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Comparative evaluation of natural and acid-modified layered mineral materials as rimifon-carriers using UV/VIS, FTIR, and equilibrium sorption study

Nedyalka Georgieva1* and Zvezdelina Yaneva1

Abstract: The encapsulation of rimifon on natural (NZ) and acid-modified (AMZ) zeolites was investigated by UV/VIS, FTIR, and equilibrium sorption studies in aqueous medium. The UV/VIS and FTIR spectral investigations provided data on the nature and characteristics of the drug–zeolite complexes. The probable host–guest interactions during rimifon encapsulation in AMZ include van der Waals interactions, as well as H-bonds established between the O-atom from the carbonyl (>C=O) group and N-pyridine/N-hydrazine atoms in rimifon and zeolite OH-groups. The maximum experimental equilibrium sorption capacity of AMZ (q_{max} = 7.17 mg/g) was approximately 24 times higher than that of NZ. Baudu and Fritz–Schlunder isotherms almost overlapped and seemed to be the best-fitting models with regard to the experimental equilibrium data of rimifon sorption on AMZ. The unique properties of AMZ and the established high extend of rimifon encapsulation proved the possibility of its successful application as rimifon-carrier for environmental and medical purposes.

Subjects: Analytical Chemistry; Environmental Chemistry; Health and Social Care; Medicinal & Pharmaceutical Chemistry

Keywords: rimifon; zeolite; sorption; FTIR; UV/VIS spectrophotometry

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1. Introduction

Rimifon (isonicotinylhydrazine, isoniazid, 4-pyridinecarboxylic acid hydrazide) is a key pharmaceutical drug recommended by the World Health Organization for the complex treatment of infections caused by *Mycobacterium tuberculosis* (Deosarkar, Sawale, Tawde, & Kalyankar, 2015; Georgieva & Gadjeva, 2002; Sabitha, Ratna, & Reddy, 2010). Rimifon is slowly permeated through the stomach and is mainly absorbed through the intestine because it occurs in the protonated form at acidic pH. Therefore, it can be considered as a good candidate for the development of site-specific release formulations (Kundawala, Patel, Patel, & Choudhary, 2011). Besides, due to the short biological half-life of the drug, it has to be administrated once daily in the treatment of tuberculosis for a six-month period. Thus, the development of controlled release dosage forms would clearly be advantageous. Hence, to improve therapeutic efficacy and patient compliance, to reduce adverse effects, and to decrease the dose and dosing frequency, controlled release preparations of antitubercular drugs are essential (Sabitha et al., 2010).

Contrary to the traditional applications of clay minerals, novel attempts have been explored to develop new potential aspects as drug carriers, protecting matrix, release controlling agents, and chemical modifiers (Raghvendra & Saraswathi, 2012). Recent studies are directed to investigate the potentially exciting pharmacological applications of smectite clays, mesoporous silicas, and zeolites for the encapsulation of different ions and molecules to obtain subsequent delayed release (Auerbach, Carrado, & Dutta, 2003). Several toxicological studies proved that natural zeolites are nontoxic and safe materials in human and veterinary medicine (Kralj & Pavelic, 2003). Moreover, cell culture studies proved the possible use of zeolites as biomaterials (Rimoli et al., 2008). Vlača et al. (2011) established that α-cyano-4-hydroxycinnamic acid (CHC) molecules could be encapsulated in NaY zeolite supercages, without structural modification or loss of crystallinity of the zeolite framework, while the drug molecule retains its molecular integrity. The application of the CHC–NaY complex led to an inhibition of cell viability up to 110-fold when compared to the nonencapsulated drug. The FT-IR and FT-Raman studies of Akyuz and Akyuz (2008) and the investigations of Raghvendra and Saraswathi (2012) were based on the preparation of isoniazid–intercalated montmorillonite and saponite nanocomposites, analytical analyses of the host–guest interactions, and in vitro release studies.

From environmental aspect, however, due to the extensive use of rimifon in medicine (Brock, Isaza, Egelund, Hunter, & Peloquin, 2014; Georgieva & Gadjeva, 2002; Nureen, Iqbal, Khan, & Basit, 2012), it could be attributed to the group of “emerging” contaminants (Ames & Gold, 1990). According to literature data after oral administration, <20% of isoniazid substance is excreted unchanged by humans into wastewater (Sasu, Metzger, Kranert, & Kummerer, 2015; Westwood et al., 2005). Besides, approximately two-thirds of the population in the developing world has no hygienic means of disposing excreta and an even greater number lack adequate means of disposing of total wastewater (Rose, 1999). Thus, it is a common practice to discharge untreated sewage directly into water bodies or onto agricultural land (“water reuse”), causing significant health, economic, and environmental risks (Bdour, Hamdi, & Tarawneh, 2009; Sasu et al., 2015). These pharmaceutical biologically active substances are active even in small amounts as they pollute natural waters and soil, destroy or inhibit the activity of certain microorganisms that are important for the ecosystems, and harm human health. Consequently, the development of innovative techniques for their removal from wastewaters is significant perspective. Efficient removal of tetracycline (95.5%) by HCl-modified zeolite under different conditions was established by Zou et al. (2012). The adsorption capacity of beta zeolites toward ketoprofen, hydrochlorothiazide, and atenolol was strongly dependent on both the solution pH and Al-content of the adsorbent. Atenolol was readily adsorbed on the less hydrophobic zeolite, under pH conditions with predominant electrostatic interactions, while ketoprofen adsorption was mainly driven by hydrophobic interactions. For undissociated molecules, the adsorption capability increased with the increase in hydrophobicity (Pasti et al., 2013).

The aim of the present study was to investigate and compare the physicochemical, spectral (UV/VIS, FTIR) characteristics, and sorption capacity of natural (NZ) and acid-modified zeolite (AMZ) as potential rimifon-carriers, and to assess their possible applicability for medical/environmental purposes.
2. Experimental

2.1. Biologically active compound
Rimifon was obtained from Bristol-Myers Squibb Co. (Connecticut, USA). Its physicochemical and molecular characteristics are presented in Table 1.

2.2. Natural zeolite
The natural zeolite (NZ) used in the present study was supplied by Bentonite AD (Kurdzhali City, Bulgaria). It characterized with: pore volume—0.11 cm³/g; density—1.10 g/cm³; specific surface area—37.1 m²/g; and clinoptilolite content—87% (Allen, Ivanova, & Koumanova, 2009). Prior to the sorption experiments, the mineral composite was thoroughly washed several times with distilled water to remove dust and any adhering substances.

2.3. Acid modification of NZ
The acid modification of natural zeolite was accomplished by treatment with 4-mol/dm³ HCl in a batch mode under vigorous stirring for 4 h at 25 ± 1°C. It was then washed several times with distilled water until neutral reaction. The absence of Cl⁻ anions in the infiltrate was identified by a quality reaction with 0.1-mol/dm³ AgNO₃.

The natural and acid-modified materials were oven dried at 373 K for 48 h. The prepared samples were stored in airtight containers for further studies. They were fractionated by sieving. The used fraction from both sorbents was 0.5–1.0 mm.

2.4. Surface chemistry characterization of NZ and AMZ
Surface chemistry of NZ and AMZ was characterized by Boehm titration, pH of zero charge, and FTIR.

Acidic and basic sites on the sorbents were determined by the acid–base titration (potentiometric titration) method proposed by Boehm (Boehm, 1994). The total acidic sites were neutralized using NaOH (0.1 mol/dm³) while the basic sites were neutralized with HCl (0.1 mol/dm³). The potentiometric titration curves were obtained by plotting the volume of titrant (VNaOH, VHCl, cm³) against the recorded pH.

The zero surface charge (pH_PZC) characteristics of NZ and AMZ were determined using the solid addition method (Hameed, 2010). 40 cm³ of 0.1 mol/dm³ NaCl solution was transferred to a series of 250 cm³ stoppered conical flasks. The pH_i values of the solutions were adjusted between 2 and 11 by

Table 1. Physicochemical and molecular characteristics of rimifon

| Characteristic                        | Value                        |
|---------------------------------------|------------------------------|
| Molecular formula                     | ![Molecular formula](image)  |
| CAS number                            | 54-85-3                      |
| Molecular mass                        | 137.139 g/mol                |
| Molecular volume                      | 111.5 ± 3.0 cm³/mol          |
| Flash point                           | 142.7 ± 23.2°C               |
| Boiling point                         | 312.3 ± 25.0°C at 760 mm Hg |
| Density                               | 1.1 ± 0.1 g/cm³              |
| log K₆₉₉                               | −0.70                        |
adding either 0.1-mol/dm$^3$ HCl or 0.1-mol/dm$^3$ NaOH. The total volume of the solution in each flask was exactly adjusted to 50 cm$^3$ by adding NaCl solution of the same strength. The pH of the solutions was then accurately noted. 0.5 g of NZ/AMZ was added to each flask, and the flasks were securely capped immediately. The suspensions were then kept shaking for 24 h and allowed to equilibrate for 0.5 h. The final pH values of the supernatant liquids were noted. The difference between the initial and final pH (pH$_i$) values ($\Delta$pH) was plotted against pH$_i$. The point of intersection of the resulting curve with abscissa, at which pH 0, gave the pHPZC. pH was measured using pH-meter Consort C931, Belgium.

2.5. FTIR spectroscopy
The functional groups present in the fresh and drug-loaded sorbents were characterized by a FTIR. FTIR spectra of fresh NZ, AMZ, and rimifon-loaded zeolites were obtained with KBr disk technique in the range of 400–4,000 cm$^{-1}$ using TENSOR 37 Bruker FTIR spectrometer (Bruker Optik GmbH, Germany).

2.6. UV/VIS spectrophotometry
Rimifon concentrations were measured with UV/VIS spectrophotometer DR 5000 Hach Lange (Germany), supplied with 10-mm quartz cells. All spectra were recorded in the UV region at $\lambda = 262$ nm with 2-nm slit width, 900-nm/min scan speed, and very high smoothing. The standard curve at pH 5.6 was linear over the range of the tested concentrations ($R^2 = 0.9996$).

2.7. Equilibrium sorption studies
Equilibrium sorption experiments were carried out by agitating predetermined mass of NZ/AMZ with 50 cm$^3$ of rimifon solutions with initial concentrations in the range of 5–100 mg/dm$^3$ at temperature $T = 19 \pm 2^\circ$C. The initial pH of the single-component solutions was in the range of 6.5–7.3. The sorbate/sorbent systems were agitated on IKA®KS 130 Basic Shaker at 180 rpm. Equilibrium was established after 72 h. Then, the drug solutions were separated from the adsorbent by centrifugation with Heraeus Labofuge 200 (Thermo, Electron Corporation) at 5,300 g for 20 min and filtered using 0.45-μm membrane filters (LCW 916, Hach Lange, Germany) to ensure the solutions were free from adsorbent particles before measuring the residual rimifon concentration.

The corresponding values of rimifon solid phase concentrations ($q_e$) were calculated by the mass balance equation (Equation 1):

\[
(c_o - c_e) \cdot V = (q_e - q_o) \cdot w
\]

where $c_o$ (mg/dm$^3$) is the initial rimifon concentration in the liquid phase, $q_o = 0$ and $w$ (g) is the sorbent mass.

All experiments were carried out in triplicate, and the average values were taken to minimize random error. Blanks containing no adsorbate and replicates of each adsorption point were used for each series of experiments.

2.8. Mathematical modeling
The equilibrium sorption behavior of rimifon on NZ and AMZ in the present research was modeled by the Langmuir, Freundlich, Redlich–Peterson, Khan, Sips, Baudu, Fritz–Schlunder equations, and the multilayer isotherm model (Table 2) by means of nonlinear analyses.

2.9. Error analysis
The nonlinear regression Chi-square ($\chi^2$) test was employed as a criterion to evaluate the quality of model isotherms fitting. The Chi-square can be represented by Equation 12:

\[
\chi^2 = \sum \left( \frac{(q_{e,exp} - q_{e,cal})^2}{q_{e,cal}} \right)
\]
where $q_{e}^{exp}$ is the equilibrium adsorption capacity from the experiment (mg/g) and $q_{e}^{cal}$ is the equilibrium capacity calculated according to the applied model (mg/g). A small value of $\chi^{2}$ indicates that data from the model are similar to the experimental values, whereas a large value of $\chi^{2}$ points out the difference between them. In order to confirm the best-fitting isotherms, the data-set using the Chi-square test, combined with the values of the determined correlation coefficients ($R^{2}$), sum of squares of errors (SSE), mean squared errors (MSE), and root-mean-square errors (RMSE) has to be analyzed.

### 3. Results and discussion

#### 3.1. Physicochemical and spectral characterization of NZ and AMZ

**3.1.1. Potentiometric titration**

Test for the determination of acidic and basic sites and functional groups present on the mineral sorbents was determined by potentiometric titration. In order to gain closer inside of the surface properties of NZ and AMZ for acidic sites, suspensions in 0.1 mol/dm$^3$ HCl were potentiometrically titrated with 0.1-mol/dm$^3$ NaOH (Figure 1). Likewise, the NaOH suspensions of both zeolites were potentiometrically titrated with 0.1-mol/dm$^3$ HCl for the determination of basic sites (Figure 2). The respective zero-order and first derivative potentiometric titration curves of NZ and AMZ are presented in Figures 1 and 2.

The results from the titration permitted the qualitative and semi-quantitative determination of the nature and number of active (acidic and basic) sites present on the mineral materials. According to the experimental data, the acidic and basic sites for NZ were estimated to be 2.5 and 6.3 mmol/g,
respectively, and for AMZ—2.4 and 6.85 mmol/g, respectively. Thus, the observed higher concentration of acidic sites as compared to that of the basic ones determined the acidic surface of both layered mineral materials. However, the acidic nature of the AMZ surface was more pronounced.

3.1.2. Point of zero charge

It is observed from Figures 3 and 4 that the surface charge of NZ is zero at pH 7.345, and AMZ is zero at pH 2.5.

Hence, the pH_{pzc} of NZ and AMZ is 7.345 and 2.5, respectively.
3.1.3. FTIR analyses of fresh NZ, AMZ, and rimifon-loaded AMZ

The adsorption of an organic molecule on mineral surface, or the formation of intercalates, gives rise to changes in the vibrational spectra of the interacting species. In order to determine the interaction mechanism of adsorbed rimifon molecules by zeolites, the vibrational wavenumbers of adsorbed molecules were carefully investigated by taking into account the coordination effects through the endocyclic and exocyclic N-atoms and through the >C=O group. The FTIR spectra of solid rimifon, drug-loaded NZ, and drug-loaded AMZ, measured within the range of 4,000–400 cm⁻¹, are presented in Figure 5 and the wavenumbers of the characteristic vibrations are shown in Table 3.

In the 2,700–2,600 cm⁻¹ region of the FTIR spectra of the rimifon-treated NZ and AMZ there were not observed any bands which could be attributed to N–H stretching vibrations, indicating that cationic surface species were not generated on the mineral surface. When coordination occurs through

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Figure 3. pH_{pzc} of NZ.

Figure 4. pH_{pzc} of AMZ.
the O-atom of the carbonyl group, a negative shift is expected in the \( \nu(C=O) \) mode of the coordinated molecule with respect to the free ligand. Thus, in the rimifon treated NZ and AMZ, the \( \nu(C=O) \) mode was observed at a lower wavenumber than in the pure drug substance. In the solid rimifon, the amino group H-atoms and the >C=O group are expected to be involved in H-bonding interactions. The ring breathing mode of rimifon around 1,000 cm\(^{-1}\) is obscured by the strong Si–O stretching mode of aluminosilicates. Since the Si–O stretching mode frequency is significantly affected by changes in swelling and orientation of the zeolite platelets, the ring mode of rimifon around 1,000 cm\(^{-1}\) was not analyzed.

![Figure 5. FTIR spectra of rimifon, fresh AMZ, and drug-loaded AMZ.](image)

| \( \nu (\text{cm}^{-1}) \) | Rimifon-loaded NZ | Rimifon-loaded AMZ | Rimifon |
|--------------------------|--------------------|--------------------|--------|
| 3625                     | Lattice termination silanol groups | Lattice termination silanol groups |        |
| 3620                     | Asymmetric stretching vibration of H\(_2\)O | Asymmetric stretching vibration of H\(_2\)O |        |
| 3445, 3427               | Symmetric stretching vibration of H\(_2\)O | Symmetric stretching vibration of H\(_2\)O |        |
| 1666.42, 1645.20, 1637, 1633.63 | Bending vibration of H\(_2\)O, \( \nu(C=O), \delta(NH_2) \) | Bending vibration of H\(_2\)O, \( \nu(C=O), \delta(NH_2) \) | \( \nu(C=O) \) |
| 1602.77, 1554.65         | —                  | —                  | \( \nu_{\text{ring}} \) |
| 1217, 1220.88, 1203.52   | Internal tetrahedra asymmetric stretching vibrations, \( \delta(CH) \) | Internal tetrahedra asymmetric stretching vibrations, \( \delta(CH) \) | \( \delta(CH) \) |
| 1056.94, 1053.08         | Si–O stretching mode of aluminosilicates, Al(III) in the octahedral position, \( \nu_{\text{ring}} \) | Si–O stretching mode of aluminosilicates, Al(III) in the octahedral position, \( \nu_{\text{ring}} \) | \( \nu_{\text{ring}} \) |
| 894, 842.35              | —                  | —                  | \( \gamma(CH) \) |
| 796.56, 792              | Internal tetrahedra symmetric stretching vibrations | Internal tetrahedra symmetric stretching vibrations |        |
| 700–600                  | Octahedral sites occupied by divalent central atoms, \( \gamma(CH) + \tau_{\text{ring}}, \delta_{\text{ring}} \) | Octahedral sites occupied by divalent central atoms, \( \gamma(CH) + \tau_{\text{ring}}, \delta_{\text{ring}} \) | \( \gamma(CH) + \tau_{\text{ring}}, \delta_{\text{ring}} \) |
| 464                      | O–T–O bending vibration | O–T–O bending vibration |        |
The incorporation of the pharmaceutically active compound in zeolite displayed variations in the intensity of relevant bands on the FTIR spectra of the rimifon-loaded zeolites (Figure 5). In addition to the strong bands caused by the host zeolite, the FTIR spectra for the system drug-encapsulated zeolite exhibited shifting of the bands in the region from 2,500–2,000 cm⁻¹ to lower frequencies. Besides, the vibrational bands at 3,620 and 3,419 cm⁻¹, which were attributed to adsorbed water, and the band at 1,645 cm⁻¹, characteristic of C=O vibration/C=C bonding/C=N bonding, characterized with lower transmittances.

The 1,203 and 1,056 cm⁻¹ bands corresponded to asymmetric stretching vibration modes of internal T–O bonds in TO₄ tetrahedra (T=Si and Al). The 796 cm⁻¹ band were assigned to the stretching vibration modes of O–T–O groups (Tomečková et al., 2012). Most of the octahedral sites were occupied by divalent central atoms, thus the O–H bending bands were shifted to wavenumbers in the range of 700–600 cm⁻¹ (Amorim et al., 2012). The OH stretching band of the strongly H-bonded zeolitic water, observed in the 3,400 cm⁻¹ region of the FTIR spectra, shows a decrease in frequency indicating that intercalated rimifon molecules involve H-bonds with the zeolitic water molecules. Although for the prepared drug-carrier system, the strong bands assigned to the vibration of the zeolite structure dominated the FTIR spectra; the characteristic rimifon FTIR vibrational bands in the rimifon-loaded AMZ spectra provided evidence for the presence of the drug in the zeolite matrix.

The probable host–guest interactions during rimifon encapsulation in zeolite include van der Waals interactions and H-bonds established between the O-atom from the carbonyl (>C=O) group and N-pyridine/N-hydrazine atoms in rimifon and zeolite OH-groups.

In the FTIR spectra of fresh NZ, rimifon and rimifon-loaded NZ (Figure 6), the bands with a peak at 3,400–3,600 cm⁻¹ were assigned to OH-stretching, and the vibrations at 1,645 cm⁻¹ were referred to bending vibration of adsorbed water molecules associated with K and Ca in the channels and cages in the zeolite structure. The software package CS Chem 3D ultra was used to calculate the Connolly molecular surface area of rimifon molecule—137.135 Å². The comparison of the dimensions of rimifon molecules with those of zeolite channels and pores: (1) micropores (<1.5 nm) and (2) mesopores (1.5–16 nm) revealed that there were no spatial limitations for the drug molecules to enter the micro- and mesopores of the zeolitic matrix.
3.2. Equilibrium studies

During the equilibrium sorption studies, it was established that the maximum experimental equilibrium capacity of NZ toward rimifon was \( q_{\text{max}} = 0.3 \text{ mg/g} \), while that of AMZ—approximately 24 times higher—\( q_{\text{max}} = 7.17 \text{ mg/g} \). The experimental equilibrium data of rimifon sorption by NZ and AMZ (Figure 7) were described by eight mathematical models through nonlinear regression analyses.

The values of the calculated isotherm parameters and error functions for both studied systems are presented in Table 4. The monolayer sorption capacities determined by the Langmuir model were consistent with the experimental data for both drug–zeolite systems—\( K_L/a_L = 0.358 \text{ mg/g} \) for NZ and 7.71 mg/g for AMZ (Table 4).

The significantly lower extend of rimifon encapsulation by natural zeolite (E 22%) as compared to that of the acid-modified mineral (E 97%) was due to HCl modification, which resulted in dissolution of some amorphous nonzeolitic materials that block the pores of natural zeolites. Besides, some cations and impurities were eliminated from the zeolite channels and replaced by H-atoms of smaller diameter. Consequently, the volume of the vacancies in channels and cavities increased leading to higher sorption capacity (Inglezakis & Zorpas, 2012). According to the Bronsted and Lewis theory, dissolution of natural zeolites in acid solution occurs because of the acidic behavior of the aluminosilicate structure in the presence of H\(^+\) ions in the solution (Margeta, Logar, Šiljeg, & Farkas, 2013).

Similar results were obtained by Zou et al. (2012). The sorption removal capacity of HCl-zeolite toward tetracycline was relatively higher at low pH. The adsorption removal rate of wastewater containing 0.1 mmol/L tetracycline was 95.5% when the dosage of treated zeolite was 0.05 g.

Figure 8 presents the experimental equilibrium data of rimifon sorption on AMZ and the applied eight model isotherms. Obviously, the Redlich–Peterson isotherm characterized with the highest \( R^2 \) value (\( R^2 = 0.9962 \), Table 4). However, the lowest and identical \( \chi^2 \) values (\( \chi^2 = 0.0703 \)) were obtained for Baudu and Fritz–Schlunder models.

The predicted by Baudu model maximum sorption capacity of AMZ (\( q_e = 4.169 \text{ mg/g} \)) was lower than the experimentally obtained, while that of the Fritz–Schlunder model (\( q_{\text{FS}} = 6.917 \text{ mg/g} \)) was close in value. According to the plots in Figure 8, both isotherms almost overlapped and seemed to be the best-fitting models with regard to the experimental equilibrium data of rimifon sorption on
### Table 4. Values of isotherm parameters and error functions for the systems rimifon-NZ and AMZ-rimifon

| System                    | Rimifon-NZ | Error functions | Rimifon-AMZ | Error functions |
|---------------------------|------------|----------------|-------------|----------------|
| **Model**                 | Parameter  | Error functions| Parameter   | Error functions|
| **Langmuir**              | $K_L = 0.043$ | $R^2 = 0.8930$ | $K_L = 2.5786$ | $R^2 = 0.9890$ |
|                           | $a_L = 0.120$ | $SSE = 0.0030$ | $a_L = 0.3342$ | $SSE = 0.4830$ |
|                           | MSE = 0.0010 | RMSE = 0.0152  | MSE = 0.0270 | RMSE = 0.1630  |
|                           | $\chi^2 = 0.0152$ | $\chi^2 = 0.7457$ |             |                 |
| **Freundlich**            | $K_F = 0.0860$ | $R^2 = 0.8090$ | $K_F = 2.7380$ | $R^2 = 0.9870$ |
|                           | $n_F = 0.3400$ | $SSE = 0.0060$ | $n_F = 0.2940$ | $SSE = 0.4990$ |
|                           | MSE = 0.0020 | RMSE = 0.0292  | MSE = 0.0002 | RMSE = 0.1246  |
|                           | $\chi^2 = 0.0292$ | $\chi^2 = 0.0705$ |             |                 |
| **Redlich–Peterson**      | $K_R = 0.0270$ | $R^2 = 0.9230$ | $K_R = 11.4980$ | $R^2 = 0.9910$ |
|                           | $b_R = 0.0130$ | $SSE = 0.0020$ | $b_R = 3.3860$ | $SSE = 0.0860$ |
|                           | $n_R = 1.4520$ | $MSE = 0.0010$ | $n_R = 0.7700$ | $MSE = 0.2930$ |
|                           | $\chi^2 = 0.0115$ | $\chi^2 = 0.0705$ |             |                 |
| **Sips**                  | $q_S = 0.3170$ | $R^2 = 0.9090$ | $q_S = 3.2170$ | $R^2 = 0.9910$ |
|                           | $K_S = 0.0600$ | $SSE = 0.0030$ | $K_S = 0.4800$ | $SSE = 0.3460$ |
|                           | $m_S = 11.4730$ | $MSE = 0.0010$ | $m_S = 0.2500$ | $MSE = 0.0860$ |
|                           | $\chi^2 = 0.0137$ | $\chi^2 = 0.0712$ |             |                 |
| **Multilayer isotherm**   | $Q_m = 1.7210$ | $R^2 = 0.9190$ | $Q_m = 5.5888$ | $R^2 = 0.9962$ |
|                           | $K_1 = 0.0190$ | $SSE = 0.0030$ | $K_1 = 0.7685$ | $SSE = 0.5350$ |
|                           | $K_2 = 0.0380$ | $MSE = 0.0010$ | $K_2 = 0.0091$ | $MSE = 0.1340$ |
|                           | $\chi^2 = 0.0112$ | $\chi^2 = 0.1676$ |             |                 |
| **Khan**                  | $q_K = 1.3100$ | $R^2 = 0.9200$ | $q_K = 2.3130$ | $R^2 = 0.9910$ |
|                           | $b_K = 0.0240$ | $SSE = 0.0030$ | $b_K = 3.6190$ | $SSE = 0.3440$ |
|                           | $a_K = 2.1610$ | $MSE = 0.0010$ | $a_K = 0.7540$ | $MSE = 0.0860$ |
|                           | $\chi^2 = 0.0111$ | $\chi^2 = 0.0709$ |             |                 |
| **Baudu**                 | $q_B = 1.7220$ | $R^2 = 0.9230$ | $q_B = 4.1690$ | $R^2 = 0.9910$ |
|                           | $b_B = 0.0150$ | $SSE = 0.0030$ | $b_B = 1.6530$ | $SSE = 0.3420$ |
|                           | $x = 0.4410$  | $MSE = 0.0010$ | $x = -0.4420$ | $MSE = 0.1140$ |
|                           | $y = -0.4050$ | $RMSE = 0.0350$ | $y = -0.1890$ | $RMSE = 0.3380$ |
|                           | $\chi^2 = 0.0117$ | $\chi^2 = 0.0703$ |             |                 |
| **Fritz–Schlunder**       | $q_{FS} = 0.0030$ | $R^2 = 0.8660$ | $q_{FS} = 6.9170$ | $R^2 = 0.9910$ |
|                           | $K_{FS1} = 3.6470$ | $SSE = 0.0040$ | $K_{FS1} = 0.9890$ | $SSE = 0.3420$ |
|                           | $K_{FS2} = 0.1100$ | $MSE = 0.0040$ | $K_{FS2} = 1.6330$ | $MSE = 0.1710$ |
|                           | $m_1 = 2.3250$  | $RMSE = 0.0660$ | $m_1 = 0.7440$  | $RMSE = 0.0440$ |
|                           | $m_2 = 2.0590$  | $\chi^2 = 0.0188$ | $m_2 = 0.5560$  | $\chi^2 = 0.0703$ |
AMZ. Due to the increased number of isotherm parameters in both empirical models, they simulate the model variations more accurately. In the case of sorptive processes of organic macromolecules like drugs having different types of functional groups, the factors affecting sorption are large. So, in the absence of a theoretical model that could account for the chemical heterogeneity of the surface, and simultaneous prevalence of different sorption mechanisms, isotherm models having a greater number of model constants are able to predict the system behavior better.

4. Conclusion
The present study provided the following general findings. The acidic and basic sites were quantified as 2.5 and 6.3 mmol/g, respectively, for NZ, and as 2.4 and 6.85 mmol/g, respectively, for AMZ; therefore, the mineral surfaces were acidic. The maximum experimental equilibrium sorption capacity of AMZ ($q_{\text{max}} = 7.17 \text{ mg/g}$) was approximately 24 times higher than that of NZ. The observed FTIR sorbent spectral differences before and after rimifon encapsulation indicated that the probable host–guest interactions during the drug encapsulation in AMZ include van der Waals interactions, as well as H-bonds established between the O-atom from the carbonyl (>C=O) group and N-pyridine/N-hydrazine atoms in rimifon and zeolite OH-groups, electrostatic and hydrophobic–hydrophobic interactions between hydrophobic parts of the drug molecule and the sorbent. The applicability of the Baudu and Fritz–Schlunder models to the experimental data outlined the possibility of multilayer sorption of rimifon molecules and/or a heterogeneous distribution of active sites on the sorbent surface.

The unique properties of AMZ and the established high extend of rimifon encapsulation proved the possibility of its successful application as rimifon-carrier for environmental and medical purposes.

Nomenclature

- $a_K$: Khan model exponent
- $a_L$: Langmuir isotherm constant, dm$^3$/mg
- $a_R$: Redlich–Peterson isotherm constant, dm$^3$/mg
$b$  Redlich–Peterson isotherm constant ($0 < b < 1$)

$b_B$  Baudu equilibrium constant

$b_K$  Khan equilibrium constant

$C_p$  equilibrium sorbate concentration in the liquid phase, mg/dm$^3$

$C_o$  initial sorbate concentration in the liquid phase, mg/dm$^3$

$d_p$  particle diameter, mm

$K_1$  equilibrium constant for the first layer adsorption in the multilayer isotherm model

$K_2$  equilibrium constant for multilayer adsorption in the multilayer isotherm model

$K_F$  Freundlich isotherm constant, dm$^3$/g

$K_{FS1}$  Fritz–Schlunder equilibrium parameter

$K_{FS2}$  Fritz–Schlunder equilibrium parameter

$K_L$  Langmuir isotherm constant, dm$^3$/g

$K_r$  Redlich–Peterson isotherm constant, dm$^3$/g

$K_S$  Sips equilibrium constant

$\log K_{ow}$  octanol/water partition coefficient

$m_1$  Fritz–Schlunder model exponent

$m_2$  Fritz–Schlunder model exponent

$m_S$  Sips model exponent

MSE  mean squared error

$n_F$  heterogeneity factor in the Freundlich model

$q_B$  Baudu maximum sorption capacity, mg/g

$q_p$  equilibrium sorbate concentration in the solid phase, mg/g

$q_{FS}$  Fritz–Schlunder maximum sorption capacity, mg/g

$q_K$  Khan maximum sorption capacity, mg/g

$Q_m$  maximum monolayer adsorption capacity in the multilayer isotherm model, mg/g

$q_S$  Sips maximum sorption capacity, mg/g

$q_t$  sorption capacity at time $t$, mg/g

$R^2$  correlation coefficient

RMSE  root mean square error

SSE  sum of squares of error

$T$  temperature, K

$t$  time, min

$V$  solution volume, dm$^3$, cm$^3$

$w$  sorbent mass, g

$x$  Baudu isotherm parameter

$y$  Baudu isotherm parameter

$\lambda$  maximum absorbance wavelength, nm

$\chi^2$  Chi-square error

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