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Performance of HDTMA-Br-Modified Indonesian Zeolite as a Drug Carrier Candidate for Diclofenac Sodium

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Abstract

Diclofenac sodium is a non-steroidal anti-inflammatory drug with a relatively short release time. This short release time promotes a more frequent drug consumption and could lead to side effects in the stomach, e.g., gastrointestinal disorders, gastrointestinal bleeding, and gastric ulcers. A drug delivery system with a slow-release activity is one of the promising technologies to control the drug amount released to the stomach. A surfactant-modified natural zeolite as a carrier for diclofenac sodium has been used in this study. This study focused on the preparation, characterization, and slow-release performance of HDTMA-modified natural zeolite as a carrier for diclofenac sodium. The zeolite underwent chemical and physical activation, as well as milling prior to use. It was proven that the zeolite used was dominated by mordenite and clinoptilolite with high stability properties towards acid treatments, as indicated by the XRD patterns. A modification of the zeolite surface using HDTMABr was also successfully performed, indicated by the appearance of peaks at wavenumbers of 2923.05 cm-1 and 2853.39 cm-1 (symmetrical and asymmetrical CH2 strains of HDTMA molecules, respectively) in the FTIR spectra. The synthesized HDTMA-modified natural zeolite also showed an excellent surface property such as surface area, pore-volume, and size, as indicated by the BET-BJH isotherms on the nitrogen adsorption. The slow-release performance of the zeolite-based drug delivery system was studied by investigating the adsorption-desorption behavior of HDTMA-modified zeolite towards diclofenac sodium. The HDTMA-modified zeolite adsorbed the diclofenac sodium of 54.01% at a pH of 7.5, the contact time of 60 min, and the initial concentration of 100 ppm. The adsorbed diclofenac sodium of 73.95% could be released from the HDTMA-modified adsorbent for 8 h, mimicking the time length of drug metabolism in the human body.

1. Introduction

Diclofenac is a non-steroidal anti-inflammatory drug (NSAIDs) derived from phenylacetic acid. However, c.a 20% of patients showed unexpected symptoms such as gastrointestinal disorders, gastrointestinal bleeding, and gastric ulcers [1]. Meanwhile, this medicine should be taken regularly to maintain its therapeutic effect due to its short release time (2-3 hours). The increase in the frequency of drug consumption could increase the more significant side effects, indeed.

A drug delivery system that can extend diclofenac sodium's working time is necessary to control its amount released into the stomach. As a consequence, it may minimize the side effects of the drug on the stomach. A drug delivery system's activity is mainly determined by the route of metabolism, the type of carrier, and the destination of the drug [2]. The drug delivery system's activity in this study would be mainly controlled by the type of carrier used as an immobilizer.

Porous materials such as zeolites and clay could be used as carriers for the drug delivery system [3]. Various

studies on zeolite as carriers in drug delivery systems have also been implemented [4, 5, 6]. Zeolites are a potential matrix that controls drug release by forming a homogeneous complex between the matrix and the drugs [7] and show the ability to desorp drug molecules in acidic conditions [8]. However, very little information could be obtained on the development of Indonesian natural zeolite as a carrier in a drug delivery system. The adsorption-desorption behavior of Indonesian natural zeolite as a carrier candidate for diclofenac sodium in the drug delivery system would be investigated in this study.

The adsorption capacity of Indonesian natural zeolites could be improved through an activation process, such as acid or base activation [9], thermal activation (calcination) [10], or modification using certain chemical compounds [11, 12]. Also, the adsorption capacity of the natural zeolites could be enhanced by increasing their surface area as an important parameter in their function as a carrier of drugs [13]. Changing the zeolites' size smaller by milling or grinding was an effective method [14].

The natural zeolites generally have a negatively charged surface [15]. To be able to adsorb drug molecules in the drug delivery system, changing the negative charge to the suitable one (positively charged surface for diclofenac sodium adsorption) is crucial. In this study, the modification of zeolite's surface using HDTMABr surfactant was carried out to enable the natural zeolite to adsorb the diclofenac sodium molecules as a part of the drug delivery system. The diclofenac sodium molecules would be better adsorbed on the zeolites modified by an HDTMABr cationic surfactant than other cationic surfactants, such as benzalkonium chloride [16]. Moreover, the zeolites modified by HDTMA-based cationic surfactant were stable in high ionic strength and a wide range of pH environments [17]. The drug molecules would be attached at the surfactant's active sites (on the zeolite's surface) through an ad-solubilization, surface solubilization, or co-adsorption effect [16]. The adsorption behavior of diclofenac sodium over the surfactant-modified natural zeolite was evaluated and compared to that without HDTMABr surfactant modification. The desorption behavior of diclofenac sodium adsorbed on the HDTMA modified natural zeolite to evaluate the slow-release performance of the drug delivery system developed in this study was also justified.

2. Methodology

This study was carried through several steps, i.e., the preparation and characterization of the HDTMA-modified natural zeolite, adsorption of diclofenac sodium over the modified natural zeolite, and the desorption of the adsorbed diclofenac sodium from the surface of the modified natural zeolite. A repeated experiment was applied in all adsorption-desorption experiments to show good data reproducibility. A well-fitted standard curve (with an R^2 of 0.99) was used to determine the diclofenac sodium concentration in the sample solution.

2.1. Materials and instrumentation

The carrier for the drug delivery system was developed based on Indonesian natural zeolite purchased from Gunung Kidul. The zeolite was pre-treated using a 6 N hydrochloric acid solution (purchased from E. Merck). The zeolite modification was performed using HDTMABr (Merck, 97%) to produce an adsorbent with a positively charged surface. The drug used to evaluate the HDTMA-modified zeolite performance in the drug delivery system was diclofenac sodium purchased from Aasrti Drugs Ltd.

The crystalline structure of original and HDTMA-modified natural zeolite was analyzed using a PANalytical Xpert'3 Powder X-ray diffractometer. A Perkin-Elmer Frontier Spotlight 200 type-Fourier transform infrared spectrophotometer was used to evaluate the electronic structure of the HDTMA-modified natural zeolite as the confirmation of the success of the modification. The porosity of the HDTMA-modified natural zeolite was measured using a Quantachrome Nova 1200e surface area analyzer. The adsorption and desorption behaviors of the diclofenac sodium were evaluated by monitoring the change in diclofenac sodium concentration in the adsorption system using a Genesys 10UV UV-visible spectrophotometer.

2.2. Preparation and characterization of HDTMA-modified natural zeolite

The natural zeolite with a particle size of 230 mesh used in this study underwent a pre-treatment process through a sequential chemical and physical activation prior to modification using an HDTMABr surfactant. The chemical activation was carried out through an acid treatment using 1 M hydrochloric acid solution for 2 h under stirring. The zeolite was then dried in an oven for 4 h at 105°C. This acid treatment was followed by a physical activation, as previously reported [18]. The latter was carried out by heating zeolite in a furnace at 600°C for 2 h at atmospheric pressure. As previously reported [19], a milling process was carried out after these two activation processes using a PPF-UG shaker mill with a speed of 720-900 rpm for 10 h. The pre-activated and -milled zeolite of 10 g was added into 100 mL of 0.2 M HDTMABr surfactant solution. The obtained mixture was stirred using a magnetic stirrer for 24 h at room temperature, filtered, and washed until bromide-free solid was obtained (indicated by no precipitate was detected by $AgNO_3$ solution). The obtained solid was then dried in an oven at 105 ℃ for 5 h.

To confirm the success of the modification of the natural zeolite with the HDTMA surfactant, the HDTMA-modified natural zeolite was analyzed by means of an FT-IR spectrophotometer. The change in the crystalline structure of the natural zeolite, activated zeolite, activated and milled zeolite, and HDTMA-modified natural zeolite was evaluated using an X-Ray diffractometer. The crystallite size of the zeolites was calculated using the Scherrer equation as previously reported [20]. The change in the HDTMA-modified natural zeolite porosity compared to the activated and

milled zeolite was investigated through a BET adsorption isotherm using a surface area analyzer.

2.3. Adsorption of diclofenac sodium

The adsorption behavior of diclofenac sodium over the HDTMA-modified natural zeolite was studied at ambient temperature and atmospheric pressure. The HDTMA-modified natural zeolite of 0.1 g was mixed with 10 mL of diclofenac sodium solution at various pH, initial concentration, and contact time, as presented in Table 1. Each mixture was shaken out with a shaking incubator at 250 rpm. Experiments using natural zeolite and activated, and milled zeolite were also carried out at a specific condition for comparison.

Table 1. The experimental design matrix in the adsorption of diclofenac sodium over the HDTMA-modified zeolite at various conditions.

# experiment	Contact time (min)	pH	The initial concentration of diclofenac sodium solution (ppm)
1	30	6.5	50
2	30	6.5	75
3	30	6.5	100
4	30	7.5	50
5	30	7.5	75
6	30	7.5	100
7	30	8.5	50
8	30	8.5	75
9	30	8.5	100
10	30	9.5	50
11	30	9.5	75
12	30	9.5	100
13	60	6.5	50
14	60	6.5	75
15	60	6.5	100
16	60	7.5	50
17	60	7.5	75
18	60	7.5	100
19	60	8.5	50
20	60	8.5	75
21	60	8.5	100
22	60	9.5	50
23	60	9.5	75
24	60	9.5	100
25	120	6.5	50
26	120	6.5	75
27	120	6.5	100
28	120	7.5	50
29	120	7.5	75
30	120	7.5	100
31	120	8.5	50
32	120	8.5	75
33	120	8.5	100
34	120	9.5	50
35	120	9.5	75
36	120	9.5	100

The adsorbents were then separated from the solution. These adsorbents were used in the desorption to study the slow release performance of the HDTMA-modified natural zeolite for adsorbed diclofenac sodium. The obtained solution (filtrate) was analyzed using a UV-Vis spectrophotometer at a wavelength of 297 nm to measure diclofenac sodium concentration, which was not adsorbed into the adsorbents. The concentration of sodium diclofenac adsorbed on the surface of adsorbents was determined from the difference in diclofenac sodium concentration before adsorption from that after adsorption. The percentage of the adsorbed diclofenac sodium was determined by using Equation (1).

$$Adsorbed\ DS\ (\%) = \frac{C_{adsorbed}}{C_{initial}} x100\% \quad (1)$$

2.4. Desorption of diclofenac sodium

The desorption behavior of diclofenac sodium over the HDTMA-modified natural zeolite was carried out at a highly acidic condition mimicking gastric juice's acidity (a pH of 1.2). The adsorbed diclofenac sodium on the surface of HDTMA-modified natural zeolite was desorbed using an HCl solution with a pH of 1.2. Each mixture was shaken out using a shaking incubator at room temperature at a stirring rate of 250 rpm during various time-release (0.5-8 h). The solution was then separated from the adsorbents. The diclofenac sodium concentration, released from the adsorbents over a specific release time, was measured using a UV-Vis spectrophotometer. The percentage of the desorbed diclofenac sodium was determined over the amount of the adsorbed diclofenac sodium, as shown in Equation (2).

$$Desorbed\ DS\ (\%) = \frac{C_{desorbed}}{C_{adsorbed}} x100\% \quad (2)$$

3. Results and Discussion

3.1. Characteristics of HDTMA-modified natural zeolite

The natural zeolite from Gunung Kidul Indonesia shows a brownish white appearance due to the presence of impurities. The soluble impurities could be removed by washing using demineralized water, whereas the insoluble impurities could be removed by acid treatment. This study used 1 M HCl solution as a chemical activator due to its ability to dissolve impurities and arrange the balance cations on the zeolite's surface, resulting in the zeolite with a uniformly charged surface. Hydronium ions from the HCl solution would be easier to replace by HDTMA+ cations from HDTMABr surfactants [11]. This kind of treatment might cause structural damage in the zeolite [21]. After each acid treatment, a physical activation (calcination) was needed to re-arrange the zeolite's morphological structure and improve its structural porosity [11], e.g., porosity.

The activated natural zeolite underwent a milling process prior to modification with HDTMABr surfactant. It was observed that there were no significant changes in the physical appearance of the zeolites after milling. The milling process only caused a change in the size of the zeolites. Meanwhile, the zeolite modification using HDTMABr surfactant caused the change in the color of the modified zeolite to a pale reddish-brown. The observed color change might be due to the binding of the HDTMABr surfactant to the zeolite's surface.

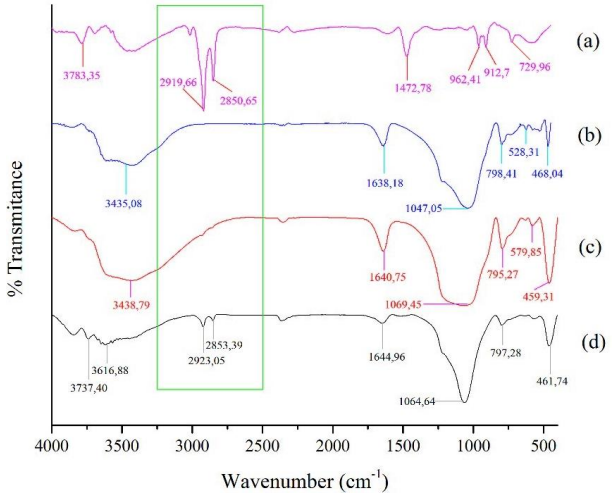

Figure 1. FTIR spectra of (a) HDTMABr, (b) natural zeolite, (c) activated zeolite after milling process, and (d) HDTMA-modified natural zeolite.

Moreover, the change in the zeolites' electronic structure during chemical and physical activations, milling, and modification using HDTMABr surfactant could be confirmed by the spectra shown in Figure 1. The original natural zeolite (Figure 1(b)) generally has a typical absorption area at wavenumbers around 1300-300 cm^{-1}, indicating the presence of tetrahedral bonds of $(SiO_4)^{4-}$ and $(AlO_4)^{5-}$ [22]. A peak at a wavenumber of 468.04cm^{-1} indicated the internal bending vibration of Si-O/Al-O while the external bending vibration of Si-O/Al-O at wave number 798.41 cm^{-1} [22]. Furthermore, symmetrical O-Si-O and asymmetric O-Al-O strains were observed at wavenumbers of 528.31 cm^{-1} and 1047.05 cm^{-1}, respectively [22]. In addition, a broad peak at wavenumbers of 3435.08 cm^{-1} and 1638.18 cm^{-1} indicated O-H strain and O-H bending vibrations, respectively [22].

The chemical activation seemed to cause changes in the intensity of some peaks (528.31 cm^{-1}, 1047.05 cm^{-1}, and 3435.08 cm^{-1}). Shifts in wavenumbers in the milled activated zeolite spectrum (Figure 1 (c)) were also observed. The shifts were observed in the symmetrical O-Si-O strain, from a wavenumber of 528.31cm^{-1} to 579.85 cm^{-1}, and an asymmetric O-Al-O strain from a wavenumber of 1047.05 cm^{-1} to 1069.45 cm^{-1} [21]. These shifts might be caused by the re-arrangement of the zeolite structures due to the activation using acid solution [23].

The IR spectrum of HDTMABr ($C_{19}H_{42}NBr$) in Figure 1(a) shows typical peaks appear at wavenumbers of 2919.66 cm^{-1} and 2850.65 cm^{-1} which are symmetrical and asymmetrical strains of CH_2, respectively. The peak at a wavenumber of 1472.78 cm^{-1} associated with the asymmetric CH_3 strain of $(CH_3)_3N^+$ bond was also observed [24]. The changes in the electronic structure of the zeolites with the presence of $HDTMA^+$ cations have been confirmed. The appearance of new peaks on the spectrum of the HDTMA-modified zeolite (Figure 1(c)) has proved that the modification of zeolite with HDTMABr surfactant was successfully carried out. Those observed new peaks indicated the existence of the symmetrical and asymmetrical strains of CH_2 [25]. Besides, a change in the peak shape and intensity associated with the -OH group and the emergence of a new peak at a wavenumber of 3737.30 cm^{-1} resulted from the interaction of the negative charge around Al in the zeolite structure with $HDTMA^+$ cation was also observed. This change was also observed at the peak at a wavenumber of 1047.05 cm^{-1} due to the replacement of Si^{4+} by $HDTMA^+$ cation [24].

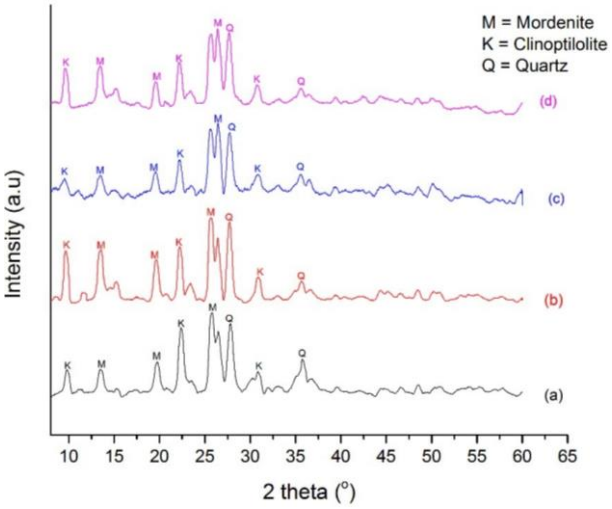

Figure 2. XRD patterns of (a) natural zeolite, (b) activated zeolite, (c) activated zeolite after milling process, and (d) HDTMA-modified natural zeolite.

In addition to its electronic structure, the change in the zeolite's crystalline structure was also evaluated in this study. The diffractogram in Figure 2(a) shows that Indonesian natural zeolite has several typical diffractions at 2θ of 13.56°; 19.75°; 25.77°; 26.38°, and 27.80°, which indicated the presence of mordenite minerals [26] as a constituent of the natural zeolite. Other diffractions at 2θ of 9.93, 22.34, and 30.59 degrees were associated with clinoptilolite minerals [26], while the diffractions at 2θ of 27.80 and 35.90 degrees were designated for the presence of quartz [26]. Thus, the natural zeolite used in this study was dominated by mordenite and clinoptilolite minerals with small quantities of quartz, as was also reported elsewhere [27].

Chemical and physical treatments, milling, and modification of zeolites using HDTMABr surfactant apparently did not cause significant changes in the zeolite structure. A decrease and/or increase in the intensity of some peaks possibly be caused by chemical activation using hydrochloric acid solution resulting in the Si/Al ratio changes in the zeolite framework [28], leading to the changes in the diffraction intensity. The milling process did not change the structure of zeolites. Milling is a physical process that would not conceptually change the structure of zeolites. Moreover, the structure changes due to the modification of the activated zeolite with HDTMABr surfactant were not observed in this study. It indicated that surfactants that are on the surface of zeolite are in small number.

The activated zeolite showed a larger pore volume than natural zeolite, from 0.047 to 0.069 cm^3/g, as shown in Table 2. This might be related to the impurities' release from the zeolite pores increasing in

the zeolite's pore volume. After the milling process, the zeolite's pore volume slightly decreased compared to the activated zeolite. Furthermore, the modification of zeolite with HDTMABr surfactant caused a decrease in the zeolite pore volume to 0.041 cm^3/g. The binding of $HDTMA^+$ cations possibly caused this to zeolites resulting in the smaller observed pore volume. Therefore, the HDTMA-modified zeolite was mesoporous [29]. Please note that the pore size of 2-50 nm is classified as a mesopore, while that < 2 nm and > 50 nm is micro and macropores, respectively [30].

Table 2. Surface area, pore-volume, average pore size, and crystallite size of various adsorbents.

Adsorbents	Surface area (m^2/g)	Pore volume (cm^3/g)	Average pore size (Å)	The crystallite size (nm)
Natural zeolite	15.46	0.047	61.26	240.95
Activated zeolite	22.59	0.069	61.34	121.81
Activated zeolite after milling	20.92	0.063	59.81	80.29
HDTMA-modified zeolite	21.69	0.041	37.31	194.93

The crystallite size of the zeolites prepared in this study was also investigated to study the effect of the fore-mentioned treatment on the zeolites' physical properties, as can be seen in Table 2. The milling process was able to reduce the crystallite size by 66.67% from its initial size. However, an increase in the size of HDTMA-modified zeolite was observed; more than two-fold of the pre-activated and milled zeolite size, but no more than that of the natural zeolite before the activation process (bulk material). The binding of the HDTMA cations on the pre-activated and -milled zeolite surface was the possible reason for this increase in the crystallite size. It might be due to replacing the smaller H^+ ion on the zeolite surface with the bigger $HDTMA^+$ ion.

As shown in Table 2, the physical and chemical activation possibly caused a significant increase in the zeolite surface area from 15.46 to 22.59 m^2/g. An increase in the surface area was observed for the activated zeolite after the milling process, reaching 20.92 m^2/g. This increase might indicate the smaller size of the zeolite after the milling process. A slight increase in the surface was also observed for the HDTMA-modified zeolite. This insignificant increase in the surface area of the HDTMA-modified zeolite was possibly due to the existence of bulky $HDTMA^+$ cations occupying active sites on the zeolite surface. Therefore, there was no linear increase in the surface area of the HDTMA-modified zeolite by decreasing the crystallite size.

3.2. Adsorption of diclofenac sodium

The HDTMA-modified zeolite role as a carrier for diclofenac sodium in the developed drug delivery system was investigated by studying the adsorption behavior of diclofenac sodium on the HDTMA-modified zeolite. Three different parameters were studied in the adsorption of diclofenac sodium over the HDTMA-modified zeolite. The adsorption data were analyzed using a response surface method of Minitab 17, as is presented in Figures 3, 4, and 5.

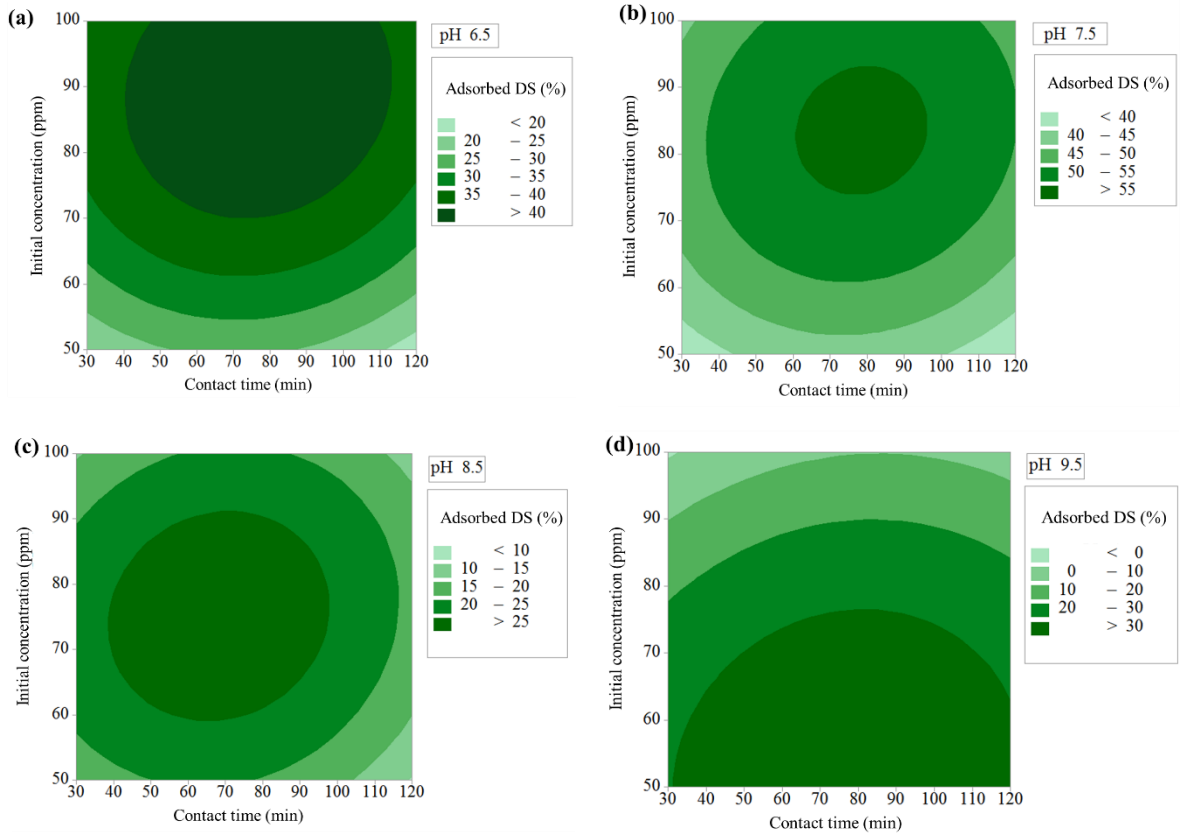

Figure 3. Percentage of adsorbed diclofenac sodium on the HDTMA-modified zeolite at a pH of (a) 6.5, (b) 7.5, (c) 8.5, and (d) 9.5.

The three figures showed that the highest uptake of diclofenac sodium was observed at the adsorption pH of 7.5, the initial sodium concentration diclofenac of 100 ppm, and the contact time of 60 min. Diclofenac sodium of 54.01% could be adsorbed on the HDTMA-modified zeolite at this condition. The environment's acidity showed a significant effect on the adsorption behavior of diclofenac sodium over the HDTMA-modified zeolite, as shown in Figure 3. The high solubility of diclofenac sodium at a pH above 6.5 enabled diclofenac sodium molecules to interact with HDTMA cations on the HDTMA-modified zeolite surface [31].

At a pH greater than pKa of diclofenac sodium (pKa = 4), diclofenac sodium was ionized [6]. The diclofenac group becomes negatively charged by releasing Na^+. Moreover, at a pH of 7.5, a significant number of diclofenac anions possibly resulted in the aqueous solution [31]. The anions would be adsorbed at the HDTMA-modified zeolite surface through an electrostatic $HDTMA^+$ cation-diclofenac anion interaction [32]. This interaction possibly occurred between the negatively charged carboxyl group of diclofenac anions and the positively charged HDTMA cations on the modified zeolite surface [33]. A decrease in the adsorbed diclofenac sodium was observed at pHs of 8.5 and 9.5 (Figure 3c and 3d) due to decreased interaction between HDTMA-modified zeolites and diclofenac anions. The increase in pH causes OH's concentration in the solution to increase, which causes a decrease in positive charge on the surface of HDTMA-modified zeolite [33].

The adsorbed diclofenac sodium increased by increasing the initial concentration of diclofenac sodium solution from 50 ppm to 100 ppm, as presented in Figure 4. However, when the concentration of sodium diclofenac solution increased to 200 ppm (it was not shown in the RSM graph due to its single data at a pH of 7.5 and contact time of 60 min only), the adsorbed diclofenac sodium decreased by ~18%. This might be due to the limited number of active sites on the HDTMA-modified zeolite leading to the limited interaction between the adsorbent and the adsorbate [34]. Also, at high concentrations of diclofenac sodium solution, clumping of the adsorbent might occur, resulting in a decrease in the number of active sites [6]. As a result, the adsorption capacity of HDTMA modified zeolite against diclofenac sodium was also reduced.

The third parameter investigated in this study related to diclofenac sodium's adsorption behavior over the HDTMA-modified zeolites was contact time. The adsorption with a contact time of 60 min showed the highest adsorption of diclofenac sodium solution over the HDTMA-modified zeolite. More than 50% of diclofenac sodium solution (with a concentration of 100 ppm) was adsorbed on the HDTMA-modified zeolite. This might indicate that the adsorbent was still in an unsaturated condition and able to adsorb the adsorbate. After 60-minutes of contact time, the surface of the adsorbent was saturated with the adsorbed diclofenac sodium. This phenomenon would promote the desorption or re-release of the adsorbate molecules from the adsorbent surface, resulting in a decrease in the adsorption of diclofenac sodium solution [34].

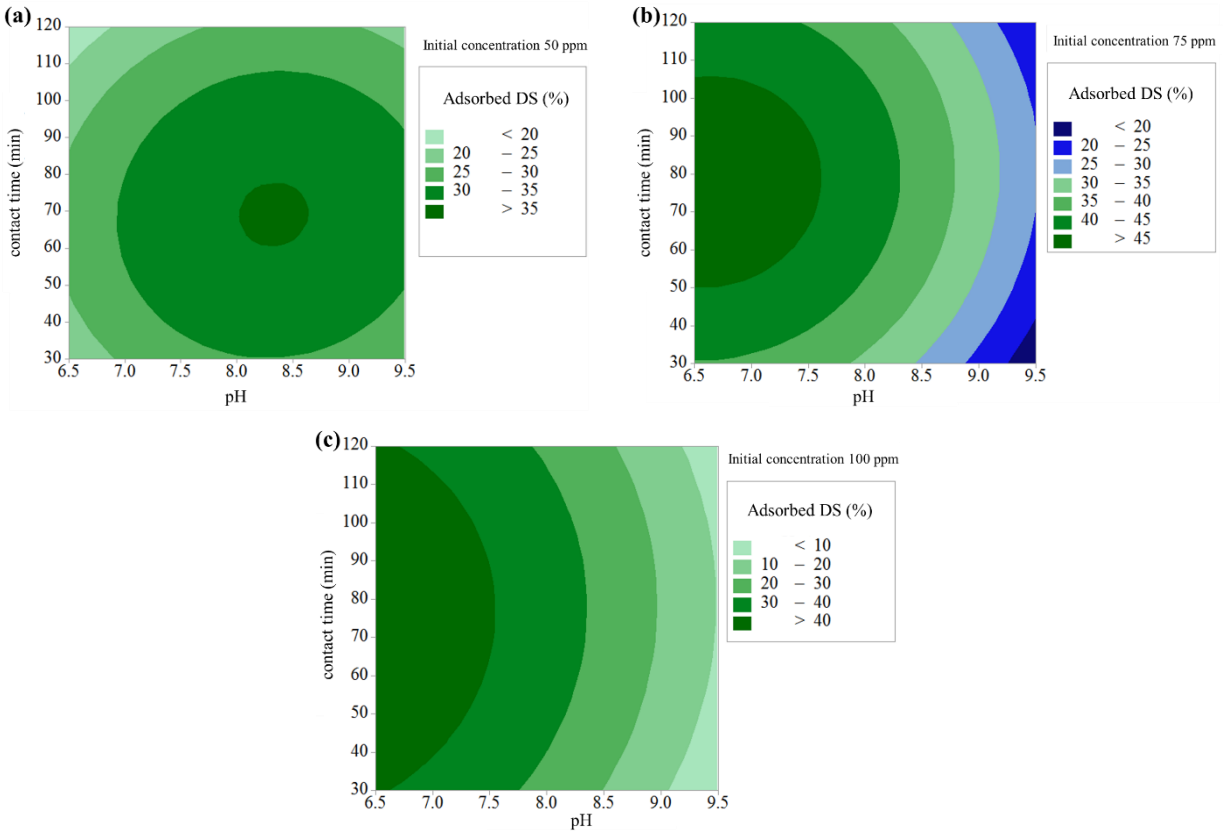

Figure 4. Percentage of adsorbed diclofenac sodium on the HDTMA-modified zeolite at an initial concentration of diclofenac sodium of (a) 50 ppm, (b) 75 ppm, and (c) 100 ppm).

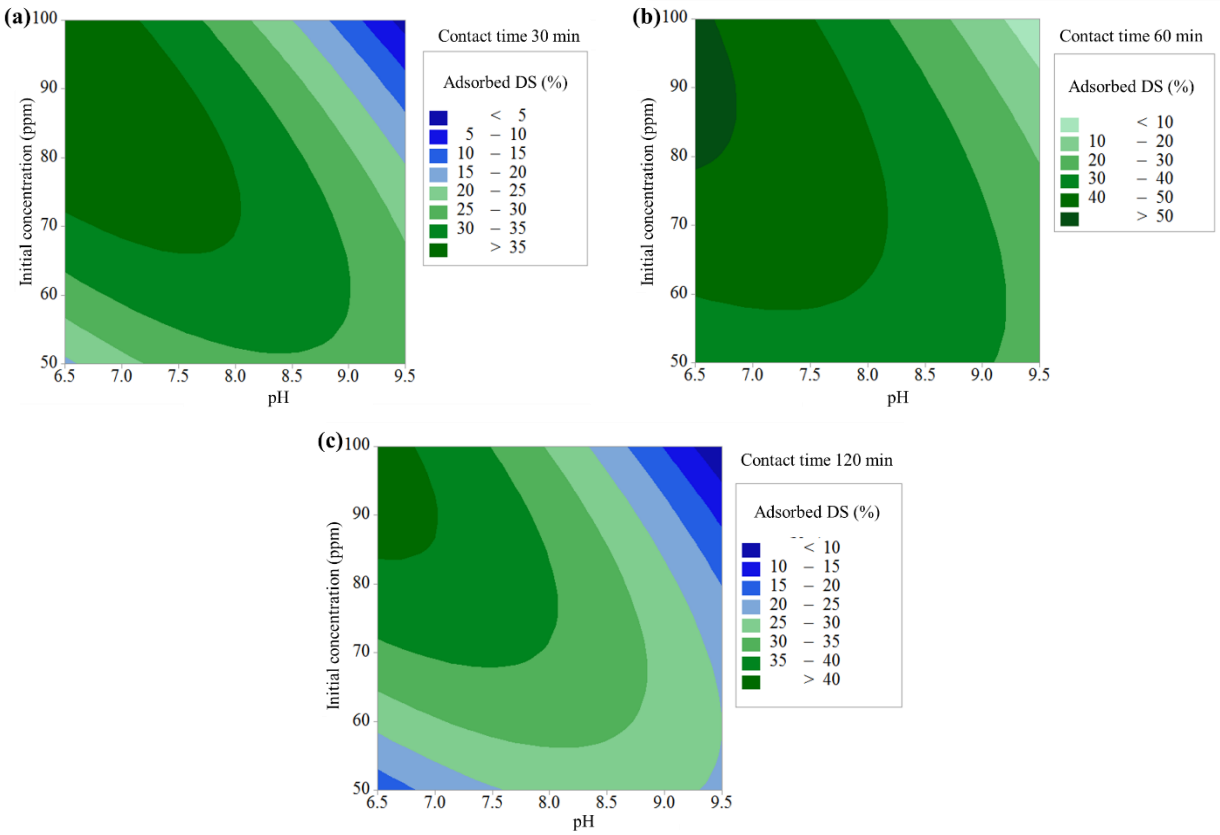

Figure 5. Percentage of diclofenac sodium adsorbed on the HDTMA-modified zeolite with a contact time of (a) 30 min, (b) 60 min, and (c) 120 min.

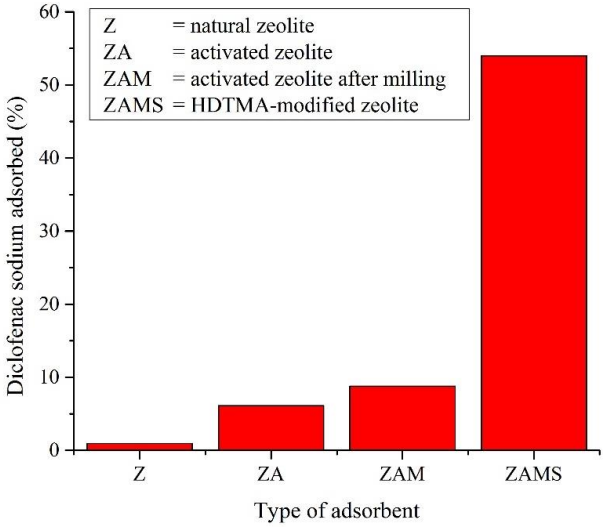

Figure 6. The amount of diclofenac sodium adsorbed on various adsorbents at a pH of 7.5, an initial concentration of diclofenac sodium solution of 100 ppm, and a contact time of 60 min

The adsorption behavior of diclofenac sodium solution over other adsorbents, i.e., natural zeolite, activated zeolite, activated-milled and HDTMA-modified zeolite, was also investigated in this study as a comparison. The adsorption was carried out at the same condition, i.e., at a pH of 7.5, an initial concentration of diclofenac sodium solution of 100 ppm, and a contact time of 60 min. The amount of adsorbed diclofenac sodium over various zeolites is presented in Figure 6. Without any pre-treatment, the ability of the natural zeolite to adsorb diclofenac sodium solution was meager. It might be due to the presence of impurities on the surface and pores of the zeolite. The impurities might prevent diclofenac sodium molecules from being adsorbed on the surface of the natural zeolite. After chemical and physical activations, the adsorption of diclofenac sodium solution significantly increased by 561% (from 0.92 to 6.09 %), possibly due to the loss of impurities from the surface of the activated zeolite. Besides, the increase in the zeolite surface area after the activation process might be the reason; the higher the surface area of an adsorbent, the higher the adsorption ability [35].

Furthermore, a considerable increase (by 43%) in the amount of diclofenac sodium adsorbed on the activated-milled zeolite surface was also observed. This increase was accompanied by a slight decrease (by 7.4 %) in the surface area of the corresponding zeolite, indicating an agglomeration that might be more susceptible for the zeolite with a smaller crystallite size (please see Table 2) [36]. This decrease in the crystallite size would improve the adsorption efficiency through the ion exchange mechanism [36]. The ion exchange mechanism could be enhanced because of removing the exchangeable cations in the activated-milled zeolite structure.

Figure 6 shows that the HDTMA-modified zeolite was the best adsorbent among various adsorbents in this study under the same conditions. The presence of $HDTMA^+$ cations on the zeolite surface seemed to play a vital role in the adsorption process [37]. Zeolites have a negatively charged surface. Therefore, a modification

was urgently required to allow diclofenac sodium molecules to be adsorbed. $HDTMA^+$ cations would be able to electrostatically interact with diclofenac anions (from diclofenac sodium molecules dissolved in water) [25]. This phenomenon is called ad solubilization, surface solubilization, or co-adsorption, designating an organic drug molecule binding to a surfactant on the surface of zeolite [32].

3.3. Desorption of diclofenac sodium

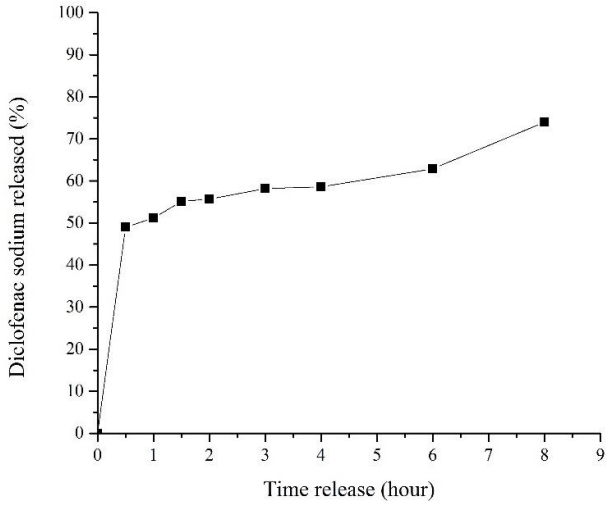

Figure 4. The amount of diclofenac sodium desorbed from the surface of HDTMA-modified zeolite at various time releases.

The release performance of diclofenac sodium from the HDTMA-modified zeolite adsorbent was evaluated by studying diclofenac sodium's desorption behavior from the adsorbent. A gradual release of diclofenac sodium was investigated over 0.5 to 8-hours release time, mimicking the generally prescribed frequency of medication. The adsorbed diclofenac sodium of 49% was released from the HDTMA-modified zeolite over a half-an-hour release time, as is shown in Figure 7. An insignificant increase in the desorbed diclofenac sodium from the adsorbent was observed by increasing releasing time. It was shown that the drug delivery system (diclofenac sodium on the HDTMA-modified zeolite carrier) in this study was able to control the release of diclofenac sodium molecules gradually.

Interestingly, not all of the adsorbed sodium diclofenac could be released within 8 hours; only 73.95% diclofenac sodium was released from the HDTMA-modified zeolite carrier. The remaining sodium may be released into the body for a longer time (more than 8 hours). Despite its limitation in releasing the adsorbed diclofenac sodium (less than 70% within 8 h), these findings are better than that previously reported; only 30% of the adsorbed diclofenac sodium was released from the carrier surface during an 8-h period [16].

4. Conclusion

The modification of zeolite using HDTMABr surfactant was successfully carried out in this study. This was indicated by the presence of symmetrical and asymmetrical vibrations of CH_2 at wavenumbers of 2923.05 cm^{-1} and 2853.39 cm^{-1}. The HDTMA-modified zeolite showed a remarkable ability to adsorb diclofenac sodium compared to other zeolite-based adsorbents investigated in this study. The condition appropriate for diclofenac sodium adsorption was at a pH of 7.5, an initial concentration of diclofenac sodium of 100 ppm, and a contact time of 60 min. The presence of $HDTMA^+$ cations on the HDTMA-modified zeolite surface allows an electrostatic interaction between diclofenac anions (from diclofenac sodium dissolved in water) and HDTMA cations (on the surface of the HDTMA-modified adsorbent). The HDTMA-modified zeolite could be a promising drug carrier. It could release ~74% of the adsorbed diclofenac sodium within 8 h (the normal period of therapeutic dose) in the acidic environment mimicking the acidic condition of the stomach.

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