Application of molecularly imprinted polymer designed for the selective extraction of ketoprofen from wastewater

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ABSTRACT

A molecularly imprinted polymer (MIP) that is selective to ketoprofen was synthesized and applied in the adsorption of the target compound from water. The MIP was synthesized using a bulk polymerization method at high temperatures (60–80°C), where ketoprofen, 2-vinylpyridine, ethylene glycol dimethacrylate, toluene and 1,1′-azobis(cyclohexanecarbonitrile) were used as template, functional monomer, cross-linker, porogen and initiator, respectively. Non-imprinted polymer (NIP) was synthesized similarly to the MIP but in the absence of ketoprofen. From molecular dynamics simulation, the nature of interactions that occurred between the template and the functional monomer were found to be based on hydrogen bonding. This was confirmed experimentally, where a high extraction efficiency of ≥ 90% was obtained at acidic conditions (pH 5) due to the protonation of ketoprofen. A contact time of 45 min was sufficient for the maximum adsorption of ketoprofen from 10 mL spiked water using 8 mg of the adsorbent. MIP showed greater selectivity than NIP by achieving a relative selectivity coefficient of 7.7 towards ketoprofen in the presence of structurally related pharmaceuticals. Furthermore, the order of sorption onto the MIPs from water was ketoprofen > fenoprofen > gemfibrozil. From a modelling perspective, the Langmuir adsorption isotherm and pseudo-second-order kinetic model gave the best fit, with maximum adsorption capacity of 8.24 $mg{\cdot}g^{-1}$ and sorption rate constant of 0.25 $mg{\cdot}g^{-1}{\cdot}min^{-1}$ for MIP. This was translated to chemisorption of ketoprofen onto the homogeneous MIP binding sites. This work demonstrated the great potential of MIP in selective recognition of ketoprofen from wastewater relative to closely related compounds.

Keywords: ketoprofen, molecularly imprinted polymer, water, adsorption, molecular dynamics simulation, hydrogen bonding

INTRODUCTION

The presence of pharmaceutical compounds in surface water and wastewater has been known since the 1960s (Stumm-Zollinger and Fair, 1965). Pharmaceuticals are known as biologically active compounds that have a particular mode of action in humans and animals (Tiwari et al., 2017). Since the 1960s, the occurrence and fate of pharmaceuticals in the environment have attracted the devotion of the scientific community to assess the effectiveness of environmental policies (Kermia et al., 2016; Patrolecco et al., 2016; Pena et al., 2008; Zorita et al., 2008). In recent times, pharmaceuticals have been recognized as a class of environmental pollutants and they are becoming increasingly problematic contaminants of either surface water or groundwater around industrial and residential communities.

The sources of pharmaceuticals in surface water include wastewater treatment plants (WWTPs), households, effluent from pharmaceutical industries, and health service centres (Bayen et al., 2013; Félix–Cañedo et al., Kyzas et al., 2015; Santos et al., 2005). Pharmaceuticals such as ketoprofen are easily transported from wastewater to other water matrices. This is due to water being a good carrying medium for polar and semi-polar compounds (Pavlović et al., 2007). Globally, ketoprofen is a well-known pollutant in water matrices (Hanamoto et al., 2016; Martinez-Sena et al., 2016; Spongberg et al., 2011). However, there are very few recent studies on the occurrence of ketoprofen in South African aqueous environments (Agunbiade and Moodley, 2016; Madikizela et al., 2014; Zunngu et al., 2017). In surface water and wastewater, ketoprofen is usually detected with other non-steroidal anti-inflammatory drugs (NSAIDs) (Laven et al., 2009; Togola et al., 2007; Yu et al., 2013).

Due to the complexity of environmental samples, selective analytical methods are required for the analysis of compounds such as ketoprofen. Nowadays, molecularly imprinted polymers (MIPs) are being designed to improve the selectivity of analytical methods. Molecular imprinting technology is used for the preparation of highly specific binding sites for small molecules (Madikizela et al., 2016). The imprinting process involves the generation of cavities containing functional sites which are complementary to the target analyte with respect to shape, size and functional groups, within a highly cross-linked polymer matrix (Farrington and Regan, 2007; Gholivand et al., 2012). Most commonly, during molecular recognition the target compounds interact with MIP through non-covalent bonding, ionic interaction and hydrophobic interaction methods (Feng et al., 2009). For a MIP to possess such interactions, polymerization is usually carried out following bulk polymerization, in situ polymerization, suspension polymerization, and multi-step-swelling polymerization approaches (Dai et al., 2012; Ferrari et al., 2003; Murray and Örmeci, 2012).

Since an optimal target molecule and functional monomer interaction has a determining impact on successful imprinting, the choice of appropriate monomers plays

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a critical role in a successful imprinting process (Kubo and Otsuka, 2016). The best functional monomers are normally selected based on a trial-and-error method, which is expensive and time-consuming (Augusto et al., 2010; Rostamizadeh et al., 2012; Sobiech et al., 2014). Nowadays, with the advent of computational chemistry, the computer-aided study of MIPs has been investigated as a rational and fast technique to search for optimal imprinting conditions (Rostamizadeh et al., 2012). Also, the use of molecular dynamics simulations and computational screening to identify functional monomers capable of strong interaction with the target molecule has been investigated (Dong et al., 2009; Rostamizadeh et al., 2012).

Although, the molecular imprinting technique has been widely used for polymer synthesis, few studies have applied computational modeling in order to investigate interactions that occur between target molecule and functional monomer. Molecular dynamics simulations are a powerful tool to investigate complex systems made of thousands of atoms, at reasonable computational costs (Monti et al., 2006; O'Mahony et al., 2007; Riahi et al., 2009). The properties of molecules are affected by the surrounding environment and accurate molecular dynamic simulations must include a proper description of the existing interactions. Simulations are based on classical mechanical force fields that describe non-covalent interactions, H-bonding, van-der-Waals forces, π–π interactions and electrostatic interactions (Dong et al., 2009). Molecular dynamics simulation, in canonical ensemble at constant atom number, volume and temperature (NVT), has been utilized to fully understand the interactions of pharmaceuticals with 2-vinylpyridine (Madikizela et al., 2016; Riahi et al., 2009).

With ketoprofen being a well-known water contaminant, it is vital to synthesize a MIP for it and vigorously study how it interacts with this sorbent. MIPs play a crucial role in sample preparation through the selective extraction of target compounds from various matrices; therefore, it is important to understand the sorption mechanisms in order to carefully design them. There is detailed information on the application of molecular dynamics simulation to study the interactions between the templates and functional monomers used in molecular imprinting; however, the complex for ketoprofen and 2-vinylpyridine has never been studied. Therefore, this is the first detailed study to use molecular dynamics simulations for the evaluation of ketoprofen recognition by MIPs. The aims of the present study were to study the factors that affect the adsorption of ketoprofen onto MIP synthesized using bulk polymerization process and to investigate the adsorption mechanism.

EXPERIMENTAL

Chemicals

Ketoprofen (≥ 98%), 2-vinylpyridine (97%), HPLC-grade methanol (≥ 99.9%), 1,1′-azobis-(cyclohexanecarbonitrile) (98%), ethylene glycol dimethacrylate (98%), HPLC-grade chloroform (≥ 99.8%) and toluene (99.7%) were purchased from Sigma-Aldrich (Steinheim, Germany). HPLC-grade acetonitrile (≥ 99.9%) and glacial acetic acid (100%) were purchased from Merck (Darmstadt, Germany). Formic acid (approx. 98%) and fenoprofen (≥ 97%) were purchased from Fluka (Steinheim, Germany). Gemfibrozil was purchased from J & H Chemicals Co. Ltd (Hangzhou, China).

Molecular dynamics simulation

Molecular dynamics simulations were executed in order to understand the nature of molecular interactions that occur between 2-vinylpyridine as functional monomer and ketoprofen as the template. These were performed in canonical ensemble at constant NVT. Discover Module of Materials Studio (version 7.0) was used to perform the simulations. In this work, COMPASS force field was used to calculate the intermolecular interaction energy and bond length between ketoprofen and 2-vinylpyridine. This was done after the optimum conformation of the ketoprofen-2-vinylpyridine configuration was established; thereafter, ketoprofen was removed from the system which allowed for a single-point energy calculation for 2-vinylpyridine. Then, a single-point energy calculation was performed on ketoprofen only. Prior to the execution of molecular dynamics simulations, all structural configurations were subjected to energy minimization for geometry optimization using minimizer incorporated in the discover module of Materials Studio. For minima calculation, a maximum iteration of 100 000 was used with an ultra-fine convergence level. This resulted in molecular dynamic simulation using NVT lasting for 100 ps with a time step of 1 fs. Similar conditions were applied to investigate the interactions that occur between 2-vinylyridine and its competitors (fenoprofen and gemfibrozil).

Synthesis of molecularly imprinted polymer

The synthesis of MIP for ketoprofen has been published in our previous work (Zunngu et al., 2017). The synthesis was carried out by mixing 25 mg of ketoprofen with 54 µL of 2-vinylpyridine. The mixture was stirred at room temperature in a 50 mL round-bottomed flask containing 10 mL of acetonitrile/toluene (1:9, v/v) porogenic mixture for 30 min. Thereafter, the reaction vessel was placed on ice to prevent premature polymerization. Ethylene glycol dimethacrylate (4.77 mL) and 100 mg of 1,1′-azobis-(cyclohexanecarbonitrile) were added. The mixture was purged with nitrogen gas for 10 min, sealed and stirred in an oil bath at 60°C for 16 h to initiate polymerization. After 16 h, the temperature was increased to 80°C and maintained for 24 h to achieve a solid monolith polymer. The polymer was dried to constant mass at 80°C followed by grinding and sieving to collect particles that ranged from 25 to 90 µm in diameter. The control, non-imprinted polymer (NIP) was synthesized and treated likewise, with the omission of ketoprofen in the reaction mixture. Thereafter, both MIP and NIP particles were washed repeatedly with a mixture of acetic acid: acetonitrile (1:9, v/v) until ketoprofen could not be detected by the former in the high performance liquid chromatography (HPLC) system.

Instrumentation

A Shimadzu HPLC (Kyoto, Japan) system that consisted of an online mobile phase degasser unit (Model: DGU-20A5), 20 µL sample loop, pump (Model: LC-20AT), and UV/visible detector (Model: SPD-20A) was used for the determination of the pharmaceuticals. The mobile phase conditions consisted of a mixture of acetonitrile and 0.2% formic acid in water (60:40, v/v) at a flow rate of 1 mL·min^{-1}. Separation of the analytes was performed on a Gemini C_{18} HPLC column with dimensions of 150 mm × 4.6 mm × 5 µm obtained from Phenomenex (California, USA). Shimadzu LC solutions

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software was used for data collection and processing. Detector wavelength was set at 255 nm.

Spectroscopic characterizations were done by nuclear magnetic resonance (NMR) and Fourier-transform infrared (FTIR) techniques. Agilent VNMRS Wide Bore 500 MHz NMR spectrometer with a ^{1}H frequency of 500 MHz and a ^{13}C frequency of 125 MHz was used. The spectra were acquired utilizing a dual-channel 4 mm Chemagnetics TM T3 HX MAS probe using 4 mm zirconia rotors. The cross-polarization (CP) spectra were recorded at 25°C with proton decoupling using a recycle delay of 10 s. The CP pulse power parameters were optimized for the Hartmann-Hahn match using a glycine standard sample. The radio frequency fields for the match were γCB1C = γHB1H ≈ 55 kHz. The contact time for cross-polarization was optimized to 2.0 ms. Magic-angle-spinning (MAS) was performed at 10 000 revolutions per second (10 kHz). FTIR used was equipped with attenuated total reflection (Perkin Elmer, Llantrisant, United Kingdom) with solid samples analysed without any treatment.

A scanning electron microscopy (SEM), JOEL model JSM 6700F (Tokyo, Japan) was used to study the polymer morphology.

Surface area, total pore volume and average pore diameter for both MIP and NIP were evaluated using the Flow Prep 060 instrument from Micromeritics (Aachen, Germany).

The zeta potentials for MIP dispersed in water adjusted to pH 5 and 9 were determined at 25°C using a zeta instrument (Model: Nanosight NS 500) obtained from Malvern Instruments Limited (Worcestershire, UK).

Optimization of adsorption parameters

Parameters that could influence the adsorption of ketoprofen onto MIP were optimized. In our previous work (Zunngu et al., 2017), it was clearly demonstrated through the application of molecularly imprinted solid-phase extraction (MISPE) that the performance of the NIP for adsorption of ketoprofen yields poor results when compared to MIP. Therefore, the focus of the present study was based more on adsorption of ketoprofen onto MIP. Initially, 10 mL of ketoprofen standard (1 mg·L^{-1}) was prepared in 3 organic solvents (acetonitrile, toluene and chloroform), and the adsorption process into 8 mg of MIP was allowed to occur overnight. This was important as the nature of the solvent used to dissolve the target compound is known to influence the batch adsorption capacity for the MIP (Kizhakekuthiathottil and Beena, 2011; Navarro-Villoslada et al., 2004). The ketoprofen standard prepared in water was treated likewise. Extraction efficiency was determined in each case.

Thereafter, adsorption parameters in the batch mode, such as sample pH (3–9), polymer mass (8–25 mg), contact time (5–60 min) and initial concentration of target molecule (0.001–70 mg·L^{-1}), were optimized for the uptake of ketoprofen by MIP sorbent from water solutions. This was done by holding all the other parameters constant while varying one. For example, when monitoring the effect of polymer amount, the sorbent mass was changed from 8 to 25 mg, while contact time, adsorption medium and its volume, sample pH, and concentration of ketoprofen in spiked solutions were kept constant. Each experiment was repeated 3 times. In each case, the extraction efficiency or the adsorption capacity was calculated using Eqs 1 and 2, respectively.

$$\text{Extraction efficiency (\%)} = \frac{(C_0 - C_e)}{C_o} \times 100 \quad (1)$$

$$\text{Adsorption capacity (mg·L}^{-1}) = \frac{(C_o - C_e)V}{W} \quad (2)$$

where C_o and C_e are the initial concentration (mg·L^{-1}) before the adsorption and the final concentration (mg·L^{-1}) of target compound remaining in solution after adsorption, respectively. V and W represent the volume (L) of the solution and the mass (g) of the polymer, respectively.

Selectivity studies

The selectivity of the MIP for ketoprofen was tested in batch rebinding experiments using optimum conditions, which were 10 mL of deionized water spiked with 1 mg·L^{-1} of each of the analytes (ketoprofen, fenoprofen and gemfibrozil). Thereafter, the concentration of the un-adsorbed compounds in solution were measured by HPLC. This was followed by the determination of the distribution coefficients (K_d (mL·g^{-1})) using Eq. 3. Thereafter, the selectivity coefficients for the adsorption of ketoprofen in the presence of the competing species was calculated using Eq. 4. Furthermore, the selectivity of the MIP in relation to the NIP was measured using the relative selectivity coefficient (K') which was calculated using Eq. 5.

$$K_d = \frac{(C_0 - C_e)}{WC_e} V \quad (3)$$

$$K = \frac{K_d \text{ (ketoprofen)}}{K_d \text{ (competitor)}} \quad (4)$$

$$K' = \frac{K(\text{MIP})}{K(\text{NIP})} \quad (5)$$

RESULTS AND DISCUSSION

Synthesis of molecularly imprinted polymer

Computational analysis of a pre-polymerization mixture

Synthesis of the MIP for ketoprofen was performed using standard reagents that are normally used when preparing polymers for acidic pharmaceuticals (Sun et al., 2008). Such reagents may be commonly used, but for the success of molecular imprinting it is always important to evaluate the possible interactions that will occur in the pre-polymerization complex. In this case, the nature of interactions that occur between the widely used 2-vinylpyridine and ketoprofen were investigated. Prior to the execution of molecular dynamics simulations, the Mulliken charges for all the atoms present in ketoprofen (Fig. 1a) and 2-vinylpyridine (Fig. 1b) were assigned (Table 1). From the Mulliken charges, it was observed that hydrogen bonding could occur where the nitrogen atom (6N) of 2-vinylpyridine will accept the proton (33H) from the carboxylic group of ketoprofen. Molecular dynamics simulation confirmed this observation (Fig. 1c). The resulting bond distance between the binding atoms of the two compounds was 1.837 Å. In previous studies, the hydrogen bond distances reported were in the range of 1.646 to 2.160 Å (Han et al., 2017; Madikizela et al., 2016; Puzio et al., 2013; Suriyanarayanan et al., 2017). Furthermore, the binding energy (ΔE) for the complex that results from the interactions

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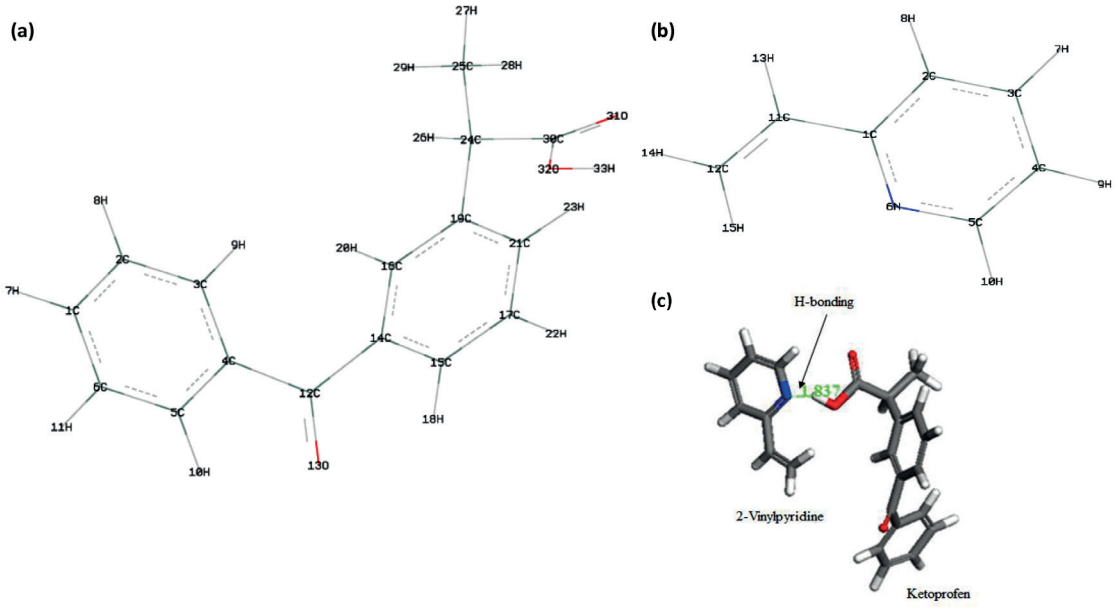

Figure 1
Molecular interactions between ketoprofen (a) and 2-vinylpyridine (b) to form the complex (c)

TABLE 1
Mulliken charges of ketoprofen and 2-vinylpyridine

Ketoprofen			2-vinylpyridine		
Atom number	Atom	Atomic charges	Atom number	Atom	Atomic charges
1	C	−0.090	1	C	0.192
2	C	−0.068	2	C	−0.103
3	C	−0.097	3	C	−0.103
4	C	0.026	4	C	−0.104
5	C	−0.062	5	C	0.051
6	C	−0.103	**6**	**N**	**−0.314**
7	H	0.112	7	H	0.100
8	H	0.132	8	H	0.082
9	H	0.129	9	H	0.089
10	H	0.156	10	H	0.095
11	H	0.114	11	C	−0.105
12	C	0.263	12	C	−0.254
13	O	−0.473	13	H	0.097
14	C	0.015	14	H	0.118
15	C	−0.065	15	H	0.161
16	C	−0.102			
17	C	−0.113			
18	H	0.158			
19	C	0.031			
20	H	0.144			
21	C	−0.091			
22	H	0.115			
23	H	0.102			
24	C	−0.099			
25	C	−0.386			
26	H	0.127			
27	H	0.165			
28	H	0.184			
29	H	0.111			
30	C	0.515			
31	O	−0.459			
32	O	−0.714			
33	**H**	**0.323**			

between 2-vinylpyridine and ketoprofen was used to quantify the strength of the hydrogen bonding. Binding energy was calculated using Eq. 6, as explained in previous studies (Farrington, Regan, 2007; Madikizela et al., 2016):

$$\Delta E = E_{(complex)} - E_{(template)} - E_{(2\text{-vinylpyridine})} \quad (6)$$

The obtained binding energy for the complex that is formed by ketoprofen and 2-vinylpyridine was −11.97 Kcal·mol^{-1}, which corresponded well with the binding energies obtained in other similar complexes (Farrington et al., 2006; Gholivand et al., 2012; Madikizela et al., 2016; Zhang et al., 2008). Therefore, these results confirmed the existence of hydrogen bonding between ketoprofen and 2-vinylpyridine.

Characterization of the synthesized polymers

Scanning electron microscopy

Scanning electron microscopy (SEM) was used to study the polymer morphology. The results (Fig. 2) clearly show the differences between the morphology of the MIP (Fig. 2a) and NIP (Fig. 2b). It was observed that the surface of the MIP is rougher, resulting in the availability of more surface area for ketoprofen adsorption, and has large pore sizes compared to the NIP. The pores on the surface improved the mass transfer of ketoprofen from the solution to the pores of the sorbent. This suggested that polymer morphology influenced the extraction of the target molecule from water.

Brunauer, Emmett and Teller analysis

Brunauer, Emmett and Teller (BET) results given in Table 2 show a greater surface area (209 m^2·g^{-1}) for the MIP than the NIP (95 m^2·g^{-1}). Previous work has shown that a MIP with a higher surface area yields a higher adsorption capacity than its corresponding NIP with lower surface area (Dai et al., 2012; Song et al., 2015). It was also observed that the MIP had

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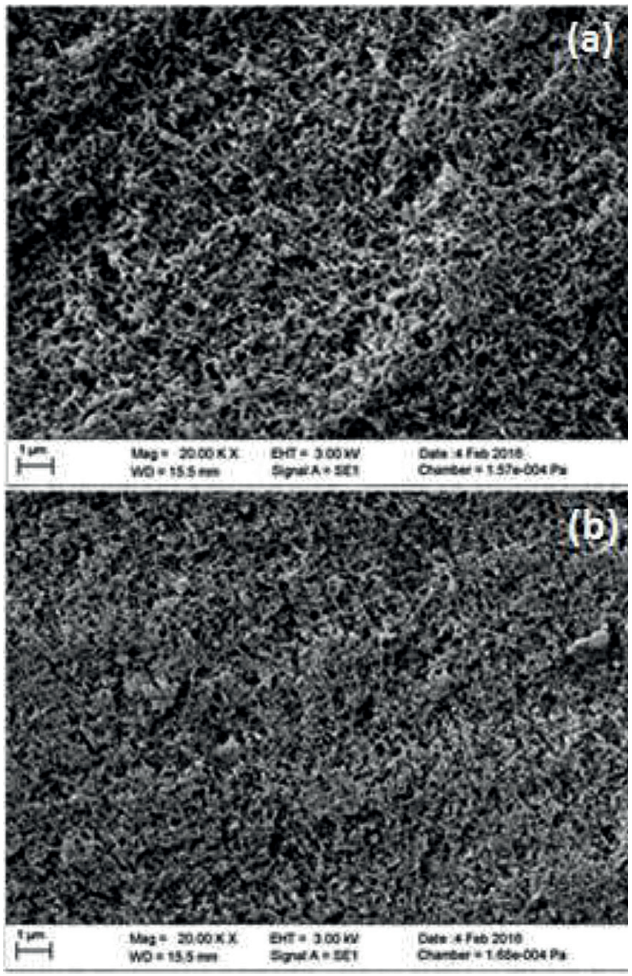

Figure 2
SEM micrographs of (a) MIP and (b) NIP

a higher total pore volume than the NIP. This corresponds well with SEM results, which were translated to MIP having larger pore sizes compared to the NIP. Furthermore, a bigger total pore volume for MIP implies that it has a higher sample load capacity than the NIP (Farrington and Regan, 2007). The average pore diameters for both MIP and NIP fall in the range of 2–50 nm, which indicates mesoporous structures in both polymers (Cormack and Elorza, 2004).

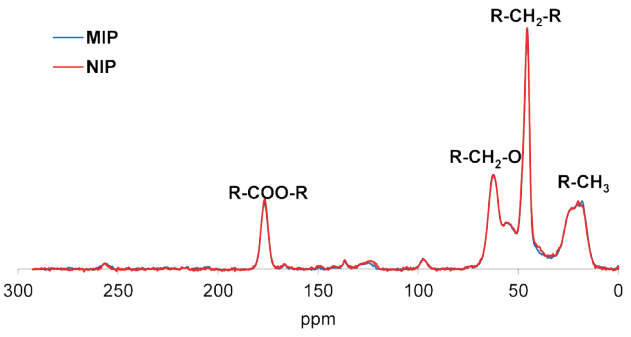

Figure 3
Solid-state 13C CP/MAS NMR spectra of the MIP and NIP

TABLE 2
Brunauer, Emmett and Teller analysis of polymers

Polymer	Surface area ($m^2 \cdot g^{-1}$)	Total pore volume ($cm^3 \cdot g^{-1}$)	Average pore diameter (nm)
MIP	209	0.59	11.3
NIP	95	0.30	12.6

Spectroscopic characterization of the synthesized polymers

The solid-state ^{13}C CP/MAS NMR spectra for both MIP and NIP were identical (Fig. 3), implying the identical arrangement of carbon atoms in the polymeric network. The assigned major signals corresponded well with those given for MIPs and NIPs synthesized with similar reagents (Skogsberg et al., 2007; Madikizela and Chimuka, 2016 a). In addition, methyl (17 ppm), methylene (61 ppm) and CO_2R (175 ppm) groups were all observed in the spectra, as expected due to the nature of imprinting, which uses a large amount of ethylene glycol dimethacrylate as a cross-linking monomer (Fig. 3). These strong resonances in the aliphatic region were associated with the cross-linking and functional monomers (2-vinylpyridine), whereas at the far end carbonyl grouping in CO_2R is clearly visible, which is in good agreement with observations made elsewhere (Kizhakekuthiathottil and Beena, 2011; Skogsberg et al., 2007; Sobiech et al., 2016).

Similar structural arrangements for MIP and NIP were further confirmed with FTIR (Fig. 4). Strong intensities for C=O and C-O groups at ≈1 765 and ≈1 382 cm^{-1} indicated the high degree of cross-linking (EGDMA) agent in the polymer network (Pakade et al., 2011; Wang et al., 2009). The appearance of C-N stretch at ≈1 323 cm^{-1} in all polymers' spectra was caused by the presence of cyanide groups in polymers that originate from the functional monomer and initiator. FTIR spectra of the polymers were identical in all peaks, which was an indication that they were similarly synthesized with the same pre-polymerization reagents, with only the omission of ketoprofen for NIP.

Optimization of parameters for the adsorption of ketoprofen by molecularly imprinted polymer

Effect of adsorption medium

This study is based on the adsorption of ketoprofen from water; however, the uptake of the compound from different solvent

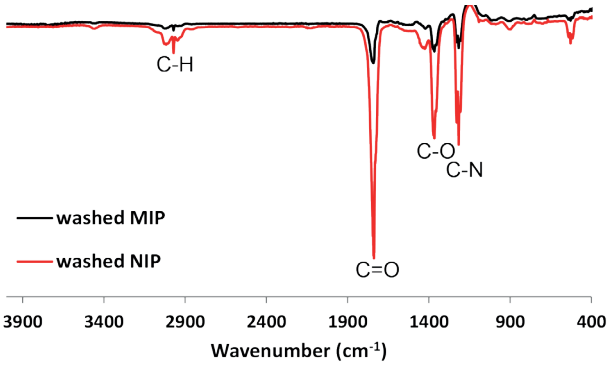

Figure 4
FTIR spectra of the synthesized MIP and NIP

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conditions was evaluated. The following organic solvents in the order of increasing polarity were investigated; toluene, chloroform and acetonitrile. In each case, other parameters were held constant while varying the extraction medium. The highest extraction efficiency (97%) was achieved when ketoprofen was dissolved in water (Fig. 5). This was followed by good extraction efficiencies obtained when ketoprofen was extracted from chloroform (82%) and toluene (62%). Both chloroform and toluene are less polar than acetonitrile while ketoprofen has a polar group. This could easily promote the adsorption of polar ketoprofen onto MIP particles from chloroform and toluene while there are strong interactions between ketoprofen and acetonitrile. In addition, toluene was used in the porogenic mixture; therefore, similarly to our previous results, the adsorption occurs better in a solvent that was applied as porogen (Madikizela et al., 2016).

Furthermore, in the same previous study, Madikizela et al. (2016) observed low extraction efficiency in polar organic solvents due to the possible competition for hydrogen bonding in the MIP cavity that could occur between solvents and target compounds. Thereafter, subsequent experiments were conducted using water as the adsorption medium.

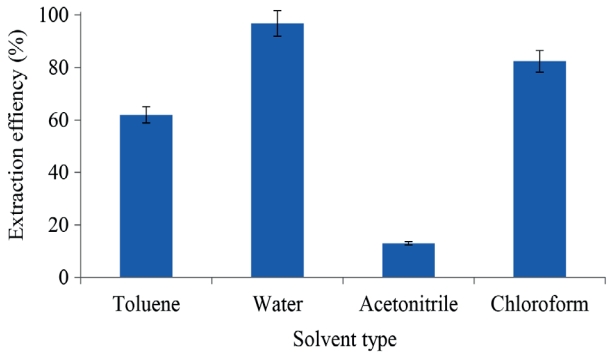

Figure 5

Effect of solvents on the extraction efficiency of ketoprofen by MIP sorbent. Experimental conditions: sample pH (unadjusted neutral), contact time (45 min), polymer mass (8 mg), sample volume (10 mL) and concentration of ketoprofen (1 mg·L^{-1}) (n = 3).

Effect of sample pH

The pH of the sample solution affects both the aqueous chemistry and the binding sites of the polymer, which in turn have an influence on the adsorption process (Madrakian et al., 2013). In the current study, pH was varied from 3 to 9 while other extraction conditions were kept constant. The results (Fig. 6) indicate that the extraction efficiency was higher at acidic pH, which was significantly reduced as the pH was increased. This is in agreement with the findings reported in literature, where it has been demonstrated that at low water pH there is an increase in adsorption of acidic compounds to polymers with monomers containing nitrogen (Meischl et al., 2016). This could be explained by the protonation of acidic compounds in acidic media which results in adsorption through hydrogen bonding, as computationally demonstrated earlier. In order to avoid the excess usage of acids during pH adjustments, pH 5 was selected as optimum pH and used in the experiments that followed. This was further elaborated using the results from zeta potential (Fig. A1), where a MIP was dispersed in water under acidic and basic conditions. The average zeta potential of MIP at pH 5 and 9 were –30.3 mV and –15.6 mV, respectively. This means that the surface was more negatively charged at pH 5 than pH 9 which resulted in strong adsorption of protonated ketoprofen at acidic conditions.

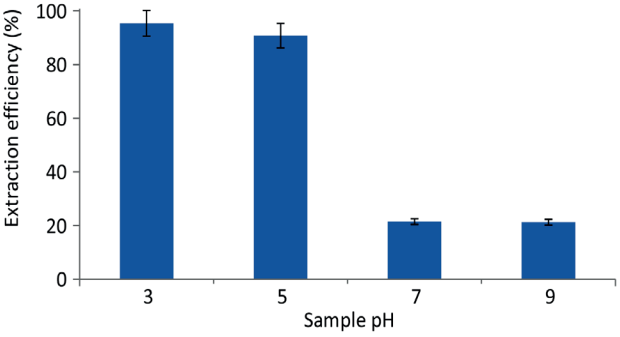

Figure 6

Effect of sample pH on the extraction efficiency of ketoprofen by MIP sorbent. Experimental conditions: 10 mL water, contact time (45 min), polymer mass (8 mg) and concentration of ketoprofen (1 mg·L^{-1}) (n = 3).

Effect of contact time

The relationship between the amount of ketoprofen adsorbed and contact time with the MIP is shown in Fig. 7, where the other experimental conditions were fixed. In the studied time range (5–60 min), the extraction efficiency varied from 75% to 80%. In comparison, in our previous study we observed that the maximum adsorption of NSAIDs onto MIP could be achieved in as little as 2 min of contact time (Madikizela and Chimuka, 2016b). However, in order to ensure that there is sufficient contact between ketoprofen and MIP, 45 min was used in subsequent experiments.

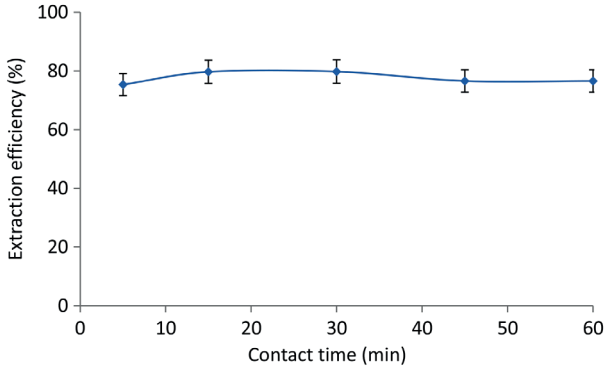

Figure 7

Effect of contact time on the extraction efficiency of ketoprofen by MIP sorbent. Experimental conditions: 10 mL water, sample pH 5, polymer mass of 8 mg and concentration of ketoprofen at 1 mg·L^{-1} (n = 3)

Effect of polymer mass

The effect of polymer amount was investigated by varying the mass of the MIP from 8 to 20 mg while the other experimental conditions were kept constant. In the studied adsorbent mass range, it was observed that the extraction efficiency was roughly independent of the polymer amount (Fig. 8), as the extraction efficiency varied slightly from 98 to 100%. This

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means that any amount of MIP from 8 mg and more could be able to extract 1 mg·L^{-1} of ketoprofen efficiently. Furthermore, this implies that the equilibrium had already been established when the minimum mass of the MIP (8 mg) was used. Normally, for lower masses, the extraction efficiency is expected to increase before attainment of equilibrium, where the increase in mass is directly proportional to the available adsorption sites (Tavengwa et al., 2013). In addition, the concentration of ketoprofen reported in South African wastewater is in the range of 0.38 to 6.40 µg·L^{-1}, which could indicate that any amount of MIP selected in this study is able to adsorb the acidic drug from environmental samples (Agunbiade and Moodley, 2016; Madikizela et al., 2014). Therefore, 8 mg of MIP was used in subsequent experiments.

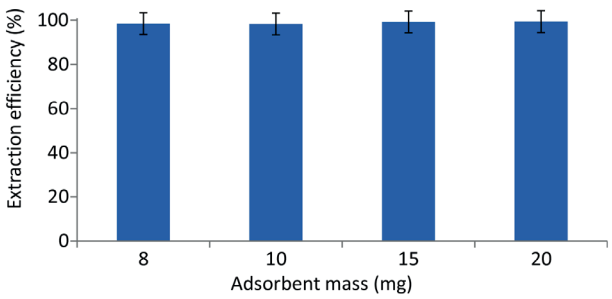

Figure 8
Effect of polymer amount on the extraction efficiency of ketoprofen by MIP sorbent. Experimental conditions: 10 mL water, sample pH 5, contact time of 45 min and concentration of ketoprofen at 1 mg·L^{-1} (n = 3).

Effect of initial concentration

This experiment was carried out by varying the initial concentration of ketoprofen while keeping other parameters constant. The adsorption capacity increased linearly as a function of initial concentration; this was observed until 60 mg·L^{-1} (Fig. 9). A small increase in adsorption capacity was observed in the concentration range of 60 to 70 mg·L^{-1}. This could indicate that the MIP was reaching saturation at higher concentrations. Due to the concentration of ketoprofen being expected at µg·L^{-1} levels in environmental samples, initial concentrations exceeding 70 mg·L^{-1} were not investigated. In any case, this experiment was carried out in order to understand how the concentration of ketoprofen affects its adsorption onto the MIP. This is important as it enables the determination of the maximum adsorption capacity for the MIP.

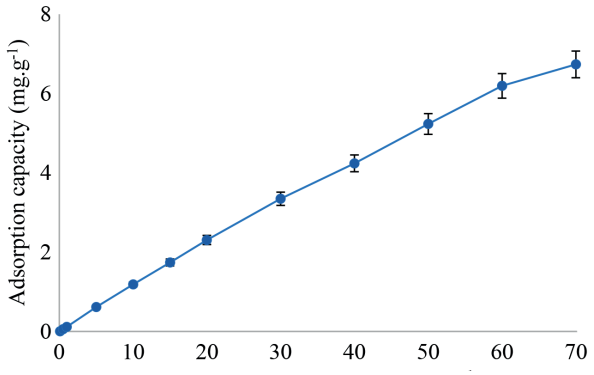

Figure 9
Effect of initial concentration of ketoprofen on the extraction efficiency of ketoprofen by MIP sorbent. Experimental conditions: 10 mL water, sample pH 5, contact time of 45 min, and polymer mass of 8 mg (n = 3).

Selectivity of MIP

The selectivity of the MIP was assessed using standard equations (Eqs 3–5) described earlier (Tavengwa et al., 2014; Xu et al., 2012). In the experimental set-up, deionized water was spiked with 1 mg·L^{-1} of ketoprofen in the presence of equal amounts of fenoprofen and gemfibrozil used as competitors in a multi-component system. Fenoprofen and gemfibrozil are themselves acidic pharmaceuticals having similar physico-chemical properties and size as ketoprofen (Table A1). Due to the presence of the carboxylic group in their chemical structures as well as ketoprofen, they are expected to form hydrogen bonds with 2-vinylpyrine used as functional monomer in molecular imprinting. Based on the molecular dynamics study, the hydrogen bonds between competitors and 2-vinylpyridine occur similarly to that between ketoprofen and 2-vinylpyridine (Fig. A2).

The adsorption of pharmaceutical drugs into MIP was allowed to equilibrate using the optimized experimental conditions. The K_d values obtained for adsorption of ketoprofen, fenoprofen and gemfibrozil on MIP were 1 065, 16 and 175 mL·g^{-1}, respectively (Table 3). This translated to the selectivity coefficient of 67 for the MIP. In comparison to the NIP, the relative selectivity coefficient (K') of 7.7 for the MIP was observed. This indicated that the selectivity is 8 and 2 times greater for ketoprofen in the presence of fenoprofen and gemfibrozil, respectively, compared to the NIP. These results indicated that the MIP was highly selective for ketoprofen recognition, relative to the NIP, in aqueous samples which resulted in a low selectivity coefficient (Mata et al., 2014). The order of sorption onto the MIP was ketoprofen > fenoprofen > gemfibrozil. Although ketoprofen and its competitors have similar size and functional groups, the MIP selectivity towards ketoprofen is influenced by molecular recognition due to differences in the shape of the target compound and its competitors.

Molecularly imprinted polymer surface adsorption mechanism

Pseudo-first-order (Eq. 7) and pseudo-second-order (Eq. 8) kinetic models were used to investigate the nature of adsorption for ketoprofen on MIP.

TABLE 3
Distribution coefficients, selectivity coefficients and relative selectivity coefficients for the MIP and NIP

Polymer	K_d (mL·g^{-1})		K	K'	K_d (mL·g^{-1})		K	K'
	Ketoprofen	Fenoprofen			Ketoprofen	Gemfibrozil		
MIP	1 065	15.9	67	7.7	1 065	175	6.1	2.03
NIP	265	30.3	8.7	-	265	89	3.0	-

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$$\log(Q_e - Q_t) = \log Q_e - \frac{k_1 t}{2.303} \quad (7)$$

$$\frac{t}{Q_t} = \frac{1}{k_2 Q_e^2} + \frac{1}{Q_e} t \quad (8)$$

where: Q_t is the adsorption capacity (mg·g^{-1}) at any time t (min); Q_e is the adsorption capacity at equilibrium (mg·g^{-1}); k_1 and k_2 are pseudo-first-order (min^{-1}) and pseudo-second-order sorption rate constants (mg·g^{-1}·min^{-1}), respectively (Madikizela and Chimuka, 2016b). The correlation coefficients (R^2) obtained for pseudo-first-order and pseudo-second-order models were 0.014 and 0.996, respectively. These indicate that the data fitted well with the pseudo-second-order kinetic model, which translates to the chemisorption of ketoprofen onto MIP particles. This was likely to be through H-bonding between the nitrogen atom of 2-vinylpyridine and the hydrogen atom in the carboxylic group of ketoprofen. The H-bonding of the template and the functional monomer was confirmed by computational modelling studies, as discussed earlier. Pseudo-second-order further meant that the target compound gets adsorbed onto two or more active binding sites on the surface of the MIP (Mata et al., 2014). The calculated adsorption capacity at equilibrium (Q_e) for MIP, based on the favourable pseudo-second-order model, was 3.22 mg·g^{-1}, whereas the experimental value was 0.12 mg·g^{-1}. The pseudo-second-order sorption rate constant (k_2) obtained for MIP when employing the kinetics models was 0.25 mg·g^{-1}·min^{-1}.

Isothermal analysis of the polymers was done using Eqs 9 and 10 for the linearized forms of the Freundlich and Langmuir isotherms, respectively.

$$\log Q = \frac{1}{n} \log C_e + \log \alpha \quad (9)$$

$$\frac{C_e}{Q} = \frac{C_e}{Q_{max}} + \frac{1}{Q_{max} K_L} \quad (10)$$

where: Q is the amount of the adsorbed molecule at equilibrium (mg·g^{-1}), n is the Freundlich exponent depicting the adsorption intensity, C_e is the equilibrium concentration of the target molecule (mg·L^{-1}), α is the adsorption capacity of the target molecule (mg·g^{-1}), Q_{max} is the maximum adsorption capacity (mg·g^{-1}) and K_L is the Langmuir adsorption equilibrium constant (Madikizela and Chimuka, 2016b; Mata et al., 2014). Linear plots were obtained for both Langmuir and Freundlich isotherms (Fig. A3); however, the larger R^2 for MIP (Table 4) in the Langmuir model indicates that the monolayer adsorption of ketoprofen at homogeneous binding sites was dominant. In addition, the results depicted in Table 4 show the Q_{max} of 8.7 mg·g^{-1} for MIP obtained from the Langmuir isotherm, which is close to the experimental maximum adsorption capacity shown in Fig. 9. Furthermore, the calculated n values (Table 4) are greater than 1, which indicates a favourable adsorption process, but due to low α values indicating the adsorption capacity, the Freundlich model was not considered as the best isotherm. A similar observation has been reported in literature, where comparable R^2 values for both Langmuir and Freundlich isotherms were achieved but due to the closeness of the Q_{max} values to the experimental adsorption capacity, the Langmuir model was described as the best fit (Pakade et al., 2017).

Environmental application

Data presented in this work describe the nature of adsorption for ketoprofen onto MIP particles. In a recent study, it has been demonstrated that the MIP prepared in this study is capable of adsorbing ketoprofen from wastewater (Zunngu et al., 2017). In this study (Zunngu et al., 2017), MIP was packed in the solid-phase extraction (SPE) cartridge and applied as sorbent in the determination of ketoprofen from wastewater using HPLC. Furthermore, the reported recovery obtained for wastewater spiked with ketoprofen was 68%, whereas the method detection limits of 0.23 and 0.17 µg·L^{-1} were achieved for wastewater influent and effluent, respectively. Upon application for environmental monitoring of ketoprofen in wastewater treatment plants, the drug was quantified in 3 wastewater influents and effluents at concentration ranges of 22.5–34.0 and 1.14–5.33 µg·L^{-1}, respectively. Despite the MIP's successful application as SPE sorbent in our previous work (Zunngu et al., 2017), there was no detailed information on the nature of binding and factors that could affect ketoprofen adsorption from contaminated water. Such information is important in order to ensure the complete removal of ketoprofen from contaminated water.

CONCLUSION

In this study, molecular dynamics simulation has indicated that ketoprofen interacts with 2-vinylpyridine through hydrogen bonding, which was further confirmed experimentally, where maximum adsorption of ketoprofen on MIP occurred under acidic conditions. Under acidic conditions, ketoprofen is protonated, which results in strong interactions with the nitrogen atom of 2-vinylpyridine in the MIP. Also, high extraction efficiency for ketoprofen molecules was observed, which is related to the high binding energy that was obtained for ketoprofen-2-vinylpridine complex in the molecular dynamics simulation. Furthermore, 2-vinylpyridine was computationally demonstrated as the suitable functional monomer in the synthesis of MIP for ketoprofen. The synthesized MIP was characterized by SEM, which showed that the surface of the MIP was rougher when compared to the NIP. Based on BET analysis, MIP had a larger surface area and total pore

TABLE 4
Data extracted from the adsorption isotherms

Polymer	Langmuir			Freundlich		
	R^2	K_L (L·mg^{-1})	Q_{max} (mg·g^{-1})	R^2	n	α
MIP	0.992	0.21	8.7	0.989	2.11	1.80
NIP	0.991	0.15	9.4	0.992	2.05	1.82

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volume than the NIP, which resulted in higher sample load capacity. The NMR results showed no differences in the chemical shifts obtained for MIP and NIP, which indicates that both polymers were chemically equivalent. Similar FTIR spectra were as a result of both MIP and NIP having a similar backbone structure. Although similarities were observed for both MIP and NIP in NMR and FTIR data, selectivity experiments proved MIP to be more selective to ketoprofen, due to the imprinting effect, in the presence of fenoprofen and gemfibrozil. Selectivity was observed to be 8 and 2 times greater for ketoprofen in the present of fenoprofen and gemfibrozil, respectively, compared to the NIP. The extraction efficiencies achieved for the ketoprofen when using MIP were between 70 and 100%. From the perspective of contact time, kinetics of sorption followed the pseudo-second-order model, further emphasizing the chemisorption mechanism. Using the initial concentration data, the Langmuir adsorption isotherms provided the best fitting model, which indicated that chemisorption of ketoprofen occurred on the homogeneous binding sites of the MIP.

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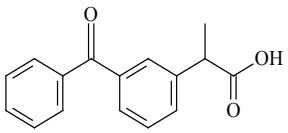
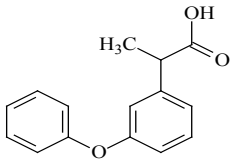
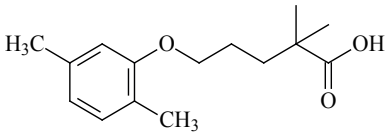
APPENDIX

TABLE A1
Chemical structures and physicochemical properties of ketoprofen and compounds used as competitors (Naghdi et al., 2018)

Chemical compound	Chemical structure	MW	*p*Ka	Log K_{ow}	Water solubility (mg·L^{-1})
Ketoprofen		254	4.29	3.12	51
Fenoprofen		242	4.21	3.90	Slight
Gemfibrozil		250	4.45	4.77	11

MW: molecular weight (g·mol^{-1})

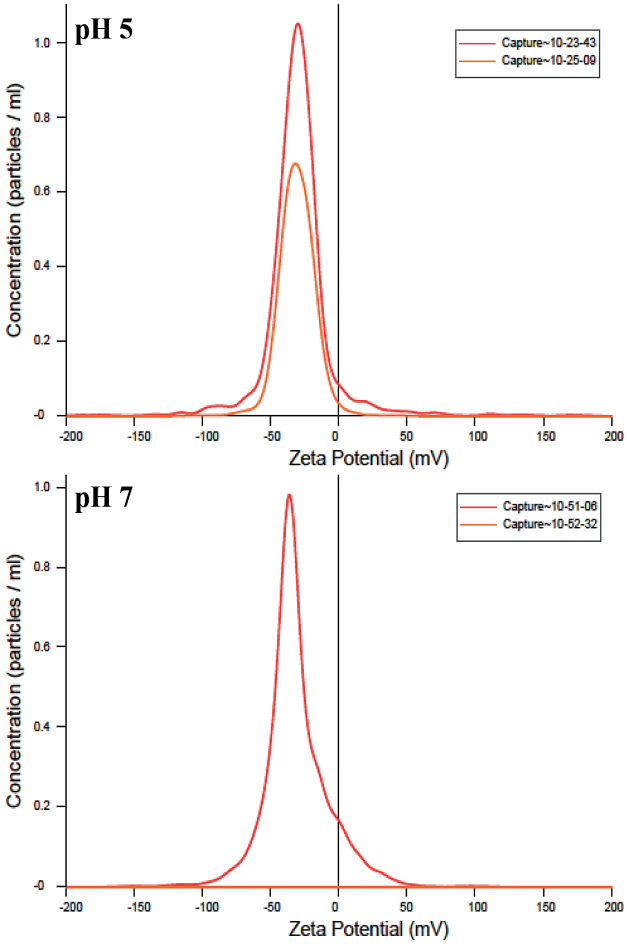


Figure A1
Zeta potential curves for MIP dispersed in water at pH 5 and pH 9

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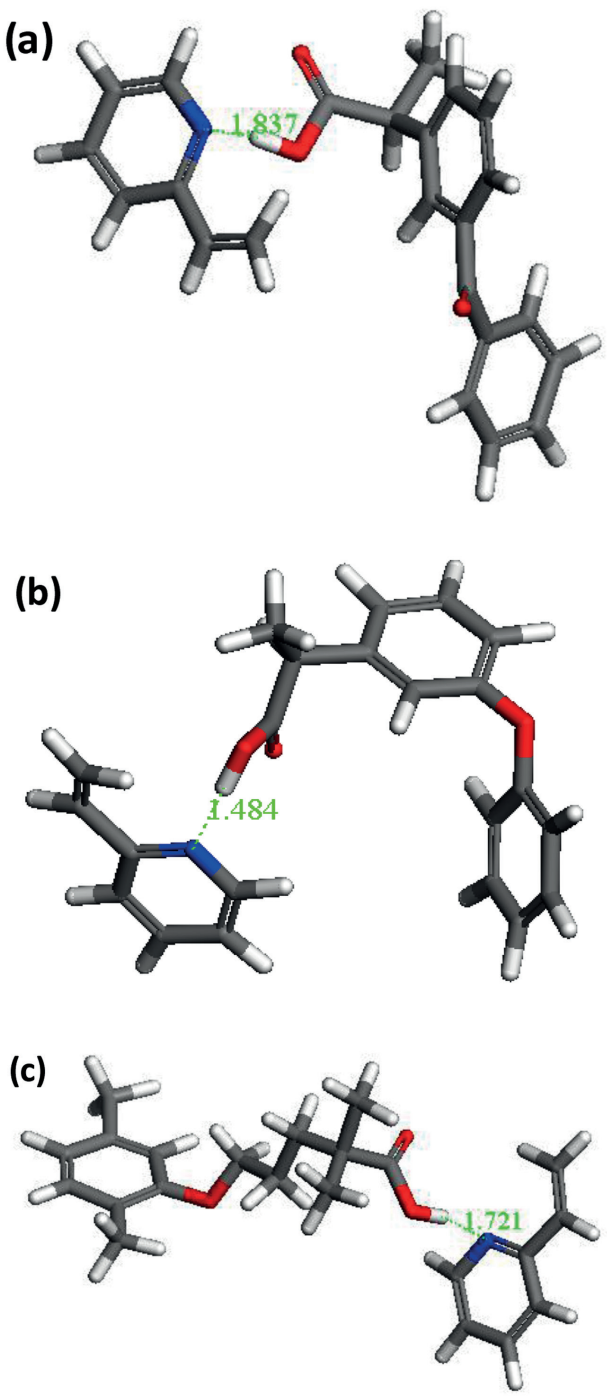

	Bond distance (Å)	ΔE (Kcal.mol^{-1})
Ketoprofen	1.837	-11.97
Gemfibrozil	1.721	-16.32
Fenoprofen	1.484	-18.20

Figure A2
Complex formation between ketoprofen and 2-vinylpyridine (a), fenoprofen and 2-vinylpyridine (b), and gemfibrozil and 2-vinylpyridine (c)

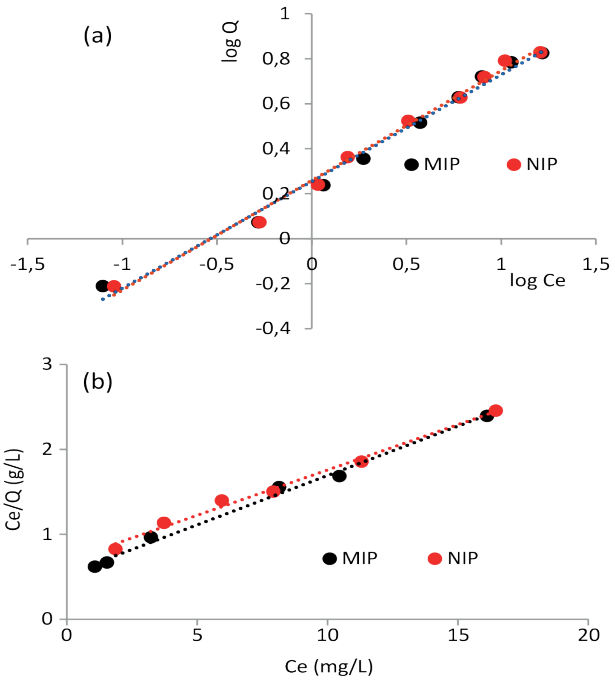

Figure A3
(a) Freundlich and (b) Langmuir plots of both MIP and NIP

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