MOLECULARLY IMPRINTED POLYMER FOR THE REMOVAL OF DICLOFENAC FROM WATER: SYNTHESIS AND CHARACTERIZATION.

[1,3]Nurlin Abu Samah, [1]María-Jesús Sánchez-Martín, [2]Rosa Mª Sebastián, [1]Manuel Valiente, [1]Montserrat López-Mesas*

[1] Universitat Autònoma de Barcelona, Centre Grup de Tècniques de Separació en Química (GTS), Química Analítica, Departament de Química, 08193 Bellaterra, Spain.

[2]Universitat Autònoma de Barcelona, Química Orgànica, Department of Chemistry, 08193 Bellaterra, Spain.

[3]Faculty of Industrial Sciences & Technology, Universiti Malaysia Pahang, Lebuhraya Tun Razak, 26300 Pahang, Malaysia.

E-mail*: montserrat.lopez.mesas@uab.cat

Abstract

Contaminant of Emerging Concerns (CECs) have been introduced as one type of recalcitrant pollutant sources in water. In this study, the non-steroidal anti-inflammatory drug diclofenac (DCF) has been removed from water solutions using Molecularly Imprinted Polymer (MIP), synthetized via bulk polymerization with allylthiourea (AT) as the functional monomer and using DCF as template (MIP-DCF). DCF detection has been performed by UV spectrophotometer. From the kinetic study in batch mode, approximately 100% of removal is observed by using 10 mg of MIP-DCF, with an initial concentration of 5 mg L^{-1} of DCF at pH 7, within three minutes and agitated at 25ºC. In continuous flow mode study, using a cartridge pre-packed with 10 mg of MIP-DCF, a high adsorption capacity of 160 mg DCF/g MIP was obtained. To study the porosity of MIPs, scanning electron microscopy (SEM) has been used.

In order to characterize the chemical interaction between monomer and template, the pre-polymerization mixture for MIP and DCF has also been studied by ^{1}H NMR. One of the chemical shift observed has been related to the formation of a complex between amine protons of thiourea group of AT with carboxylic acid on DCF. In conclusion, the developed MIP works as a good adsorbent for DCF removal, and is selective to DCF in the presence of indomethacin and ibuprofen.

Keywords: Molecularly imprinted polymer, diclofenac, contaminant of emerging concerns

1.0 Introduction

Organic micropollutants are typically released into the environment via wastewater discharges and land application of bio-solids, thus, contaminating the groundwater and surface waters that are used as drinking water resources.[1] Although the concentration is at trace level, they pose a risk to human health especially when micropollutants are found after the wastewater treatment plant[2], releasing the treated water for human's need, such as tap water. Contaminant of Emerging Concerns (CECs) include organic compounds persistent towards the conventional wastewater treatments. The best way to vanish them is the degradation using advanced oxidation processes (AOPs). However, problems may arise due to the potentially toxic transformation products than can be formed during the degradation process. These AOPs treatments are practiced and applicable, but there are also other methods to consider based on recovery techniques to separate such compounds from water.

Diclofenac ((2-(2,6-dichlorophenylamino)phenylacetic acid, DCF) is commonly used in medical care as analgesic, anti-arthritic and anti-rheumatic agent[3] and it is one of the most frequently detected pharmaceuticals in the aquatic environment, river and surface waters.[4] It is considerably stable under normal environmental conditions, being photodecomposition the most probable decomposition pathway for its onsite elimination.[5] Even at very low concentrations of this drug, adverse effects in different organisms have been observed for instance the diet cycle of fish species such as bream, roach and stickleback was disturbed by the presence of DCF in water. These kinds of fish species were abundant at the lowland river where the majority of persistent organic pollutants could be found, especially CECs. It has also been stated that organic chemical emissions to water might cause certain fish species to come under pressure.[6]

It is certainly needed to remove these compounds from water. Common water treatments are photodegradation and sorption processes mainly using carbon. A photodegradation study has been developed at pilot scale[5], but the main drawback is the formation of toxic by-products. On the other hand, the sorption process using carbon as a sorbent would remove all the organic components included nutrients which are necessary for the aquatic life. Hence, new materials need to be developed to remove and, if possible, to recover pharmaceuticals since the price of drugs and pharmaceutical production such as DCF or ibuprofen is unstable in the market.

Molecularly-imprinted polymers (MIPs) are synthetic materials with artificially generated recognition sites able to selectively interact with a target molecule in front to closely-related compounds. Recently, MIPs are attracting widespread attention due to their prominent selectivity properties[7]. Bulk polymerization is the most popular and general method to prepare MIPs due to its attractive properties, such as rapidity and simplicity in preparation, with no requirement for sophisticated or expensive instrumentation, and purity in the produced MIPs.[8]

In the literature, the imprinted polymer using DCF as template, MIP-DCF, has been synthetized

in many ways including bulk polymerization[9] and precipitation polymerization[10]. According to Sun[9], MIP-DCF has been developed using different types of monomer such as 2-vynilpyridine (2-VP) but the loading capacity was relatively low probably due to low effective functional sites able to interact with the molecule. On the other hand, the precipitation polymerization method is used due to its highly selective properties and total sorption amount; however, it required a high volume of porogen solvent during polymerization to produce the particles.

In the present work, the use of MIPs as removal technique of DCF from water has been proposed, to avoid DCF to reach human consumer waters, and being an opportunity to be recovered. Bulk polymerization has been chosen to synthetize a new MIP using DCF as a template (MIP-DCF) and thiourea groups. The synthesized MIP-DCF has been characterized and the pre-polymerization mixture of the complex formed between functional monomer and template has also been studied.

2.0 Materials & Methods

Reagents: Sodium Diclofenac (DCF-Na) and ibuprofen were from Cayman Chemical, United States with purities higher than 99%. Indomethacin (IDM), 1-allylthiourea (AT), acrylamide (AM) and ethylene glycol dimethacrylate (EGDMA) were 98-99% of purity from Sigma Aldrich (Spain). Figure 1 shows the chemical structure of some of the used compounds. 2,2-azobisisobutyronitrile (AIBN), 98%, was from Acros Organic (Belgium). Acetic acid (TLC grade) and hydrochloric acid were from J.T. Baker (96% and 37-38% of purity respectively). Sodium hydroxide (98%) was purchased from Panreac (Spain). Chloroform and acetonitrile (HPLC grade) were from VWR Company (Spain). Acetonitrile-d_3, analytical grade, was from Sigma Aldrich (Spain). Methanol, HPLC grade, from VWR Company, (Spain). Deionized water and nitrogen gas 99 % of purity was used.

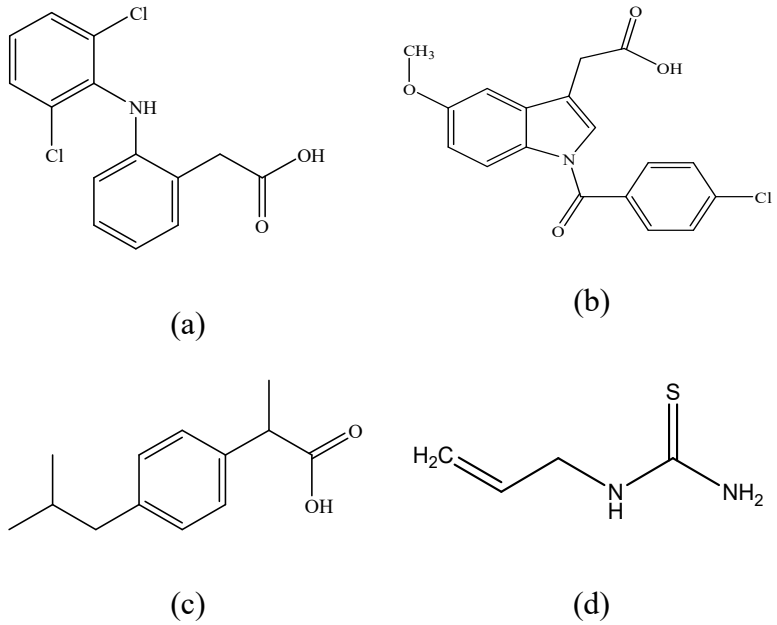


Figure 1. Chemical structure of (a) DCF, (b) IDM, (c) IBU and (d) AT.

Intrumentation: Water bath from E. Gabarro A-G (Germany). Soxhlet extraction apparatus from VWR company (Spain). Centrifuge from Orto Alresa model Digicen (Spain). Mortar grinder from Retsch (Germany). UV double-beam spectrophotometer from UNICAM, model UV-2 200 (USA). 400 MHz Nuclear Magnetic Resonance (^{1}H NMR) (Germany) (self-serviced at Servei de Ressonància Magnètica Nuclear (SeRMN), Universitat Autònoma de Barcelona, Spain).

2.1 Synthesis of MIP using DCF as template

To synthetize MIP-DCF, firstly DCF was converted into its acidic (DCF) form by dissolving the commercially available sodium salt (DCF-Na) in water (7 mg/mL) and acidifying the solution with HCl (equimolecular amount). The final solution was stirred for 10 min using a magnetic stir bar. Since DCF is insoluble in water, it immediately precipitates.[11] Afterwards,

the mixture was filtered using 0.45 µm filter paper and a vacuum apparatus and the precipitate was washed with dilute HCl (0.001 N) and water to remove any sodium chloride and unreacted DCF-Na. Finally, the powder was allowed to dry at room temperature, collected and stored in a clear glass vial.[12]

To prepare the MIP, the procedure based on Kugimiya's synthesis was followed[13], using DCF as template instead of phenylphosphonic acid or diphenyl phosphate. Diclofenac (DCF, 1.0 mmol), 1-allylthiourea (AT, 4.0 mmol), ethylene glycol dimethacrylate (EGDMA, 20 mmol), and 2,2-azobisisobutyronitrile as an initiator (AIBN, 0.12 mmol) were dissolved in 4.0 mL of acetonitrile.[13] The solution was sonicated and purged with nitrogen for 5 min to remove oxygen present in the solution.[9] Then, the sealed solution was polymerized at 60°C in a water bath for 24 h. Resulting polymer was successively washed with methanol/acetic acid (9:1, v/v) in a Soxhlet apparatus to remove DCF used as template.[14,15,16] A final washing step using 25 mL of methanol for three cycles was performed and polymer was centrifuged at 5300 rpm for 3 min to remove residual acetic acid. The supernatant methanol was analyzed using UV spectrophotometer at 280 nm in order to confirm that there was no template eluting from the polymer particles. Afterwards, the polymer was dried at 60°C under vacuum overnight and stored at room temperature.[14] Finally, the polymer was ground using automated mortar for 5 min and sieved several times to yield particle size between 28 µm and 100 µm. The non-imprinted polymer (NIP) was synthetized using the same procedure described above, but without the addition of a template, to evaluate the sorption capacity of the polymer itself and to discriminate from the absorption of the selective sites of MIP.

2.2 Kinetics

10 mg of MIP-DCF were added into 5 mL tubes. Then 2 mL of 5 mg/L of DCF solution were transferred to the tubes[14] and covered with aluminium foil. Since the solubility of DCF in water

is low[17] (2.37mg/L) a mixture of acetonitrile and water (5% v/v) has been used to dissolve it. The solution was agitated, and aliquots were collected at the desired time up to 120 min and filtered using a syringe filter (mesh size: 0.22 μm). The absorbance value at 280 nm (λmax) was measured by UV spectrophotometry. The procedure was performed in triplicate. The percentage of removal (% removal) was calculated using Equation 1 where C_i is the initial concentration of analyte and C_f is the final concentration after sorption. The concentration was obtained from a calibration curve of absorbance versus concentration. The same procedure was followed using NIP instead of MIP-DCF.

$$\%\, removal = \frac{C_i - C_f}{C_i} \times 100\% \qquad \textbf{Equation 1}$$

2.3 Total adsorption study

Batch mode: In order to characterize the total sorption or saturation profile of MIP-DCF, the analysis of the adsorbed amount for different initial concentrations of DCF in batch mode have been done. DCF solutions from 1 to 25 mg/L were prepared, limited by the solubility, in 5% of acetonitrile/water (pH 7) at room temperature. 2 mL of the different solutions of DCF were placed into 5 ml tubes. On the other hand, 10 mg of MIP-DCF or NIP were individually added to the different tubes. Then, the solutions were agitated for 1 h, covered using aluminium foil. Finally, they were filtered using a syringe filter (0.22 μm) and analyzed by UV spectrophotometry.

Continuous flow mode: Molecularly imprinted solid phase extraction (MISPE) was used. 10 mg of MIP-DCF was accurately weighted and placed in a cartridge of 1.5 mL of capacity. 2 L of DCF 15 mg/L in acetontrile/water (5% v/v) was prepared. Then, the solution was loaded

into the cartridge using a peristaltic pump at 1.67 mL/min of flow rate. The solution eluting from the cartridge was collected in fractions of 5 mL the first 50 mL, and afterwards, fractions of 50 mL. The solution was continuously-flowing until the absorbance measurements reached the plateau. Finally, all the fractions were analyzed via UV spectrophotometry. The procedure was performed in duplicate.

2.4 Effect of pH

DCF solutions of 15 mg/L were prepared at different pH, ranging from 3 to 12. Two mL of the solutions were added to different tubes containing 10 mg of MIP-DCF and agitated for 1 h. Then, they were filtered using a syringe filter (0.22 μm) and measured by UV spectrophotometry.

2.5 Porosity study

MIP and NIP were visualized by using Field Emission Scanning Electron Microscope (FESEM). The MIP particles were distributed on carbon disc attached to the pin stubs. The parameters were set as follows: EHT: 1kV, Mag: 34.63KX, WD: 4.1 mm for scale 1μm, or EHT: 1 kV, Mag: 16.20 KX, WD: 3.3 mm for scale 2 μm.

2.6 Selectivity study

Few selectivity studies are found in the literature and sometimes are conducted in individual solutions containing the interference only and not in a mixture containing both, analyte and interference.[18] Selectivity can be defined as the ability of differentiating and quantifying the analyte in the presence of other components from its matrix.[19] Hence, in our study two components in a mixture, analyte and interference, were analyzed together. To perform the study, 2 mL of the studied mixture solution consisting of DCF and ibuprofen (IBU) or

indomethacin (IDM) as interference, in 5 mg/L each, were added to 10 mg of MIP-DCF in 5 mL tubes. The solutions were covered using aluminium foil and agitated for 1 h, then filtered using a syringe filter (pore size: 0.22 μm). All analysis were done in triplicate and the solutions were analyzed by UV spectrophotometry.

2.7 Pre-polymerization study via ^{1}H NMR

The pre-polymerization process takes place when the functional monomer interacts with actives sites of the template, previous to the addition of the crosslinker. A non-covalent molecular imprinting approach was followed to prepare the MIP. Molecular recognition of the template molecule by imprinted polymers is based on the intermolecular interaction between the template molecule and functional groups in the polymer. Thus, to study the interaction between the template molecule and the monomer in pre-polymerization complexes it is important to predict the recognition mechanism of the imprinted polymer.

In the present work, the interaction between DCF as template and AT as monomer in pre-polymerization complexes was studied by ^{1}H NMR spectroscopy which is nowadays widely used within the field of molecular imprinting.[20] To do so, three samples were prepared with a fixed concentration of template (DCF), 0.05 mol/L, and varying concentration of monomer (AT), 0.10 mol/L (a), 0.30 mol/L (b) and 0.50 mol/L (c) in acetonitrile-d_3. ^{1}H NMR spectra were acquired at room temperature in a 400 MHz spectrometer.

3.0 Results and Discussion

3.1 Kinetics

For DCF removal by MIP-DCF, the kinetic experiment shows important differences between MIP-DCF and NIP. According to the results obtained, more than 95% of DCF was removed

by MIP-DCF whereas less than 30% removal for NIP was achieved (Figure 2). It means that the binding is mainly due to the imprinted sites of DCF which creates specific interactions in the MIP-DCF, consequence of a well-templating procedure in the cross-linked polymers and not by the polymer itself (NIP). Moreover, the MIP-DCF is able to eliminate the 95% of DCF from the solution in 3 minutes.

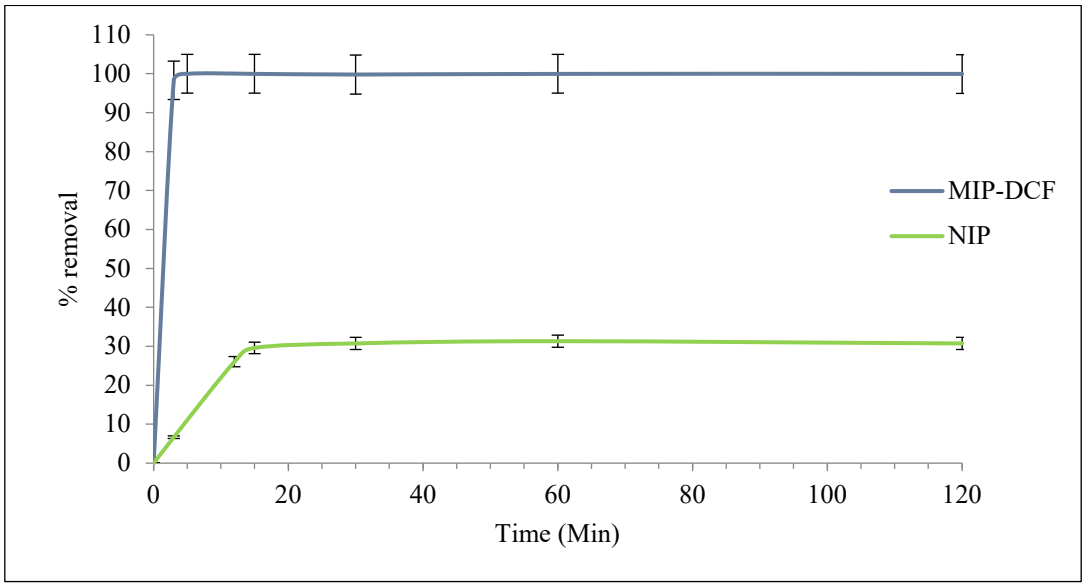


Figure 2. Percentage of removal of DCF (initial concentration 5 mg/L) by MIP-DCF and NIP in batch mode.

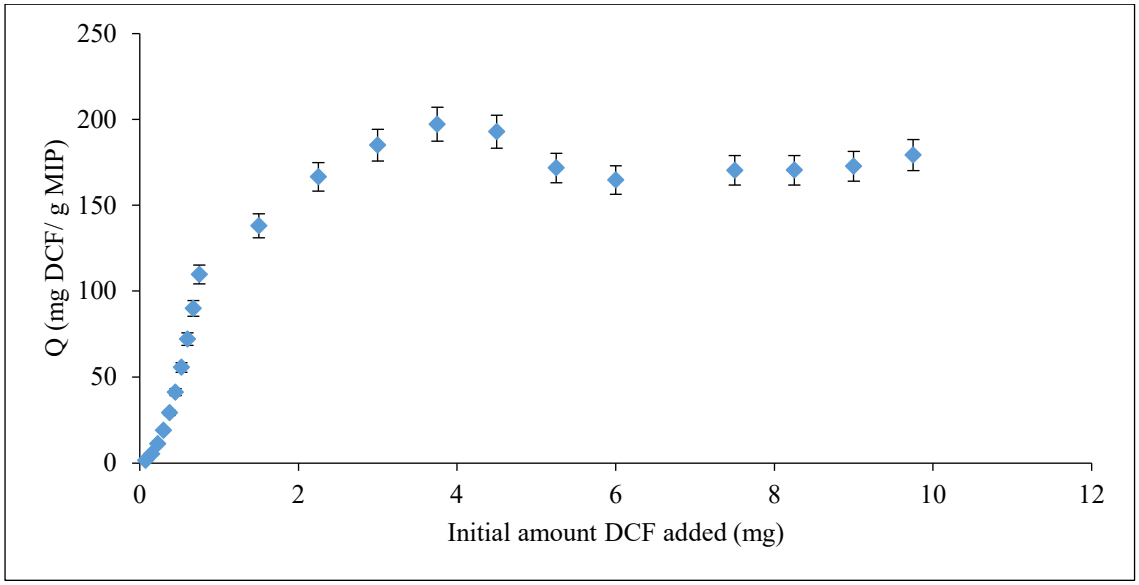
3.2 Adsorption capacity studies

Batch mode

The efficiency of the removal by MIP-DCF within the range of 1 to 25 mg/L has been studied. The total sorption capacity, Q (mg DCF/ g MIP-DCF), increases proportionally to DCF initial concentration. The linear regression equation obtained for the adsorption capacity was Q = 0.1956[DCF] - 0.0795 with R^2 equals to 0.9999.

230 ***Continuous flow mode***

231 Since the total sorption of the target molecule using batch mode did not reach a plateau, due to
232 the low solubility of DCF, molecularly imprinted solid phase extraction (MISPE) was
233 suggested as an alternative methodology. The total saturation obtained was 170 mg DCF/g
234 MIP-DCF (0.0058 mmol of DCF sorbed into 10 mg of MIP-DCF) as observed in Figure 3.



235

236 **Figure 3.** Sorption capacity (Q) of MIP-DCF after loading 15 mg/L DCF solution in a column
237 containing 10 mg of polymer in continuous flow mode.

238

239 **3.3 Influence of pH**

240 pH commonly affects the process of removal if the target molecule contains acid or/and basic
241 functional sites. According to the study carried out by Asiabi,[7] MIPs fabricated tend to isolate
242 the target molecule at neutral pH. However, it depends on the target molecule and the functional
243 sites in the cross-linked polymer. In the present study, pH range from 3 to 12 was studied. From
244 the obtained results, the percentage of removal obtained for pH lower than 7 was above 80%
245 for MIP-DCF. But since the pK_a for DCF is around 4.1 and due to the low solubility of the
246 neutral form, in acidic medium the compound precipitates being removed from the solution.

Figure 4 shows the sorption capacity at different pH values where it is observed that the best range for the highest removal by sorption process can be selected at pH range 5-7.

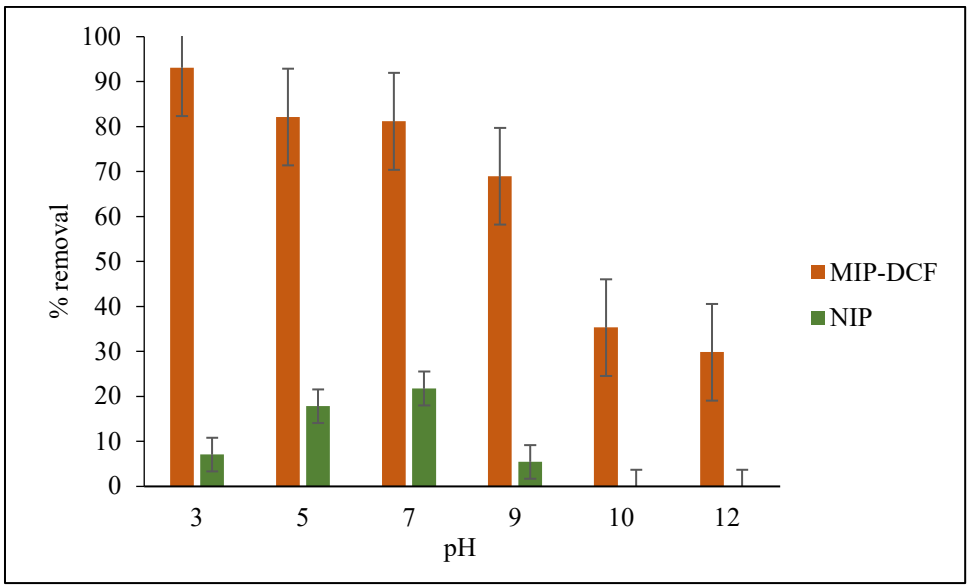
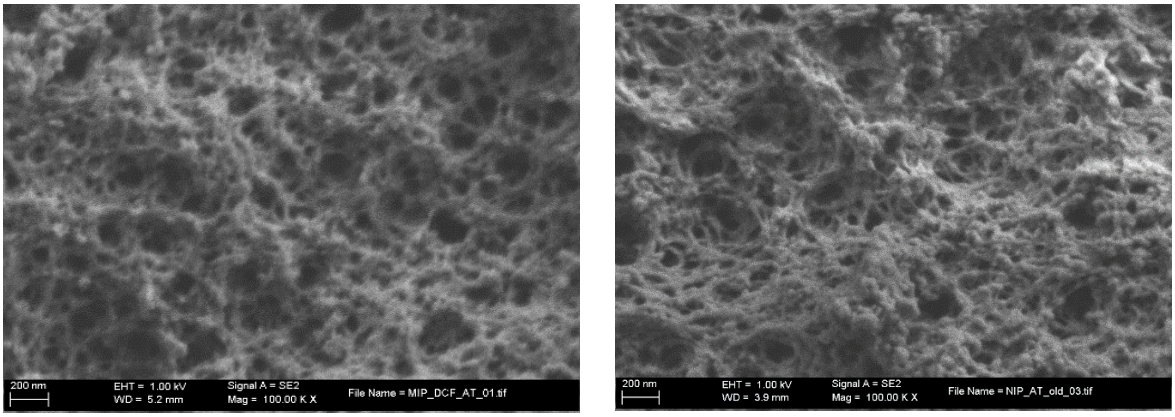


Figure 4. % removal of DCF in different pH solutions (pH 3 – pH 12) using 10 mg of MIP-DCF and NIP, and 2 ml of 15 mg/L of DCF, medium: acetonitrile/water (5% v/v) and agitated for 1 h.

3.4 Porosity study

The SEM picture of MIP-DCF and NIP are shown in Figure 5a and 5b respectively. It is seen that the pores size for MIP-DCF (5a) is more homogeneous than NIP (5b) and in average the pore size is about 200 nm of size for MIP-DCF and slightly lower to NIP, so the porosity of the material seems to be increased by the use of the template.



(a) (b)

Figure 5. SEM pictures for (a) MIP-DCF and (b) NIP with AT as the functional monomer at magnificence 100 kV; EHT at 1.00 kV and scale 200 nm.

3.5 Selectivity study

Simultaneous detection of two components in a mixture consisting of DCF and indomethacin (IDM) or ibuprofen (IBU) was carried out via UV-spectrophotometry. For the quantification, different calibration curves for each target molecule at its maximum wavelength, 260 nm for IDM, 280 nm for DCF and 220 nm for IBU, were done. The selectivity studies were carried out by MIP-DCF as a sorbent in two different mixtures, Mixture 1, containing IDM and DCF and Mixture 2, with DCF and IBU at 5 mg/L each respectively.

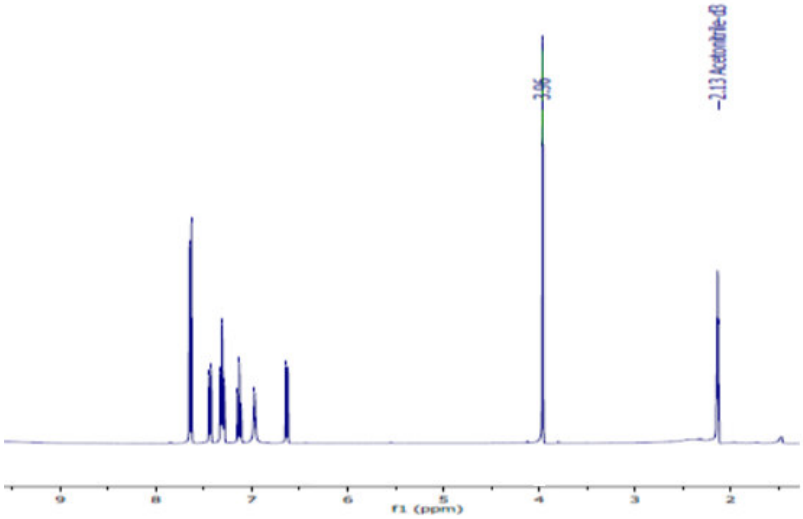
In Mixture 1, DCF adsorption was found to be 100±5% and 57±1% for IDM. For Mixture 2, IBU was not adsorbed by the MIP-DCF. It could be explained because the functional sites on the template can interact selectively with the target molecule. As can be seen in Figure 1, in the three molecules there is a carboxylic acid functional group able to interact with thiourea groups through a double hydrogen bond interaction, promoting stable cyclic structures. This type of interaction has been studied by Li and co-workers.[21] Formation of these type of complexes has also been used during the last years for enantioselective organocatalysis.[20] However, if only this type of interaction would exist between the template and the MIP-DCF

279 all three molecules could be recognized, specially the smaller one, IBU, which was not the
280 case. It should be highlighted that an amino group is also present in DCF, that should also
281 interact with thiourea moieties through the formation of a hydrogen bond between the N atom
282 of the amine and protons of thiourea group. Taking into account pK_b of both phenylamino
283 group (aprox. 11) and thiourea (aprox. 15), the interaction in the other sense should not happen.
284 This type of interaction is also not possible with IDM. This molecule contains an amide group,
285 whose nitrogen atom presents low basicity and nucleophilicity. This fact could explain the low
286 selectivity to IDM. From another side, IBU does not contain any other nucleophilic functional
287 group in its structure, hence, its sorption by MIP-DCF was approximately zero.
288 On the other hand, the size of the molded cavities in the template is a paremeter to take into
289 account since IDM is lightly bigger than DCF (the template molecule) what would explain the
290 lower removal of the first one.
291

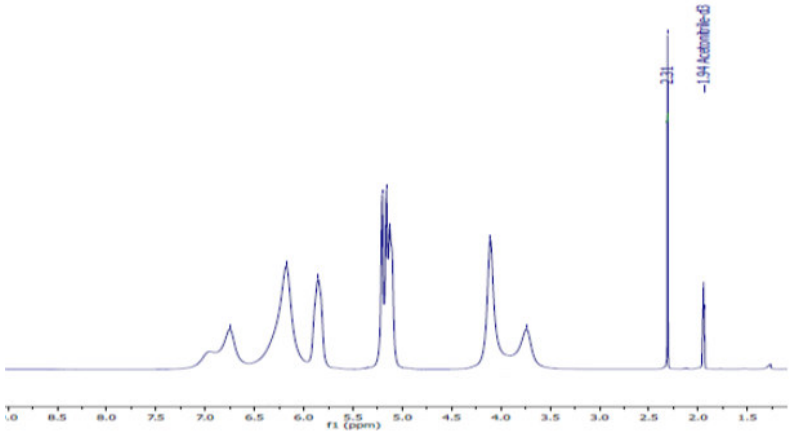
292 **3.6 Pre-polymerization study using ^{1}H NMR spectroscopy**

293 In the present work, simulated and experimental spectra were obtained for DCF and AT (Figure
294 6). In the experimental spectrum of pure AT, the observed peaks were broad because thiourea
295 functional sites have tendency to react via intermolecular and intramolecular reaction.
296 However, the experimental and the simulated spectra of pure DCF in acetonitrile-d_3 were very
297 similar. The simulation was done by using ChemDraw Ultra version 8.0 (data not shown).

(a)



(b)



298 **Figure 6.** ^{1}H NMR spectra of experimental (a) pure DCF and (b) pure AT in 1 mL of
299 acetonitrile-d_3 at 400 MHz.

300

301 In the pre-polymerization mixture, ^{1}H NMR has been used to study the interaction between
302 monomer (AT) and template (DCF). The results show more than one active functional sites so
303 it could be estimated that the synthesized MIP will have high affinity towards the analyte in
304 the sorption process as observed experimentally.
305 In order to produce high number of active imprinted sites on the imprinting polymer, it is well
306 known that the ratio between monomer and template is crucial,[9,20,22] an according to the

literature, the mmol ratio between monomer and template is optimum at 4:1. The structure of the complex formed between DCF and MIP is suggested in Figure 7. ChemDraw version 8.0 software has been used for this purpose.

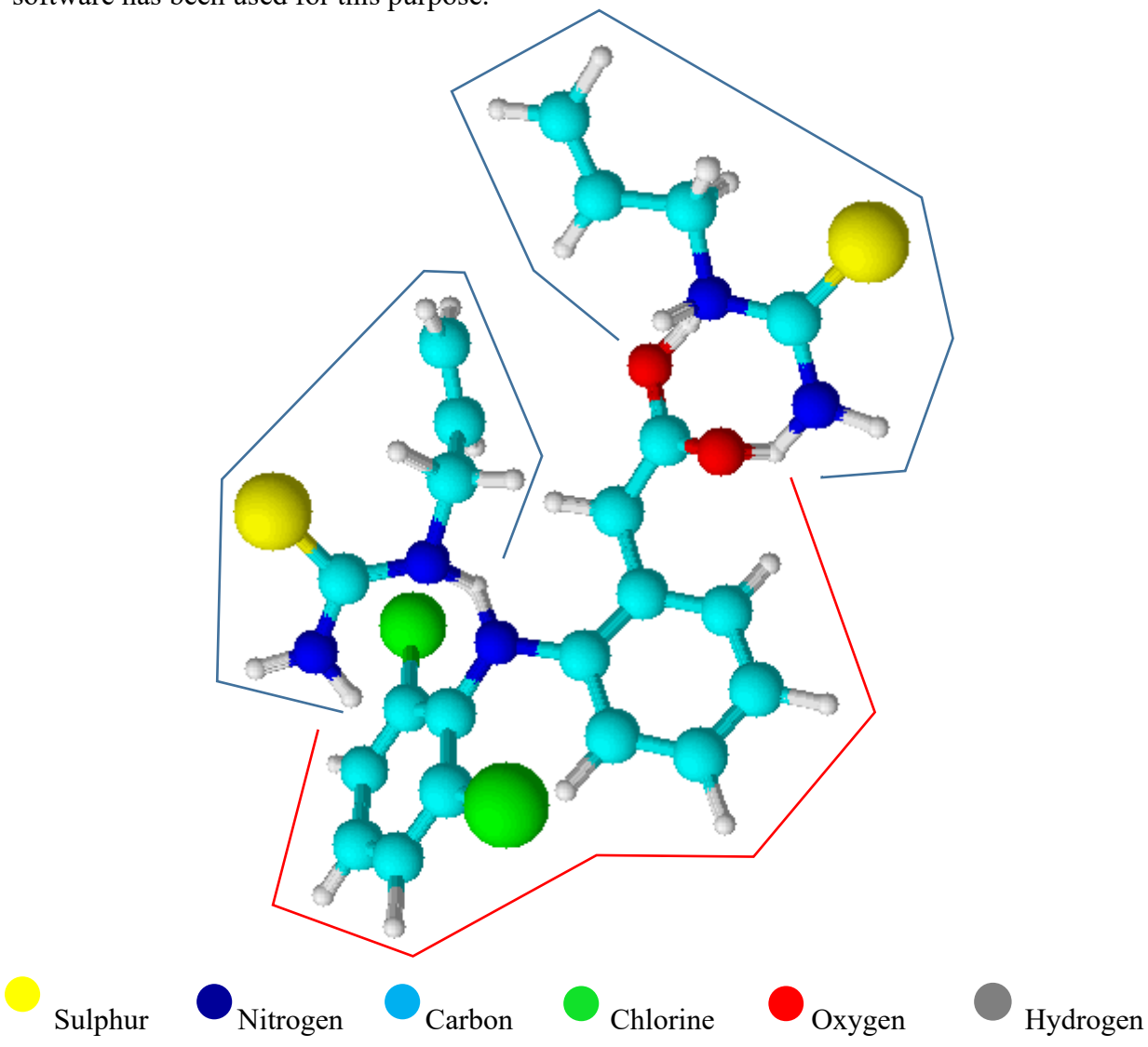


Figure 7. Complexes structure formed between DCF (—) and AT (—) with two active functional sites.

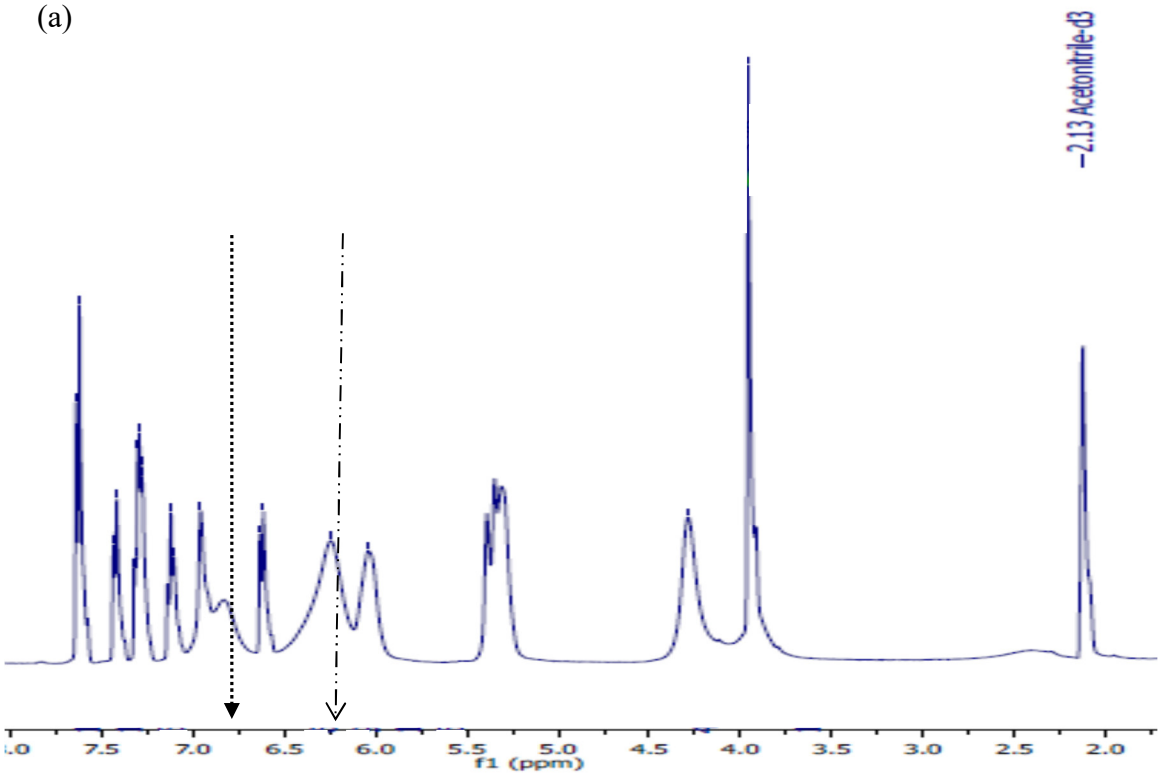
^{1}H NMR spectra for mixtures of 0.05 mol/L DCF and (a) 0.1 mol/L AT (b) 0.3 mol/L AT and (c) 0.5 mol/L AT in 1 mL of acetonitrile-d_3 at 400 MHz are shown in Figure 8. From the spectroscopy results, a chemical shift was observed from 6.3 ppm in mixture with 0.1 mol/L AT concentration to 6.45 ppm in mixture at higher AT concentration corresponding to the

protons of amino moieties of thiourea group of AT molecule bonded to the carboxylic acid at DCF molecule via hydrogen bonding. Generally, the reaction involved for pre-polymerization seems to forward the process as the results obtained for mixtures a, b and c showed that peaks in pure DCF or pure AT decreased and certain significant peaks could not be found in the mixtures spectra.

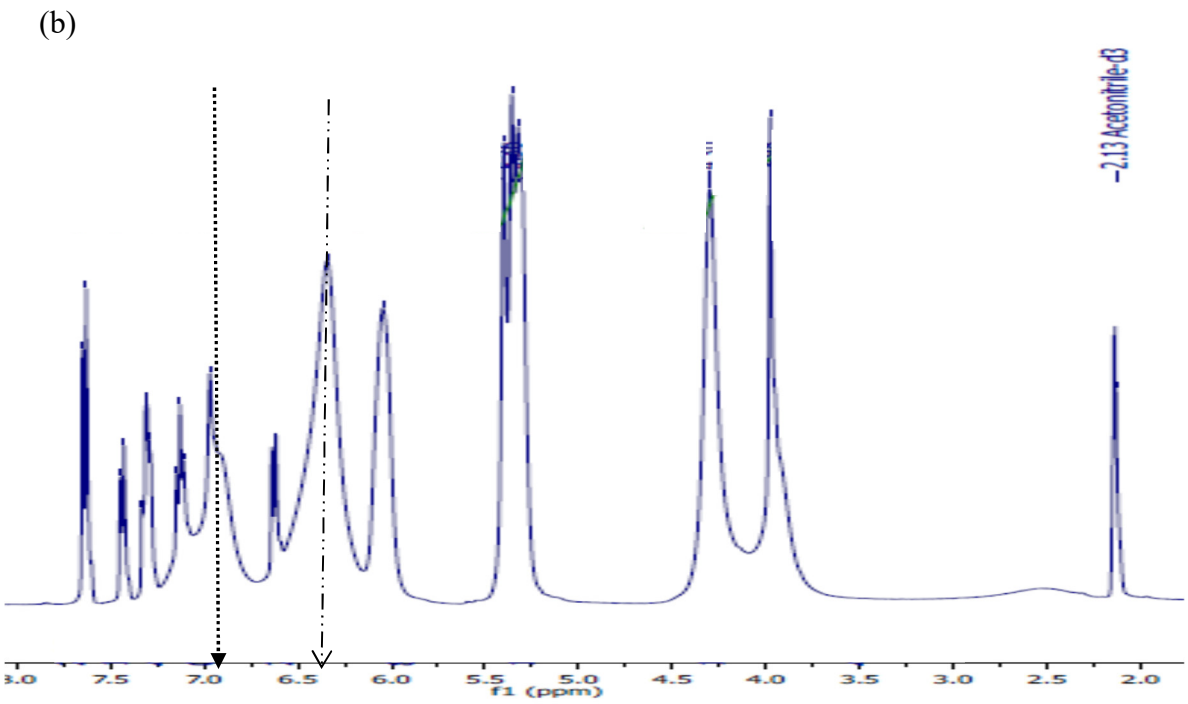
Similar finding was reported by Li[21] for the reaction between an aromatic thiourea and carboxylic acid to form a complex used as catalyst in cationic ring opening polymerization. In their work, when the amount of 1,3-bis-(3,5-bis(trifluoromethyl)phenyl) thiourea (TU) (functional monomer) was increased at fixed trifluoroacetic acid (TFA) (template) concentration, the chemical shift was downfield from 7.83 ppm to 7.94 ppm. The authors stated that TU as anion receptor coordinated with carboxylate by double hydrogen bonding interactions, and was expected to stabilize the anion and lower the pKa of the oxy-acid, thus allowing the increase of the electrophilicity of the activated cationic substrate. In the present case, slight downfield chemical shift was observed for acidic proton of DCF that agrees with the more acidic behavior of the proton when the complex between AT-DCF is formed.

Moreover, in our work, a peak is downfield from 6.6 ppm to 6.9 ppm due to hydrogen bonding between nitrogen atom amine group of DCF and a hydrogen nitrogen atom of thiourea group at AT. Similar finding was reported by Sun[9] in which a chemical shift was downshield from 7.70 ppm to 7.82 ppm, when a pyridine moiety interacts with amino group of DCF.

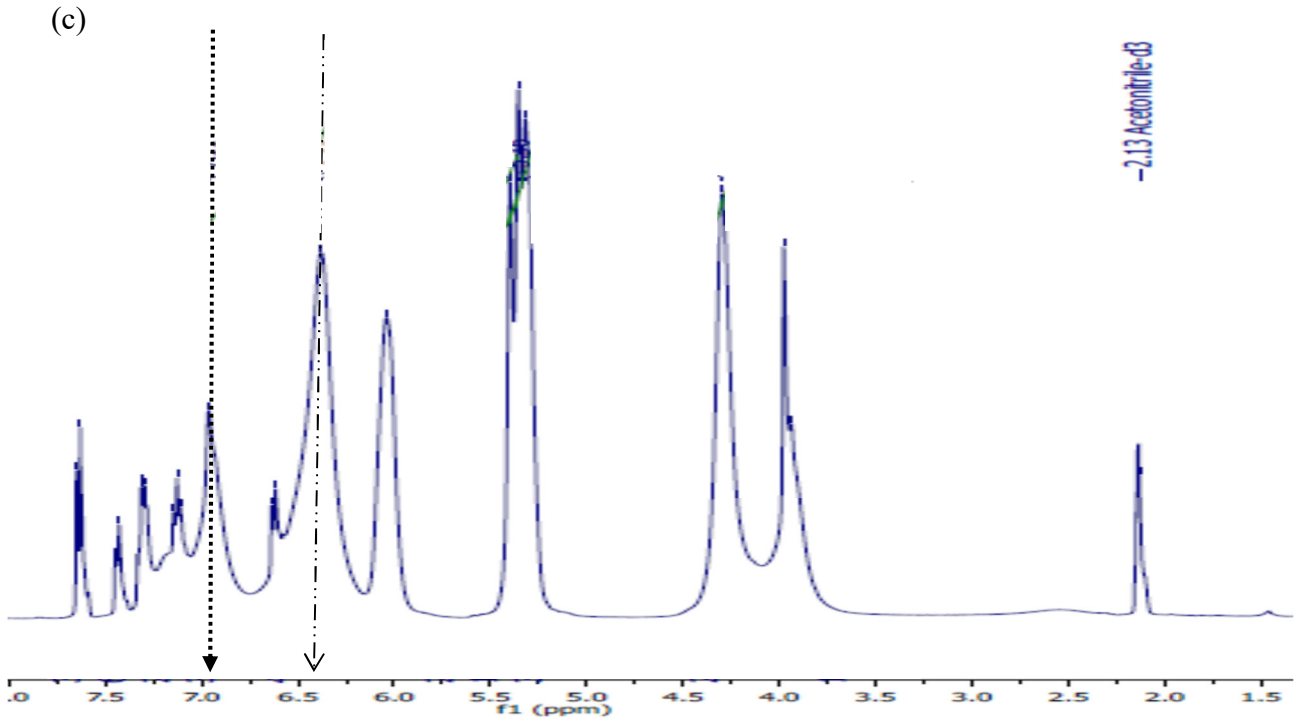
(a)



340



341



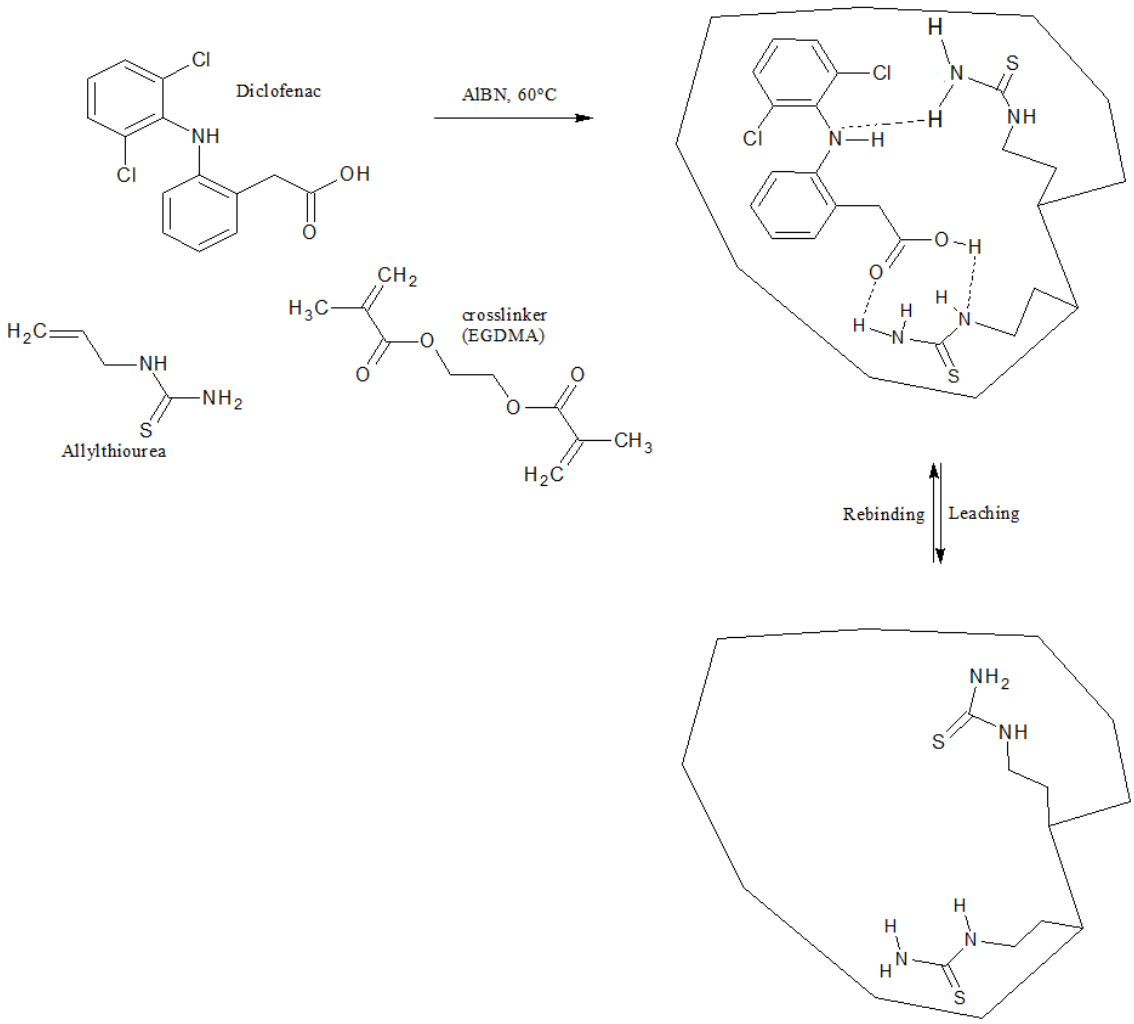
342 **Figure 8.** ^{1}H NMR spectra of mixtures of 0.05 mol/L DCF and (a) 0.1 mol/L AT (b) 0.3 mol/L

343 AT and (c) 0.5 mol/L AT in 1 mL of acetonitrile-d_3 at 400 MHz

344

However, Sun[9] used 2-vynilpyridine (2-VP) as the functional monomer for synthesizing the polymers MIPs. The clear difference between the two monomers (2-VP and AT) is that there is only one active functional site on 2-VP molecule whereas there are two active functional sites on AT molecule. When 2-VP and DCF were in contact at the pre-polymerization stage at least two non-covalent bonds were formed, one was an ionic interaction (acid DCF-base pyridine ionic pair formed) and another one was hydrogen bonding between NH proton of DCF and nitrogen atom at pyridine ring with pK_b at 8.8. In this case, pyridine is more basic than aniline contained in DCF with pK_b value in range of 9-13. Interaction between AT and acid group of DCF is strong and well fixed, generating a well ordered complex formed by two hydrogen binding (as a chelate interaction). Moreover, the possibility of having an additional hydrogen bond between, once more, protons of thiourea moieties and the nitrogen atom of aniline group of DCF, can promote a higher selectivity compare with the system of 2-VP.

Based on the commented results, the mechanism of the reaction to form MIP-DCF is proposed in Figure 9 (ChemDraw version 8.0 software has been used). In the proposed mechanism, there are two active functional sites on one AT molecule.



360 **Figure 9.** Scheme of proposed reaction mechanism of DCF and AT as the functional monomer
361 in MIP-DCF formation.

362

363 **4.0 Conclusion**

364 A new molecularly imprinted polymer (MIP) with DCF as the template using allylthiourea
365 (AT) as the monomer via bulk polymerization was successfully synthetized. One of the
366 significant findings to emerge from this study is that there was more than 90% of efficiency
367 removal within 3 min by MIP-DCF compared to NIP. The present work is much faster and less
368 laborious. pH of the solution during removal processes also has been tested and the best pH
369 value in order to achieve the highest sorption capacity is at pH below 7. The selectivity study

shows that the N-H functional group located at the center of DCF compound favored the reaction with the active functional sites of the MIP. Hence, DCF was favored to be trapped into the cavities compared to IDM and IBU. The preliminary experimental results obtained in pre-polymerization stage study were consistent to the suggested scheme reaction of MIP synthesis. The presence of the thiourea moieties allow not only a double interaction with the acid group of DCF, but also most probably generates an extra hydrogen bond interaction with N atom of aniline group in DCF. This triple interaction should promote a well-ordered template that could be responsible of the high removal % and the selectivity among other acidic pharmaceutical moieties.

Acknowledgements

The authors thank Spanish Project CTM 2015-65414-C2-1-R, Skim Latihan Akademik IPTA (SLAI) by Ministry of Higher Education, Malaysia and Universiti Malaysia Pahang, Malaysia for financial support.

References

1. Murray, A. & Örmeci, B. Application of molecularly imprinted and non-imprinted polymers for removal of emerging contaminants in water and wastewater treatment: A review. *Environ. Sci. Pollut. Res.* **19,** 3820–3830 (2012).

2. Bueno, M. J. M. *et al.* Occurrence and persistence of organic emerging contaminants and priority pollutants in five sewage treatment plants of Spain: Two years pilot survey monitoring. *Environ. Pollut.* **164,** 267–273 (2012).

3. Pérez-Estrada, L. a. *et al.* Photo-fenton degradation of diclofenac: Identification of main intermediates and degradation pathway. *Environ. Sci. Technol.* **39,** 8300–8306

(2005).

4. Huber, C. *et al.* Emerging pollutants and plants – Metabolic activation of diclofenac by peroxidases. *Chemosphere* **146,** 435–441 (2016).

5. Pérez-Estrada, L. A. *et al.* Decomposition of diclofenac by solar driven photocatalysis at pilot plant scale. *Catal. Today* **101,** 219–226 (2005).

6. Johnson, A. C. *et al.* Do concentrations of ethinylestradiol, estradiol, and diclofenac in European rivers exceed proposed EU environmental quality standards? *Environ. Sci. Technol.* **47,** 12297–12304 (2013).

7. Asiabi, H., Yamini, Y., Seidi, S. & Ghahramanifard, F. Preparation and evaluation of a novel molecularly imprinted polymer coating for selective extraction of indomethacin from biological samples by electrochemically controlled in-tube solid phase microextraction. *Anal. Chim. Acta* **913,** 76–85 (2016).

8. Chen, L., Xu, S. & Li, J. Recent advances in molecular imprinting technology: current status, challenges and highlighted applications. *Chem. Soc. Rev.* **40,** 2922–2942 (2011).

9. Sun, Z., Schüssler, W., Sengl, M., Niessner, R. & Knopp, D. Selective trace analysis of diclofenac in surface and wastewater samples using solid-phase extraction with a new molecularly imprinted polymer. *Anal. Chim. Acta* **620,** 73–81 (2008).

10. Dai, C. M., Zhou, X. F., Zhang, Y. L., Liu, S. G. & Zhang, J. Synthesis by precipitation polymerization of molecularly imprinted polymer for the selective extraction of diclofenac from water samples. *J. Hazard. Mater.* **198,** 175–181 (2011).

11. Khazaeinia, T. & Jamali, F. A comparison of gastrointestinal permeability induced by diclofenac- phospholipid complex with diclofenac acid and its sodium salt . **6,** 352–

359 (2003).

12. Burke, J. Diclofenac Salts: Their Synthesis, Characterization and Lyophilization Cake Characteristics. (2007).

13. Kugimiya, A. & Takei, H. Preparation of molecularly imprinted polymers with thiourea group for phosphate. *Anal. Chim. Acta* **564,** 179–183 (2006).

14. Yang, T., Li, Y. H., Wei, S., Li, Y. & Deng, A. Development of a selective molecularly imprinted polymer-based solid-phase extraction for indomethacin from water samples. *Anal. Bioanal. Chem.* **391,** 2905–2914 (2008).

15. Puoci, F. *et al.* Spherical Molecularly Imprinted Polymers (SMIPs) via a Novel Precipitation Polymerization in the Controlled Delivery of Sulfasalazine. *Macromol. Biosci.* **4,** 22–26 (2004).

16. Lagha, A. A Molecularly Imprinted Polymer for the Selective Solid-Phase Extraction of Ibuprofen from Urine Samples. *Open Chem. Biomed. Methods J.* **4,** 7–13 (2011).

17. Fini, A., Laus, M., Orienti, I. & Zecchi, V. Dissolution and Partition Thermodynamic Functions of Some Nonsteroidal Anti-Inflammatory Drugs. *J. Pharm. Sci.* **75,** 23–25 (1986).

18. Amiri, A., Mohammad, A., Shabani, H., Dadfarnia, S. & Khodadoust, S. Spectrochimica Acta Part A : Molecular and Biomolecular Spectroscopy Solid phase microextraction of diclofenac using molecularly imprinted polymer sorbent in hollow fiber combined with fiber optic-linear array spectrophotometry. *Spectrochim. Acta Part a Mol. Biomol. Spectrosc.* **147,** 26–30 (2015).

19. Poole, C. F. Mike S. Lee: Mass Spectrometry Handbook. *Chromatographia* **75,** 1341–1342 (2012).

20. Dai, C.-M., Geissen, S.-U., Zhang, Y.-L., Zhang, Y.-J. & Zhou, X.-F. Selective removal of diclofenac from contaminated water using molecularly imprinted polymer microspheres. *Environ. Pollut.* **159,** 1660–1666 (2011).

21. Li, X. *et al.* Thiourea binding with carboxylic acid promoted cationic ring-opening polymerization. *Polymer (Guildf).* **84,** 293–303 (2016).

22. Dai, C. meng *et al.* Removal of carbamazepine and clofibric acid from water using double templates-molecularly imprinted polymers. *Environ. Sci. Pollut. Res.* **20,** 5492–5501 (2013).