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Cellulose acetate/P4VP-b-PEO membranes for the adsorption of
electron deficient pharmaceutical compounds

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Abstract

The prevalence of pharmaceutical compounds in surface and groundwater presents a rising threat to human health. As such, the search for novel materials that serves to avoid their release to the environment or for the remediation once in the water effluent is of utmost importance. The present work describes the fabrication of a cellulose acetate (CA) membrane modified with the block copolymer Poly(4-vinylpyridine-*b*-ethylene oxide) (P4VP-*b*-PEO) crafted for the specific targeting and adsorption of electron deficient pharmaceuticals. The electron deficient pharmaceuticals (EDPs) under study were Sulfamethoxazole, Sulfadiazine, and Omeprazole. The results as part of this work present a thorough characterization of the prepared membranes by FTIR, Contact Angle, and SEM images. Moreover, results show that adsorptive character of the membrane correlates with the relative electron deficiency and spatial orientation of the contaminant. Interestingly, the addition of a nominal 1% of P4VP-*b*-PEO to the cellulose matrix helps to increase the adsorption efficiency of the membranes at least two-fold in most cases. For the compounds studied, the prepared membrane has a higher efficiency towards Omeprazole, followed by Sulfamethoxazole and Sulfadiazine. This work may serve to inspire the design and fabrication of selective soft materials for the adsorption and remediation of contaminants of emerging concern.

Keywords: Sulfamethoxazole, Sulfadiazine, Omeprazole, electron deficient pharmaceuticals, water remediation, soft materials

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3 **1. Introduction**
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6 The ability of a society to provide fresh water for hygiene and consumption to the population
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8 is perhaps one of the most important items for the sustained growth of developing countries and
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10 the expansion of urban areas. Nevertheless, with the increase in population and urbanization, the
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12 release of toxic compounds to the environment and surface water also increases. The sources of
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14 contamination in surface and ground water are diverse, including: agricultural, industrial, oil
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16 pollution, sewage and wastewater¹ among many others.
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21 In recent years, the Environmental Protection Agency (EPA) has become very proactive in
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23 informing the community about the contaminants of emerging concern (CECs). CECs are a class
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25 of contaminants of diverse origins that are typically detected at trace levels in surface and
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27 groundwater (i.e. ppb, ppt). Examples of CECs are: pesticides, hormones, antibiotics, over-the-
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29 counter medications, agricultural byproducts, industrial chemicals, petroleum-based chemicals
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31 and others². A recent study conducted by Bai et.al (2018) accounts for the presence of numerous
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33 pharmaceuticals, pesticides and waste-indicator compounds in the metropolitan area of Denver,
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35 Colorado³. Findings like this one are of concern since even at low levels some CEC's are quite
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37 harmful to human health⁴. The biggest concern related to the presence of CECs in surface and
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39 groundwater is their potential to act as endocrine disruptor compounds (EDCs). There is vast
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41 evidence in the cited literature that the absorption of EDCs is the cause of hormone blockage or
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43 mimic and may cause prenatal development, metabolic diseases and other health-related issues.⁵
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Also, the concern exists that these compounds may affect aquatic life⁶ and their presence in groundwater has been correlated to disrupted microorganismal composition in communities and a rise of antibiotic resistant strains⁷. Other studies have suggested that the presence of certain CECs in water may lead to fish species to uptake considerable amounts of the compounds, which will ultimately be ingested by humans⁸.

Although in principle, the processes employed in wastewater treatment plants may remove CECs; this is not always the case^{9, 10}. In fact, some of these processes do not account as actual removal methods, and the byproducts that are created such as organochlorine specie can be more toxic than the initial compounds¹¹⁻¹⁵. As a strategy to cope with the presence of CECs in surface and groundwater, researchers have proposed the use of activated carbons¹⁶, nanofiltration¹⁷⁻¹⁹, reverse osmosis²⁰, ultrafiltration, degradation with microorganisms, and electrooxidation, among others²¹. Nevertheless, the adsorption of CECs with activated carbon is a preferred method because of the material's porosity (surface area), which allows for effective adsorption of the contaminants^{22, 23}. However, the production of activated carbon demands considerable amounts of energy and activated carbon pores can easily undergo fouling, drastically reducing its adsorption efficiency^{24, 25}.

Materials scientists have sought multiple solutions to mitigate the disadvantages of activated carbon by directly attending the drawbacks of the material²⁶ or fabricating alternative carbonaceous materials. For example, Turk Sekulic et al. reported a phosphorised carbonaceous adsorbent that was capable of sustaining π - π EDA interactions with their contaminants of interest with a maximum adsorption of 99 %²⁷. Further alternative materials for the removal of CECs have been fabricated in the form of cationic surfactants and organo-montmorillonites^{28, 29}.

Certainly, the use of membranes is considered quite promising and a viable technology that can be employed to remove CECs from wastewater and drinking water.³⁰ Membrane technologies such as forward osmosis (FO) and reverse osmosis (RO) have been extensively studied for the rejection of CECs. However, these methods still rely on physical rejection, and as such there is no selectivity, and organic fouling is still an issue³¹⁻³⁶. Despite the advances in polymer synthesis and membrane production technologies, insufficient or no research has been performed to tackle the water remediation of CECs. This is a consequence of the lack of selectivity and poor cost-effectiveness of polymers used in commercial purification membranes. We hypothesize that porous adsorption membranes are a feasible strategy to overcome the deficiencies of these common methods. Adsorption can be controlled by the addition of specific functionalities to polymeric rearrangement producing high porosity. These functionalities can also allow the reusability of the membranes by reversible adsorption as a response to external stimuli.

Thus, herein we propose the manufacture and study of a cellulose acetate based membrane capable of adsorbing CECs that are electron deficient pharmaceuticals (EDPs). In this study, we used phase inversion to fabricate a membrane out of cellulose acetate (CA) modified with Poly (4-vinylpyridine-b-ethylene oxide) (P4VP-b-PEO), two polymers capable of sustaining electrostatic interactions with positively charged molecules. Cellulose acetate (**Figure 2a**) is ubiquitously regarded as a resilient and biodegradable support for water purification membranes³⁷. Additionally, P4VP-b-PEO (**Figure 2b**) was chosen because our previous studies suggest that it is capable of sustaining electrostatic π - π interactions with the deactivated rings of the EDPs³⁸ as seen in **Figure 2c**. We embedded the block copolymer P4VP-b-PEO into the cellulose acetate support and tested the membrane in a gradient of electron-deficient pharmaceuticals (EDPs), establishing

a correlation between the general electronegativity of the EDPs and the adsorption capacity of the membrane.

The EDPs studied are two antibiotics and a commonplace pharmaceutical: Sulfamethoxazole (SMX), Sulfadiazine (SDZ), and Omeprazole (OMZ), respectively. The first two are sulfonamide antibiotics frequently prescribed to treat bacterial infections in humans and animals³⁹. These compounds pose the serious threat of altering microorganismal communities and inducing antibiotic resistance as is reported extensively in the literature⁴⁰⁻⁴³. Omeprazole is a highly accessible nonprescription medication used to treat heartburn, and it is characterized for its chemical instability⁴⁴. This compound is prone to quick degradation due to numerous environmental factors such as pH, heat, and light⁴⁴. More interesting is the fact that these degradation intermediates are highly electron deficient and may serve to validate the model membranes in this work⁴⁵. These three pharmaceuticals were chosen because they are substituted with prominent electron withdrawing groups, as are many other pharmaceuticals. According to the World Health Organization, the selected compounds are frequently found in most groundwater studies, in a varying range of regions and concentrations ranging from parts per billion to parts per million⁴⁶. Hence, the current study focuses on fabricating and evaluating a CA supported membrane capable of adsorbing EDPs studying the intertwine between the relative electron deficiency of the compounds and the membrane's adsorbing capacity. This work provides a feasible approach to the targeted removal of EDPs from aqueous media using environmentally friendly and sustainable components.

2. Experimental

2.1. Materials

Cellulose acetate (CA; 39.8 wt. % acetyl, Mn ~ 30,000), acetone HPLC plus (99.9%), N,N-Dimethylacetamide reagent plus (DMAc, 99%), analytical standard Sulfamethoxazole (SMX), analytical standard Sulfadiazine (SDZ), and analytical standard Omeprazole (OMZ) were purchased from Sigma Aldrich (St. Louis, MO, USA). Poly(4-vinyl pyridine -b-ethylene oxide) (P4VP-b-PEO, 20 kDa – 5 kDa) was purchased from the Polymer Source Inc. (Dorval, QC, Canada). All reagents were used without further purification. A polyester mesh with 105 μ m mesh openings and 52% open area was purchased from ELKO Filtering Co, LLC. Nanopure water from an Aries FilterWorks Gemini High Purity Water System (18.23 M-Ohm/cm) (Berlin, NJ, USA) was used to conduct all experiments.

2.2 Preparation of CA/P4VP-b-PEO membranes

CA membranes reinforced with polyester mesh were prepared by non-solvent induced phase separation (NIPS) process as published elsewhere^{47, 48}. Casting solutions were prepared dissolving 17 % wt. CA and varying concentrations of P4VP-b-PEO (0, 1 % wt) in 2:1 w/w acetone: DMAc. Solutions were left to magnetically stir at 400 rpm for 48 hours at room temperature. A polyester mesh was attached to a clean glass plate using metal clips. Dissolved polymer solutions were casted over the polyester mesh using a film casting doctor blade (MTI Corp. Richmond, CA, USA) adjusted to 150 μ m. Films were allowed approximately 5 s for evaporation of the solvents before they were immersed in nanopure water (non-solvent) for 10 min. Finally, membranes were cut to a specific size, rinsed, and stored in nanopure water.

2.3 Characterization of the membranes

2.3.1 Fourier-Transform Infrared (FTIR) Spectroscopy

CA Membranes were characterized by Fourier-transform infrared (FTIR) spectroscopy using a Bruker Tensor 27 attenuated total reflectance (ATR) spectrometer (Billerica, MA, USA). The spectral width ranged from 400–4000 cm^{-1} for 64 accumulation scans and 4 cm^{-1} of resolution.

2.3.2 Scanning Electron Microscopy

In order to assay the surface morphology of the CA membranes, a JEOL 6480LV scanning electron microscope (Peabody, MA, USA) in the secondary electron imaging (SEI) mode with 15 kV accelerating voltage.

2.3.3 Contact Angle measurements

The wettability of the CA membranes was tested by contact angle measurements performed with a Krüss drop shape analyzer DSA25S (Krüss Optronic, Hamburg, Germany) at room temperature. Membranes were cut to obtain 1 cm^2 pieces that were fixed to the stage of the instrument using carbon tape. To start the analysis, a 4.50 μL nanopure water droplet was released from a syringe with a 25-gauge flat needle (0.51 mm inner diameter, 0.26 mm outer diameter) onto the surface of the sample. Images of the drop were recorded every 0.5 s up to 120 s (to avoid changes due to evaporation of the drop) and analyzed in real-time using the Advance software (version 1.8).

2.4 Computational analysis

Spartan 16 (Wavefunction Inc., Irvine, CA, USA) was used to model the molecules SMX, SDZ, and OMZ in order to generate their electron-density maps. Calculations were performed based on Density Functional Theory (DFT), and geometries of the molecules were optimized at BLYP/6-31G*.

2.5 Adsorption batch tests of Sulfamethoxazole, Sulfadiazine, and Omeprazole using the CA membranes

2.5.1 Adsorption comparison between 17% CA and 1% P4VP-b-PEO 17% CA

17% CA and 1% P4VP-b-PEO (composite) membranes of uniform size and weight were exposed to separate 30 mL solutions of 30 ppm SMX, SDZ, and OMZ, respectively at 25 °C and 250 rpm in a Brunswick Shaker Incubator Series 2000 for 4 h. Afterwards, the membranes were removed, and the solutions were analyzed by UV-vis. A Shimadzu UV Spectrophotometer UV-1800 was used to obtain the absorbance of both, the solutions exposed to the membranes and controls to calculate their respective concentrations. In order to obtain the equilibrium adsorption amount of the membranes, we used the following formula,

$$q_e = \frac{(C_0 - C_e)V}{w}$$

where q_e is the equilibrium adsorption amount (mg/g), C_0 is the initial concentration of SMX, SDZ or OMZ (mg/L), C_e is the equilibrium concentration of SMX, SDZ or OMZ after the adsorption (mg/L), V is the volume of the pharmaceutical solutions, and w is the mass of the CA membrane before the experiment was carried out. All experiments were performed in triplicate.

2.5.2 Adsorption as a function of time

Membranes cut into rectangular shapes with consistent area and weights were exposed to 30 mL solutions of 30 ppm of SMX, SDZ, and OMZ, respectively at 25 °C and 250 rpm in a Brunswick Shaker Incubator Series 2000. The adsorption equilibration times ranged from 5 min to 24 h.

2.5.4 Cyclic reusability testing

In order to assay the reusability of the material, membranes were exposed to 30 mL solution of each pharmaceutical for a contact time of 1 hr at 25 °C and 250 rpm. Afterwards, the membranes were immersed in EtOH 95 % wt. for 20 min and later in nanopure water for 10 min under the

same experimental conditions. Membranes were dried with compressed air and used for another batch adsorption cycle. All solutions were measured using UV-vis, and the equilibrium adsorption amount (q_e) was calculated for each cycle.

3. Results and discussion

Foremost, the structures of the pharmaceuticals under study must be taken into consideration. As seen in **Figure 1**, the three compounds under study vary in their spatial arrangement as well as their degree of electron withdrawing substitution. The central feature to the π - π interactions with P4VP-PEO lies in the electron deficient aromatic ring that can be appreciated in the electron density maps of each molecule. **Figure S1** shows the highly electron deficient degradation intermediates of Omeprazole.

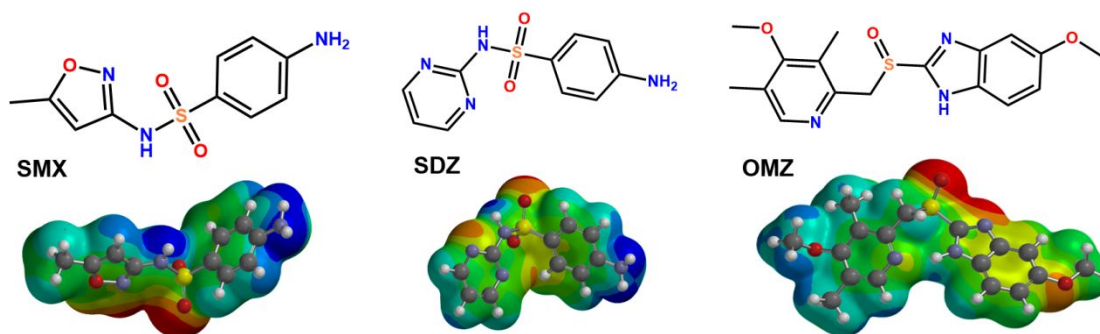


Figure 1. The molecular structures for the pharmaceuticals under study.

Figure 2 depicts the polymeric constituents of the composite membrane, cellulose acetate (**Figure 2 a**) and P4VP-PEO (**Figure 2 b**), as well as the electron donor acceptance (EDA) interactions between the pyridine ring of the block copolymer and the aromatic rings of the EDPs.

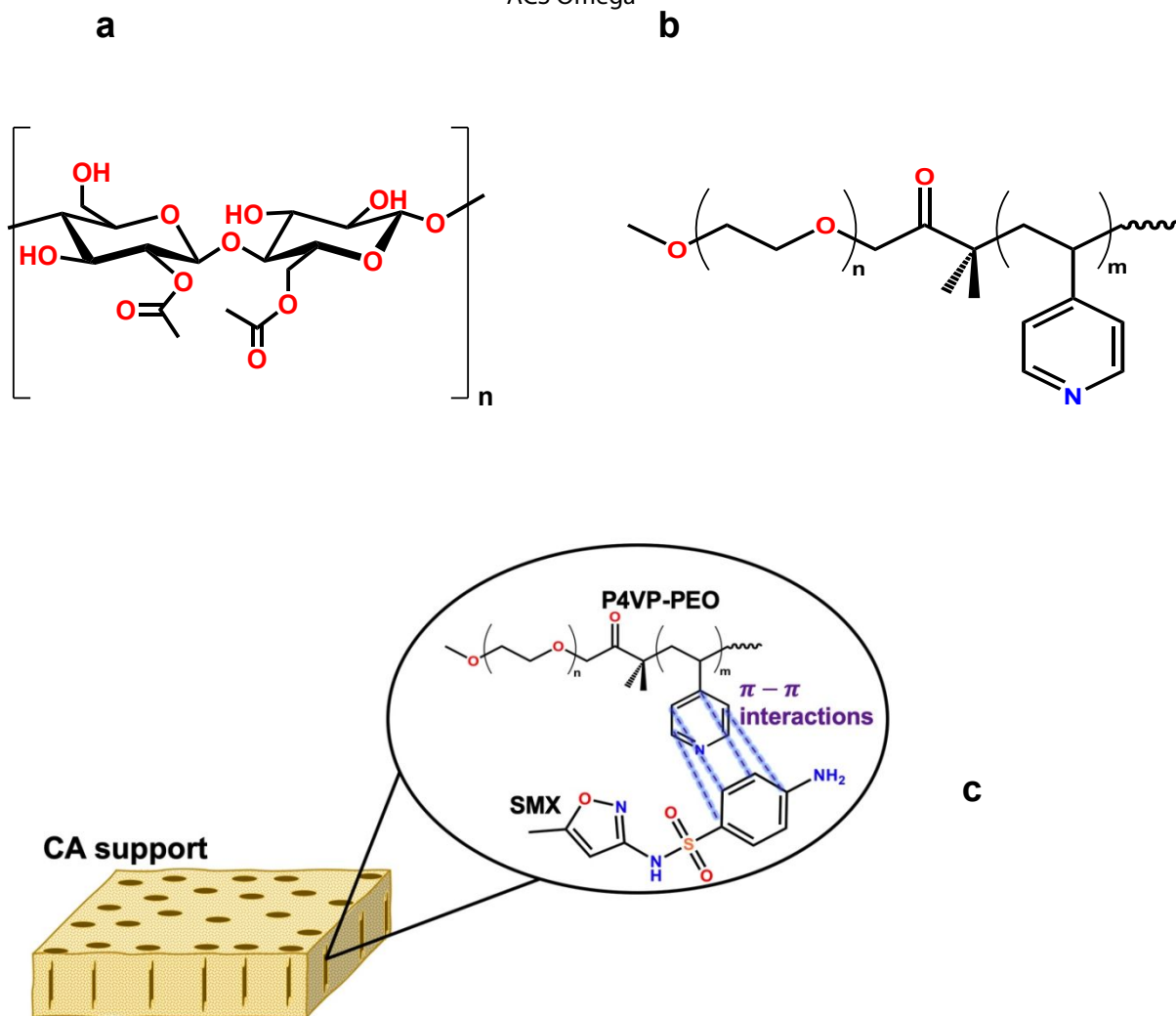
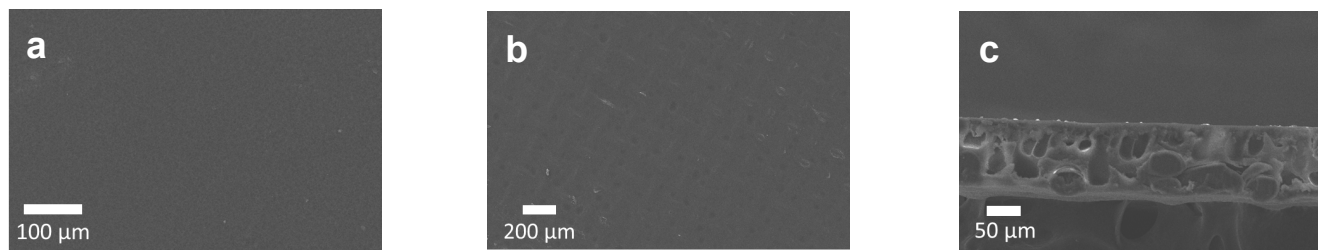


Figure 2. The materials for the prepared membrane (a) Cellulose acetate, (b) P4VP-b-PEO, and (c) a schematic of the EDA interactions that take place on the aromatic rings of the EDPs and the pyridine ring of P4VP-b-PEO.

Before exploring the capacity of the membrane to adsorb the compounds of interest, it was of utmost importance to verify the membranes physical characteristics. First, SEM micrographs were obtained for both the CA membrane and the composite membrane as seen in **Figure 3**. Upon analyzing the composite membrane, it can be observed that the front and back sides are smooth surfaces with minor deformations (**Figure 3 a** and **Figure 3 b**, respectively). However, the cross-section of the membrane (**Figure 3 c**) shows a large number of pores which are formed during the nucleation that occurs during phase separation due to the nucleation effect that occurs during



precipitation⁴⁹. Even though the presence of pores is confirmed, no apparent connection or channels between the pores can be detected in the top and bottom surfaces of the membrane. This implicates that the flow of water through the membrane would be limited due to the disconnection between the inner pore structures, whilst minimizing the surface area for the OH groups to interact with the EDPs. On the other hand, the composite membrane displays small pores in the front side and large pores in the back side (**Figure 3 d** and **Figure 3 e**, respectively). Moreover, the cross-section (**Figure 3 f**) showed hierarchical pores that connect both sides of the membrane, suggesting the potential flux of water through the membrane since porosity and pore connectivity are directly related to permeability⁵⁰. **Figure S2** shows that increasing the concentration of P4VP-b-PEO induces more hierarchical pores. This behavior can only be explained by the presence of P4VP-b-PEO. During phase separation, the hydrophilic ethylene oxide chains of the block copolymer allow a higher water (non-solvent) penetration in the CA matrix, changing the overall nucleation effects.

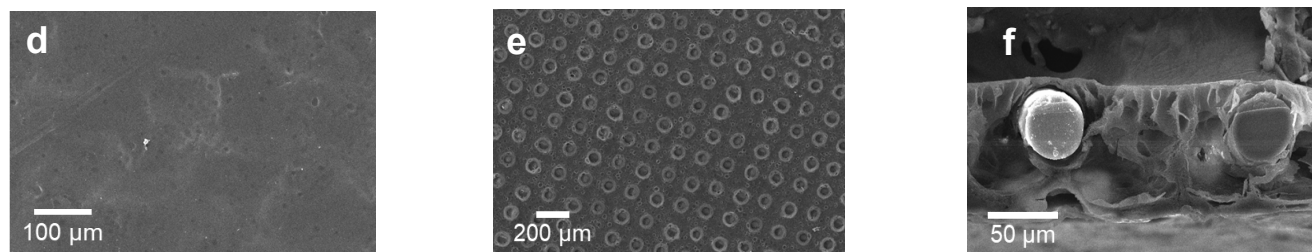


Figure 3. SEM micrographs of pristine CA and composite membranes. The micrographs show the (a) front side, (b) back side and (c) cross section of CA membranes. SEM micrographs of (d) front side, (e) back side and (f) cross-section of the composite membranes.

In order to prove the chemical integrity of the composite membrane, FTIR was performed, and the spectra shows the different functional groups found in CA, P4VP-b-PEO, and the composite membrane. **Figure 4 a** shows the FTIR spectra of both membranes and the block copolymer by itself. Hence, a thorough analysis of the spectra for the composite membrane is described as follows. A signal *ca.* 1730 cm^{-1} that corresponds to the carbonyl of the acetyl group can be easily observed. Also, the band at 1370 cm^{-1} corresponds to the bending vibration of methylene groups ($-\text{CH}_2$) and the intense band at 1217 cm^{-1} corresponds to the ($-\text{C}-\text{O}$) stretching vibration. Moreover, a sharp band around 1030 cm^{-1} corresponds to the glycosidic ring stretching⁵¹. Despite the lack of difference between the CA membrane and the P4VP-b-PEO modified membrane, a close inspection reveals a new band at 1596 cm^{-1} (inset spectra) that is likely due to vibrations of the pyridine ring that are also present in the spectrum of P4VP-b-PEO⁵². It should be noted that the low intensity of that band is somewhat expected since the FTIR method used only analyzes the surface of the material while P4VP-b-PEO is expected to be mostly embedded in the material.

Another important measure of these types of materials is related to the surface energy of the membrane that can be quantitatively assessed by contact angle measurements. **Figure 4 b** shows the contact angle results for both the CA membrane and the composite membrane. Considering

that the CA used in this study has a 39.8% wt. substitution, membranes were expected to have considerable wettability. In the case of the CA membrane, the contact angle is 60° at time 0 s. After 120 s, the value decreases to 50° due to water penetration, a process mediated by diffusion through the membrane. When examining CA membranes modified with P4VP-b-PEO, a similar result is observed (contact angle of 60°) since P4VP-b-PEO is not expected to change the hydrophilicity/hydrophobicity of the membrane. However, after 120 s, there is no apparent change in the contact angle. This phenomenon can be attributed to the hydrophobic air molecules found within the superficial pores that come into contact with the water droplet and, therefore, reduce penetration of the membrane with water. Thus, the observed hydrophobic effect may not be inherently attributed to the membrane's chemical composition rather than the morphology of the pores.

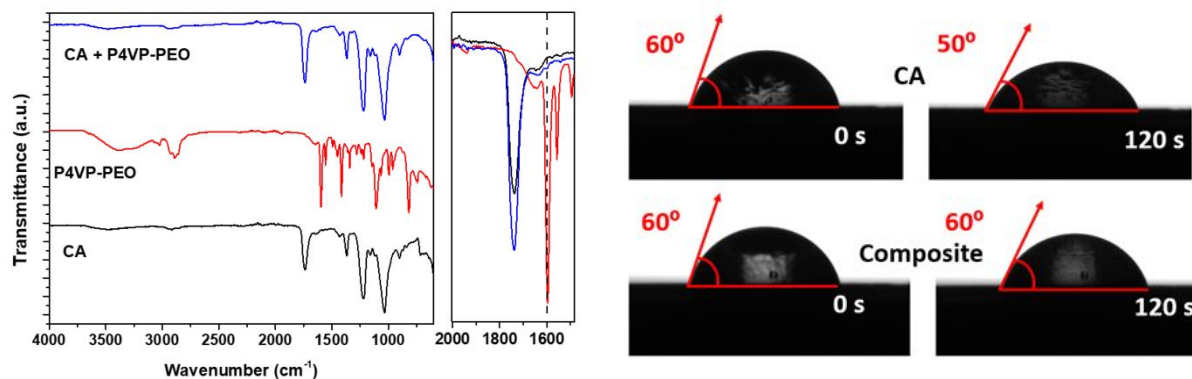


Figure 4. (left) FTIR spectra for CA, P4VP-b-PEO, and the composite membrane and (right) contact angle measurements for both membranes

In order to determine the enhancing effect of adding P4VP-b-PEO, single-point contact time experiments were carried out with both membranes. The single-point contact time experiments shown in **Figure 5 a** indicate that modifying the membrane with 1% P4VP-b-PEO induces a nearly four-fold increase of OMZ adsorption and a two-fold increase in SMX adsorption. It should be noted that the high adsorbance of OMZ can be due to the highly electron deficient degradation intermediates of OMZ. So forth, SDZ adsorption is minimal; however, an increase in adsorptivity can be detected. These results suggest the CA has a notable adsorptive character due to the coulombic interactions that occur between the OH groups and the partially positive regions in the EDPs under study in strong agreement with related CA adsorption studies⁵³. The addition of the P4VP-b-PEO drastically enhances the adsorption capacity of the membrane likely due to the expected π - π interactions of the benzoyl groups, which increase in adsorptivity as the benzene rings in the EDPs become chemically deactivated. **Figure S3** shows that a higher concentration of P4VP-b-PEO leads to higher adsorption. A directly proportional correlation can be found between adsorption efficiency and contaminant electron deficiency. This correlation can be due to both increased surface area of the CA support due to the pores as well as the π - π interactions between

the block copolymer and positively charged regions of the EDPs which supports that the composite membrane is more likely to promote electrostatic interactions with EDPs at increasing electron deficiency. **Figure 5 b** depicts the correlation between pharmaceutical absorptivity and electron deficiency.

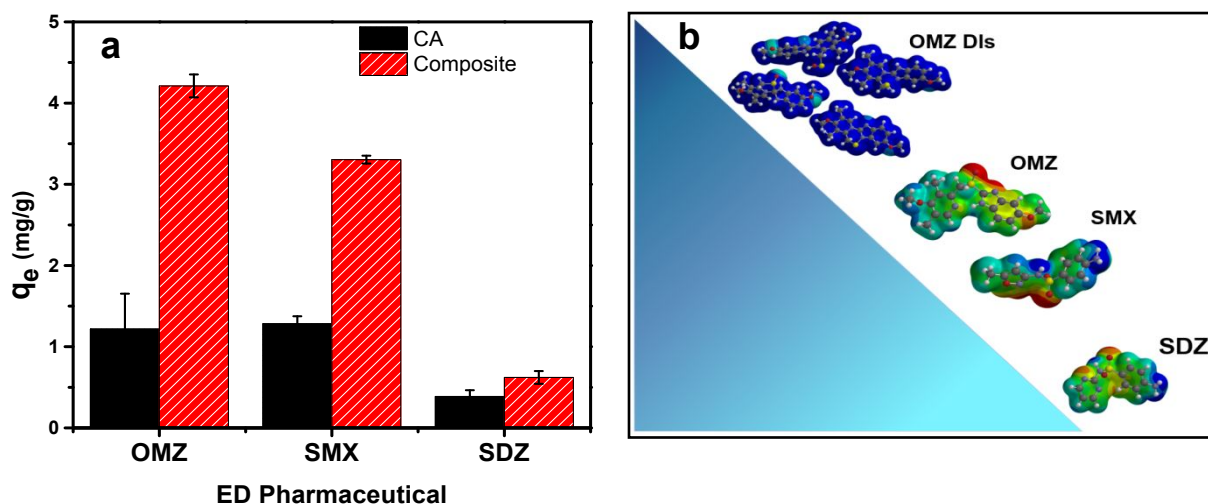


Figure 5. (a) Barplot of the adsorption capacities of the CA membrane and the composite membrane and (b) a representative figure of the adsorption trend from greatest to least ED: OMZ Degradation Intermediates (OMZ DIs), OMZ, SMX, and SDZ.

The adsorptive trend of the pharmaceuticals with the composite membrane can be explained by a combination of the electron deficiency of each molecule as well as the spatial orientation of the relatively positive aromatic rings. For the OMZ IDs, the electron density maps shown in **Figure S1** display the positively charged atoms throughout the cleaved OMZ molecules inducing the highest observed electron deficiency in this study: this allows the pyridine ring in the P4VP-b-PEO to easily adsorb the degradation intermediates. In the case of OMZ, the sulfonamide group hosts a double bond between sulfur and oxygen. This arrangement leads to a strong electron withdrawing effect that can be seen on the electron density maps in **Figure 2** which provides an

interaction site for the pyridine ring from P4VP-b-PEO. In the case of SMX and SDZ, the spatial arrangement effect is crucial to the difference in membrane adsorption values of each membrane since both of these groups display similar electronic character. Both SMX and SDZ are fitted with a primary nitrogen and a sulfonamide group on the aromatic ring of interest. However, the spatial arrangement of the aromatic rings in SMX can be described as the rings being in intercepting planes. This allows for the pyridine ring of the P4VP-b-PEO to interact freely with the ring of interest since the spatial orientation allows for the electron deficient ring to be isolated in space. On the other hand, SDZ has two rings bent in space with a vertex at the sulfonamide. The spatial arrangement that the molecule assumes creates a relatively narrow angle in which the pyridine ring from the P4VP-b-PEO cannot interact freely with the electron deficient ring in the plane that faces away from the sulfonamide group.

In order to determine maximum adsorption capacity at the tested concentration (30 ppm), kinetic experiments were carried out for each of the pharmaceuticals. As demonstrated in **Figure 6 a**, the hierarchy of adsorption from the single-point experiments (4 hrs) is also observed at longer times (24 hrs). Most notably, OMZ has not reached equilibrium at 24 hours. This can be due to the ED degradation intermediate species that are generated as the experiment transcurrs ⁴⁵. These statements are supported by **Figures S4 and S5** which encompass preliminary Isotherm and thorough kinetic characterization for the composite membrane in EDP solution.

The reusability is an important feature, specifically because it can reduce costs for the final application while increasing the operational life of the material . Herein, we test the reusability of the composite membrane for 5 cycles with each of the EDPs. Interestingly, after the initial cleaning cycle, all the adsorption valaues slightly increased (See **Figure S6**). This increment can be attributed to interactions between the EtOH and either the ethylene oxide chains or the hydroxyl

groups of the CA. Thereafter, the results were consistent for 4 cycles **Figure 6 b**. This consistency confirms that the material is efficient after continuous usage, and it suggests that cleaning the membranes with EtOH optimizes the adsorption capacity of the composite membrane.

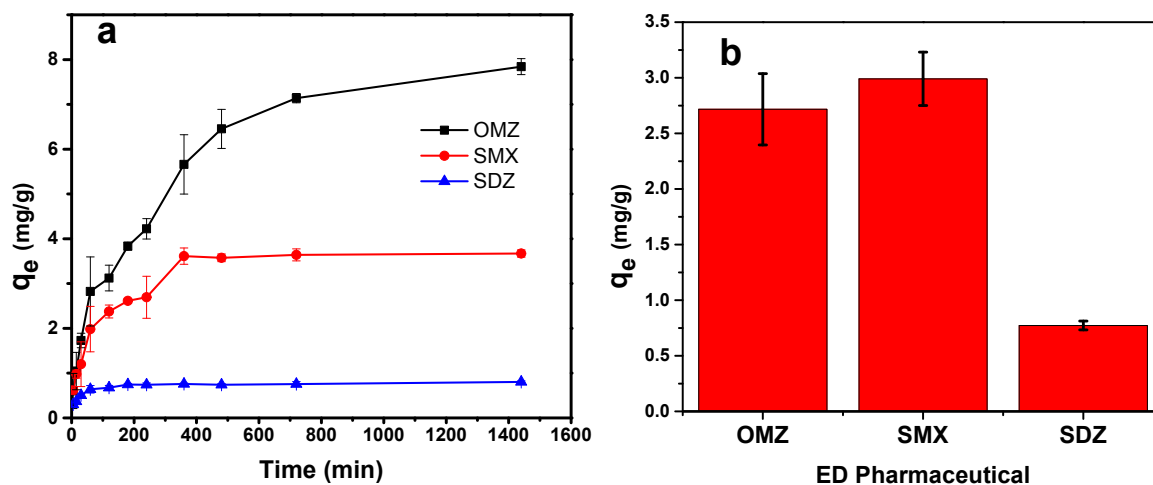


Figure 6. (a) Adsorption capacity of the CA/P4VP-b-PEO as a function of contact time from 1-1500 min, and (b) CA/P4VP-b-PEO membrane reusability for cycles 2-5 for each pharmaceutical compound tested.

The presented results encompass a thorough characterization of the membrane's composition as well as a demonstration of the adsorptive trend displayed by the composite membrane and the pharmaceuticals under study.

4. Conclusion

The study reveals that the composite membrane is capable of adsorbing electron deficient contaminants from aqueous media at low concentrations with a higher efficiency than the unmodified CA membrane. Most importantly, the composite membrane demonstrates an affinity towards adsorbing EDPs at increasing electron deficiency taking into consideration their spatial arrangement and relative electron deficiency. Although other materials show a higher adsorption

capacity for aqueous contaminants, this membrane presents our preliminary works in eco-friendly membranes fabricated for adsorption of specific electron deficient molecules, mainly pharmaceuticals, that present alarming and unprecedented threats in ecosystems and human life. Future works include exploring supports other than CA, and more inexpensive additives than block copolymers.

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Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript. L.P-P is the main author of this work.

Notes

The authors declare no competing financial interest. TOC figure is free domain and prepared by the main author LPP.

Supporting Information

The supporting information includes degradation intermediates of omeprazole, SEM images of 3% P4VP-PEO composite membrane, kinetic experiments, preliminary isotherm experiments, and reusability experiments.

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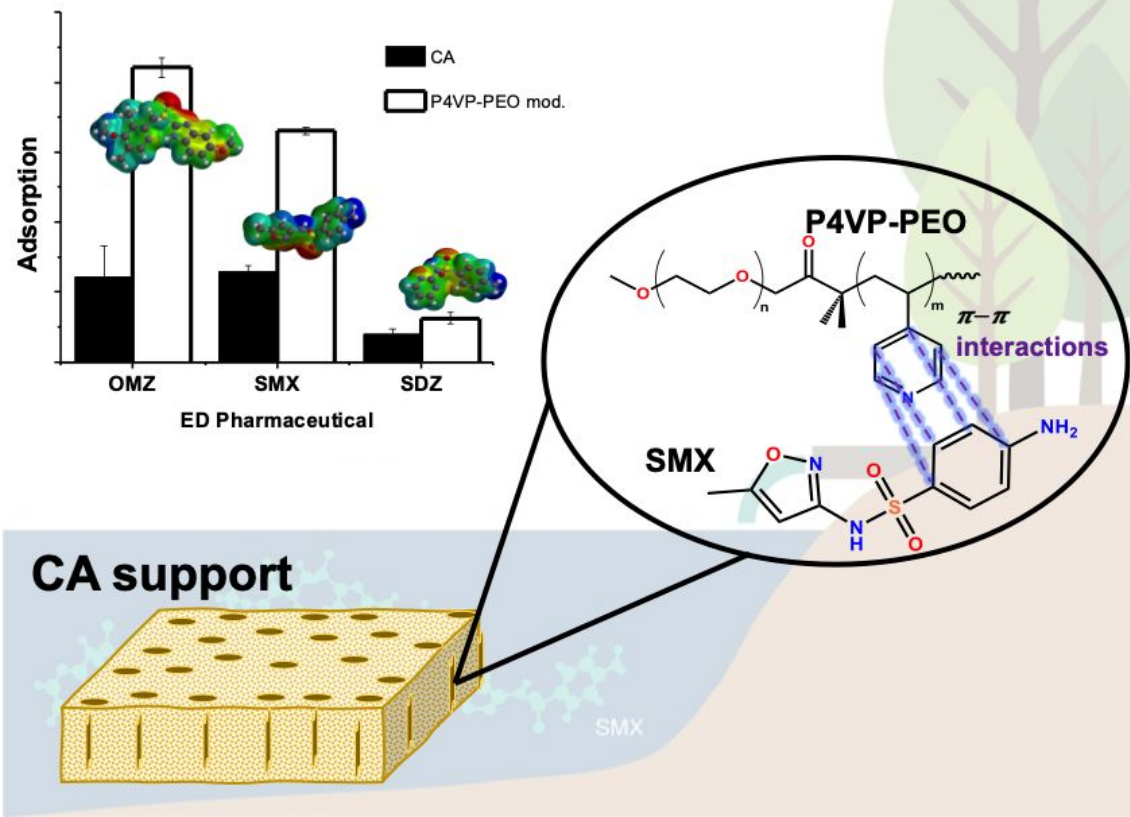
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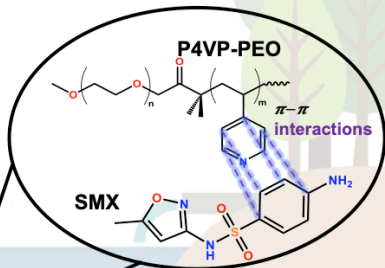
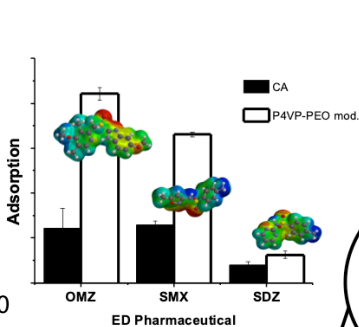
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