Diffusion Coefficients of Water in Biobased Hydrogel Polymer Matrices by Nuclear Magnetic Resonance Imaging

Kenneth M. Doll,[1] Karl E. Vermillion,[2] George F. Fanta,[3] Zengshe Liu[1]

[1]*Bio-Oils Research, Unit, U.S. Department of Agriculture/National Center for Agricultural Utilization Research/ Agricultural Research Service, 1815 North University Street, Peoria, Illinois 61604*
[2]*Functional Foods Research Unit, U.S. Department of Agriculture/NCAUR/Agricultural Research Service, 1815 North University Street, Peoria, Illinois 61604*
[3]*Plant Polymer Research Unit, U.S. Department of Agriculture/NCAUR/Agricultural Research Service, 1815 North University Street, Peoria, Illinois 61604*

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ABSTRACT: The diffusion coefficients of water in biobased hydrogels were measured with a simple NMR method. This method tracked the migration of deuterium oxide through imaging data that was fit to a diffusion equation. The results show that a 5 wt % soybean-oil-based hydrogel gave an aqueous diffusion of 1.37 ($\pm$0.21) $\times$ 10^{-9} m^2/s. The value for a 0.5 wt % saponified starch–polyacrylonitrile graft copolymer was 1.28 ($\pm$0.26) $\times$ 10^{-9} m^2/s, which remained about the same at increased polymer content in the hydrogel. For comparison, a commercially available acrylic polymer was evaluated with the same methodology and was found to have a diffusion coefficient of 7.6 ($\pm$1.3) $\times$ 10^{-10} m^2/s, about half that of the biobased products studied here. These parameters are of significant interest in the development of controlled release applications. © 2012 Wiley Periodicals, Inc. J. Appl. Polym. Sci. 000: 000–000, 2012

Key words: biodegradable; diffusion; drug delivery systems

INTRODUCTION

Diffusion is a fundamental property of a material and is crucial in many applications. The diffusion of aqueous liquids within a gelatinous matrix is of specific importance in absorbance, cosmetics, and controlled flavor encapsulation applications. In the drug-delivery area, a biocompatible gel's ability to appropriate a quantity of an organic molecule and then appropriately deliver it to the target area is a key feature.[1–4]

To achieve the desired moisture uptake and release properties, certain structural features are required. Most important are polar groups in the structure that are open enough to allow sufficient interaction with water. However, the material must also be crosslinked enough to remain insoluble and of sufficient physical strength to hold together. Theories of the physical aspects of hydrogel structure date back many years[5–7] and examples made using naturally sourced materials, such as starch,[8] cellulose,[9] aspartic acid,[10–16] and citric acid[17–21] are common.

The two materials studied herein were prepared by significantly different strategies to achieve these goals. A highly absorbent saponified starch-based polymer can be prepared by the grafting of the acrylonitrile onto starch and then the saponification of the polyacrylonitrile with aqueous alkali (Scheme 1) through a process where a hydrolyzed form of the dried saponified starch–polyacrylonitrile is obtained. This highly absorbent material has been shown to absorb up to 650 times its own weight in deionized water, and a number of practical applications for this polymer have been suggested.[22] The other material was prepared via a crosslinking reaction of soybean oil (Scheme 2) catalyzed by a Lewis acid,[23,24] followed by the hydrolysis of the material with a base to free up the carboxylate structures already present in the material.[25] The product has been studied in drug use applications,[26] where it was shown to dramatically increase the efficacy when used as part of a drug system to fight multidrug resistant cancer cells.[27]

The use of NMR to characterize gels is not entirely new[28,29] and has been used to distinguish species in a few cases. For example, the method reported by Kossel and Kimmich[30] tracks the migration of an isotope through a polymer matrix by the comparison of

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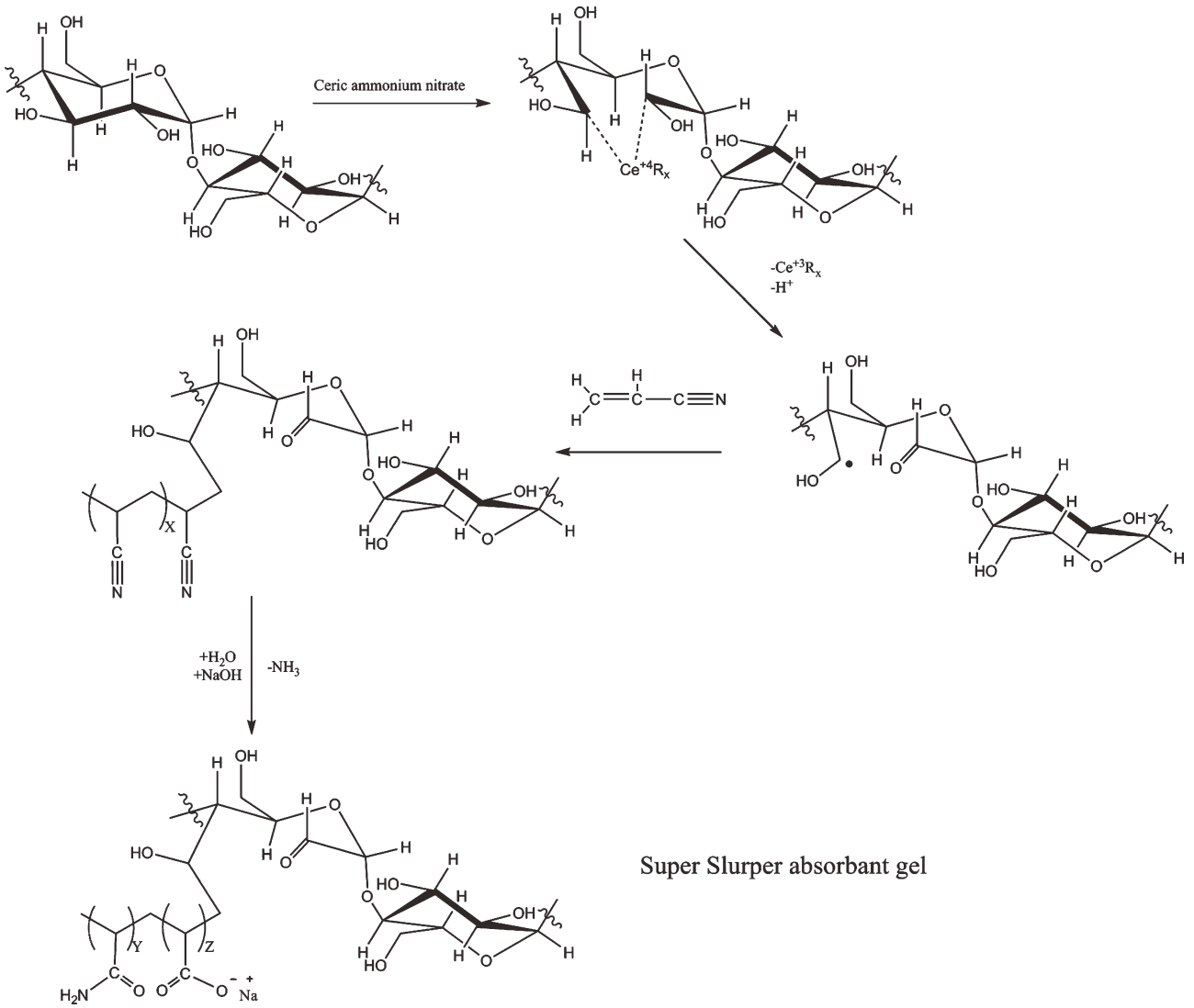
Correspondence to: K. M. Doll (kenneth.doll@ars.usda.gov).



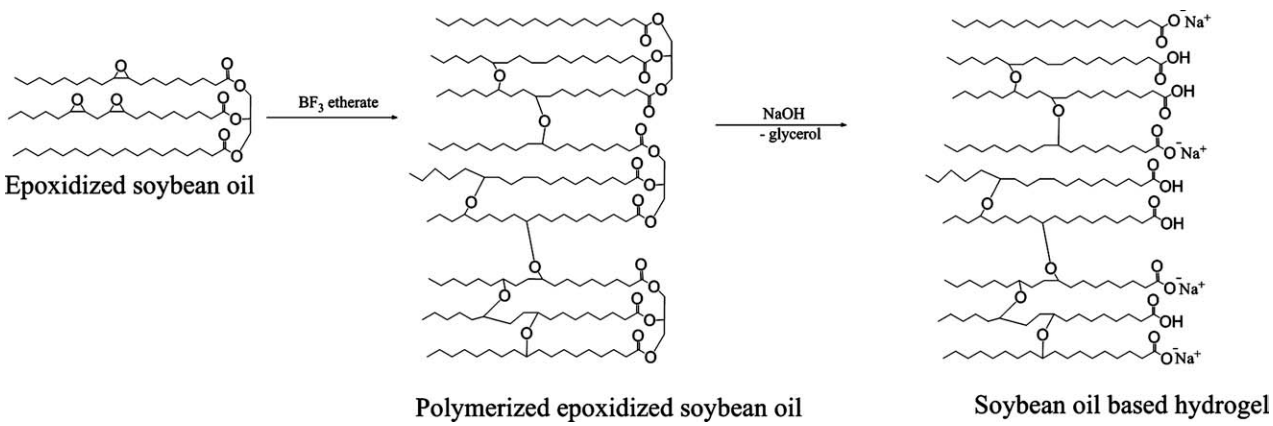
Scheme 1 Synthetic process for the production of the saponified starch–polyacrylonitrile gel used in this study.

NMR images taken over a period of time. However, the diffusion coefficient (D) of water in these two well-characterized[31,32] gelatinous materials mentioned previously has not been previously evaluated by NMR or any other method.

EXPERIMENTAL

Materials and methods

Epoxidized soybean oil (Vikoflex 7170, Arkema, Philadelphia, PA), boron trifluoride diethyl etherate



Scheme 2 Synthetic process for the production of the soybean-oil-based hydrogel used in this study.

(Sigma-Aldrich, St. Louis, MO, redistilled), ethanol [Sigma-Aldrich, American Chemical Society (ACS) reagent, 200 proof, 99.5%], sodium hydroxide (Fisher Scientific, Fair Lawn, NJ, 97.5%), hydrochloric acid (Sigma-Aldrich, ACS reagent), acetic acid (Fisher Scientific), crystal violet (Sigma-Aldrich, ACS reagent), and deuterium oxide (Sigma-Aldrich, 99.96 atom %) were used as received. Methylene chloride (Fisher Scientific) was dried with molecular sieves before use. Water was run through a filtration system (Barnstead, part of Thermo Fisher Scientific, Asheville NC, Easypure II) until the resistance was 18 MΩ/cm or higher. A commercially available acrylic hydrogel resin (Carbopol high-performance polymer, Noveon, Cleveland, OH) was obtained as a free sample from the manufacturer and was used as received.

The saponified starch–polyacrylonitirle material (SGP 502 Super Slurper) was a research sample (Henkel Corp., Minneapolis, MN) that was synthesized through literature methods.[31,33] In short, acrylonitrile was graft-polymerized onto gelatinized starch in the presence of ceric ammonium nitrate. In the reaction, a ceric–starch complex was formed, breaking the glucopyranosyl unit of the starch and forming reactive free radicals that were capable of reacting with the acrylonitrile to form polyacrylonitrile grafts. In the second step, the starch–polyacrylonitrile graft copolymer was saponified with aqueous sodium hydroxide to convert the nitrile substituents to sodium carboxylate and carboxamide.

The soybean-oil-based hydrogel was also synthesized by literature methods.[24,32] Typically, epoxidized soybean oil was dissolved in methylene chloride and cooled to 0°C in an ice bath. Boron trifluoride etherate (~ 1.3 wt %) was added dropwise to the solution and allowed to react for 3 h. Ethanol was added to deactivate the catalyst; this was followed by rotary evaporation at 70°C to form an insoluble white powder. Hydrolysis was performed by suspension in 0.4*N* NaOH, filtration, and then precipitation with 1.0*N* HCl. The product was washed with 10% acetic acid and dried *in vacuo*.

This polymer was characterized by many physical and spectral methods, including FTIR spectroscopy, gel permeation chromatography, differential scanning calorimetry and thermogravimetric analysis.[24] These results confirmed the complete reaction of the epoxide group and showed the overall stability of the structure.

NMR methodology and curve fitting

All NMR spectra were collected on a Bruker Avance 500 spectrometer (Boston, MA) with a gradient 5-mm Broadband Observe (BBO) probe at 27°C. The pulse program for acquisition was the Bruker standard imgegp1d2h, and initial processing was done with Topspin 1.3 patchlevel 8 (Boston, MA). A total of 32 transients per time point were acquired. Calibration with a phantom was performed immediately before each run.

Figure 1 Visual determination of diffusion in the 0.3% saponified starch–polyacrylonitrile gel. The photographs were taken at 1 day (left) and 9 days (middle). An analogous experiment with the die layer on the bottom is also shown after 9 days (right).

Mathematical derivations and justification for the equation used in determination of D are available elsewhere (Fig. 1).[34–36] Curve fits [eq. (1)] were performed by KaleidaGraph 3.6 software running on a Dell (Austin, TX) Optiplex 760 with a 2.99-GHz Intel Core 2 Duo CPU (Santa Clara, CA) and a Microsoft Windows XP operating system. The diffusion equation as a function concentration and distance is as follows:

$$C(x,t) = \frac{1}{2} C_0 erfc\left(\frac{x}{2\sqrt{Dt}}\right) \quad (1)$$

where *erfc* is the error–function complement, t is the diffusion time. and C_0 is the initial concentration.

Hydrogel preparation

The hydrogels were prepared by the blending of the resin powder with an appropriate amount of water, water/dye solution, or deuterium oxide with gentle stirring. The gels were transferred to a graduated cylinder or a standard 5-mm NMR tube via a long-tipped pipette. The concentrations were chosen on the basis of obtaining a gel that was transferable but still capable of forming distinct layers. In the soy-based hydrogel, this was 5 wt %. In the saponified starch–polyacrylonitrile system, the concentrations used were 0.75 and 0.5 wt %.

Visual method of diffusion evaluation

A graduated cylinder was used for the visual measurement of D. Saponified starch–polyacrylonitrile gels of 0.3 and 0.6 wt % were prepared, and a

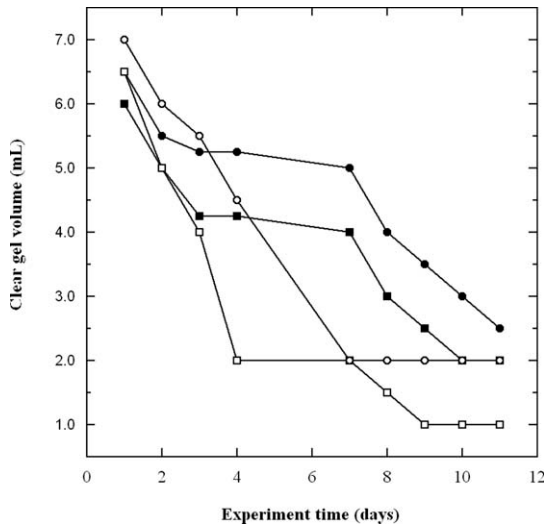


Figure 2 Visual determination of diffusion in the saponified starch–polyacrylonitrile gel: (□, ■) 0.6 wt % and (○, ●) 0.3 wt % dye in (■, ●) the top layer and (□, ○) the bottom layer.

minimal amount of crystal violet dye was added to half of each gel. A volume of about 7 mL of clear gel was added to the cylinder, and an equal quantity of dyed gel was added. A similar experiment was performed with the layers in reverse order to check for effects of gravity. The diffusion was observed, and the amount of clear gel was determined visually (Fig 1).

RESULTS AND DISCUSSION

A visual method was used to give a qualitative analysis of the diffusion of solution in the gel matrix. The saponified starch–polyacrylonitrile gel was prepared at 0.3 and 0.6 wt %, with and without crystal violet dye. In a 25-mL graduated cylinder, the gels were carefully layered, the dye behavior was observed, and the progress was monitored. From this qualitative data (Fig. 2), a couple of observations could be made. First, changes in the weight percentage of the gel within this range did alter the observed volume change, which was 2.2 ±0.8 mL each day over the first 8 days. Second, the order of the layers did not cause a change in the results; this showed the apparent lack of gravitational effects on this experiment. However, this experiment was far from the quantitative data that is needed to compare hydrogels in advanced applications. It was also potentially convoluted by effects of the diffusion of the dye and difficulty in determining the gel volumes.

The NMR method is capable of much greater resolution than the visual method. Instead of a dye in the gel, the migration of the solvent itself, deuterium oxide, was monitored. With a simple NMR method, the position of the deuterium in the sample could be tracked. The resultant positions are shown (Fig. 3), and D was calculated via the mathematics of Crank and Park.[34] This was a slightly different approach than the Cyclic Cross-polarization (CYCLCROP) method of Kossel and Kimmich[30] but with similar effect. In Kimmich's method, a specialized pulse sequence is used to indirectly detect ^{13}C on the proton NMR frequency through cross-polarization. In the method used here, deuterium imaging was used, which directly detected the amount of deuterium at its physical location in the NMR tube. This was also different than the approach of using a diffusion probe or the spin–spin and spin–latice relaxational studies used for similar purposes.[28] In those techniques, the mobility of the species is determined by specific interactions with the substrate that are measured. The method here focused on the position of the species.

There are some mathematical parameters and assumptions that need to be defined and mentioned. A function (C) was used for concentration, which was a function of time (t) and position in the tube (x). The value *erfc* is the error function compliment, a well-studied mathematical function. With these parameters, the diffusion equation can be used to calculate D. An assumption here was that the diffusion of the deuterium oxide into the water layer was equal to that of water into the diffusion layer. Second, eq. (1) is valid for diffusion from an impermeable boundary source inside a cylinder, which must be long relative to the distance diffused. In other words, all diffusion is in the same direction and is not limited by the container. To ensure the validity of this assumption, only data collected between 5 and 10 min was used in the determination of the D

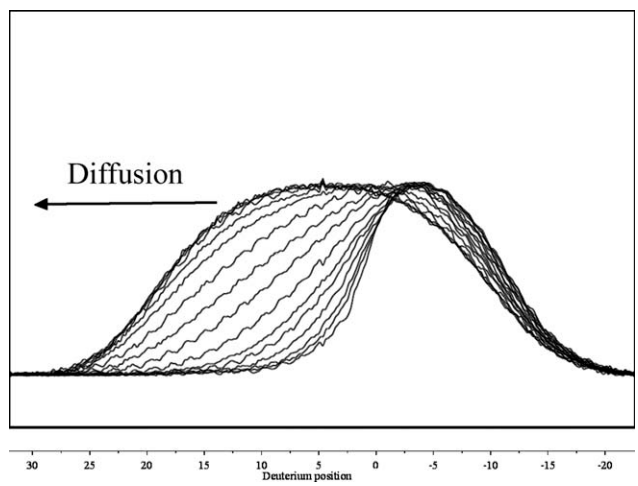


Figure 3 ^{2}H-NMR magnitude image of a sample of the soy-based hydrogel over time. The initial spectrum shows the deuterium in the bottom of the tube on the right side of the figure. Each successive spectrum (180, 300, 600, 1200, 1800, 7200, 14,400, 28,800, 57,600, 129,600, 172,800, and 216,000 s) tracks the deuterium's new position. The spectra for other gel systems were similar.

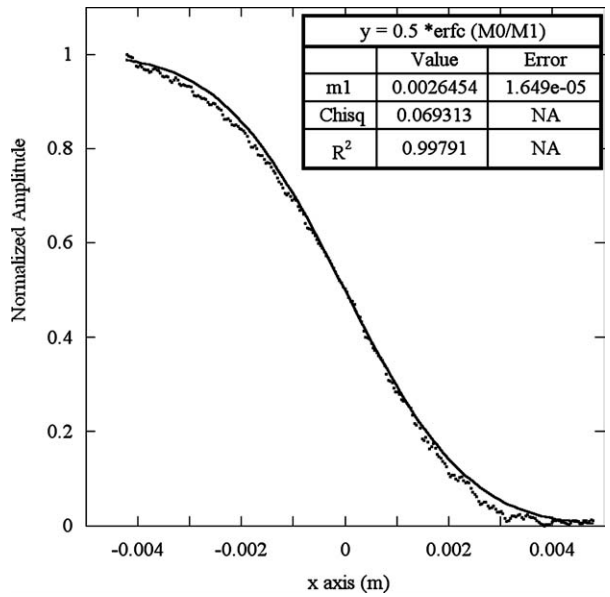


Figure 4 Curve fit of the data for the diffusion of deuterium oxide in 5 wt % soybean-oil-based hydrogel at 10 min. The curve fits for the other gel systems were similar. In this fit, ''y'' is the normalized amplitude, M0 is the position along the x axis of the tube, and ''m1'' is equal to 2 times the square root of the diffusion coefficient multiplied by the elapsed time. Chisq and R squared are related to the quality of the fit with lower values of Chisq and R squared close to 1 indicating superior fit. Because time is known, the diffusion coefficient is calculated from M1.

values, even though later data was at least qualitatively illustrative. Using this window of time also minimized the impact of potential time differences when we took the initial spectrum. The third assumption, that the order of the layers did not affect the result, was confirmed experimentally by identical experiments with the composition of the layers reversed. The reported results are an average of data from experiments in both configurations, although either layering gave results that demonstrated that there was no systematic effect caused by the layering geometry.

To fit the data, some manipulation had to be performed. First, the region of diffusion in the spectrum had to be isolated and normalized. Next, the x axis had to be converted to a distance value; we did this by taking the image of an NMR tube with a 0.85-cm blank phantom and using that known volume value to calibrate the axis. The curve was then mathematically moved to place the 0 value of the x axis at the inflection point of the curve. In cases where the diffusing deuterium oxide layer was in the bottom of the tube, a multiplier of -1 was used to reverse the axis to ensure that the data fit the positive form of the equation. The resultant data was a satisfactory fit [eq. (1)], with typical coefficient of determination (R^2) values greater than 0.98 (Fig. 4). The resultant fit gives the value $2(Dt)^{1/2}$, containing D and time (t), which is a known value for each curve. The reported D is an average value of the D values found in the 5–10 min data, where our earlier assumptions were most valid. It is also an average of multiple experiments with a reported standard deviation.

The D values of these biobased hydrogels are reported in Table I. For comparison purposes, a commercially available hydrogel was also studied by this method. The results show that the diffusion in the biobased hydrogel polymers was between 1 and 1.5×10^{-9} m^2/s. The commercially available acrylic-based hydrogel had D values of about half of the value of those of the biobased materials. It was interesting to compare this result to those available in the literature. The fastest possible aqueous diffusion expected would be the self-diffusion of water with itself, which has been studied extensively in previous experiments[37–39] and was determined to be 2.4×10^{-9} m^2/s. On the slower end, water has a D value of 1.2×10^{-10} m^2/s under some conditions in a highly crosslinked carbohydrate–borax hydrogel.

This technique has the possibility of being applied generally to other molecules of potential interest. With appropriately labeled compounds, essentially any molecule can be tracked through a media with NMR imaging. Additionally, although deuterium has a convenient signal, ^{13}C or ^{17}O could be used as well. The labeled compound would be suspended in the gel and appropriately layered with a gel that did not contain the labeled compound. The use of ^{31}P-NMR is also a possibility and, because of its high abundance, chemical labeling would not be necessary.

CONCLUSIONS

The values obtained for the D values of biobased hydrogel systems were measured, and these values showed their promise for use in encapsulation applications. Overall, these materials showed more rapid release than those observed in literature systems and that of the polyacrylic resin used for comparison in this study. Both the saponified starch–polyacrylonitrile and the soy-based hydrogel had similar D

TABLE I
The diffusion coefficients of biobased hydrogels and a commercially available acrylic hydrogel polymer

Hydrogel	Diffusion coefficient (10^{-9} m^2 s^{-1})
Soy based gel 5 wt%	1.37 ± 0.21
Saponified starch polyacrylnitrile 0.75 wt%	1.35 ± 0.24
Saponified starch polyacrylonitrile 0.5 wt %	1.28 ± 0.26
Commercially available acrylic hydrogel 5 wt%	0.76 ± 0.13

values, and the use of a higher loading ratio had little effect; this indicated that there is still a considerable amount of study necessary to tailor the controlled release of aqueous molecules from these materials.

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