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Synthesis, Characterization and Optimization of Magnetite Molecularly Imprinted Polymer for Application in the Removal of Non-Steroidal Anti Inflammatory Drugs (NSAIDS)

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ABSTRACT

Diclofenac (DCF) remains one of the most extensively used sold anti-inflammatory and analgesics that have been in use for an extended period. It has been widely detected in aquatic environments at concentrations that are indicative of detrimental environmental effects in addition to its inclusion on the EU's first watch list therefore, its removal from the environment is crucial. In this study**,** a selective Molecularly Imprinted Polymer (MIP) was synthesized via a bulk polymerization strategy with methacrylic acid (MAA) as the functional monomer, ethylene glycol dimethacrylate (*EGDMA*) as the cross-linker, Azobisisobutyronitrile (AIBN) as initiator and Diclofenac sodium (DCF) as the template molecule. The structure of the prepared MIP/ NIP was characterized by Fourier Transform Infrared Spectroscopy (FTIR), Scanning Electron Microscope (SEM) and Transmission Electron Microscopy (TEM). Several parameters influencing the adsorption efficiency of the MIP were optimized via the batch adsorption experiment. The results revealed that the maximum removal efficiency of the MIP (79%) was achieved at the optimized conditions of pH 2, 10 mL of 10 mg/L of adsorbate solution at 60 min contact time which was higher than its corresponding non molecularly imprinted polymer (NIP) which was (57%). The result of the reusability study showed that the adsorbent can be reused up to five cycles, hence it is efficient and promising for the removal of diclofenac from aqueous media.

Keywords: NSAIDs, optimization, removal, reusability, selectivity

INTRODUCTION

Recently, pharmaceutical compounds have been recognized as important emerging environmental contaminants due to their incomplete removal in sewage treatment plants (Park & Myung, 2015). it can be discharged into the aquatic environment either as the parent drug or its metabolites. NSAIDs (Non-Steroidal Anti-Inflammatory Drugs) are one of the most prominent and frequently recommended pain killer medicines that can be purchased over the counter, without a medical prescription from healthcare professionals in most countries and this, in turn, increases the chances for consumption and hence, their presence in the environment (Jedynak *et al*., 2019; Yamkelani *et al*., 2019). It exhibits an incredible spectrum of properties, including effects on fever, joint pain, headache and rheumatism. It is considered a "contaminant of emerging concern" and was included in the Watch List of EU Decision 2015/495 (Sathishkumar *et al*., 2019; Lonappan *et al*., 2016). This compound accumulates and results in adverse consequences if it enters the human body more than needed (Raouf *et al*., 2018; Lagha *et al*., 2011). The toxicity of diclofenac in birds, animals, aquatic animals, and plants has been reported based on in vitro/in vivo assessments. These compounds are harmful to humans and aquatic life even at low concentrations and have been detected in environmental water samples in concentrations ranging from ng/L to µg/L (Guo *et al*., 2019; Fontes *et al*., 2018; Kumirska *et al*., 2012). NSAIDs compounds enter the aquatic environment through various sources that include households, wastewater treatment plants (WWTPs), hospitals and industrial units (Madikizela *et al*., 2018). Recent studies indicate that diclofenac exhibits toxic effects on aquatic organisms even at (ng/L) concentrations in the environment (Fontes *et al*., 2018). Apart from the chronic and acute toxicity due to medication, it may also pose an adverse ecological risk to non-targeted organisms through biomagnification in the food chain (Sathishkumar *et al*., 2019).Among the several emerging pollutants, NSAIDs particularly, diclofenac are the most common compounds

detected in the environment due to their large consumption throughout the world (Cantarella *et al*., 2019). Frequently DCF is not completely removed from wastewater treatment plants. Moreover, the elimination of these compounds is often swept into WWTP (Lagha *et al*., 2011). A high number of research studies have demonstrated the inability of WWTPs to completely remove pharmaceuticals during the sewage treatment processes (Gao *et al*., 2018; Jiang *et al*., 2017; Madikizela & Chimuka, 2017; Almeida *et al*., 2017; Paxéus, 2004).Therefore, the occurrence of NSAIDs in the environment has become the issue of major concern due to their potential ecotoxicity into the environment as they severely affect the aquatic and terrestrial organisms at different trophic levels (Sharma & Kaushik, 2017). The extent to which they can be eliminated during wastewater treatment has become an active topic of research. DCF can interact with other inorganic contaminants such as Hg(II), Pb(II), and Sn(II) to form complexes (Refat *et al*., 2014). Consequently, the properties of DCF can change completely and become another potential pollutant possessing antibacterial and cell destruction properties (Lonappan *et al*., 2016). The molecularly imprinted polymer is a smart adsorbent material with high selectivity capable of rebinding the template molecule after the template is removed from the polymer matrix (Asman *et al*., 2015). In this study, MIP towards diclofenac has been synthesized via a non-covalent imprinting protocol and fortified with magnetic properties for easy separation by an external magnetic field. Several parameters influencing the adsorption behavior of DCF have been optimized and will be used for future adsorption study. The Possible interaction mechanism between diclofenac sodium and methacrylic acid was also evaluated.

MATERIALS AND METHODS

Reagents and chemicals

Diclofenac sodium salt, 99 % methacrylic acid (MAA), 98% ethylene glycol dimethacrylate (EGDMA) and Azobisisobutyronitrile (AIBN) were supplied by Sigma Aldrich (St Loius, Missouri, US). $FeCl_2.4H_2O$ and ferric chloride hexahydrate ($FeCl_3.6H_2O$), from R&M Chemicals (Edmonton, Canada) was used to synthesize the magnetite nanoparticles. 28% Ammonia solution was purchased from Merck, Darmstadt, Germany. Ethanol, methanol, and acetonitrile were supplied by Merck, Darmstadt, Germany. All reagents and chemicals were of analytical grade and were used without further purifications.

Instrumentation

A pH meter (Eutech pH 700) was used for pH measurement. Shaker (IKA, KS4000 I control) was used to shake the solution at different speeds and temperatures, an external magnetic field was used for the MSPE process. Uv-vis spectrophotometer (Perkin Elmer Lambda 35) was used to detect the residual analyte.

Preparation of Magnetite Nanoparticles (Fe_3O_4)

Magnetite nanoparticles (Fe_3O_4) were prepared according to the method documented by Yusoff *et al.* (2017) with slight modifications. The magnetic nanoparticles (MNPs) were synthesized with the molar ratio 1 : 2 by dissolving 0.86 g of $FeCl_2{\cdot}4H_2O$ and 2.34 g of $FeCl_3{\cdot}6H_2O$ in 40 mL of ultrapure water and was stirred for 30 min at 600 rpm. 5 mL of NH_3 was added after the solution was heated to 90 ℃ and the reaction mixture was continuously stirred for an hour. The resultant nanoparticles were then washed with ultrapure water five to six times to remove any unreacted chemicals. The product was separated by the application of an external magnet and dried in a vacuum oven overnight at 60℃.

Preparation of Magnetite Molecularly Imprinted Polymer

The MIP was prepared as reported with minor modifications (Li *et al*., 2018). The target template diclofenac sodium (0.1 mmol) and MAA (0.8 mmol) were dissolved in acetonitrile (20 mL) in a round bottom flask. The mixture was then stirred for 8 h at room temperature for pre-polymerization. Secondly, the developed Fe_3O_4 particles (0.2 g) were added to the solution followed by an ultrasonic treatment (60 W) for 15 min. Then, EDMA (3.0 mmol) was added as a cross-linker followed by the addition of AIBN (0.3 mmol) as an initiator and Polymerized at 60 ℃ in an inert atmosphere (nitrogen) for 24 h. The MIP product was washed with methanol/acetic acid (9:1, *v/v*) to remove the template molecules in the polymers until no templates were detected in the supernatant by Uv-vis at 276nm. Finally, the products were dried in a vacuum oven at 50 ℃ overnight. Similarly, the non-imprinted polymer was prepared in the same way without the target template.

Characterization Techniques

The adsorbent was characterized using A Perkin Elmer FTIR (Waltham, Massachusetts, the US in the range of 4000 – 400 cm^{-1} with 32 scans using the KBr method, SEM analysis was conducted with a Fei quanta FeG 650 model (Czech, Republic). The TEM images were captured by the FEI CM 12 instrument.

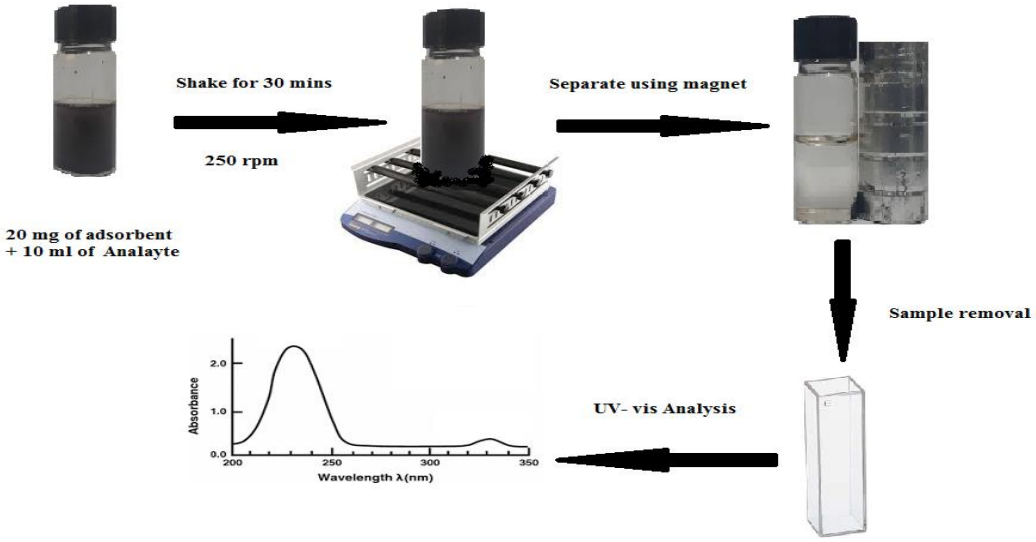
Batch Adsorption Study

The removal process was conducted via the batch adsorption experiment (Anne *et al*., 2018). In a glass vial containing 20 mg of the adsorbent material and 10 mL of a known concentration of the analyte (diclofenac sodium). The vial was placed on a mechanical shaker equipped with a thermostatic water bath at various temperatures (298K, 333 K and 338K) and a speed of 250 rpm for 30 min. The effect of several

parameters influencing the adsorption efficiency of diclofenac such as pH, contact time, temperature and initial concentration and sorbent dosage were examined. The adsorbent was separated with the aid of an external magnetic field and the supernatant was analyzed using the Uv-vis spectrophotometer (Perkin Elmer) at 276 nm. The removal percentage of diclofenac was by Equation (1)

$$\text{Removal efficiency (\%)} = \frac{(C_0 - C_f)}{C_0} \times 100 \qquad (1)$$

where C_O is the initial analyte concentration and C_f is the final concentration in mg/L respectively.



Scheme 1. Illustration of the diclofenac removal process

Optimization of Adsorption Parameters

Several parameters were optimized to obtain the optimum conditions for the removal of diclofenac in aqueous media. Each of the analysis was done in triplicate.

Effect of Adsorbent Dose

The amount of sorbent was studied by varying the sorbent dose from 5-80 mg to obtain the optimum dose for the removal process. 10 mL of 10 mg/L of analyte solution, 30 mg of sorbent material and shaking time of 30 min was used. The concentration of the analyte remaining after the removal process was analyzed using the Uv-vis spectrophotometer (Yusoff *et al*., 2018).

Effect of Adsorbate pH

The effect of pH was conducted by adjusting the solution to the desired pH using 0.01M NaOH or 0.01M HCl using a pH meter. The removal conditions: 10 mL of 10 mg/L of adsorbate solution, 30 mg of adsorbent material and shaking time of 30 min were used. The supernatant was collected using a magnet and the concentration of the analyte was monitored using the Uv-vis spectrophotometer (Madrakian *et al*., 2015).

Effect of contact time

The effect of contact time was studied in the range of 10-120 min. the removal conditions: 10 mL of 10 mg/L of analyte solution, 30 mg of sorbent material at pH and agitated using an incubator shaker and the supernatant analyzed with Uv-vis spectrophotometer after the removal process (Yusoff *et al*., 2018).

Effect of Concentration and Temperature

Equilibrium studies were performed at various initial concentrations of the analytes within the range of 0–100 mg /L in 10 mL of an aqueous solution of the analytes with a sorbent dosage of 30 mg at a pH of 2 at three different temperatures, namely, 298 K, 333 K, and 338 K, and the solution was later agitated at 250 rpm for 30 min the residual amount of diclofenac was determined by Uv-vis spectrophotometer (Yusoff *et al*., 2018).

Reusability Study

The reusability procedure was conducted by using 30 mg of the same sample up to five times for the removal of diclofenac. After each use, the adsorbents were washed three times with 3 mL of methanol followed by washing with 3 mL ultra pure water three times. The adsorbent was then dried at 60 °C before being reused in the next removal cycle (Yu & Yang, 2017).

RESULTS AND DISCUSSION

Characterization of Powdered Products

SEM and TEM analysis was conducted to elucidate the surface morphologies and the results are shown in Figure 1. TEM was conducted to show the core shell structure of the materials. It was observed

that both the MIP and NIP are spherical which is uniformly distributed in Figure 1 (a) and (b) respectively. The result of SEM shows that the surface of MIP Figure 1 (c) is smoother than NIP Figure 1 (d) suggesting an increase in the surface area. Hence, the high uptake of NSAIDs by the material. The FT-IR spectra Figure 1 (e) provide direct proof for the successful synthesis of molecularly imprinted polymers because MIP and NIP had similar peaks except for slight spectral shifts. No peaks of the template molecule were observed in the MIP showing complete removal of the template from the polymer matrix. The strong peaks of Fe-O related to the magnetite phase show that the material possesses magnetic properties (Mahdavi *et al.*, 2013). Table 1 depicts the Assignment of functional groups for Fe_3O_4, MIP and NIP spectra and their respective wavenumbers.

Table 1: Assignment of functional groups for Fe_3O_4, MIP and NIP spectra

Wavenumber (cm^{-1})	Functional groups assigned
3397	O-H stretching vibrations
2918	C-H stretching vibrations
1739	C=O stretching vibrations
1642	C=C stretching vibrations
596-597	Fe-O stretching vibrations

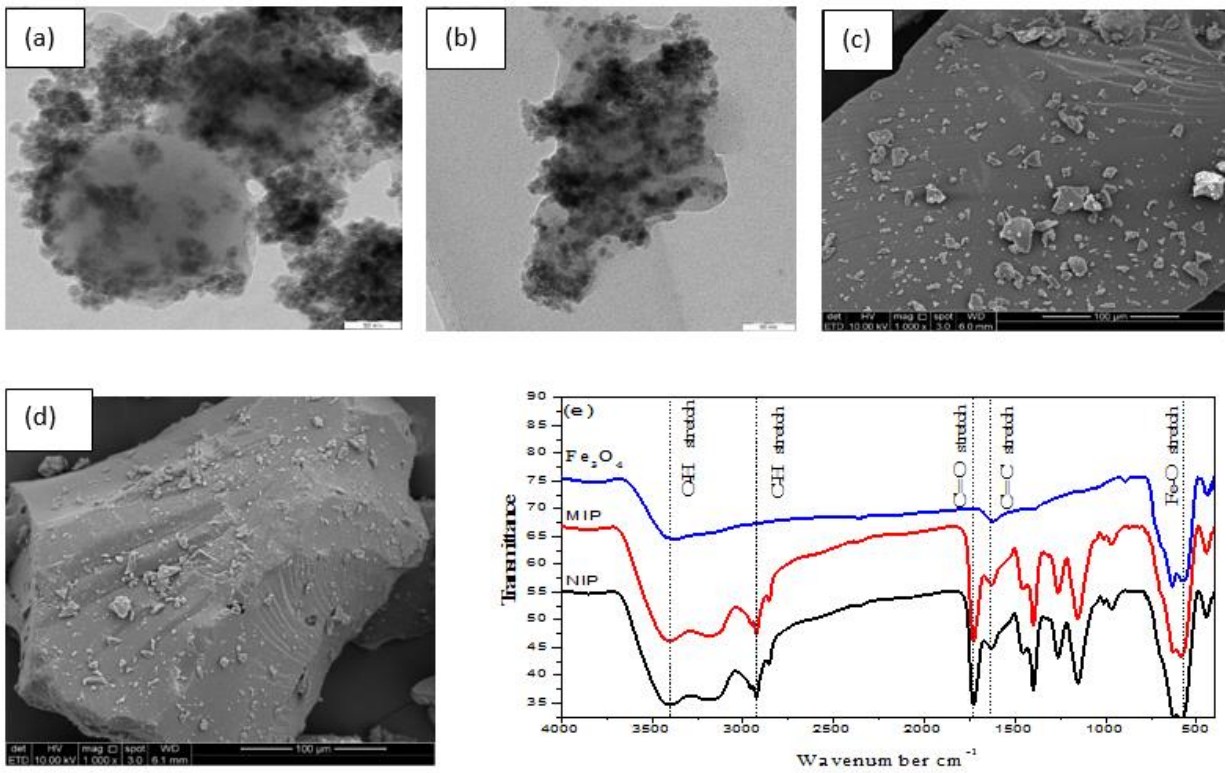
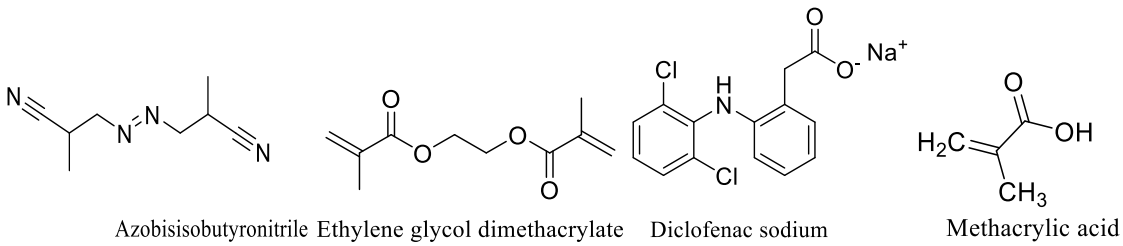


Figure 1. (a) TEM for MIP (b) TEM for NIP (c) SEM for MIP (d) SEM for NIP (e) FT-IR spectra Fe_3O_4, MIP and NIP



Scheme 2: Molecular structures of MIP components.

Optimizations of Adsorption Parameters

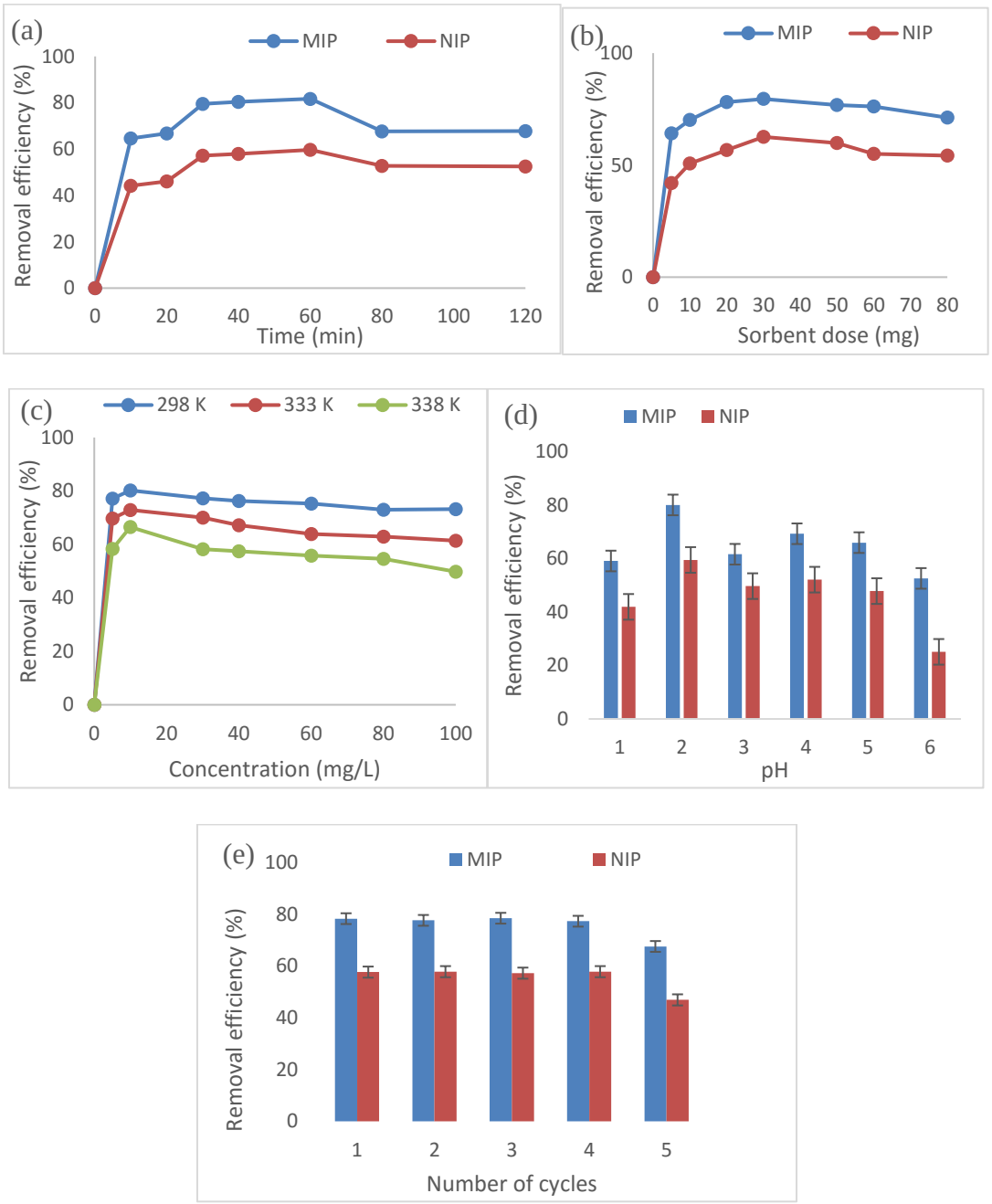


Figure 2: (a) Effect of contact time (b) Effect of sorbent dose (c) Effect of initial concentration and temperature (d) Effect of sample pH (e) Reusability for adsorption study

Effect of Contact Time

The effect of contact time on the removal of DCF from aqueous solutions onto MIP and NIP was conducted by varying contact time ranging from 10-120 min while keeping the adsorbent amount, adsorbate concentration and pH constant. Generally, the process was faster at the beginning of the experiment. The higher sorption rate at the initial period can be attributed to the increase in the number of the vacant sites on the adsorbent available at the initial stage (Habib, 2013) and the maximum removal of 60% and 81% (NIP and MIP respectively) was achieved at 60 min depicted in Figure 2 (a). After 60 min the removal efficiency dropped gradually, both materials attained equilibrium at 80 min. This could be attributed to the unavailability of active sites in the sorbent material. Therefore, 60 min was chosen as the optimized time for the removal in subsequent studies.

Effect of Sorbent Dosage

The effect of sorbent dosage on the adsorption process can be carried out by preparing

an adsorbent-adsorbate solution with different amount of adsorbents added to fixed adsorbate solution concentration and mixed until equilibrium is attained. The effect sorbent dose, on the uptake of DCF by MIP and NIP, was investigated at varying sorbent dose (5-80 mg), while keeping all other parameters constant. the result is depicted in Figure 2 (b). It was observed that the removal of DCF by the adsorbent materials increases with an increase in dosage rapidly at the initial stage and the maximum removal of MIP (81%) and NIP (57%) respectively were achieved using 30 mg adsorbent dose. The removal percentage dropped afterward. The decrease in the removal efficiency of DCF may be attributed to two reasons. The increase in sorbent dose at constant DCF concentration and volume will lead to saturation of sorption sites and secondly, it may be due to particulate interaction such as aggregation resulting from high sorbent dose (Ofomaja, 2008). In this study, 30 mg was selected as the optimized sorbent dose.

Effect Initial Concentration and Temperature

The effect of initial concentration and temperature on the adsorption efficiency of DFC was conducted at, 30 mg sorbent dose, initial concentration 10-100 mg/L, adsorption time 30 min, temperature 298 K, 303 K, 338 K and stirring speed 250 rpm. The result is depicted in Figure 2 (c). 298 K gave the best removal percentage increasing the temperature resulted in the decrease in removal efficiency due to the adsorbed molecules having greater energies, and therefore, becoming more likely to release from the surface of the adsorbent. (Elamin *et al*., 2019). As the concentration increases the removal efficiency decreases due to the saturation of the active sites of the sorbents by the sorbate.

The Effect of pH

The effect of pH in aqueous solution is an important parameter in the adsorption process (Auwal & Hossen, 2018). The value of the solution pH will determine the surface charge of the adsorbent, which will, in turn, affect the interaction between the adsorbate and adsorbent. The pH of the system exerts a profound influence on the adsorptive uptake of adsorbate molecules most probably due to its influence on the surface properties of the adsorbent and ionization or dissociation of the adsorbate molecule. The study was performed under varying pH conditions, ranging from pH 1- 9. 30 mg of adsorbents, 60 minutes of contact time, and 10 mL of 10 mg/L DCF solution at 298K. the pK_a of DCF is reported to be 4.20 (Jug & Mura, 2018). The results are depicted in Figure2(d). The highest removal was obtained at pH less than the pKa of the analyte (pH 2) below thepK_a value, DCF is present as neutral DCFH (a protonated form of DCF) while, after this value, it exists in its anionic form (DCF^-). From these considerations, the results can be rationalized. Specifically, at pH 2, DCF was protonated by the excess of H^+ in water, which reduces the pollutant/adsorbent electrostatic attraction (Rizzi*et al*., 2019).The optimal pH for the adsorption of diclofenac sodium onto MIP and NIP was pH 2 and was adopted for further studies.

Reusability study

Reusability is an important indicator to evaluate the efficiency and cost-effectiveness of any adsorbent.Reusability analysis was carried out to study the stability of MIP and NIP, as presented in Figure 2 (e). The adsorbents were stable up to five cycles (adsorption/desorption) with a high removal efficiency and started to decrease in efficiency on further recycling.The removal efficiency at the fifth cycle was 67 % and 47% for MIP and NIP respectively. This shows that the material is stable, economical and renewable adsorbent which has a prospect in the efficient removal of DCF from aqueous samples.

CONCLUSION

MIPs were successfully synthesized by crosslinking the crosslinker and functional monomers which can be combined with template molecule by some non-covalent bond (hydrogen bonding). The cavities remaining in the polymer could selectively capture the template molecule after the removal of the template from the polymer matrix. Moreover, the MIP and NIP have been successfully applied in different harsh conditions such as extremes concentrations, high temperature, and pH. The materials demonstrated promising physiochemical stability because it can be reused up to five consecutive cycles, which make them ideal materials for separation technique and will be applied for further adsorption study.

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