CHEMISTRY OF MATERIALS

Article

Cite This: *Chem. Mater.* 2019, 31, 7080−7084

pubs.acs.org/cm

Ionic Hydrogel for Accelerated Dopamine Delivery via Retrodialysis

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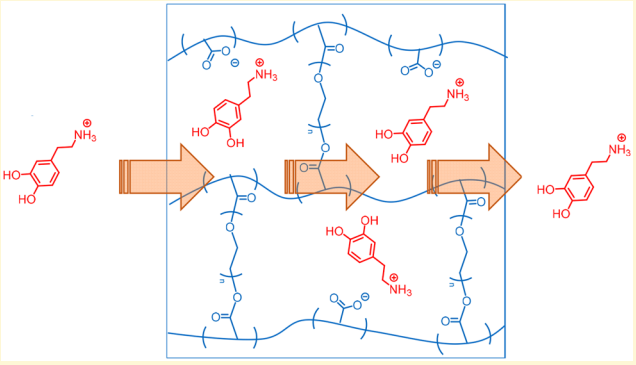
Supporting Information

ABSTRACT: Local drug delivery directly to the source of a given pathology using retrodialysis is a promising approach to treating otherwise untreatable diseases. As the primary material component in retrodialysis, the semipermeable membrane represents a critical point for innovation. This work presents a new ionic hydrogel based on polyethylene glycol and acrylate with dopamine counterions. The ionic hydrogel membrane is shown to be a promising material for controlled diffusive delivery of dopamine. The ionic nature of the membrane accelerates uptake of cationic species compared to a nonionic membrane of otherwise similar composition. It is demonstrated that the increased uptake of cations can be exploited to confer an accelerated transport of cationic species between reservoirs as is desired in retrodialysis applications. This effect is shown to enable nearly 10-fold increases in drug delivery rates from low concentration solutions. The processability of the membrane is found to allow for integration with microfabricated devices which will in turn accelerate adaptation into both existing and emerging device modalities. It is anticipated that a similar materials design approach may be broadly applied to a variety of cationic and anionic compounds for drug delivery applications ranging from neurological disorders to cancer.



Local drug delivery directly to the source of a given pathology using implantable materials and devices is a promising approach to treating otherwise untreatable diseases. This approach is particularly attractive for pathologies where systemic drug treatments have been ineffective due to an inability to reach the target and/or serious side effects from off target drug interactions. Concentration-driven diffusion via retrodialysis (also known as reverse microdialysis) is among the most widely reported local drug delivery techniques to date with numerous applications in both research and the clinic.[1,2] Retrodialysis involves the delivery of compounds across a semipermeable membrane typically using a microdialysis probe loaded with a perfusate solution of drugs. The technique is simple to apply and offers the benefit of continuous drug delivery with minimal local pressure increase.

As the primary material component in retrodialysis, the semipermeable membrane represents a critical point for innovation. New membrane materials could expand applications to allow for efficient delivery of low-concentration drug solutions and to accelerate delivery of drugs with poor stability. Likewise, new membrane materials that are compatible with microfabrication techniques could allow for adaptation of recently reported material/device architectures that mitigate the foreign body response. This is particularly important as the foreign body response is well-known to limit the long-term efficacy of medical implants for drug delivery and sensing.[3−6]

Previous work on microdialysis membranes has suggested that incorporation of fixed ionic groups within the membrane can affect the diffusion rate of charged compounds.[7] We aimed to explore if this effect could also be leveraged for retrodialysis membranes. To that end, we report here on a hydrogel based on polyethylene glycol diacrylate (PEGDA) and a new ionic monomer, dopamine acrylate (iDAA). The iDAA monomer was formulated with dopamine (+) as the counterion to each acrylate (−) fixed ionic group. This also ensured optimal permeability for controlled amounts of dopamine within the membrane.

Dopamine is a neurotransmitter known to play an important role in controlling movement and emotions.[8,9] The death of dopamine-producing cells has long been implicated in Parkinson's disease, and thus local delivery of dopamine and dopamine-like compounds has been the subject of much research.[10−13] PEGDA based materials have been used extensively for biological applications[14−16] and can be photopatterned in a manner compatible with standard microfabrication procedures.[17,18] Hydrated PEGDA based

Special Issue: Jean-Luc Bredas Festschrift

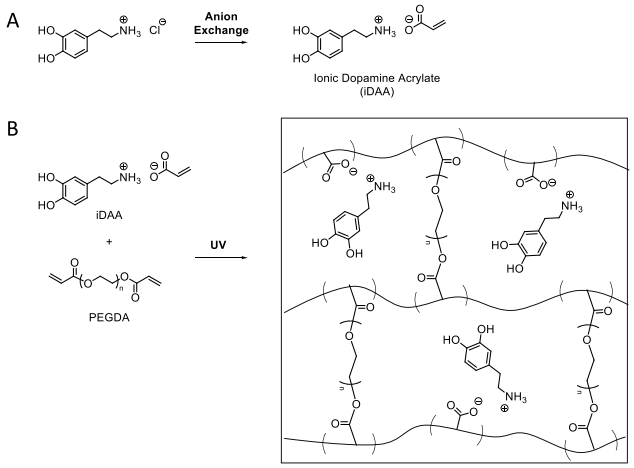
Received: May 31, 2019
Revised: July 26, 2019
Published: July 29, 2019

DOI: 10.1021/acs.chemmater.9b02135
Chem. Mater. 2019, 31, 7080−7084

membranes are also known to have tunable swelling ratios and to be semipermeable allowing a variety of compounds to diffuse through.[14,19] The combination of biocompatibility, processability, and permeability makes PEGDA a suitable candidate for retrodialysis applications.

As shown in Scheme 1, the iDAA monomer was prepared exchanging the Cl^- in dopamine hydrochloride with acrylate

Scheme 1. (A) Formation of iDAA by Exchange of Cl(−) with Acrylate(−) and B) Combination of PEGDA, iDAA, and H_2O with a Photoiniator and UV Light To Form PEGDA-iDAA



(−) using an anion exchange resin (Alfa Aesar, Amberlyst A-26), see Methods for detailed synthetic procedures and NMR. iDAA was then mixed with deionized water (up to 1 M), equal volumes of PEGDA (Mn 575, Sigma-Aldrich) and 2 wt % 2-hydroxy-2-methylpropiophenone, and a biocompatible photoinitiator (Darocur 1173, Sigma Aldric). The mixed solution was deposited as desired and exposed to ultraviolet (UV) light (100 $\mu J/cm^2$, AnalytikJena UVP Cross-linker) for 30 min to form a fully cross-linked PEGDA-iDAA membrane (see Scheme 1B). The composition of the PEGDA-iDAA membranes was confirmed with FTIR (Figure S1). Membranes were also prepared with methyl acrylate (MA) in place of iDAA to provide a comparison to a noncharged membrane. Following UV exposure, membranes were soaked in phosphate buffered saline (PBS 0.01M) for at least 4 h, replacing with fresh PBS solution on an hourly basis. The membranes were observed to be stable in PBS with no visible degradation up to six months. Likewise, membranes were found to exhibit only modest swelling in PBS solution with an increase in weight content of no more than 11%. The observed stability and minimal swelling suggest a highly cross-linked membrane. The limited swelling is particularly important for integration with microfabricated devices as excessive swelling can otherwise stress nonswelling materials leading to cracking and issues with adhesion.

As an initial test of compatibility with microfabricated devices, PEGDA-iDAA membranes were directly patterned onto the end of a 220 μm wide neural probe with an integrated microfluidic channel[20] (Figure 1). The patterning of the membrane, 200 μm across, was made possible by selected UV exposure of the deposited membrane solution using standard photolithography techniques (SUSS MicroTec MJB4). Adhesion to the parylene surface of the neural probe was aided by

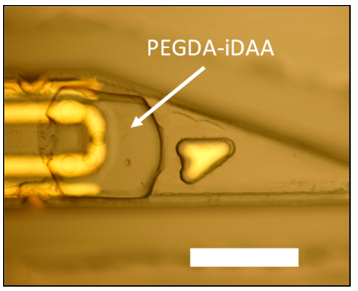


Figure 1. Image of PEGDA-iDAA membrane patterned at the end of the neural probe with an integrated microfluidic channel. Scale bar 200 μm.

pretreatment with methacryloxypropyl trimethoxysilane (Silane A 174, Sigma-Aldrich) following previously reported procedures.[21] As with the free-standing membranes, the PEGDA-iDAA membranes on the microfluidic probes exhibited excellent stability with no signs of degradation in PBS, suggesting that the material is well suited for retrodialysis applications.

Following the processability testing, the diffusion/uptake of molecules in the PEGDA-iDAA membrane was explored by soaking the membranes in aqueous solutions with charged dye molecules. In particular, to understand the effect of fixed anionic groups in the membrane, three membrane compositions with varying fixed anion concentrations were compared: PEGDA-MA with 500 mM concentration of MA, PEGDA-iDAA-MA with 50 mM concentration of iDAA and 450 mM concetnration of MA, and PEGDA-iDAA with 500 mM concentration of iDAA. Each membrane was soaked in 1 mM and 10 mM phenol red solutions (pH 10). After 1 h, the membranes were removed from the solution, gently patted dry, and photographed. They were then placed in a concentrated NaCl solution (2 M) for 1 h during which time absorbed dye was released into the NaCl solution. A fixed volume of the NaCl solution was then taken for UV−vis measurements to gauge the relative concentration of phenol red. The same procedure was followed using fresh membranes with methylene blue in place of phenol red. The photographed membranes and UV−vis results are shown in Figure 2A for phenol red (450 nm) and Figure 2B for methylene blue (670 nm). The absorption data was normalized by volume of the membrane to account for variations in dimensions.

Prior to soaking membranes in dye solutions, they were observed to be transparent with only negligible absorption across the visible spectrum. After soaking in phenol red, the membranes took a yellow hue that increased with increasing concentration, suggesting some uptake of the anionic dye. The absorbed concentration of phenol red was found to be greatest in the uncharged PEGDA-MA membrane with decreasing uptake as the concentration of iDAA increased. This can be understood by considering that the fixed acrylate(−) groups in the PEGDA-iDAA membrane act as an electrostatic barrier to the diffusion/uptake of anionic compounds as is typical for polyanions.[22] In contrast, the opposite trend was observed when membranes were soaked in the cationic methylene blue solution with increasing uptake of methylene blue as the iDAA content increased. In fact, the normalized absorption from methylene blue was more than 10-fold higher for the PEGDA-iDAA membrane compared to the PEGDA-MA membrane. We posit this phenomenon can be explained by considering that the fixed acrylate(−) groups are each compensated by a

DOI: 10.1021/acs.chemmater.9b02135
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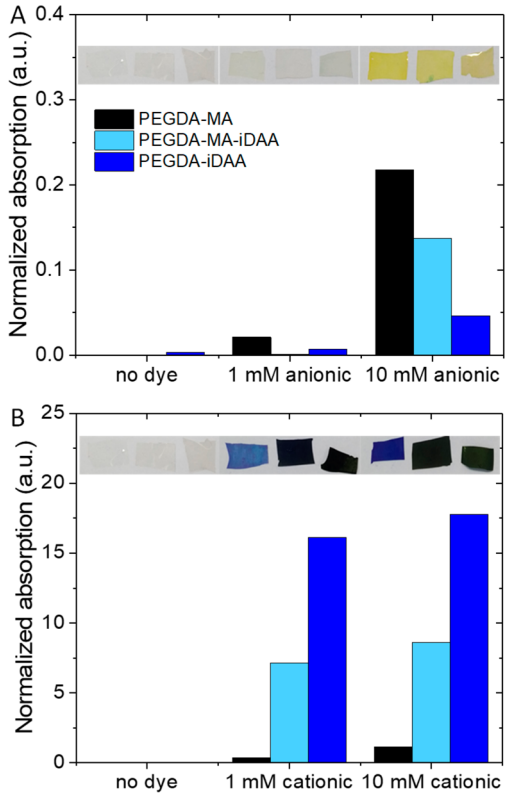

Figure 2. (A) Normalized absorption at 450 nm for PEGDA-MA, PEGDA-MA-iDAA, and PEGDA-iDAA membranes before and after soaking in 1 mM and 10 mM phenol red solutions with images of the corresponding membranes above each bar (membrane width approximately 1 cm each). (B) Normalized absorption at 670 nm for PEGDA-MA, PEGDA-MA-iDAA, and PEGDA-iDAA membranes before and after soaking in 1 mM and 10 mM methylene blue solutions with images of the corresponding membranes above each bar (membrane width approximately 1 cm each).

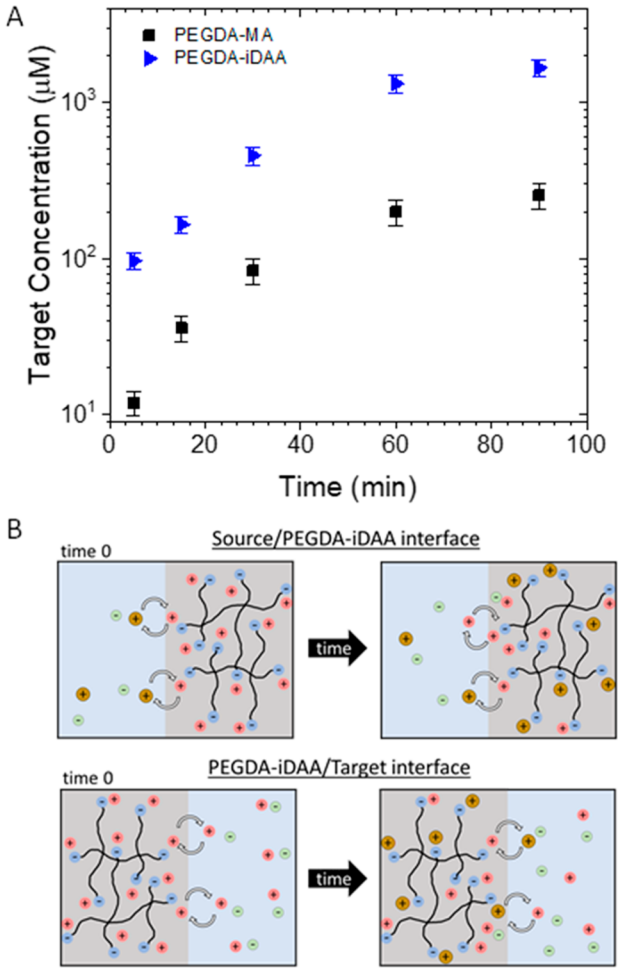

Figure 3. Concentration of dopamine measured in the Target well as a function of time using PEGDA-iDAA and PEGDA-MA membranes with an initial dopamine concentration of 12 mM in the Source well. The inset illustrates the relative ionic concentration in the Source, membrane, and Target. (B) Schematic showing ion exchange at the Source/PEGDA-iDAA interface (top) as well as the PEGDA-iDAA/Target interface (bottom) at time zero and after some minutes. Brown cations represent dopamine with sodium represented by red cations, fixed acrylate anion in blue, and chlorine anions in green.

counterion in the form of a freely moving cation. Initially the counterions are primarily Na+, and upon introduction of methylene blue(+) some portion of the counterions are exchanged. The higher concentration of fixed ions and counterions in the membrane compared to concentration of the dye solution drives a higher uptake of the cationic methylene blue within the membrane than would be expected in the absence of fixed charge. Together these results indicate the charged PEGDA-iDAA membrane is well suited to preferentially transport cationic species.

Having observed the ability to preferentially uptake cationic species at an accelerated rate, the suitability of PEGDA-iDAA membranes for retrodialysis of dopamine was subsequently tested in a model system. Membranes were sandwiched between two wells with the membrane serving as a bridge material connecting the contents of each well (see Supporting Information). One well was designated as the Source side and was filled with an aqueous solution of dopamine hydrochloride. The other well served as the Target and was filled with PBS to mimic the biological environment. After a set time period, the solution in the Target was collected and analyzed with differential pulse voltammetry[23,24] to measure the amount of dopamine delivered from the Source well to the Target well (see Supporting Information). Figure 3 shows the measured concentration of dopamine in the Target as a function of time for a dopamine Source concentration of 12 mM using either the PEGDA-iDAA or the PEGDA-MA membranes. The inset illustrates the relative initial ion concentrations in the Source, membrane, and Target. It should be noted that membranes were repeatedly rinsed and soaked in saline solution to remove any residual dopamine prior to starting the dopamine diffusion experiments. For all time points, it was observed that there was nearly 10-fold more dopamine transferred from the Source to the Target with the PEGDA-iDAA membrane compared to the PEGDA-MA. This is especially noteworthy given that the Target contained smaller, more mobile cations (Na) at greater than 10 times the concentration of dopamine in the Source as such conditions are typical for drug delivery applications.[20,25,26] We posit that these results can be understood by considering that the relatively high concentration of fixed anions in the PEGDA-iDAA membrane leads to an enhanced uptake of dopamine from the Source similar to what was observed in the charged dye experiments. As the PEGDA-iDAA membrane fills with a higher concentration of dopamine compared to the uncharged PEGDA-MA membrane, this in turn creates a higher concentration gradient for dopamine

DOI: 10.1021/acs.chemmater.9b02135
Chem. Mater. 2019, 31, 7080−7084

relative to the Target and thus a higher diffusive flux. A similar phenomenon has previously been reported for cation transport in porous ion exchange membranes.[27]

This ion exchange phenomenon is illustrated in Figure 3B wherein a simplified schematic of the ion exchanges is shown at the Source/PEGDA-iDAA interface (top) as well as PEGDA-iDAA/Target interface (bottom) at time zero and after some minutes. Brown cations represent dopamine with sodium represented by red cations, the fixed acrylate anion is in blue, and the chlorine anions are in green (the low concentration of phosphate and potassium ions in the Target are excluded for clarity). As illustrated, ion exchange facilitates uptake of dopamine into the PEGDA-iDAA membrane at the Source side and which then leads to dopamine exchange with (primarily) sodium ions at the Target side. Note that this means there is also a flux of sodium from the Target to the Source by the same mechanism.

The drug delivery capacity of the PEGDA membranes was explored further using the same Source−membrane−Target setup to measure the effect of Source concentration. Figure 4

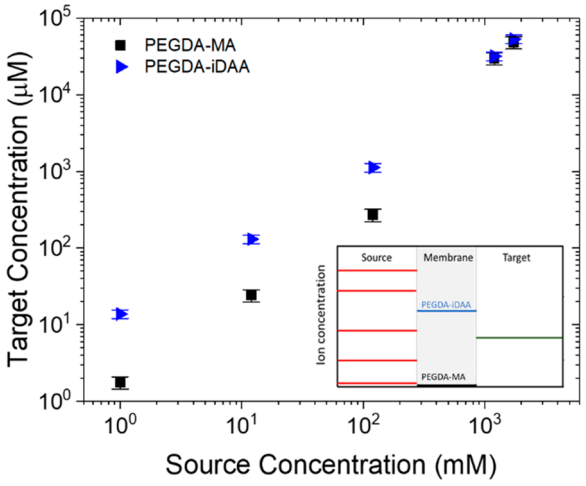

Figure 4. Concentration of dopamine measured in the Target well as a function of dopamine concentration in the Source well using PEGDA-iDAA and PEGDA-MA membranes. The inset illustrates the relative ionic concentration in the Source, membrane, and Target on a log scale.

shows the concentration of dopamine measured in the Target after 30 min for Source dopamine concentrations from 1 mM to 1.7 M. The figure inset indicates the relative ion concentrations on a log scale for each region. In the case that the Source concentration was less than the fixed ion concentration in the PEGDA-iDAA membrane (approximately 500 mM), a pronounced increase in delivered dopamine was observed relative to the PEGDA-MA membrane. However, the difference in transported dopamine was negligible between the two membranes for Source concentrations above the PEGDA-iDAA fixed ion concentration. This finding supports the notion that the fixed ions in the PEGDA-iDAA membrane drive the accelerated diffusion observed at lower Source concentrations. When the Source concentration significantly exceeds the fixed ion concentration in the membrane, it follows that after some time the concentration of dopamine in the PEGDA-iDAA membrane would be similar to that observed in the system with the uncharged PEGDA-MA membrane. Consequently, in these conditions the diffusive flux from the Source to the Target for both membrane systems is primarily a function of the Source concentration and is therefore similar in magnitude.

Altogether the results presented here suggest that the PEGDA-iDAA membrane is a promising material for controlled diffusive delivery of dopamine. The ionic nature of the membrane accelerates uptake of cationic species compared to a nonionic membrane of otherwise similar composition. The increased uptake of cations can be exploited to confer an accelerated transport of cationic species between reservoirs as is desired in retrodialysis applications. This effect can enable nearly 10-fold increases in drug delivery rates from low concentration solutions (<100 mM). Equally important, the processability of the PEGDA-iDAA membrane readily enables integration with microfabricated devices which can in turn accelerate adaptation into both existing and emerging device modalities. While the work here was focused on delivery of dopamine, we anticipate that a similar materials design approach may be broadly applied to a variety of cationic and anionic compounds for drug delivery applications ranging from neurological disorders to cancer.

METHODS

Synthesis of Ionic Dopamine Acrylate Monomer (iDAA). The synthesis of iDAA was carried out using an anionic exchange resin (AER), Amberlyst A-26 (OH) from Alfa Aesar (exchange capacity 0.8 mol/L), an excess (>10% p/V) of commercial acrylic acid (Sigma-Aldrich) in water, and 0.05 M dopamine chloride (Alfa Aesar) in methanol. The AER column was loaded with an excess of acrylic acid solution (>10% p/V). Then, a 0.05 M dopamine chloride solution in methanol was passed slowly through the column. The final product, dopamine acrylate (iDAA), was collected in the form of a methanol solution. Methanol was removed under reduced pressure, and the iDAA was characterized by ^{1}H NMR (400 MHz, Deuterium Oxide) δ 6.86−6.69 (m, 3H, aromatic), 6.13−5.60 (m, 3H, $\underline{CH_2}$=$\underline{CH}$), 3.17 (t, 2H, $\underline{CH_2}$−CH_2−NH_3), 2.82 (t, 2H, CH_2−$\underline{CH_2}$-NH_3).

Differential Pulse Voltammetry (DPV). DPV measurements were performed using a three electrode configuration with a glassy carbon working electrode, Pt-wire counter electrode, and Ag/AgCl reference electrode using an Metrohm Autolab Potentiostat (model PGSTAT128N). Glass carbon electrodes were cleaned thoroughly prior to each measurement. Unknown concentrations of dopamine were determined using a calibration curve of measured current at the 0.14 V peak for known concentrations of dopamine.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.chemmater.9b02135.

Diffusion experiment setup and example data set from differential pulse voltammetry experiments (PDF)

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Author Contributions

All authors have given approval to the final version of the manuscript.

DOI: 10.1021/acs.chemmater.9b02135
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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

The authors acknowledge funding from EPSRC (EP/S009000/1) and the European Union's Horizon 2020 research and innovation programme under the Marie Sklodowska-Curie Grant Agreement No. 823989. C.M.P. acknowledges funding from the Borysiewicz Biomedical Sciences Fellowship program. A.S.-S. acknowledges funding from the Marie Sklodowska-Curie IF BIKE Project No. 742865.

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