should be taken into account. For this purpose, we submit NZ to several washing processes using bi-distilled water, under constant stirring and room-conditions during 5 days. A solid–liquid relation of 1:100 was used, and also various replacements of the washing water were carried out. The resulting powder was labeled as washed-NZ.

2.2. Interaction procedure

Drug solutions were prepared at a concentration of 0.5 mg/ml to ensure complete solubility during the studies. The solutions were analyzed by ultraviolet spectroscopy, at different pH values (1.2, 3.0, 5.5 and 8.0), in order to know the influence of this parameter on drugs properties and stability in aqueous medium. The pH values were selected considering the typical values along the gastrointestinal tract, from 1.2 in the stomach to 8.0 in the intestine.

For interaction studies, 400 mg of each zeolite were put in contact with 100 ml of drug solution. The experiments took place at 37 °C under agitation at 300 rpm with a magnetic stirrer. After temperature stabilization, the pH of the drug-zeolite system was adjusted with HCl or NaOH solutions to the pH values mentioned above. Subsequently, the system was equilibrated for 1 h and then centrifugated. The supernatants were analyzed by ultraviolet spectroscopy (UV), while the solids were studied by infrared spectroscopy (IR). The different parameters considered for the interaction procedure mentioned above—concentration of the drugs, solution volume, pH, and temperature—match those typically used in experiments at physiological conditions (see, for example [23], where the interaction of several drugs with a clay is evaluated using an artificial stomach model).

2.3. Measurement techniques

Atomic emission spectroscopy with inductively coupled plasma (ICP-AES) was used to determine the Al, Na, Ca, K, Mg and Fe contents of the zeolitic samples. A SPECTRO spectrophotometer, model Spectroflame was employed. For each analysis 0.5 g of the material were digested using $HClO_4$, HF and HCl. X-ray fluorescence spectrometry (XRF) was employed to determine the Si content of the zeolitic materials. A Carl Zeiss Jena VRA 30 X-ray sequential spectrometer was used. For the analysis, 1 g of each sample was palletized with 0.3 g of agglutinant.

Drug solutions were analyzed before and after the interaction with the zeolitic materials by ultraviolet spectroscopy (UV). An Optizen 2120UV spectrometer was used in the wavelength interval 200–400 nm. The infrared spectroscopy (IR) analysis of the solids after the contact with the drug solution was performed using an Ati-Mattson Genesis Series Fourier-transform IR spectrometer in the wavenumber interval 4000–400 cm^{-1}. The samples were prepared using the KBr pressed-disk technique, with a 5% inclusion of the material to be analyzed.

3. Results and discussion

Table 1 shows the oxide-form chemical compositions of NZ, washed-NZ, Na-NZ, and Ca-NZ as obtained by ICP-AES and XRF. No variations in the content of Si and Al resulting of the hydrothermal treatment, were observed in the different samples, as was expected.

If we compare NZ and washed-NZ samples, the main differences between them are in the content of calcium and sodium, while the rest of the elements remain almost constant. Taking into account the experimental conditions in the washing steps, the occurrence of ion exchange processes is not probable. Besides, it is known that in sedimentary deposits the presence of small amounts of carbonates, hydroxides and volcanic glass, which may either slowly dissolve or disperse is usual [2,24]. These phases appear as thin layers on the external surface of zeolitic materials, which cannot be detected by XRD, but their presence can be inferred by chemical methods as was demonstrated by Barrer et al. [24]. Therefore, it is expected that the decrease in the levels of Ca and Na in the washed-NZ sample, will be due to the elimination of these secondary phases during the washing process. According to the chemical analysis, the amount of secondary phases removed in washed-NZ is small, around 1–2%, and for this reason it was not necessary to make any mass corrections due to the washing process.

In the case of the Na-NZ sample, a sodium enrichment is observed at the expense of the content

Table 1
Oxide-form chemical composition of the purified natural clinoptilolite NZ and its modified forms in wt.% (with the balance as H_2O)

	SiO_2	Al_2O_3	CaO	Na_2O	K_2O	MgO	Fe_2O_3
NZ	66.50	11.30	4.00	1.95	1.12	0.65	1.80
Washed-NZ	66.31	11.26	3.40	1.36	1.13	0.63	1.75
Na-NZ	66.42	11.20	1.60	4.30	1.06	0.45	1.61
Ca-NZ	66.49	11.20	4.24	0.90	1.04	0.50	1.67

of calcium (Table 1). In the Ca-NZ sample the enrichment of calcium is small and not proportional to the decrease of sodium. Although it is well known that the calcium ion exchange in clinoptilolite is less favored than that of the monovalent cations [25], a larger degree of enrichment was expected. This suggests that two opposed processes control the resulting amount of calcium in the sample Ca-NZ: (1) the slight gain of calcium due to the ion exchange process, and (2) the loss of calcium due to the removal of secondary phases (similar to the one observed in washed-NZ). In general, the hydrothermal treatments performed on NZ permit to enrich the zeolite with the mentioned cations and also to eliminate secondary phases.

Fig. 1 shows the molecular structures of metronidazole (1a) and sulfamethoxazole (1b). We have included labels that correspond to the sites where the protonation and deprotonation take place, as will be discussed later. Both molecules contain fragments that are rather rigid, e.g. the imidazole ring in the metronidazole and the benzene ring in the sulfamethoxazole, which have approximate dimensions of: 5.04×4.71 and 5.88×4.63 Å, respectively. Regarding the clinoptilolite structure, this zeolite has two parallel channels, *a* and *b*, which are connected to a third one, *c*. The mouth of the channels has nominal dimensions of: *a* 7.5×3.1 Å, *b* 4.6×3.6 Å and *c* 4.7×2.8 Å [26]. However, their real dimensions are much smaller than those mentioned above, due to the presence of the extra-framework cations. Therefore, if we compare the dimensions of the molecules with those of the channels of the clinoptilolite, we can see that the molecules are too large to enter the channels. It is clear that the interactions to be evaluated only concern the outer surface of the zeolite, which also includes the mesoporosity.

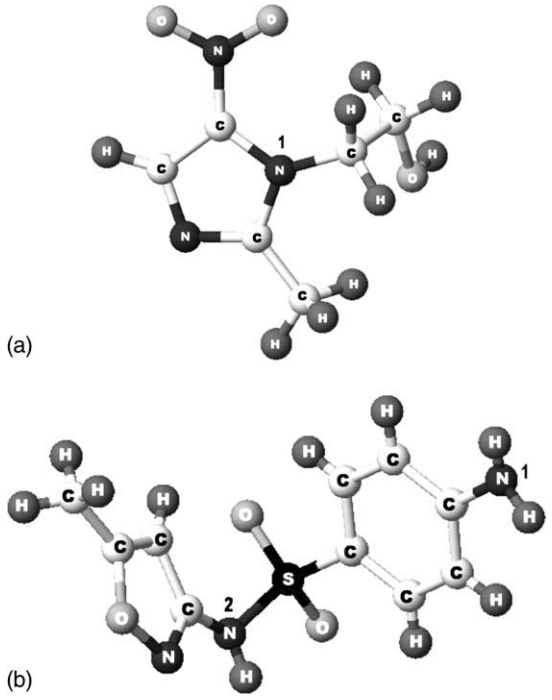

Fig. 1. Molecular structure of (a) metronidazole and (b) sulfamethoxazole. The atoms labeled by numbers correspond to the basic (1) and acid (2) sites of the molecules.

3.1. Zeolitic material-metronidazole systems

The UV absorbance spectra of 0.5 mg/ml metronidazole aqueous solutions at different pH values (1.2, 3.0, 5.5 and 8.0) before any interaction with the zeolitic materials are shown in Fig. 2. The maximum at 277 nm, which identifies metroni-

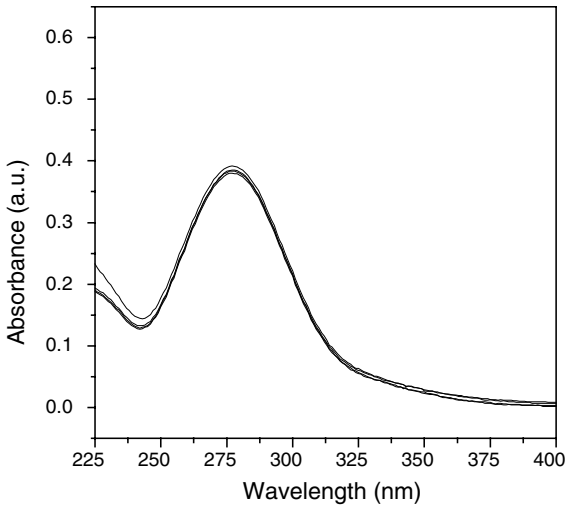

Fig. 2. UV absorbance spectra of metronidazole solutions at pH values of 1.2, 3.0, 5.5 and 8.0, before any interaction with the zeolitic materials.

dazole [27], shows a negligible dependence on pH. At pH 1.2 the metronidazole molecule is expected to be protonated due to the ionization equilibrium [28]. The protonation apparently does not affect the conjugation in the aromatic ring of the molecule, which is the main responsible for the absorption band in the UV spectrum.

Fig. 3 shows the UV absorbance spectra of metronidazole solutions before and after the interaction with NZ and washed-NZ for the different pH values studied. The drug put in contact with both zeolites does not show signs of degradation at any pH value, since the position of the maximum of absorbance remained unchanged after the interaction and no new bands that could denote the presence of degradation compounds appeared.

The differences between UV spectra of metronidazole solutions before and after the contact with NZ at the different pH values are very small, indicating a negligible variation of drug levels in solution after the interaction. We can conclude that the interaction between metronidazole and NZ is only of physical nature, and so weak that adsorption of the drug by NZ does not take place within the considered pH range.

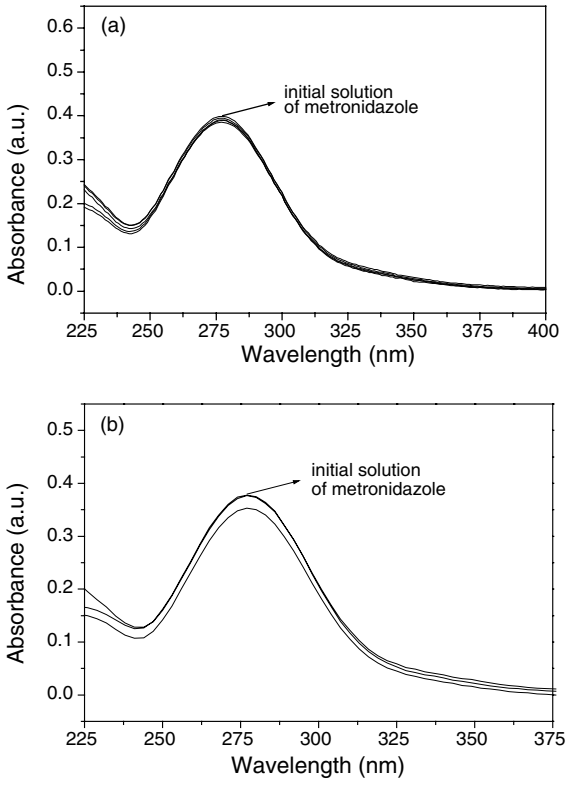

Fig. 3. UV absorbance spectra of metronidazole solutions before and after the contact with (a) NZ at pH 1.2, 3.0, 5.5 and 8.0, and (b) washed-NZ at pH 1.2 and 8.0 (from bottom to top).

In contrast with the case of NZ, the interaction with washed-NZ produces a measurable decrease in the metronidazole absorption maximum for pH 1.2. At pH 8, no relevant variation of the metronidazole content in solution was detected after the contact. This indicates that washed-NZ could adsorb metronidazole at the gastric level (pH 1.2) but not at the intestinal level (pH 8). The fact that washed-NZ only showed metronidazole incorporation at pH 1.2, could be due to the ionization equilibrium of the organic molecule, as will be discussed later. In general, this result has not a negative influence on the purpose of combined administration of this drug with the zeolite, since metronidazole is mostly absorbed in the intestine [22].

As mentioned above, no ion exchange processes take place from NZ to washed-NZ as a result of the washings. Therefore, although the elemental composition of both samples differs (see Table 1), the population of extra-framework cations should be essentially the same, which shows that the compensation cations are not related to the drug sorption by the samples. The differences in the sorption behavior of metronidazole by NZ and washed-NZ can be explained considering the phase compositional differences between them. The removal of some secondary phases, from NZ to washed-NZ, as thin layers attached on the zeolitic surface facilitates, to some extent, a more effective interaction between the drug and the zeolitic surface. Although the loss of secondary phases is small (≈1–2%), this represents an increase of around 7% in terms of metronidazole adsorption from NZ to washed-NZ. Considering that the drug sorption process takes place only at the outer surface of the crystals it is reasonable to expect such a behavior.

Fig. 4 shows the UV absorbance spectra of metronidazole solutions before and after the contact with the Na-NZ and Ca-NZ zeolites, at the

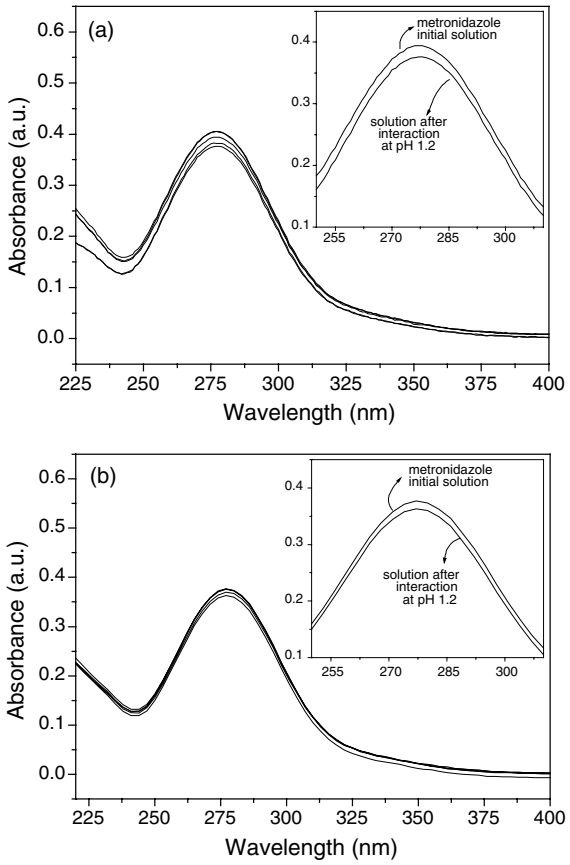

Fig. 4. UV absorbance spectra of metronidazole solutions before and after the interaction with (a) Na-NZ and (b) Ca-NZ at pH 1.2, 3.0, 5.5 and 8.0 (from bottom to top).

different pH values studied. The interaction between metronidazole and both Na-NZ and Ca-NZ does not produce any damage to the structure of the organic molecule. The larger incorporation of metronidazole by Na-NZ sample was observed at pH 1.2 (lower than in the case of washed-NZ). The results of the interaction with Ca-NZ are similar to Na-NZ, but a smaller decrease of metronidazole concentration in solution is observed. It is interesting to note that, as the pH of the metronidazole solution increases, the amount of drug adsorbed by both zeolitic materials diminishes. This fact is related to the metronidazole equilibrium as a function of the solution pH. At pHs below the metronidazole's pKa value (reported in the literature as 2.5 [28]) the molecule is protonated, while at higher pH values it is neutral. Therefore, the interaction between the metronidazole molecule and the oxygen atoms of the zeolite framework will be favored at pH smaller than the pKa value, when the molecule is positively charged. The protonated drug could also be exchanged with cations present in the pore mouths. In addition, we have found above that the cleaning of the NZ surface favors the physical adsorption of metronidazole. During the preparation of both, Na-NZ and Ca-NZ, a similar effect is expected to be one of the collateral results of the hydrothermal transformations performed on NZ. Taking into account these facts and the moderate sorption of metronidazole by the different samples, we consider that more evidence is needed for establishing a sorption mechanism.

No relevant variations in the transmittance IR spectra were observed in the zeolitic samples after the interaction with metronidazole solutions at the different pH values. The small amount of metronidazole incorporated on the zeolitic products makes its detection difficult. In addition, the most important bands of the metronidazole molecule appear at the same vibration frequencies as the zeolite bands. Considering these facts and the results of the metronidazole adsorption obtained by UV spectroscopy, we will show only the IR spectra of washed-NZ sample before and after the interaction at pH 1.2 (Fig. 5).

It is worth noting that the decrease in the metronidazole concentration in aqueous solution after the interaction with all zeolites does not exceed 8%, approximately. Furthermore, we proved that the molecule does not suffer structural modifications when it is treated with the zeolitic materials. This study constitutes an important result from the pharmaceutical point of view, since it suggests that the zeolitic products and metronidazole can be simultaneously administrated to a patient without any loss of the individual pharmaceutical effects of each substance during their transit through the gastrointestinal tract. Note that the overall results are in agreement with those reported by Lam et al. [29] regarding metronidazole–clinoptilolite interaction studies through quantum mechanical calculations.

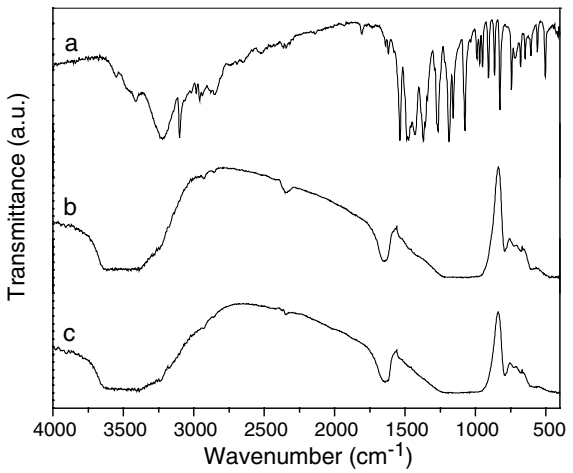

Fig. 5. IR transmittance spectra of (a) metronidazole, (b) washed-NZ, and (c) washed-NZ after the interaction with metronidazole solution at pH 1.2.

3.2. Zeolitic material-sulfamethoxazole systems

The UV absorbance spectra of sulfamethoxazole solutions (0.5 mg/ml) at different pH values (1.2, 3.0, 5.5 and 8.0), before any interaction with the zeolitic materials, are shown in Fig. 6. The absorbance maximum that identifies sulfamethoxazole shows a pronounced dependence on the pH. In an acid medium the maximum appears at 268 nm, while in a basic medium the band appears at 260 nm. Furthermore, the strong dependence between the intensity and the pH values is evident from the figure. Note that at pH below the pKa value for sulfamethoxazole (reported as 5.6 [28]) the molecule is stable in its protonated form, particularly at the free $-NH_2$ group (see Fig. 1). On the other hand, the –NH– group shows acidic properties and is able to donate the proton at high pH values. Both facts are likely to strongly affect the conjugated system of the molecule and so the UV spectrum. For this reason, we will only consider for the interaction studies the extreme pH values (1.2 and 8.0), where the sulfamethoxazole is present in solution only in its cationic and anionic form, respectively.

Fig. 7 shows the UV absorbance spectra of sulfamethoxazole solutions after the contact with all zeolitic materials at pH 1.2 and 8.0, compared to those of the drug solution before any contact with the zeolites at the same pH. The analysis of the spectra indicates that the contact of the drug with the zeolitic samples does not produce any damage on the structure of the molecule at the pH values studied. For both pH values the concentration of sulfamethoxazole practically does not diminish after the interaction with the different zeolitic materials, which indicates that this drug is

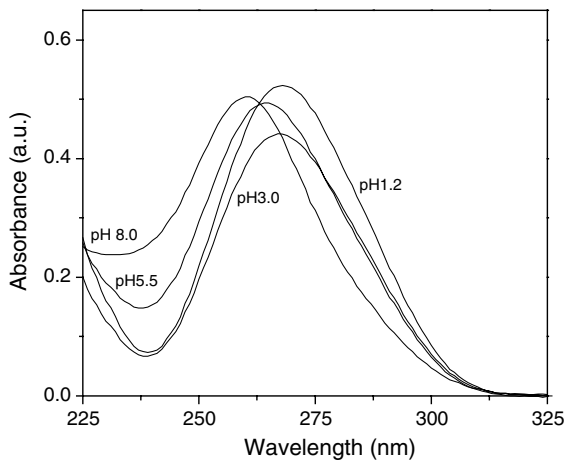

Fig. 6. UV absorbance spectra of sulfamethoxazole solutions before any interaction with the zeolitic materials at pH 1.2, 3.0, 5.5 and 8.0.

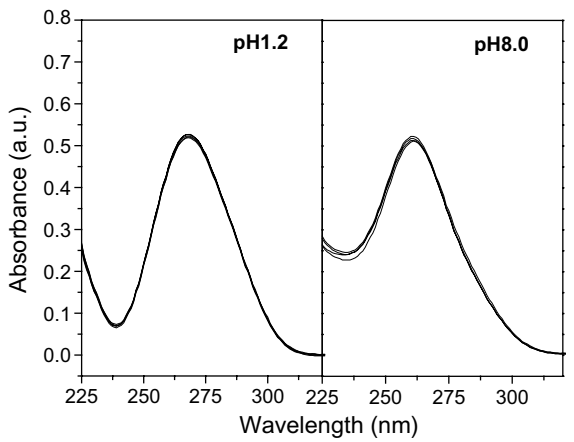

Fig. 7. UV absorbance spectra of sulfamethoxazole solutions before and after the interaction with all zeolitic materials at pH 1.2 and 8.0.

not adsorbed at all for any material. If we consider the hydrophilic character of NZ and their modified forms (Si/Al ratio ≈ 5, 3 [19]), and the non-polar character of sulfamethoxazole molecule, the weak affinity between both products in an aqueous medium, (where these zeolites show an absolute preference for water), could be explained. Since these materials do not adsorb sulfamethoxazole at any pH values studied under our experimental conditions, it is expected that their simultaneous administration does not affect the pharmaceutical effect of each product.

4. Conclusions

We have carried out interaction studies between a natural clinoptilolite and some of its modified forms with two drugs (metronidazole and sulfamethoxazole) within a wide range of pH values of pharmaceutical interest by using UV and IR spectroscopy. It was demonstrated that the organic molecules do not show signals of degradation after the contact with the different zeolitic products at any pH values. Our results indicate that metronidazole is not adsorbed on NZ, while it is adsorbed by washed-NZ, which demonstrates the influence of non-zeolitic mineral phases on the adsorption behavior of metronidazole by NZ. A moderate incorporation of metronidazole, in its protonated form, is observed for Na-NZ and Ca-NZ at pH 1.2. However, for all zeolitic products, the interaction with sulfamethoxazole showed to be negligible at the pH values considered. These results suggest that both zeolitic materials and drugs could be simultaneously administrated to a patient without any loss of the individual pharmaceutical effect of each product.

In a general way, the results obtained for the two drugs in our study indicate that the cause of the difference in the adsorptive behavior is fundamentally related with the polarity of the molecules, and the nature of the zeolitic material. The future pharmaceutical use of other zeolitic products with a higher Si/Al ratio could lead to different results, since under such conditions the adsorption of non-polar molecules would be favored.

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