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Molecularly imprinted polymers as solid-phase and dispersive solid-phase extraction sorbents in the extraction of antiretroviral drugs in water: adsorption, selectivity and reusability studies

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Abstract

The antiretroviral drugs (ARVDs) have been reported to be among the emerging water pollutants as a results attention is being paid on their analysis. This work therefore explored for the first time the multi-template MIP for the selective removal of selected ARVDs (abacavir, efavirenz and nevirapine) in wastewater, river water and tap water. The adsorption studies of a multi-template MIP were conducted by determining the effect of an increase in ARVDs concentration in solution and the effect of an increase in contact time between the sorbent and the ARVDs. High adsorption efficiencies were observed for abacavir, efavirenz and nevirapine analytes within 5 min and the maximum adsorption efficiency was observed at 60 min ranging from 94.76 to 96.93%. Adsorption kinetics showed that pseudo-second rate order was the best fitting model, while adsorption isotherms indicated that the Freundlich isotherm ($R^2 = 0.94–0.98$) best described the adsorption mechanism of ARVDs onto the MIPs. These results indicated that the electrostatic attractions influenced the multilayer coverage and chemisorption process. Selectivity studies conducted in the presence of competitors gave the recoveries between 92 and 98% for the target analytes, while they were 63–79% for competitors indicating good selectivity and strong affinity of the polymer towards the target analytes. Reusability studies showed that the MIP can be reused for up to 8 cycles with recoveries above 92% for all target ARVDs. The application of the MIP-DSPE method to wastewater, river and tap water samples gave concentrations of 28.75–178.02, 1.95–13.15 and 2.17–6.27 μg L^{-1}, respectively. These results indicate the potential unplanned consumption of ARVDs upon drinking contaminated water which could result to their resistance by the human body. Therefore, their continuous monitoring as well as investigation of their removal strategies is of paramount importance.

Keywords Dispersive solid-phase extraction, Molecularly imprinted polymer, Abacavir, Nevirapine, Efavirenz

Introduction

Pharmaceuticals are highly active chemical compounds designed to have specific physiological effects on target organs or tissues. Pharmaceuticals are not completely metabolized in the human body when ingested for the promotion of health. The indigested parts leave through urine and faecal matter into the sewage system and are transported into the wastewater treatment plants (WWTPs) (Prasse et al. 2010; Rimayi et al. 2018). The

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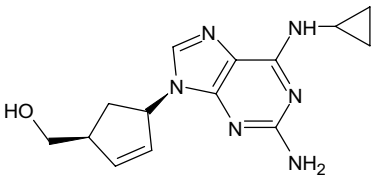
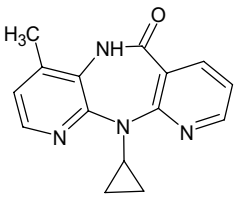
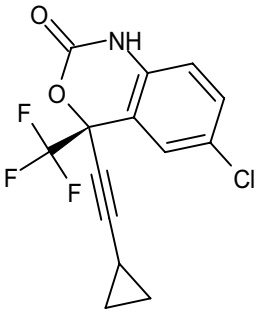
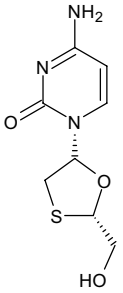
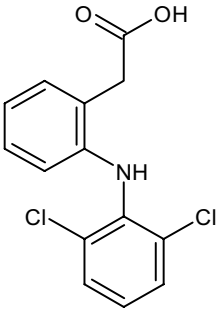
WWTPs are not designed to remove these compounds, and also, these drugs are highly soluble in water. Thus, their residues are released into the receiving rivers where they can have negative effect to aquatic animals and plants (Russo et al. 2018). The poor disposal of unused and expired drugs from household waste, pharmacies, industries and hospitals may result in their presence in WWTP as well as landfills and thus end up in ground and surface waters (Madikizela et al. 2018). Antiretroviral drugs (ARVDs) are pharmaceutical drugs used to prevent a retrovirus, such as human immune virus (HIV), from replicating and are mainly prescribed for the treatment of HIV/AIDS worldwide (Mlunguza et al. 2019). The ARVDs discharged to the rivers and WWTPs can end up in drinking water and be indirectly ingestion by the consumers leading to their accumulation in the body and hence possible drug resistance towards them (Russo et al. 2018; Schoeman et al. 2015). Exposure to high levels of ARVDs can affect the central nervous system, lipid, cardiovascular, cerebral vascular toxicity and neurological disorders (Smurzynski et al. 2011; Tijani et al. 2013; Bertrand et al. 2019; Nannou et al. 2020). This indicates the importance for their monitoring in the environmental matrices.

The behaviour of pharmaceuticals in the environment is mainly dependent on their physical properties such the solubility, pKa and octanol–water coefficient (log Kow). Octanol–water partition coefficient is used to measure how hydrophobic or hydrophilic a drug or chemical substance is (Nannou et al. 2020). Higher log Kow value indicates likeliness that a compound will be found more on a solid matrix than a liquid. Compound with smaller log Kow value (abacavir and lamivudine) has higher water solubility and thus is expected to be present in higher concentrations in water samples. On the other hand, compound with lower Kow value (efavirenz) has low water solubility and is expected to be highly adsorbed on solids (Mtolo et al. 2019). The pKa is an acid dissociation constant which can be related to strength and polarity of the acid or compound. Compound with high pKa value (abacavir) is a strong acid (completely dissociates) and has higher water solubility, while a compound with low pKa value (efavirenz) is relatively a weak acid (partially dissociates) and has low water solubility (Settimo et al. 2014). Table 1 shows the properties of some of the ARVDs.

Antiretroviral drugs are present at very low concentrations in the water bodies; hence, they require a very sensitive analytical technique for their possible determination and extraction in the water bodies. Solid-phase extraction (SPE) has been used for the extraction of many organic pollutants including pharmaceutical compounds due to its high sensitivity, and it is easy to use and fast (Fortunak et al. 2014). However, its sorbents lack selectivity especially for complex samples like environmental samples, and hence, molecularly imprinted polymers (MIPs) have been introduced as sorbents to increase selectivity and efficiency of this technique. The MIPs are easy to prepare and handle, and they have good thermal and chemical stability in comparison with SPE sorbents. They also can be applied to a wide range of compounds and can be reused with excellent reproducibility. The application of MIPs as SPE sorbents has very few but notable disadvantages such as swelling of the MIPs and loss of mass during packing into the SPE cartridge (Bitas et al. 2018). Dispersive solid-phase extraction (DSPE) incorporates direct dispersion of MIP particles into the sample under stirring/shaking and/or the use of conventional beads or magnetic nanoparticles to aid the recovery of the solid phase has been introduced to overcome MIP-SPE disadvantages (Azizi et al. 2020). After sufficient contact time between the sorbent and analyte(s), the particles are recovered by either centrifugation or magnetic field (if magnetic NPs are used). The recovered MIP particles are then introduced into an appropriate desorption solvent after a possible washing step.

Therefore, this work aim was to synthesize, characterize, and apply multi-template molecularly imprinted polymer for effective adsorption of antiretroviral drugs from wastewater and also to study the imprinted polymer's selectivity and reusability and determine the adsorption kinetics and isotherms studies on their application as DSPE sorbents for the removal of antiretroviral drugs in river water, wastewater and tap water samples. These ARVD drugs were selected due to their wide usage in the prevention of HIV replication as a result, and they have been reported to be frequently detected in water bodies worldwide (Schoeman et al. 2015; Rimayi et al. 2018; Mtolo et al. 2019; Qwane et al. 2020). For example, abacavir + lamivudine + efavirenz are the most prescribed first-line antiretroviral medications for HIV/AIDS infected people, where nevirapine is used as a replacement in case efavirenz showed to be harmful to patience (Provincial Government of the Western Cape 2018; Eckhardt et al. 2017). Accordingly, South Africa is having the highest number of HIV-infected people who are on ARVDs treatment, and higher quantities of ARVDs enter the wastewater treatment plants where they are partially removed and transferred to the receiving rivers and may reach drinking water (Mlunguza et al. 2019). The main concern about the presence of ARVDs in water bodies is that it may lead to the development of resistant strains to human beings upon unintentional consumption through contaminated food and water. This indicates the urgent need to come up with affordable,

Table 1 Physicochemical properties of selected pharmaceuticals (Abafe et al. 2018)

Name	Mw (g mol^{-1})	Structure	Kow	pKa	Solubility (mg mL^{-1})
Abacavir	286.332		1.54	5.77	77.0
Nevirapine	266.298		3.89	2.5	0.7046
Efavirenz	315.675		4.15	− 1.5	0.00855
Lamivudine	229.26		− 9.54	4.08	70.00
Diclofenac	296.148		4.51	4.3	2.5

effective and highly selective materials that can be used for simultaneous removal of ARVDs in water bodies. Hence, this work synthesized for the first time the multi-template MIP for selective removal of abacavir, nevirapine and efavirenz from South African water. Furthermore, the application of these materials for water purification will aid in preserving the scarce water that is still available in African countries.

Materials and method

Chemicals

Efavirenz, nevirapine, lamivudine and abacavir were purchased from J & H Chemical Co. Ltd (Hangzhou Zhejiang, China). 2-vinylpyridine (97%), high-performance liquid chromatography (HPLC) grade methanol (99.8%), 1,1′-azobis(cyclohexanecarbonitrile) (98%), ethylene glycol dimethacrylate (98%), diclofenac (≥ 96.5%) 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).

Apparatus and analytical methods

The SPE vacuum manifold used for the extraction of analytes was purchased from Sigma-Aldrich (Steinheim, Germany) and connected to the vacuum pump from Edwards (Munich, Germany). Empty SPE cartridges (3 mL) and frits (0.2 µm) employed for MIP packing were obtained from Biotage (Uppsala, Sweden). The samples were shaken using a FMH SHKO 20 orbital shaker from DLD Scientific cc (Durban, South Africa). Ultrasonic bath utilized for the dispersion of MIPs was bought from Science Tech (Durban, South Africa). The working frequency, power and temperature range of the ultrasonic bath were kept at 28 kHz, 300 W and 30 °C, respectively. The coffee grinding machine mixer for to homogenizing the samples was purchased from Clicks (Pietermaritzburg, KwaZulu-Natal).

A Shimadzu high-performance liquid chromatography (HPLC-2020) system equipped with a photo-diode array detector (PDA) bought from Shimadzu (Tokyo, Japan) was used for the monitoring of ARVDs in standard solutions and samples. The detection of the ARVDs was acquired at a wavelength of 254 nm. The chromatographic separation was performed on a Shim-Pack GIST C18-HP (4.6 mm × 150 mm, 3 µm) column procured from Shimadzu (Tokyo, Japan). The method was adopted from Mtolo et al. (2019), with minor modification. The optimum conditions were isocratic ES + elution with mobile phase composition of acetonitrile: 0.1% formic acid in water (70%: 30%), 0–12 min, flow rate = 0.4 mL/min, injection volume = 10 µL, wavelength = 254 nm, column Temperature = 30 °C.

A Fourier-transform infrared spectrometer from PerkinElmer (Llantrisant, UK) equipped with attenuated total reflection was used to study the vibrations of the functional groups present in the synthesized polymers. The JOEL model 6700F scanning electron microscope from JOEL LTD (Tokyo, Japan) was utilized to study the polymer morphology. Elemental composition of the polymers was studied using ThermoScientific Flash2000 organic analyser from Thermo Fisher (New York, USA). The thermal stability of the polymers was studied using Simultaneous thermal analyser 6000 PerkinElmer (Llantrisant, UK), coupled with Pyris Software. The polymers were heated from 20 to 600 °C at 10°C/min under nitrogen atmosphere flowing at 20 mL/min. The surface area and porosity of the samples were characterized by N2 Sorption measurements using Tri-Star II3020 V1.03 Brunauer–Emmett–Teller from Micromeritics (Georgia, USA). The samples were degassed overnight, under vacuum, and the temperature was held at 200 °C.

Synthesis of molecularly imprinted and non-imprinted polymers

The method for the synthesis of both the NIP (non-imprinted polymer) and MIP was adopted from Mtolo et al. 2019 and further optimized to accommodate the additional analytes. A 25 mg of the templates (abacavir, nevirapine and efavirenz) and 54 µL of 2-vinylpyridine were dissolved in 10 mL of acetonitrile/toluene (1:9, v/v) in a 100 mL round-bottom flask. The mixture was stirred at room temperature for 30 min to prepare a pre-polymerization complex. Thereafter, a 4.77 mL of EGDMA and 100 mg of 1,1′-azobis(cyclohexanecarbonitrile) were added into the reaction flask. The reaction mixture was deoxygenated with nitrogen gas for 10 min, sealed, and stirred for 16 h at 60 °C. The temperature was increased to 80 °C, and the mixture was further stirred for 24 h to ensure complete polymerization. The NIP synthesis was the same, except the addition of templates. The two polymers were washed with acetic acid/acetonitrile (1:9, v/v) using Soxhlet extraction until the templates could not be detected by the LC-PDA. Figure 1 shows a schematic illustration of the general procedure for the synthesis of MIPs using bulk polymerization technique.

Sampling

The samples were collected from one wastewater treatment plant (WWTP) in Durban (Umbilo WWTP) and one in Pietermaritzburg (Darvill WWTP). The river water samples were collected in three sampling points along Msunduzi River in Pietermaritzburg (Camps drift, Woodhouse and Bishopstowe). The tap water samples were collected from five suburbs around Pietermaritzburg (Scottsville, Oribi village, Lincoln Meade, Allandale and Napierville). The Global Positioning System coordinates for the exact location of each sewage treatment plant are Darvill (S29.59979° E30.43124°) and Umbilo (S29.84556° E30.89103°). The wastewater treatment plant receives wastewater for treatment from domestic and industrial water sources for treatment, and the treated wastewater is then discharged to the nearest river. Wastewater from each plant was collected at the inlet (where

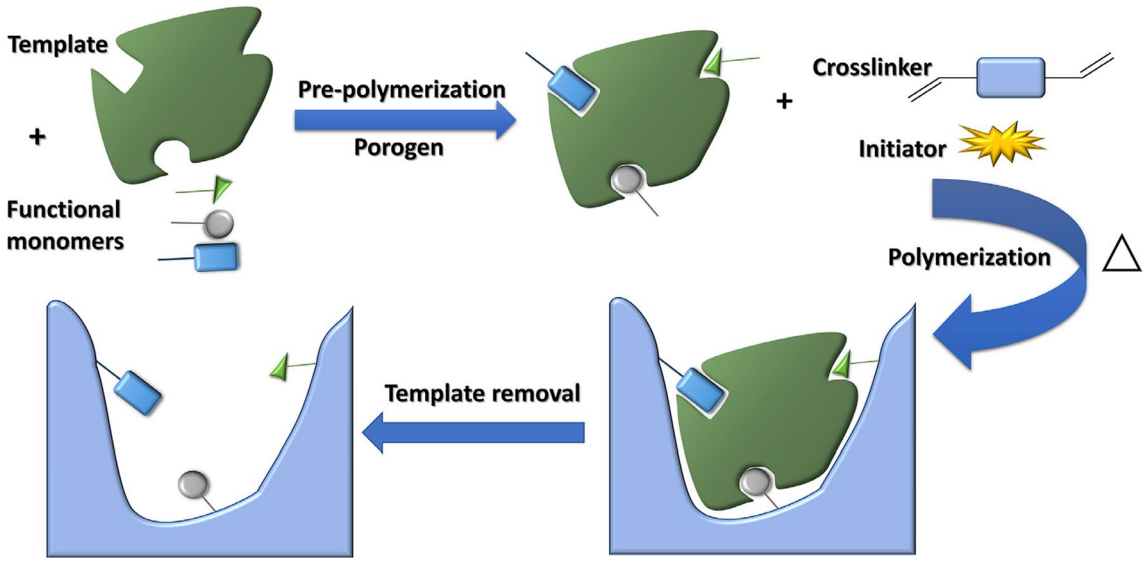


Fig. 1 Schematic illustration for the general preparation of MIPs (Azizi et al. 2020)

the treated water enters the plant) and at the exit (where the treated water is discharged into the river). The samples were collected using dark brown 2.5L water bottles and were stored in a cooler box with ice to maintain sample integrity until they get to the laboratory.

Sample preparation

The wastewater, tap water and river water samples were filtered with 0.45 µm filter paper, and the pH was adjusted to 6. This was done to ensure that the sample was free of particles, and filtration was conducted to prevent clogging of the SPE cartridge. The sample was acidified to keep the analytes in solution, to prevent formation of precipitates and to promote better interaction between ARVDs of interest and the adsorbent.

SPE, MIP-SPE, and MIP-DSPE methods

The methods for the SPE and MIP-SPE were adopted from the work published by Mtolo and colleagues, and no further optimization was done as the recoveries were within the acceptable range (Mtolo et al. 2019). A 60 mg Oasis HLB and 50 mg of MIP were separately used as SPE sorbents. For MIP-SPE, the sorbent was transferred into an empty SPE cartridge fitted with two frits using 2 mL of methanol. In both SPE and MIP-SPE, a 1 mL of acetonitrile and 1 mL of methanol were used as conditioning solvents. This was followed by passing through a 50 mL water samples to allow analytes adsorption. A 3 mL of 2% of methanol in distilled water was used to wash off impurities, while a 2 mL of acetonitrile was used to elute the adsorbed analytes. Thereafter, the eluent was reduced to 1 mL under nitrogen, filtered using 0.2 µm filter and analysed using HPLC–PDA.

The method for the MIP-DSPE was adopted from Li et al. (2016) and was further optimized. Under optimum conditions, a 40 mg of the MIP was applied to 50 mL of distilled water samples (the samples were spiked with 1 mg L^{-1} of abacavir, nevirapine and efavirenz if used for optimization) in a centrifuge tube. The MIP was dispersed using ultrasonication for 15 min. The contents in a centrifuge tube were shaken on a FMH SHKO 20 orbital shaker for 60 min at 250 rpm and then centrifuged for 5 min at 2500 rpm. The supernatant liquid was discarded, and the MIP loaded with ARVDs was transferred to an empty SPE cartridge fitted with two frits and followed by washing with 2 mL of 2% methanol in distilled water. The MIP was regenerated by eluting the compounds with 2 mL of 100% acetonitrile. The sample was reduced to 1 mL under nitrogen and filtered into HPLC vials using 0.2 µm filters and submitted for analysis.

Evaluation of the performance of MIPs prior sample preparation

The performance of the MIPs was determined prior sample preparation and analysis. This was done to ensure successful extraction of analytes with high recoveries and to determine the efficiency of synthesized MIPs.

Adsorption studies

Adsorption properties such as equilibrium adsorption capacity of the synthesized MIP particles are considered to evaluate the performance of the MIP. The MIP particles are exposed to the analyte in aqueous matrices (Sun

et al. 2016) or organic solvents such as acetonitrile (Sun et al. 2008), methanol (Yin et al. 2010), dichloromethane (Shaikh et al. 2012) or mixture of water and an organic solvent (He et al. 2016) for an experimentally determined interval to allow for complete equilibration.

The batch adsorption studies in this work were conducted using 5 mL of water. Parameters such sample pH (4–9), concentration of analytes (10–80 mg L^{-1}) and contact time (0–120 min) that could affect adsorption of ARVDs from spiked water samples were studied and optimized in batch mode. All experiments were conducted in triplicates ($n=3$), and average results were computed for each parameter under study.

Kinetics studies

The adsorption kinetics studies were conducted to assess the rate at which adsorption process of ARVDs onto the MIP sorbent occurs which is of paramount importance when developing the adsorption system. The experimental conditions used to study adsorption kinetics were 5 mL water sample spiked with 50 mg L^{-1} of ARVDs at a pH of 6. The sample was mixed with 40 mg adsorbent mass and stirred for 60 min. The data obtained were fitted on pseudo-first-order and pseudo-second-order models to describe adsorption dynamics.

Adsorption isotherms studies

The adsorption isotherms were done to understand the interaction between ARVDs and MIP sorbent and also to describe the relationship between the ARVDs amount adsorbed by the MIP adsorbent at equilibrium material and the bulk fluid phase concentration at a constant temperature (Ayawei et al. 2017). The experimental conditions used to study adsorption kinetics were 5 mL water sample spiked with 10 mg L^{-1} of ARVDs at a pH of 6. The sample was mixed with 10 mg adsorbent mass and stirred for 15 min. The data obtained were fitted on Langmuir and Freundlich isotherms to describe the best fitting isotherm.

Selectivity studies

The method used for selective adsorption studies was adopted from Qwane et al (2020) with further optimization to further demonstrate the efficiency and selectivity of the polymers. Selectivity was investigated by adsorbing10 mL of 1 mg L^{-1} spiked distilled water containing efavirenz, abacavir, nevirapine (target analytes) in the presence of competitors (lamivudine and diclofenac). The adsorption conditions employed were sample pH of 6, polymer mass of 40 mg and shaken for 60 min at room temperature using an orbital shaker. The samples were then ultrasonicated, shaken and transferred to 3 mL SPE cartridges with the MIP or NIP as sorbent safeguarded by two frits to avoid loss during extraction. All experiments were conducted in triplicates. Diclofenac is a non-steroidal anti-inflammatory drug which is used to reduce inflammation and pain, while lamivudine is an antiretroviral drug used to treat human immunodeficiency virus. These competitors were selected based on their structural similarities to the ARVDs of interest (abacavir, nevirapine and efavirenz). Their physicochemical properties influence (Table 1) their presence in water, and they have a hydroxyl group which was expected to bond onto the MIP via hydrogen bonding.

Reusability studies

The method used for reusability studies was adopted from Qwane et al. (2020) with modifications. A 10 mg of the MIP was applied to 10 mL of distilled water samples spiked with 1 mg L^{-1} of abacavir, nevirapine and efavirenz in a 50 mL centrifuge tube. The contents in a centrifuge tube were shaken on a FMH SHKO 20 orbital shaker for 10 min. The MIP loaded with ARVDs was regenerated by eluting the compounds with 100% acetonitrile using followed by 100% methanol. The same MIP was used repeatedly for eight consecutive cycles of adsorption/desorption. The analysis was done using HPLC–PDA, and thereafter, recoveries were calculated.

Results and discussion

Synthesis and characterization of polymers

The interaction of MIPs with analytes in the sample matrix is mainly through the functionalities of their monomers. Therefore, in our previous study the interaction efavirenz with 2-vinylpyridine was computationally investigated. The obtained results showed the presence of the hydrogen bonding between the nitrogen atom from 2-vinylpyridine and the hydrogen atom

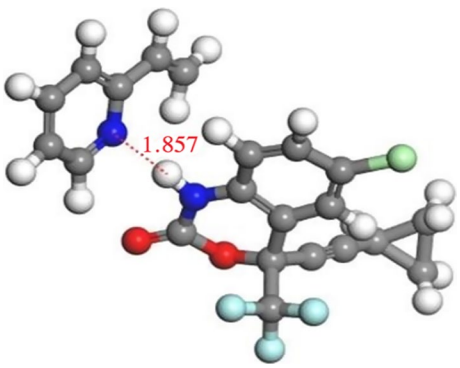


Fig. 2 Computational representation of the binding of efavirenz to 2-vinylpyridine where carbon, hydrogen, oxygen, nitrogen, fluorine and chlorine are represented by grey, white, red, blue, light blue and green round images, respectively (Adapted from Mtolo et al. 2019)

of the amine group from efavirenz and the (Fig. 2). The hydrogen bonding had a bond distance of 1.857 Å, while the 2-vinylpyridine and efavirenz complex had a binding energy of − 18 kcal/mol indicating that the MIP is expected to strongly bind with efavirenz (Molo et al. 2019). Abacavir and nevirapine also have the amine group which is expected to facilitate the hydrogen bonding with the nitrogen atom from the 2vinlypyridine functional monomer used for the synthesis of MIP in the current study.

Fourier-transform infrared

The FTIR spectroscopy was used to study the possible structural differences and similarities between the MIP and the NIP to confirm successful synthesis and removal of the templates. Characteristic bands corresponding to the symmetric and asymmetric vibrations of C-O bond of EGDMA were observed at 1141 cm^{-1} and 1249 cm^{-1}, 1137 cm^{-1} and 1249 cm^{-1}, 1144 cm^{-1} and 1250 cm^{-1} for the washed MIP, washed NIP and unwashed MIP, respectively (Fig. 3). The peak at 1720 cm^{-1} for the washed MIP and NIP and 1722 cm^{-1} for the unwashed MIP was attributed to the stretching vibrations of the C=O bond of the carboxylic acid group of EGDMA. The peak at 2951 cm^{-1} for the washed MIP, 2953 cm^{-1} for the washed NIP and 2955 cm^{-1} for the unwashed MIP corresponds to the stretching and bending vibrations of the amine group (N–H) of 2-vinylpyridine (Bakhtiar et al. 2019). The slight wavenumbers shift of the similar peaks between the MIP and NIP could be as a result of minor structural variations that might have occurred during the removal of the template from MIP.

The unwashed MIP was observed to have more intense peaks due of the strong bond vibrations within the MIP which is associated with the overlapping of bonds of the MIP with the template. The washed MIP has relatively weak peak intensity compared to the unwashed MIP due to the weakening of bond vibrations within the MIP which occurs during the washing step for the template removal. This eliminates the overlapping bonds of the MIP and template and weakening the existing bonds within the MIP. The washed NIP has a strong peak intensity compared to the washed MIP which is justified by the imprinted sites within the MIP. The washing step weakens bonds within both the MIP and the NIP, and however, the presence of cavities in the MIP also weakens the bonds which further weakens the peak intensity in the washed MIP (Chrzanowska et al. 2015).

Scanning electron microscope (SEM)

The scanning electron microscope was used to study the surface morphology of the MIP and NIP. The SEM images showed a rougher surface for the MIP and a smooth surface for the NIP (Fig. 4). The roughness is associated with

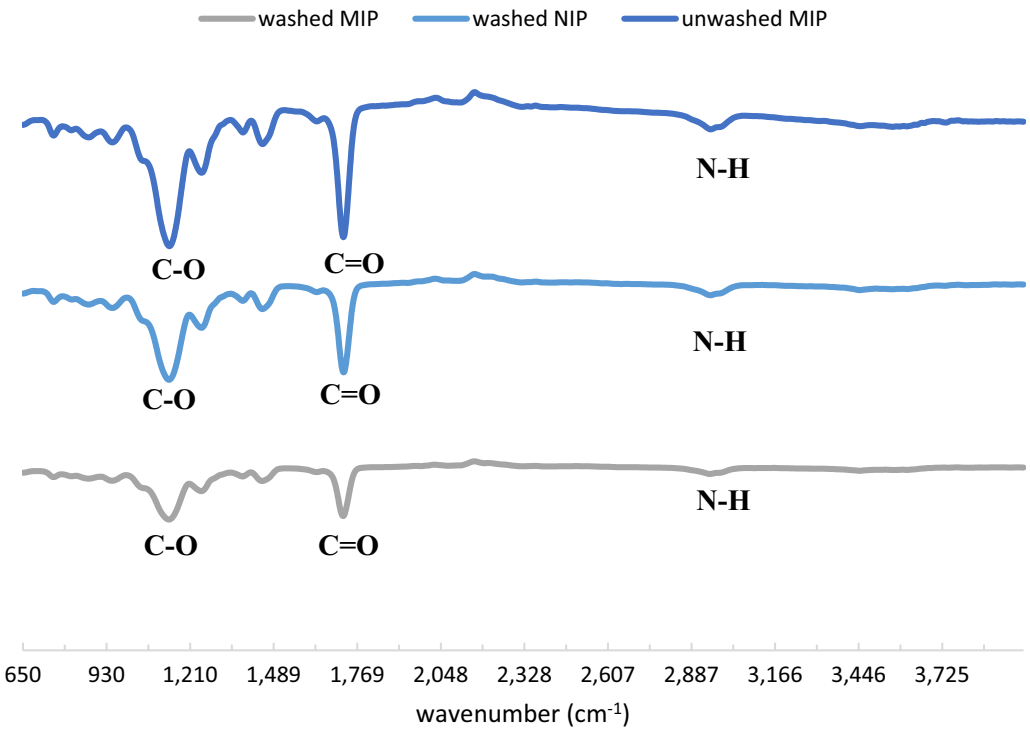


Fig. 3 FTIR spectra of the washed MIP and NIP and the unwashed MIP showing characteristic bands of functional groups present in the polymers

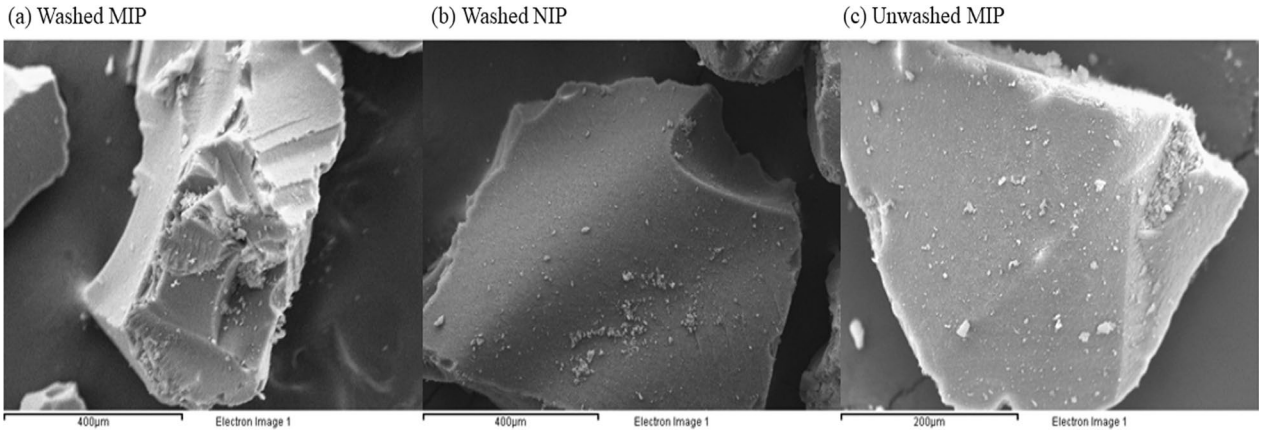


Fig. 4 SEM images of the surface of the washed MIP (**a**), washed NIP (**b**) and unwashed MIP (**c**)

Table 2 Results of the elemental composition of the MIP and NIP using the CNH analyser

Element	MIP	NIP
Elemental composition (%)		
Carbon	56.0	55.3
Hydrogen	6.4	6.4
Oxygen	37.6	37.9
Nitrogen	0.4	0.4

the presence of imprinted binding sites/cavities that were left after the removal of the template. These findings indicate that MIP has a greater ability to adsorb the analytes than the corresponding NIP (Sikiti et al. 2014). The unwashed MIP showed a smooth surface, and this could be due to that the cavities were still filled with templates. These results also correspond to the findings reported by Madikizela et al. (2016).

Elemental analysis

The elemental composition of the MIP and NIP was studied using the CNH analyser. The results obtained showed the presence of oxygen, nitrogen, carbon and hydrogen with similar percentage compositions (Table 2). This is because both polymers were synthesized using similar reagents and quantities (except for the template in the MIP) and under similar reaction conditions. The composition also shows successful template removal during the washing of the MIP post-synthesis. These results also correspond to the published findings by Qwane et al (2020).

Thermogravimetric analysis (TGA)

The stability of the synthesized MIP and NIP was studied using thermogravimetric analysis. The polymers showed a mass loss of about 2–3% at 95 °C, which is associated with the evaporation of acetonitrile (Fig. 5). Approximately 75% of the weight loss was observed at around 257 °C for the NIP and 281 °C for the MIP which were attributed to the collapse of the backbone of the polymers. Further decomposition was observed at 449 °C for both polymers. Results of similar nature were reported by Qwane et al. (2020) where the polymer backbone collapsed at 255 °C for the NIP and 355 °C for the MIP. In another study by Mtolo et al. (2019), the backbone breakdown of both polymers occurred around 250 °C. Overall, these results have shown that the MIP is more stable than its corresponding NIP.

Nitrogen physisorption analysis

Nitrogen physisorption was used to determine the surface area, pore volume and the pore diameter of the washed MIP, unwashed MIP and the washed NIP. The results obtained showed that the washed MIP had a greater surface area than the unwashed MIP and the washed NIP (Table 3). These results imply that a MIP has a higher adsorption efficiency and capacity compared to the aforementioned polymers. These findings correspond to the work published by Mtolo et al. where a higher surface area was obtained for the MIP (420 m^2/g) than the NIP (409 m^2/g), while the results reported by Qwane et al. 2020 showed equal surface area for the MIP and NIP (372 m^2/g). The washed MIP had a greater pore volume and pore diameter than the unwashed MIP and washed NIP, respectively. The average pore diameter of all three polymers falls within the

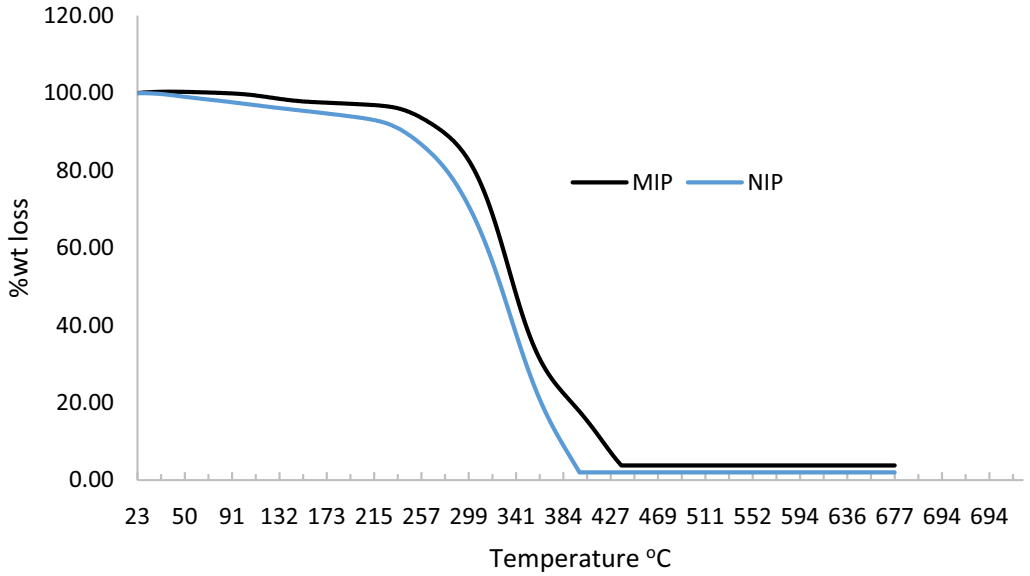


Fig. 5 TGA results showing weight loss percentage at varying temperatures

Table 3 BET results of the washed MIP, washed NIP and unwashed MIP

Polymer	Surface area (m^2/g)	Pore volume (cm^3/g)	Pore diameter (Å)
Washed MIP	457.453 ± 1.7819	0.974609	8.840
Unwashed MIP	444.0415 ± 0.5177	0.461562	8.323
Washed NIP	3,772,567 ± 0.5971	0.410385	8.209

range of 2–50 nm, and these findings indicate that the structure of the polymers is mesoporous.

Method validation

The validity of the analytical method was evaluated in terms of linearity, sensitivity, accuracy and precision. This was determined in accordance with the European Commission (EC) (2019) document no. SANTE/12682/2019. The correlation coefficients (R^2) obtained for all the analytes showed good linearity with values ranging from 0.9979 to 0.9986. Sensitivity of the analytical method was evaluated using LOD and LOQ computed from signal-to-noise ratio of 3 and 10, respectively (Table 4). The LOD (0.70–0.91 µg L^{-1}) and LOQ (1.87–2.51 µg L^{-1}) obtained for the MIP-SPE are lower than those obtained for the

Table 4 LOD, LOQ and %recoveries for ARVDs using MIP-DSPE, MIP-SPE and traditional SPE (Oasis HLB)

Analytes	LOD (µg L^{-1})		LOQ (µg L^{-1})	
	Oasis HLB	MIP	Oasis HLB	MIP
Abacavir	1.11	0.91	3.37	2.51
Nevirapine	0.89	0.70	2.73	1.88
Efavirenz	1.06	0.86	3.20	2.34
	SPE	MIP-SPE		MIP-DSPE
%Recoveries				
Abacavir	91.68 ± 0.17	99.68 ± 0.2		100.28 ± 0.15
Nevirapine	87.55 ± 0.20	97.77 ± 0.18		102.29 ± 0.19
Efavirenz	94.59 ± 0.28	97.20 ± 0.25		102.60 ± 0.2

Oasis HLB (0.81–1.11 µg L^{-1}) and (2.73–3.37 µg L^{-1}) regardless of similar preconcentration factors used for both sorbents. This indicates better sensitivity for the MIP-SPE compared to the traditional SPE and could be attributed to the ability of the MIP to selectively extract the analytes of interest imprinted on its surface while reducing matrix effects from the water samples (Mtolo et al. 2019). The SPE, MIP-SPE, MIP-DSPE methods gave analyte recoveries within the acceptable range of 80–120% which confirmed high accuracy with the %RSD ranging from 0.15 to 0.28 which confirmed high level of precision. Traditional SPE method with HLB Oasis as the sorbent gave lower recoveries compared to MIP-SPE and MIP-DSPE methods. The higher recoveries in MIP-based sorbents might have been influenced by the presence of the templates recognition sites which improves their selectivity. The traditional SPE sorbents are selective to a wide range of compounds, and thus, the competitive adsorption onto the sorbents results in less adsorption sites available for the analytes of interest leading to lower analytes recoveries. MIP-DSPE had the highest recoveries compared to both SPE and MIP-SPE which could be attributed to enough contact time between the MIP and the analytes of interest which allowed sufficient adsorption of analytes onto the cavities imprinted on the MIP.

Optimization of MIP performance

Adsorption studies

Parameters (sample pH, concentration of analytes and contact time) that could affect adsorption of ARVDs from spiked water samples were studied and optimized in batch mode. All experiments were conducted in triplicates ($n=3$), and average results were computed for each parameter under study. The adsorption efficiency (AE, %) was calculated using Eq. (1).

$$\mathrm{AE}(\%) = \frac{(C_o - C_e)}{C_o} \times 100 \quad (1)$$

where C_o and C_e are the initial and equilibrium concentrations, respectively.

The effect of sample pH The optimization of sample pH is critical and necessary in the adsorption experiments to study the structural changes or adsorbent surface charges associated with acidity or basicity of the pH of the sample. The pH range of 4–9 was investigated while keeping other experimental conditions constant. Abacavir showed a low adsorption efficiency at pH 4 for both MIP and NIP (Fig. 6) which could be attributed to the protonation of the peripheral nitrogen (NH_2) of abacavir due to its pKa value (5.06) being higher than the pH value. This change alters the structure, size and functional group (NH_2 to NH_3^+) resulting to poor recognition for binding on the MIP (Qwane et al. 2020). Also, 2-vinylpyridine (pKa = 4.89) which was used as the functional monomer exists in protonated form at Ph below its pKa values which result to repulsion between abacavir and 2-vinylpyridine and thus low adsorption capacity of abacavir at pH 4. Efavirenz and nevirapine have pKa values below the pH range assessed; thus, they were both not affected by the acidity of the sample, and hence, they had high adsorption efficiencies. At pH 6, abacavir, nevirapine and efavirenz exist as a neutral species; hence, high adsorption efficiencies were observed for both polymers. At pH 8, a slight decrease in adsorption efficiency was observed for all the analytes and the decrease became significant at pH 9. This could be linked

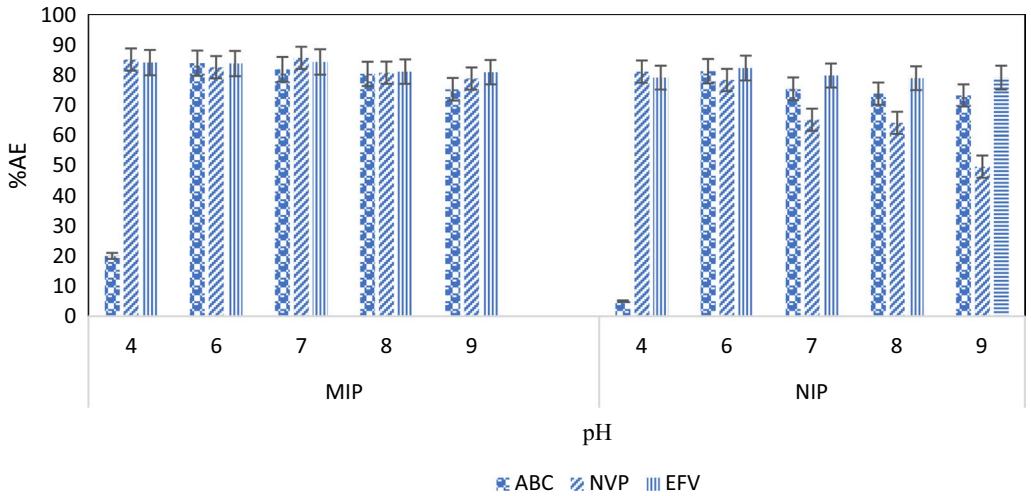


Fig. 6 Effect of pH on the adsorption efficiency. Experimental conditions were: initial concentration of ARVDs—10 mg L^{-1}, adsorbent mass—10 mg, contact time—15 min, and sample volume—5 mL

to a possible hydrolysation caused by the basicity of the sample which alters the structure of the analytes, while 2-vinylpyridine is negatively charge at basic pH resulting to poor recognition of the analytes by the cavities of the MIP and thus poor adsorption (Madikizela et al. 2017). Abacavir has low adsorption efficiency on the MIP compared to nevirapine and efavirenz, and this could be due to the polar groups present on its structure and its high-water solubility making it less likely to be completely extracted from water. The pH of 6 was therefore taken as the optimum where all analytes' recoveries were above 80%. These results agree with those reported by Dai et al. (2013) where the adsorption of clofibric acid (pKa of 3.18) was observed to decrease as the pH increases (pH of 6–12) which was associated with clofibric ionization under basic condition.

The effect of the initial ARVDs concentration The effect of an increase in the ARVDs initial concentration in spiked water samples was investigated using a concentration of 10–80 ppm. Saturation/maximum adsorption was reached at different concentration intervals for abacavir, efavirenz and nevirapine (Fig. 7). This could be due to that analytes have different adsorption intensity and affinity onto the multi-template MIP. Abacavir reached saturation at 60 ppm with 89% adsorption efficiency, nevirapine reached saturation at 80 ppm with 87% adsorption efficiency and efavirenz at 50 ppm with 87% adsorption efficiency, beyond these points absorption and desorption was observed. These results indicate that 60, 50 and 80 ppm of abacavir, nevirapine and efavirenz could saturate 10 mg of the MIP adsorbent. However, this saturation of the adsorbent is not expected in environmental water as the maximum concentration that has been reported in wastewater was 502 µg/L, 167.1 µg/L and 140.4 µg/L for abacavir, nevirapine and efavirenz, respectively (K'oreje et al. 2016, Mtolo et al. 2019, Ngwenya and Mahlambi 2023).

The effect of contact time on the adsorption of ARVDs The effects of an increase in contact time on the adsorption of ARVDs in spiked water samples were studied at a range of 5–120 min. The adsorption efficiencies showed a steady increase from 5 min of contact time to 60 min (Fig. 8). After 60 min a slight decrease was observed for all studied ARVDs which could be attributed to the saturation of MIP resulting in adsorption and desorption happening at the same time. A similar trend was observed for the NIP even though adsorption efficiencies were lower compared to the MIP. This indicated faster saturation on the NIP surface compared to MIP due to the presence of further sites suitable for the target ARVDs binding in the MIP that were left after the template removal. The adsorption efficiencies at 5 min of contact time between MIP and ARVDs were above 80%, and they increased to 96% for abacavir and 94% for nevirapine and efavirenz in 60 min of contact time. Therefore, 60 min was selected as the optimum contact time for determination of equilibrium adsorption of the polymers and kinetics. These results are comparable to the findings published by Qwane et al (2020), where the extraction efficiency achieved for MIP increased gradually from 76% in the contact time of 10 min to 90% in 60 min for abacavir. The results showed to be comparable with those obtained by Qwane et al. (2020) and Mtolo et al, (2019). The multi-template MIP synthesized in the

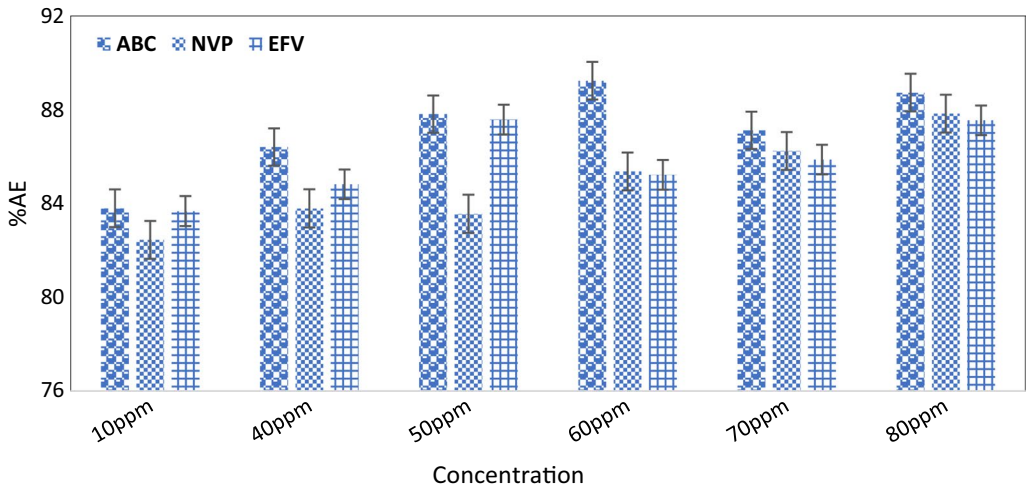


Fig. 7 Effects of concentration on the adsorption efficiency of ARVDs onto the MIP. Experimental conditions were adsorbent mass—10 mg, sample pH—6, contact time—15 min, and sample volume—5 mL

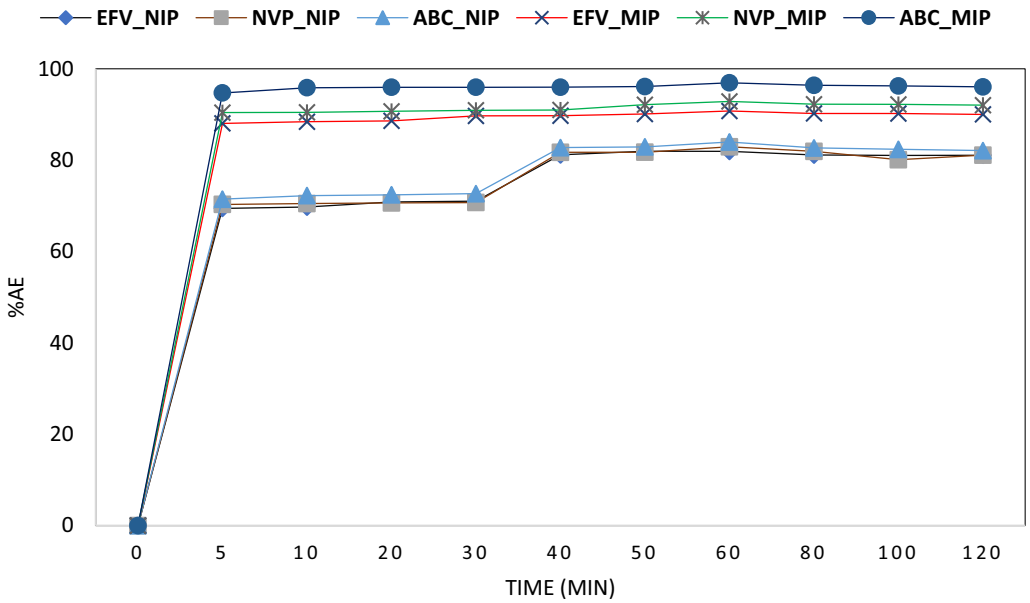


Fig. 8 Effects of contact time on the adsorption efficiency of ARVDs. Experimental conditions were: initial concentration of ARVDs—50 mg L^{-1}, sample pH—6, adsorbent mass—40 mg, and sample volume—5 mL

current study is an improvement of what exist in the literature as it can simultaneously remove three ARVs.

Kinetics modelling

To study the adsorption modelling of ARVDs onto the MIP, the data obtained in the contact time study (Fig. 8) were employed. The adsorption capacity at equilibrium (Q_e) and adsorption capacity at time t (Q_t) were calculated using Eqs. (2) and (3). The data were then fitted in pseudo-first- and pseudo-second-order kinetics using Eqs. (4) and (5), respectively.

$$Q_e = \frac{(C_o - C_e)V}{W} \tag{2}$$

$$Q_t = \frac{(C_o - C_t)V}{W} \tag{3}$$

$$\ln(q_e - q_t) = \ln q_e \frac{k1t}{2.303} \tag{4}$$

$$\frac{t}{q_t} = \frac{1}{k_2 q_e^2} + \frac{1}{q_e}t \tag{5}$$

where C_o and C_e are the initial and equilibrium concentrations, respectively, C_t is the concentration at time t, V is the volume of the analytes solution used (L), and W is the amount/mass of the polymer used for the adsorption process (g). The q_e is the adsorption capacity at equilibrium (mg g^{-1}), q_t is the adsorption capacity (mg g^{-1}) at time t (min), k_1 is pseudo-first-order adsorption rate constant (g mg^{-1} min^{-1}), and k_2 is pseudo-second-order adsorption rate constant (g mg^{-1} min^{-1}).

Linearity was used to determine the model that best fits the adsorption mechanism through analysis of the correlation coefficient (R^2) of the MIP for all three ARVDs (Fig. 9a–c). The pseudo-second-order model was found to be the best fit through linearity which was found to be one. Abacavir had the highest adsorption capacity of 24.096 mg g^{-1} compared to 23.060 and 23.055 mg g^{-1} for nevirapine and efavirenz, respectively (Table 5). These results imply that during the adsorption process of ARVDs onto the surface of the MIP, there is a transfer of electrons between the MIP and ARVDs of interest in solution/water and the process of adsorption is more chemical than physical (Qwane et al. 2020).

Adsorption isotherms

To study the adsorption mechanism of ARVDs onto the MIP, the data obtained in the study of concentration effects (Fig. 7) were further processed using the Freundlich and Langmuir Isotherms in Eqs. (6) and (7), respectively.

$$\log q_e = \log K_F + \frac{1}{n \log C_e} \tag{6}$$

$$\frac{1}{q_e} = \frac{1}{q_m K_L C_e} + \frac{1}{q_m} \tag{7}$$

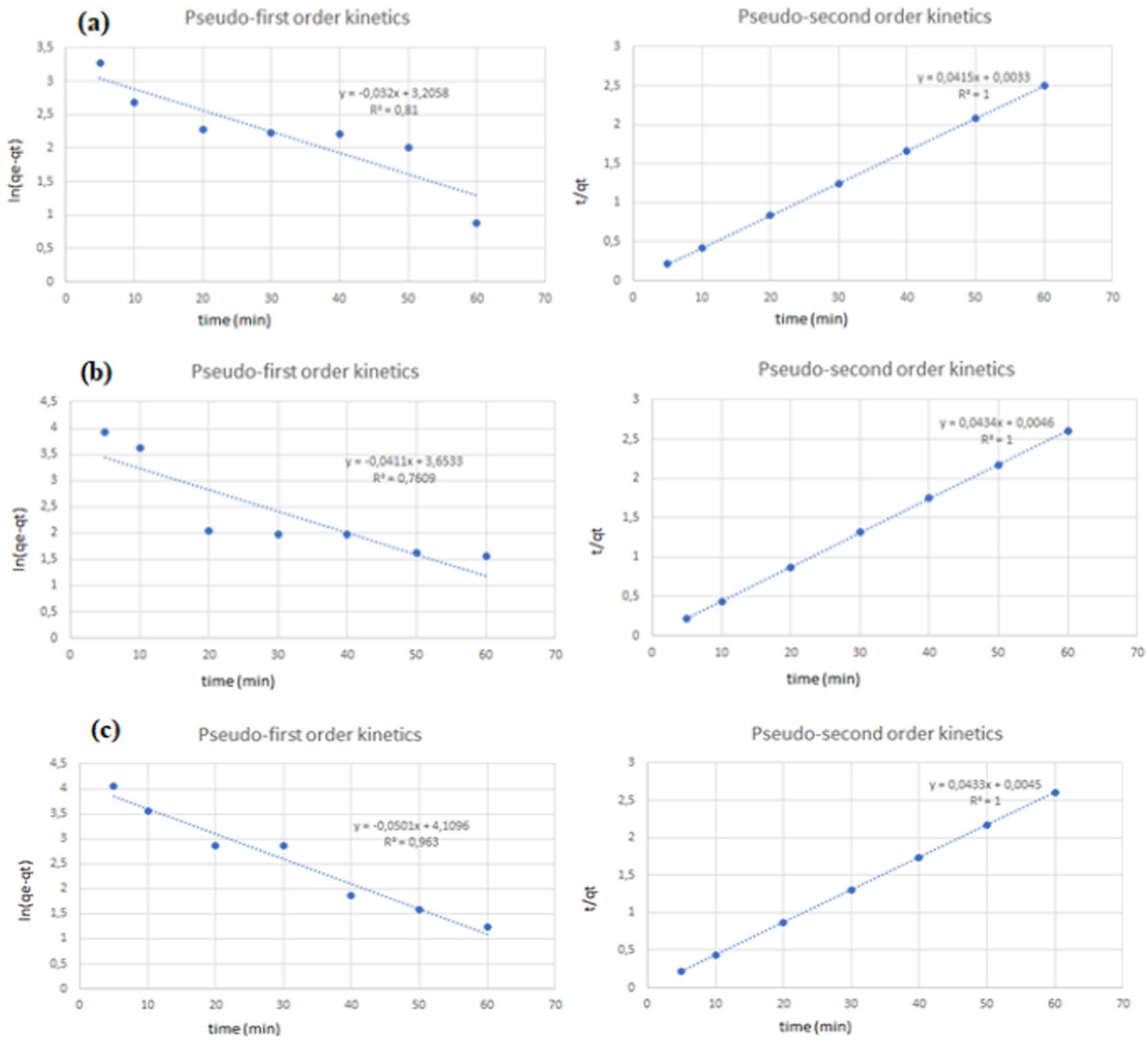


Fig. 9 Lagergren rate-order kinetics for abacavir (**a**), nevirapine (**b**) and efavirenz (**c**)

Table 5 Kinetics constants for abacavir (ABC), nevirapine (NVP) and efavirenz (EFV)

Analytes	Pseudo-first order		Pseudo-second order		
	k_1 (min^{-1})	R^2	q_e (mg g^{-1})	k_2 (min^{-1})	R^2
ABC	0.0737	0.81	24.096	0.0415	1.00
NVP	0.0947	0.761	23.060	0.0433	1.00
EFV	0.115	0.983	23.055	0.0434	1.00

where n, K_F and K_L are Freundlich and Langmuir constants, respectively. C_e is the equilibrium concentration, and q_e and q_m are equilibrium and maximum adsorption capacities, respectively.

Linearity was used to determine the model that best fits the adsorption mechanism through analysis of the correlation coefficient (R^2) of the MIP for all three ARVDs (Fig. 10a–c). The Freundlich isotherm model was found to be the best fitting model for the adsorption mechanism of ARVDs onto the MIPs with the R^2 values between 0.94 and 0.98 (Table 6), which indicated the homogeneity of the surface of the MIP. Efavirenz had the highest adsorption intensity, while abacavir and nevirapine had the lowest adsorption intensity. Adsorption intensity value (n) of efavirenz was greater than 0.7 implying that the adsorption and desorption may be observed at the same time as the concentration of the efavirenz increases. Adsorption intensity values of

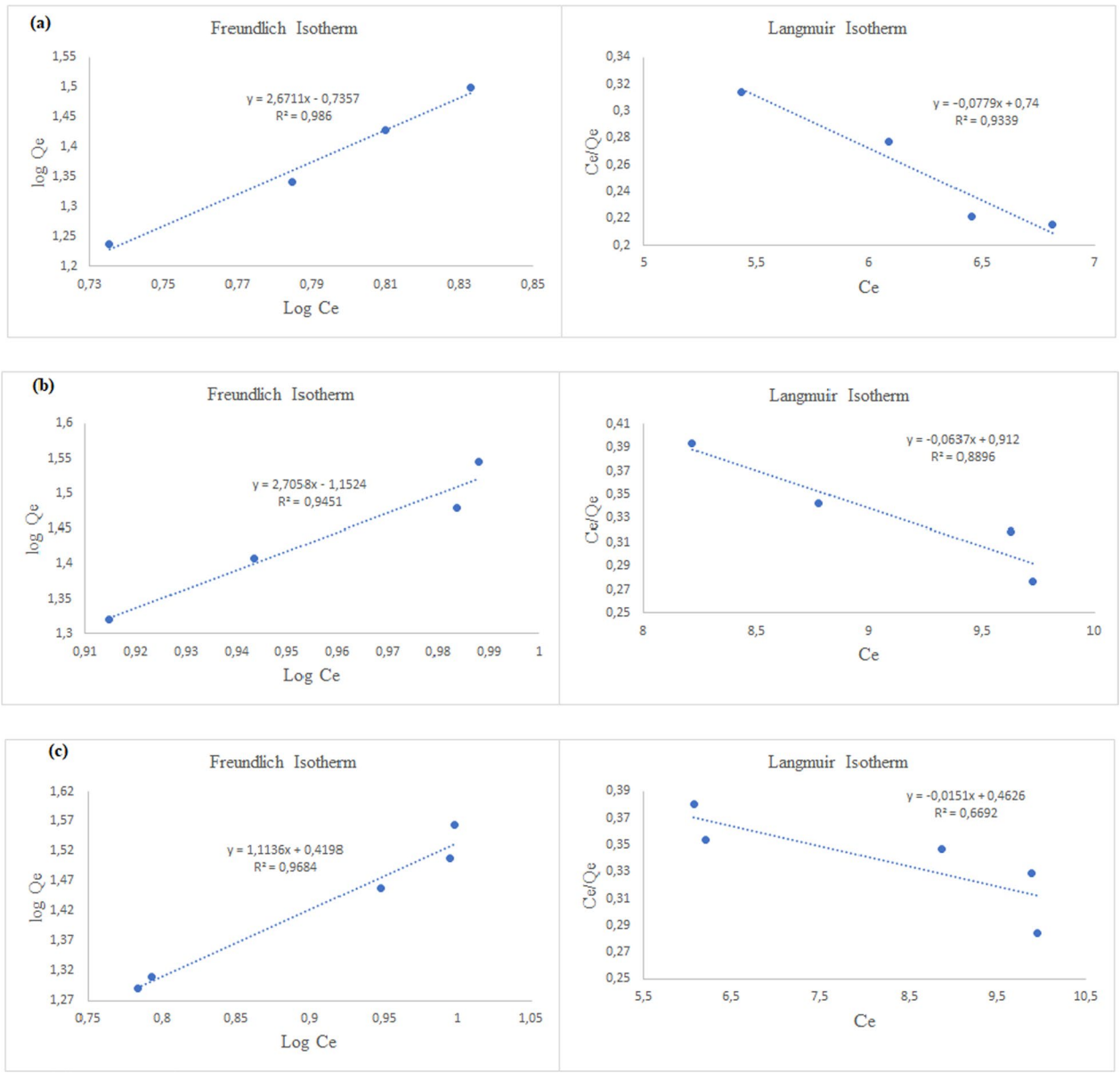


Fig. 10 Freundlich and Langmuir adsorption Isotherms for abacavir (**a**), nevirapine (**b**), and efavirenz

Table 6 Freundlich and Langmuir constants computed from Fig. 10a–c

Analytes	Freundlich constants			Langmuir constants		
	n (L mg^{-1})	K_F (mg g^{-1})(L mg^{-1})	R^2	K_L (L mg^{-1})	q_{max} (mg g^{-1})	R^2
ABC	0.37	0.0184	0.986	− 0.05765	1.35	0.9339
NVP	0.37	0.070	0.9451	− 0.0579	1.10	0.8896
EFV	0.90	2.629	0.9684	− 0.00699	2.16	0.6692

abacavir and nevirapine were less than 0.7 implying that mostly adsorption may be observed. Efavirenz had the highest adsorption affinity towards the imprinted cavities as it had higher KL value, while abacavir had the lowest of all three analytes. These results are comparable to the work published by Qwane et al. (2020),

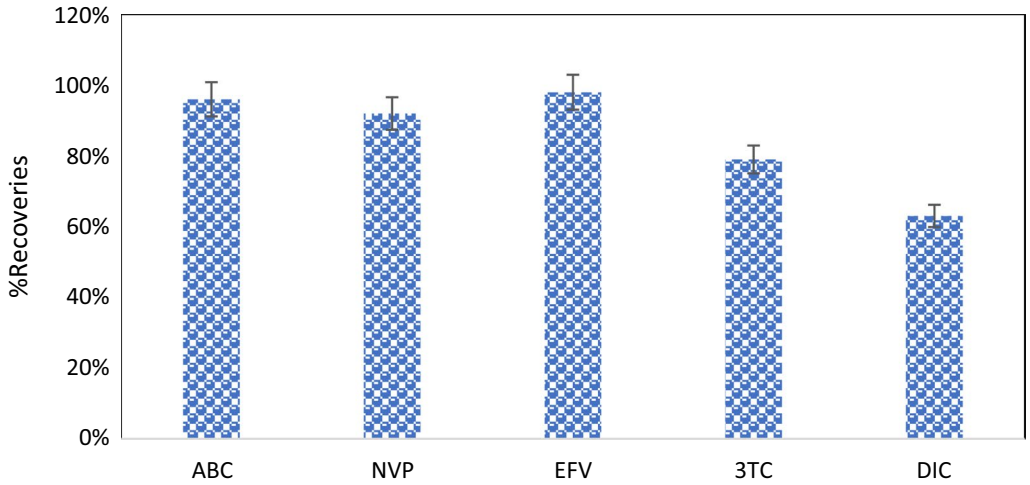


Fig. 11 Percentage recoveries of ARVDs in the presence of competitors. ABC = abacavir, NVP = nevirapine, EFV = efavirenz, 3TC = lamivudine and DIC = diclofenac. Experimental conditions were: initial concentration of ARVDs—1 mg L^{-1}, sample pH—6, contact time—60 min, adsorbent mass—30 mg, and sample volume—5 mL

where the adsorption mechanism was best described by the Freundlich isotherm which was translated to multilayer coverage for abacavir.

Selective studies

The results showed that MIP was more selective towards the ARVDs of interest with percentage recoveries ranging between 92 and 98% compared to the competitors which ranged between 63 and 79% (Fig. 11). These results were expected for the MIP since it has imprinted cavities with the same size and shape complimentary to the analytes of interest rather than competitors. The results are also corresponding to the findings published by Mtolo et al (2019) and Qwane et al (2020), where MIP was more selective to the analytes of interest compared to competitors.

Reusability studies

After the adsorption of abacavir, nevirapine and efavirenz, the MIP was regenerated with 100% acetonitrile, which removed the compounds from the cavities. This was followed by rinsing with 100% methanol, and thereafter, the regenerated MIP was re-applied for adsorption of ARVDs from spiked water samples. The recoveries were greater than 92% for eight consecutive cycles of adsorption and desorption (Fig. 12).

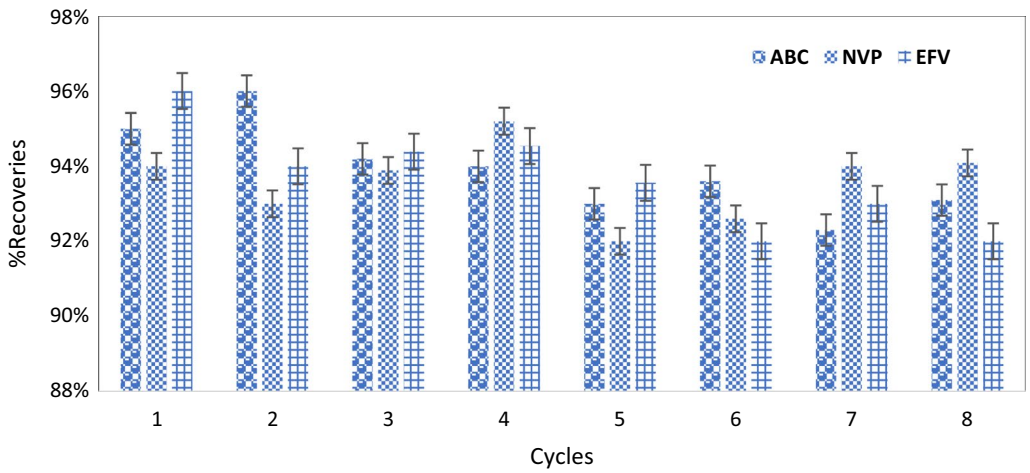


Fig. 12 Percentage recoveries of ARVDs in eight consecutive cycles. ABC = abacavir, NVP = nevirapine, EFV = efavirenz. Experimental conditions were: initial concentration of ARVDs—1 mg L^{-1}, sample pH—6, adsorbent mass—30 mg, and sample volume—50 mL

Table 7 Concentration (μg L^{-1}) of ARVDs ± %RSD detected in wastewater

	Darvill		Umbilo	
	Infl	Effl	Infl	Effl
Abacavir	167.92 ± 3.97	36.5 ± 9.66	61.24 ± 4.80	178.02 ± 4.19
Nevirapine	119.70 ± 2.24	42.07 ± 4.54	145.48 ± 4.14	104.98 ± 1.37
Efavirenz	40.76 ± 9.78	28.75 ± 9.89	48.72 ± 4.04	103.32 ± 1.46

effl effluent, *infl* influent

Table 8 Concentration (μg L^{-1}) of ARVDs ± %RSD along Msunduzi river

	Camps Drift	Wood house	Bishopstowe
Abacavir	7.85 ± 4.86	13.15 ± 7.10	n.d
Nevirapine	2.33 ± 9.71	n.q	6.38 ± 4.43
Efavirenz	n.q	2.18 ± 5.84	1.95 ± 1.82

n.d not detected, *n.q* not quantified

Application to real samples

Analysis of ARVDs in wastewater

The MIP-DSPE method was applied under optimum conditions in the determination of abacavir, nevirapine and efavirenz in wastewater samples. All the studied ARVDs were detected in all analysed samples (Table 7). The presence of efavirenz could be due to its frequent usage in combination therapy of ART accompanied by its excretion rates ranging from 14 to 61% in faeces and urine (Eckhardt et al. 2017). These findings correspond to those published by Horn et al. (2022), where efavirenz and nevirapine were frequently detected in wastewater samples at 5.1 and 134 μg L^{-1}, respectively, in 8 of 8 WWTPs studied. However, their concentrations are lower for efavirenz and comparable for nevirapine. The highest concentrations in the current study were observed at Umbilo WWTP for most ARVDs where abacavir and efavirenz also showed higher concentrations in the effluent than in the influent. This could be attributed to derivatives transforming back into parent compounds due to the water treatment processes in the WWTPs (Abafe et al. 2018).

Analysis of ARVDs in river water

River water samples were extracted using MIP-DSPE only as analysis of wastewater samples showed that it is the most selective and sensitive technique. Efavirenz was detected in all sampling points but could not be quantified in Camps Drift sampling point. Abacavir had the highest detected concentrations (7.85–13.15 μg L^{-1}). Wood house sampling point was the most polluted sampling points. This could be associated with the sampling point being located next to the municipality dump site and informal dumpsters which may potentially lead to the leaching of expired or unused ARVDs during rainfalls into the river. The concentrations observed in river water are lower than those observed in wastewater samples which could be attributed to possible dilutions during rains and floods, and when smaller rivers join mainstream rivers (Mtolo et al. 2019). The maximum concentrations of ARVDs observed were 13.15 μg L^{-1} for abacavir, 2.18 μg L^{-1} for efavirenz in Wood house sample and 6.38 μg L^{-1} for nevirapine in Bishopstowe sample (Table 8). The results obtained for efavirenz at Bishopstowe (1.95 μg L^{-1}) are closer to those reported by Mtolo and colleagues (2.45 μg L^{-1}) in the same sampling point (Mtolo et al. 2019).

Analysis of ARVDs in tap water

Tap water samples were collected from Scottsville, Oribi Village, Lincoln Meade, Allandale, Napierville. Efavirenz was the most detected in all samples, however, it was only quantified in Oribi Village sample (2.17 μg L^{-1}). Nevirapine was below detection in Lincoln Medea and below quantification in all other samples. Abacavir was quantified in higher concentrations of 5.24 μg L^{-1} in Scottsville and 6.27 μg L^{-1} in Napierville, while it was undetected in Lincoln Meade and unquantified in Oribi and Allandale. The detection of ARVDs in tap water indicates their continuous indirect congestion by humans which could result in development of resistance to ARVDs and liver toxicity.

Conclusion

The multi-template molecularly imprinted polymers were successfully synthesized via bulk polymerization. The characterization showed that the imprinted and non-imprinted polymers are structurally similar, with slight differences that confirm the presence of the imprinted binding sites on the surface of the MIP. The higher recoveries obtained for the MIP-based sorbents indicated their high accuracy compared to conventional SPE sorbent. However, MIP-DSPE is slightly more accurate than MIP-SPE which could be attributed to the improved contact step between the adsorbent and the analytes in water sample and the presence of imprinted binding sites on the MIP surface. The Freundlich isotherm and the pseudo-second rate order best described the adsorption mechanism of the ARVDs into the MIPs, which was translated into multilayer coverage and chemisorption aided by the electrostatic interactions. Selectivity studies showed that the MIP was more selective towards ARVDs of interest than the competitors. The reusability studies revealed that the MIP can be reused for up to 8 cycles without losing its high efficiency. The wastewater treatment plants were found to be contaminated with all the studied ARVDs in quantifiable amounts with the highest

concentration in abacavir. The presence of ARVDs in effluent water indicates their partial removal by the wastewater treatment processes and their contribution to the surface water pollution. Their presence in tap water is an indication of the ARVDs unintentional consumption by humans. These findings suggest the importance of the ARVDs continuous monitoring to safeguard human health and the urgency to improve the treatment technologies.

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Author contributions
PM contributed to conceptualization, methodology, resources, writing—review and editing, supervision, funding acquisition and project administration. TX was involved in data curation, conceptualization, methodology, formal analysis, validation, visualization, writing—original draft preparation, and project administration. All authors read and approved the final manuscript.

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Availability of data and materials
All data generated or analysed during this study are included in this published article.

Declarations

Competing interests
The authors declare that they have no competing interests.

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