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Pharmaceutical Retention Mechanisms by Nanofiltration Membranes

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LONG D. NGHIEM[1], ANDREA I. SCHÄFER[1], AND MENACHEM ELIMELECH[2,*]

[1] Environmental Engineering, University of Wollongong, NSW 2522, Australia

[2] Department Chemical Engineering, Environmental Engineering Program, Yale University, New Haven, Connecticut 06520-8286

* Corresponding author: Menachem Elimelech, E-mail: menachem.elimelech@yale.edu, Phone: (203) 432-2789.

Abstract

This study investigates the retention mechanisms of three pharmaceuticals — sulfamethoxazole, carbamazepine, and ibuprofen — by nanofiltration (NF) membranes. Laboratory-scale experiments were carried out with two well-characterized NF membranes, with the goal of relating pharmaceutical retention behavior to membrane characteristics, physicochemical properties of the pharmaceutical molecules, and solution chemistry. Results show that retention of pharmaceuticals by a tight NF membrane is dominated by steric (size) exclusion, whereas both electrostatic repulsion and steric exclusion govern the retention of ionizable pharmaceuticals by a loose NF membrane. In the latter case, speciation of pharmaceuticals may lead to a dramatic change in retention as a function of pH, with much greater retention observed for ionized, negatively charged pharmaceuticals. For uncharged pharmaceutical species, intrinsic physicochemical properties of the pharmaceutical molecules can substantially affect their retention. In its neutral form, ibuprofen adsorbs considerably to the membrane because of its relatively high hydrophobicity. Similarly, polarity (represented by the dipole moment) can influence the separation of molecules that are cylindrical in shape as they can be directed to approach the membrane pores head on due to attractive interaction between the molecule polar centers and fix charged groups on the membrane surface. This phenomenon is probably inherent for high dipole moment organic compounds and the governing retention mechanism remains steric in nature.

Introduction

Pharmaceuticals have been of tremendous benefit to our society for treatment and prevention of illnesses as well as promoting growth and good health. Not surprisingly, thousands of pharmaceuticals are being produced and used at vast quantities. This has, however, prompted great concern as solid evidence of widespread occurrence of pharmaceutically active compounds (PhACs) in the aquatic environment at trace levels is starting to emerge. Since they are often not fully assimilated by humans and animals during treatment, these pharmaceuticals are continuously released to the environment mostly via domestic wastewater effluent in the original or partly metabolized forms.

Currently, most wastewater treatment plants (WWTPs) are not designed to eliminate trace organic contaminants. The capacity of WWTPs to remove PhACs depends essentially on the biological treatment stage, where PhACs are removed predominantly by sorption to suspended solids and by biological degradation. Removal of several hydrophobic compounds has been reported to be positively correlated to the sludge retention time (SRT), with an SRT of at least 10 days being needed to achieve effective removal (*1*, *2*). However, many WWTPs in the United States and Europe are not designed with a long enough SRT to satisfy this requirement (*2*). The low influent concentration of PhACs and seasonal temperature changes can further complicate the problem (*1*). Some pharmaceuticals such as carbamazepine are highly persistent and have been shown to be inert to the biological treatment process (*1*, *3*). In fact, carbamazepine has even been suggested as a possible anthropogenic marker in the aquatic environment (*3*). Consequently, removal efficiencies of PhACs by WWTPs vary greatly, with the overall removal generally quite low. Not surprisingly, PhACs are ubiquitous in most secondary treated effluents and receiving freshwater bodies.

In studies carried out in many countries, including Australia, Austria, Brazil, Canada, Croatia, England, Germany, Greece, Italy, Spain, Switzerland, the Netherlands, and the U.S., more than 80 pharmaceuticals and their metabolites have been detected in aquatic environments at concentrations in the microgram per liter range or lower (*4-10*). Because pharmaceuticals are designed to be biologically active, they have the potential to affect a large variety of non-target organisms for a wide range of physiological consequences. For example, the potential for induction (*11*, *12*) or proliferation of antibiotic resistance (*11*, *13*, *14*) due to low concentrations of antibiotic

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agents in the environment is of increasing concern to scientists. Although potential chronic effects of PhACs at trace levels remain largely unknown, it is unanimously accepted that preventing such PhACs from entering the aquatic environment is essential (*2*), and a precautionary approach is required. Removal of PhACs from secondary effluents prior to water reuse is also of paramount importance, as augmentation of water supply by wastewater reuse has recently gathered substantial momentum (*15-17*).

Nanofiltration (NF) is an important technology for water recycling. Complete or near complete removal of a wide range of contaminants in secondary effluents can be achieved with NF membranes (*18-21*). However, such premise should not be generalized to all trace contaminants. As illustrated in our previous study, natural steroid hormones can adsorb (or partition) onto the membrane and subsequently diffuse through the membrane polymer (*22*). This process may result in trace contaminant removals much lower than those predicted based on a steric (size) exclusion mechanism. Furthermore, retention of trace organics by NF membranes highly depends on the compound physicochemical properties, which can be influenced by solution chemistry, particularly by the solution pH. To date, the intricate relationship between the physicochemical properties of trace organics, solution chemistry, and membrane retention behavior remains poorly understood. Delineation of the fundamental mechanisms governing trace organic contaminant removal by NF membranes will markedly enhance the use of NF membrane technology in water reuse applications.

The objective of this study is to examine the removal mechanisms of three pharmaceuticals — sulfamethoxazole, carbamazepine, and ibuprofen — by two thin-film composite NF membranes. These compounds represent different pharmaceutical groups with quite distinct physicochemical properties. Experiments were carried out with two NF membranes having well-characterized pore sizes. Retention behavior was related to the physicochemical properties of the pharmaceuticals and the membranes as well as the solution chemistry. On the basis of these results, mechanisms of pharmaceutical retention by NF membranes are elucidated and discussed.

Materials and Methods

NF Membranes. Two NF membranes, denoted NF-270 and NF-90 by the manufacturer (FilmTec Corp., Minneapolis, MN), were used in this investigation. These are polyamide thin-film composite membranes. The membranes were received as flat sheet samples. They were gently washed with deionized water (DI) to remove any preservatives and were stored in DI water at 4 °C.

Membrane Zeta Potential. Membrane surface steaming potential was measured using a commercial streaming potential analyzer (BI-EKA, Brookhaven Instruments Corp., Holtsville, NY). Details on the instrument, measurement procedure, and zeta potential calculation from the measured streaming potential are described elsewhere (*23, 24*). Streaming potential measurements were conducted in a background electrolyte solution containing 20 mM NaCl and 1 mM $NaHCO_3$ over the pH range of 2.5 to 11.0.

Pharmaceuticals. Three pharmaceuticals, namely, sulfamethoxazole, carbamazepine, and ibuprofen were selected for this study (Figure 1). The compounds were purchased from Sigma-Aldrich (Saint Louis, MO) and are reported to be of 99 % purity or higher. These pharmaceuticals represent three important drug categories. Sulfamethoxazole is an important member of the sulfonamide antibacterials and is probably the most frequently used antibiotic; carbamazepine is one of the most widely used anti-epileptic drugs; and ibuprofen is a common anti-inflammatory agent. As seen in Figure 1, the pharmaceuticals have quite distinctive functional groups. Stock solutions (1 g/L) were prepared in pure methanol for all three pharmaceuticals. The stock solutions were stored at < 4 ^{o}C and were used within 1 month.

[FIGURE 1]

Analytical Methods. A Shimadzu HPLC system equipped with a Supelco Drug Discovery C-18 column (with diameter, length, and pore size of 4.6 mm, 250 mm, and 5 μm, respectively) and

a UV detector was used to analyze pharmaceutical concentration in the feed and permeate samples. Detection wavelengths for sulfamethoxazole and carbamazepine were set at 280 nm, and for ibuprofen at 225 nm. The mobile phase for gradient elution was deionized water (buffered with 0.025 M KH_2PO_4) and acetonitrile (ACN), delivered at a constant flow rate of 1 mL/min. A gradient program for the mobile phase was set in accordance with the chromatographic behavior of the respective analytes. The total run time for each HPLC analysis was 25 min. A sample injection volume of 50 μL was used, and a typical quantification limit for all analytes under these conditions was approximately 20 μg/L. Standard curves yielded coefficients of determination (R^2) greater than 0.98 within the range of experimental concentrations in all cases. Analysis was carried out immediately following the nanofiltration experiments.

Laboratory-Scale NF Test Unit. A laboratory-scale NF/RO membrane filtration test unit was used. The unit utilizes a Dayton capacitor start motor (Dayton Electronic Manufacturing Co., Chicago, IL) coupled with a Hydra-Cell pump (Wanner Engineering Inc., Minneapolis, MN) capable of providing pressures up to 69 bar and a cross-flow of 4.2 liters per minute. Temperature of the feed reservoir was controlled using a chiller/heater (Neslab RTE 7). A seawater grade stainless steel rectangular cross flow cell with an effective membrane area of 40 cm^2 and a channel height of 2 mm was used in the test unit. Permeate flow rate was measured by a digital flow meter connected to a PC and the cross flow rate was monitored with a rotameter.

Filtration Protocol. Prior to each experiment, the membrane was stabilized at 12 bar using DI water for at least 16 hours until there was no variation in permeate flux. The feed reservoir temperature was kept constant at 20±0.1 ^{o}C throughout the experiment. Both permeate and retentate were recirculated back to the feed reservoir. In all filtration experiments, background electrolyte solution contained 20 mM NaCl and 1 mM $NaHCO_3$, and, unless otherwise stated, the pH was kept at 8.

Prior to experimenting with pharmaceuticals, 7 liters of DI water was introduced to the feed reservoir. The cross flow velocity and permeate flux were adjusted to 30.4 cm/s and 15 μm/s (54 $Lm^{-2}h^{-1}$), respectively. To achieve this permeate flux, the transmembrane pressures were set to approximately 4.5 and 6 bar for the NF-270 and the NF-90 membranes, respectively. Pharmaceuticals were then spiked into the feed reservoir to make up a concentration of 500 μg/L. Approximately 1.5 mL of feed and permeate samples were taken for analysis at specified time intervals. For experiments with variable pH, the solution was adjusted to pH 10.5 by the addition of NaOH. The pH was then incrementally dropped to 3.5 by the addition of HCl, and the system was equilibrated for 1 hour prior to sample collection for analysis at each pH value.

Results and Discussion

NF Membrane Characteristics. Membrane surface chemical characteristics are determined by a very thin polyamide layer, which makes up the active layer of the two NF membranes used in this investigation (*25*). This polyamide layer contains both carboxylic and amine functional groups that can ionize in an aqueous solution (*23, 26*). Consequently, the membrane zeta potential varies as a function of pH (Figure 2). The NF-270 membrane has an isoelectric point at approximately pH 3.5 and that of the NF-90 membrane is approximately at pH 4. At pH below the isoelectric point, the membranes have a slightly positive charge. Above the isoelectric point, the membranes are negatively charged, with the zeta potential becoming more negative as the pH increases. Since separation of ionic species by nanofiltration membranes is governed by both size (steric) exclusion and electrostatic interaction (*26-29*), this amphoteric characteristic of the membrane surface has important implications with regard to the solute retention mechanisms of the membranes.

[FIGURE 2]

The average pore radii of the membranes have been characterized in our previous study by challenging the membranes with a series of inert organic tracers of various molecular weights and

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applying a pore transport model (*22*). It was concluded that the NF-270 is a "loose" NF membrane with an average pore radius of 0.42 nm, whilst the NF-90 is a "tight" NF membrane with an average pore radius of 0.34 nm. The difference in pore size and the amphoteric nature of the membrane surface are clearly reflected in the salt (conductivity) retention behavior of these two membranes as described in Figure 3. As the pH is decreased, the membrane becomes less negatively charged (Figure 2). Consequently, electrostatic (charge) exclusion of ionic species by the membrane diminishes and completely vanishes at the isoelectric point. This results in a dramatic drop in salt (conductivity) retention by the loose NF-270 membrane as the pH decreases to 4, where a minimum retention is observed due to an absence of electrostatic repulsion at the isoelectric point (*26*). While both steric and electrostatic interactions are responsible for the separation of ionic species by the loose NF membrane, it is evident that salt retention by the tight NF-90 membrane is predominantly governed by steric exclusion. Conductivity retention by the NF-90 is substantially higher than that by the NF-270, and only a relatively small decrease in retention can be observed when the pH is reduced.

[FIGURE 3]

Physicochemical Properties of Pharmaceuticals. The biological and chemical activity of pharmaceuticals is strongly influenced by their functional groups. The chemical speciation of pharmaceuticals is governed by solution pH and the compound dissociation constants or the pK_a values (*30*). Because of differences in charge and physicochemical properties of the various species of a given pharmaceutical, their NF separation behavior may differ significantly.

The three pharmaceuticals selected for this study are markedly different in their physicochemical properties, although they all have similar molecular weights in the range between 206 and 253 g/mol (Table 1). Of a particular note is the very high dipole moment of both sulfamethoxazole and carbamazepine. These are permanent dipole moments, which are calculated using the HyperChem commercial software (*31*), and do not include the induced dipole moment resulting from the electrical field of the membrane surface. As we show later in the paper, the compound dipole moment can play an important role in retention by the NF membranes by affecting the molecule orientation as it approaches the membrane pores.

[TABLE 1]

Since carbamazepine is a base with a pKa value of 2.3, the compound is uncharged at all conditions typical of natural or waste waters. In contrast, speciation of both ibuprofen and sulfamethoxazole is expected in the pH range commonly encountered in nanofiltration processes. Sulfamethoxazole contains two functional moieties at both sides of the sulfonamide linkage (–NH–$S(O_2)$–). Consequently, sulfamethoxazole exhibits two dissociation constants, one involving the protonation of the primary aromatic amine $–NH_2$ and the other corresponding to the deprotonation of the sulfoamide –NH as illustrated in Figure 4. This figure also shows the speciation of sulfamethoxazole over the entire pH range. At pH above 5.7, sulfamethoxazole exists predominantly as an anionic species, between pH 1.7 and pH 5.7 the compound is uncharged, while at pH below 1.7 it is positively charged.

[FIGURE 4]

Solution pH can affect not only charge but also other physicochemical properties of the pharmaceuticals, particularly hydrophobicity and solubility (*32-34*). Significant variation of both hydrophobicity and solubility of several pharmaceuticals as a function of the solution pH has been reported (*33, 34*). Values for Log K_{ow} and solubility in water of the three pharmaceuticals, summarized in Table 1, were obtained from the literature. Although the corresponding pH is unknown, it is assumed that they represent characteristics of the compounds in their neutral form.

Pharmaceutical Retention by NF Membranes: General Behavior. Figure 5 presents the concentration of sulfamethoxazole, ibuprofen, and carbamazepine in both permeate and feed as a

function of time during filtration with the NF-270 and NF-90 membranes at pH 8.0. While carbamazepine is neutrally charged at the pH of the experiment, the other two compounds are negatively charged at this pH. In contrast to nanofiltration of hydrophobic trace organics, such as steroid hormones and hormone mimicking compounds which adsorb quite strongly to the membranes (*22*), these pharmaceuticals do not adsorb to the membranes at this experimental condition as evidenced from their constant feed concentrations for the duration of the runs. Sulfamethoxazole and carbamazepine have a low affinity to the membrane polymer, indicated by their relatively low log K_{ow} value (Table 1). The high log K_{ow} of ibuprofen listed in Table 1 is for the uncharged species which are prevalent below the pK_a, not for the negatively charged deprotonated species at the pH of these experiments.

[FIGURE 5]

As the experiments progress, both permeate and feed concentrations appear stable, corresponding to a constant retention over time. The contribution of electrostatic interaction to retention is evident in the nanofiltration of the negatively charged sulfamethoxazole and ibuprofen at the solution conditions (pH 8). No sulfamethoxazole or ibuprofen are detected in the permeate following filtration by the tight NF-90 membrane, while the looser NF-270 membrane also achieves a very high, but not complete removal of both compounds (Figures 5a-5d). The retention of these pharmaceuticals is higher than that of carbamazepine (Figures 5e and 5f), which is retained solely via steric interaction because it is neutrally charged above pH 2.3 (Table 1). Overall, the retention of the three model pharmaceuticals is quite high, and is attributed to the size and charge of the pharmaceutical species at this particular experimental condition (pH 8).

Pharmaceutical Retention by NF Membranes: Role of Solution pH. Retention of pharmaceuticals by NF membranes is determined by the coupled influence of the compound speciation behavior, the membrane pore size and surface charge (represented by the zeta potential), and the compound physicochemical properties (i.e., size, steric characteristics, log K_{ow}, and dipole moment). Figure 6 describes the retention of the three pharmaceuticals by the NF-90 and NF-270 membranes over the pH range 3.5 – 10.5. Over this wide pH range, the pharmaceutical compounds and the membrane display a wide variation in speciation (or charge) and physicochemical properties, thus allowing a more systematic investigation of the retention mechanisms involved. Complete or near complete retention of all three pharmaceuticals by the tight NF-90 membrane is observed over the entire pH range, despite the marked effect of pH on the charge of both the pharmaceutical compounds and the membrane surface. The retention behavior of the loose NF-270 membrane is, however, quite different. The corresponding retention behavior and associated mechanisms for each of the three pharmaceuticals are discussed below.

[FIGURE 6]

(a) Retention of Sulfamethoxazole. Solution pH affects markedly sulfamethoxazole retention by the loose NF-270 membrane. Because sulfamethoxazole transforms from a negatively charged to a neutral species as the solution pH decreases from 10.5 to 3.5, the retention by the NF-270 membrane declines dramatically from a value as high as 100% to only 25% at low pH. This decline in retention can also be attributed to a decrease in the membrane zeta potential as the solution pH decreases (Figure 2). In contrast, only a subtle but nevertheless discernible drop in retention by the tight NF-90 membrane can be observed as the solution pH decreases to below pH 6 (i.e., retention drops from 100% to 98%). This result indicates that pharmaceutical retention by this tight NF membrane is predominantly governed by steric interaction. On the other hand, both electrostatic repulsion and steric interaction are responsible for the retention of charged pharmaceuticals by the loose NF membrane.

Although the degree of sulfamethoxazole retention is markedly different for the tight NF-90 and the loose NF-270 membranes, retention behavior as a function of pH for both membranes follows a sigmoidal shape, resembling the compound speciation curve. It is interesting to note that

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the inflection point deviates slightly from the pK_a value (5.7) of sulfamethoxazole. A similar observation can also be inferred from the data reported by Bellona and Drewes (*35*). This behavior can partly be attributed to the negative proton retention often observed in an acidic solution (*26, 36*). Because the H^+ ion is more mobile or permeable than the other monovalent cations in solution (i.e., Na^+), negative retention of the more permeable ion is possible when the ratio of the more permeable ion to the less permeable ion is low (*27*). Negative proton retention of up to 400% has been reported for the loose NF-45 membrane at pH 4.5 (*36*). Due to the passage of protons through the membrane pores, local pH in the membrane pore would be lower than that at the bulk solution, which to some extent could explain the deviation between the inflection point and the pK_a value of sulfamethoxazole as seen in Figure 6a. Proton passage is more substantial for the loose NF-270 membrane where Donnan exclusion plays a more significant role (*36*). This is consistent with the fact that the deviation from the pK_a value is more significant for the loose NF-270 membrane, while it is almost negligible for the tight NF-90 membrane (Figure 6a). Negative proton retention by the NF-90 and NF-270 membranes has been confirmed by measuring the pH of the feed and permeate samples. However, the difference was found to be relatively small, in the range of 0.2 – 0.3 pH units at pH 4. Although it is possible that, due to the small pore volume, pH at the membrane pore can be significantly less than that of the bulk solution where the pH measurement takes place, it is probable that other factors may also contribute to the divergence of the inflection point from the pK_a.

(b) Retention of Carbamazepine. Carbamazepine (pK_a = 2.45, Table 1) is neutrally charged at the pH range of the experiment. Its retention by both the NF-90 and the NF-270 membranes is relatively constant, because the retention is solely governed by steric (size) exclusion (Figure 6b) in the absence of charged functional groups. In the absence of electrostatic (charge) repulsion, the compound physicochemical properties can influence the retention behavior. It is striking that the retention of the neutral species of sulfamethoxazole is significantly lower than that of carbamazepine (compare Figures 6a and 6b), despite the higher molecular weight of sulfamethoxazole compared to carbamazepine (Table 1). This phenomenon can be explained following the suggestion of Bruggen *et al.* (*37*) that organic molecules with high dipole moments (above 3 Debye) can show lower retention than molecules with approximately the same molecular weight but with a lower dipole moment. Because of the attraction between polar moieties of the molecule and the membrane fixed charged groups, the molecule is directed towards the membrane pore in an orientated instead of a random fashion. This results in a statistical propensity of the transported molecules to approach the membrane pores with a preferential orientation, in such a way that the side of the dipole which induces attraction with the fixed negative charge of the membrane pore is closer to the pore entrance. The effect is apparent when comparing the three-dimensional models of sulfamethoxazole and carbamazepine (Figure 7). The sulfamethoxazole molecule is long and cylindrical in shape with its dipole moment (5.4 Debye) acting along the main axis. By contrast, carbamazepine has a lower dipole moment (3.6 Debye) and is more bulky in shape.

[FIGURE 7]

(c) Retention of Ibuprofen. Evidence for the role of the physicochemical properties of uncharged trace organic species in retention is also apparent in the nanofiltration of ibuprofen. As the solution pH decreases to below its pK_a value of 4.9, electrostatic repulsion between ibuprofen and the membrane surface is eliminated, allowing adsorption of the uncharged ibuprofen to the membrane. While the elimination of charge repulsion reduces the removal rate, adsorption can contribute to the short-term removal of ibuprofen. Both processes occur simultaneously and their relative contributions cannot be separated. These processes are likely the cause for the decrease in the observed retention of ibuprofen by the NF-270 membrane as the pH decreases (Figure 6c).

Because of adsorption to the membrane, ibuprofen concentration in the feed decreases when the pH is reduced to below 4.9 as demonstrated in Figure 8. For runs with the tight NF-90 membrane, ibuprofen concentration in the permeate remains undetectable. However, ibuprofen concentration

in the permeate increases noticeably following filtration by the loose NF-270 membrane. Because the equivalent Stokes radius of ibuprofen calculated by the Wilke-Chang and the Stokes-Einstein equations (*38*) is 0.34 nm, smaller than the NF-270 membrane average pore size (0.42 nm), this indicates a possible convective transport of the ibuprofen through the pores of the NF-270. This behavior is quite different from the adsorption of steroid hormones to the membrane, reported in our previous studies (*22, 39*), in which permeate concentration remained low for a long time because the adsorptive capacity of the membrane had not been reached.

[FIGURE 8]

Relative Role of Steric (Size) Exclusion. When the solute-membrane interaction is purely steric, the observed retention of inert organics can be predicted by the pore transport model described in our previous publication (*22*). In this modeling approach, the key input parameters are the membrane pore radius and the inert molecule size, as well as the convective permeate flux. Predictions of retention for the NF-270 and NF-90 membranes as a function of compound molecular weight along with the experimentally determined retention values of the three pharmaceuticals (taken at a pH where the compounds are uncharged) are presented in Figure 9. Note that the conditions used for modeling and for the pharmaceutical filtration experiments are identical.

[FIGURE 9]

Steric (size) exclusion is solely responsible for retention of uncharged and non-adsorptive organic solutes. While electrostatic repulsion is absent, there is a relatively weak attraction between the molecule polar centers and fixed charge groups on the membrane surface. For compounds with sufficiently high dipole moments, such permanent dipole – fixed charge interaction can direct the molecule to approach the membrane pores in a oriented fashion and the compound three-dimensional structure becomes an important factor governing the separation process (*37*). Consequently, high dipole moment organics may exhibit lower retention than that expected based on a purely size exclusion mechanism, where the molecule approaches the membrane pore randomly and the Stokes radius is taken as an average representative size of the solute (Figure 9a). The influence of molecule polarity on retention is quite significant for compounds that are cylindrical in shape such as sulfamethoxazole (Figures 7 and 9a). It must be emphasized that, even in this case, the interaction mechanism responsible for separation remains steric in nature. Because the average pore radius of the NF-90 membrane is substantially smaller than the radii of the three pharmaceuticals used in this study, no polarity effects can be observed with this tight NF-90 membrane and the retention is nearly complete (Figure 9b).

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Table 1. Physicochemical Properties of Pharmaceuticals

Pharmaceutical	**MW** (g/mol)	**Stokes Radius** (nm)	**Solubility in Water** (mg/L)	**pK_a**	**Log K_{ow}**	**Dipole Moment** (Debye)
Sulfamethoxazole	253.3	0.38 [a]	600 [b]	pK_{a1} = 1.7 [c] pK_{a2} = 5.6 [c], 5.7 [b]	0.89 [e]	5.4 [f]
Carbamazepine	236.3	0.37 [a]	17.7 [c]	2.3 [e]	2.45 [e]	3.6 [f]
Ibuprofen	206.3	0.34 [a]	49 [d]	4.4 [d] - 4.9 [e]	3.5 [e], 4.13 [d]	1.8 [g]

[a] Calculated by the Wilke-Chang and the Stokes-Einstein equations *(38)*.

[b] Ref (*40*).

[c] Ref (*41*).

[d] Ref (*34*).

[e] Ref (*42*).

[f] estimated using HyperChem 7.0 (*31*).

[g] Ref (*43*)

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FIGURE CAPTIONS

Figure 1: Chemical structure of the three pharmaceuticals used in this study. Physicochemical properties of the compounds are described later in Table 1.

Figure 2: Zeta potential of the NF-90 and NF-270 membranes as a function of pH in a background electrolyte solution containing 20 mM NaCl and 1 mM $NaHCO_3$.

Figure 3: Salt retention (measured by electric conductivity) by the NF-90 and NF-270 membranes as a function of pH. Feed solution contained 20 mM NaCl and 1 mM $NaHCO_3$.

Figure 4: Speciation of sulfamethoxazole as a function of pH, calculated based on the pK_a values in Table 1.

Figure 5: Permeate and feed concentrations of sulfamethoxazole, ibuprofen, and carbamazepine as a function of filtration time for the NF-270 and NF-90 membranes. The feed solution contained 500 μg/L of the corresponding pharmaceutical in a background electrolyte solution containing 20 mM NaCl and 1 mM $NaHCO_3$. Other experimental conditions were as follows: cross flow velocity = 30.4 cm/s, permeate flux = 15 μm/s (54 $Lm^{-2}h^{-1}$), pH = 8, and temperature = 20 ^oC. The permeate and retentate were recirculated back to the feed reservoir during the nanofiltration run.

Figure 6: Retention of (a) sulfamethoxazole (b) carbamazepine, and (c) ibuprofen by NF-90 and NF-270 membranes as a function of the solution pH. The feed solution contained 500 μg/L of the corresponding pharmaceutical in a background electrolyte solution containing 20 mM NaCl and 1 mM $NaHCO_3$. After each pH adjustment, the system was equilibrated for 1 hour prior to sample collection for analysis. Other experimental conditions were as follows: cross-flow velocity = 30.4 cm/s, permeate flux = 15 μm/s (54 $Lm^{-2}h^{-1}$), and temperature = 20 ^oC. The permeate and retentate were recirculated back to the feed reservoir during the nanofiltration run.

Figure 7: A three-Dimensional model of sulfamethoxazole and carbamazepine, simulated using HyperChem 7.0 (*31*).

Figure 8: Feed and permeate concentration of ibuprofen as a function of the solution pH for the NF-90 membrane (top) and NF-270 membrane (bottom). The feed solution contained 500 μg/L of ibuprofen in a background electrolyte solution containing 20 mM NaCl and 1 mM $NaHCO_3$. After each pH adjustment, the system was equilibrated for 1 hour prior to sample collection for analysis. Other experimental conditions were as follows: cross-flow velocity = 30.4 cm/s, permeate flux = 15 μm/s (54 $Lm^{-2}h^{-1}$), and temperature = 20 ^oC. The permeate and retentate were recirculated back to the feed reservoir during the nanofiltration run.

Figure 9: The measured retention values of the three pharmaceuticals (open symbols) — sulfamethoxazole (S), carbamazepine (C), and ibuprofen (I) — compared to model predictions (solid line), presented in our previous publication (*22*) for retention of non-adsorptive inert organics as a function of solute molecular weight: (a) NF-270 and (b) NF-90. The retentions of these pharmaceuticals were measured at approx. pH 3.5, where the compounds they neutrally charged (Figure 6). Parameters used in the pore transport model predictions were as follows: cross flow velocity = 30.4 cm/s, permeate flux = 15 μm/s (54 $Lm^{-1}h^{-1}$), and temperature = 20 ^oC.

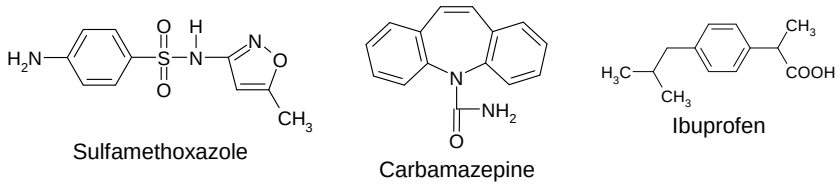

FIGURE 1

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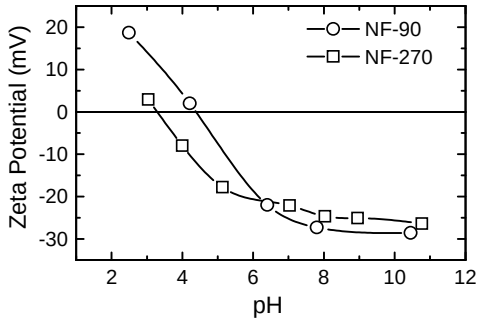

FIGURE 2

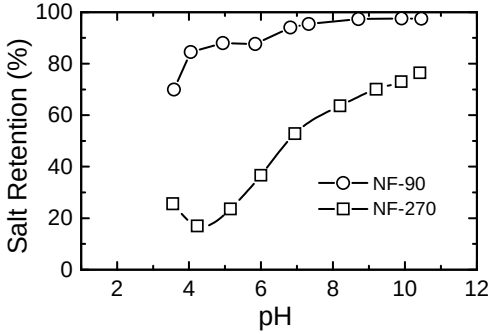

FIGURE 3

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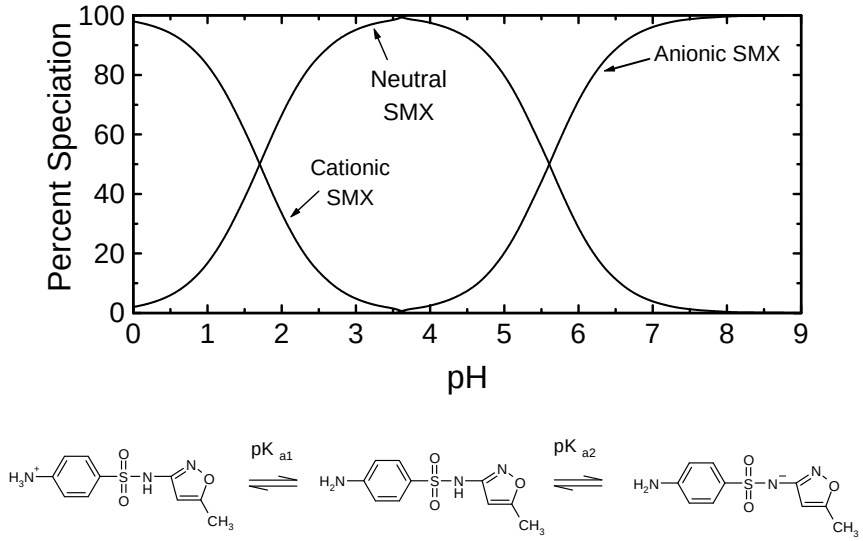

FIGURE 4

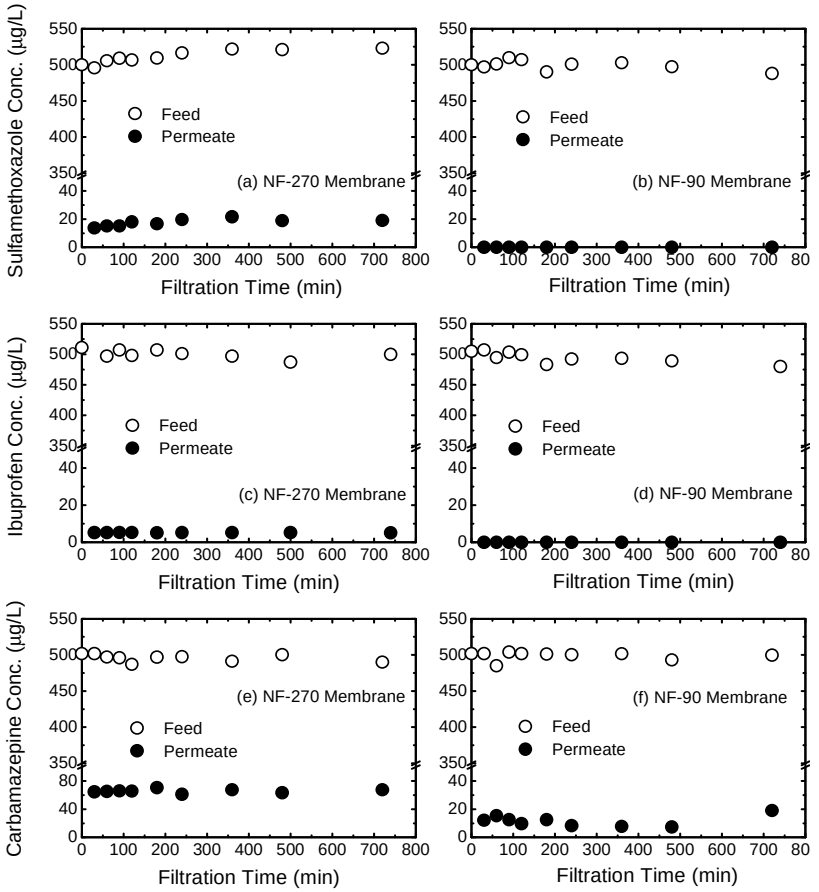

FIGURE 5

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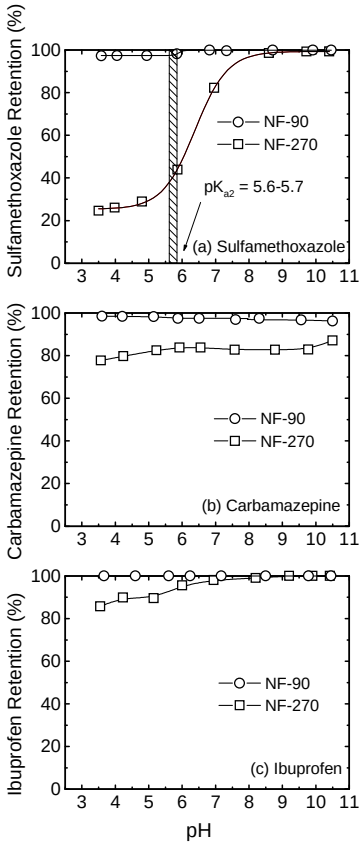
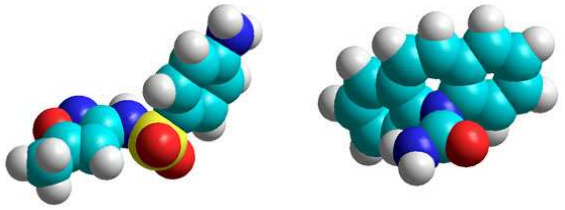


FIGURE 6



Sulfamethoxazole Carbamazepine

FIGURE 7

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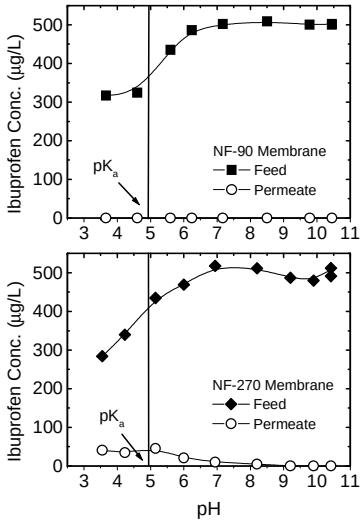

FIGURE 8

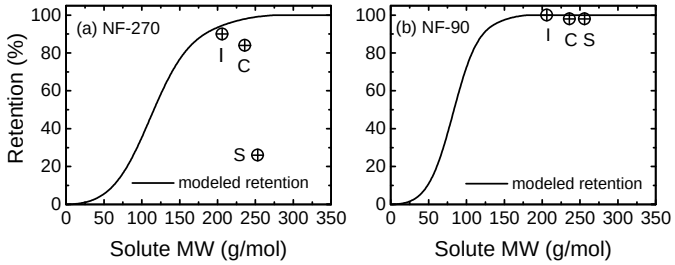

FIGURE 9

<u>BRIEF</u>

Retention mechanisms of pharmaceuticals by nanofiltration membranes are directly related to the molecule physicochemical characteristics, membrane pore size and charge, and solution chemistry.