Study of the Contribution of the State of Water to the Gel Properties of a Photocrosslinked Polyacrylic Acid Hydrogel using Magnetic Resonance Imaging

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ABSTRACT: Photocrosslinked polyacrylic acid (PAA–HEMA) hydrogels are a promising candidate for use in dermatological patch adhesives. To gain further knowledge about the properties of this gel, we investigated the T_1 relaxation time and the diffusion coefficient (D) of water in the hydrogels using magnetic resonance (MR) imaging. Hydrogels with different formulations and process factors were prepared and tested. The observed data were analyzed by ANOVA, which clarified the mode of action of the formulation and process factors based on these MR parameters. Various gel properties (i.e., gel fraction, swelling capacity, gel strength, and water-retention ability) were also measured, followed by a Bayesian network (BN) analysis. The BN allowed us to summarize well the relationships between the formulation and process factors, MR parameters, and gel properties. T_1 was associated with the swelling and water-retention properties of the hydrogel, whereas D was associated with gel formation and gel strength. Furthermore, this study clarified that T_1 and D mostly represented the hydration and water-compartmentalization effects of the hydrogel, respectively. In conclusion, the state of water seems to play an important role in the properties of the PAA–HEMA hydrogel. © 2014 Wiley Periodicals, Inc. and the American Pharmacists Association J Pharm Sci 103:3532–3541, 2014

Keywords: Bayesian network; multivariate analysis; hydrogels; imaging methods; relaxation time; MRI; hydration; state of water; diffusion coefficient

INTRODUCTION

Hydrogels are formed by three-dimensional polymer networks in an aqueous phase. They can retain a large amount of water while maintaining their mechanical strength. Currently, various hydrogels are used as adhesives for dermatological patches that are employed for local inflammation therapy and as wound dressings.[1,2] Dermatological patch adhesives exhibit a wide variety of important gel properties, including a rigid gel strength, high water-retention capacity, sufficient adhesiveness, and so on.[1,2]

Recently, we developed a novel photocrosslinked hydrogel composed of a polyacrylic acid modified with 2-hydroxyethyl methacrylate (PAA–HEMA) and evaluated it as an adhesive candidate for dermatological patches.[3–5] This hydrogel was prepared via a photochemical reaction. The exposure of an aqueous solution of the polymer to UV light triggers the reaction of the HEMA moieties, leading to the generation of inter- and intramolecular crosslinked structures with covalent bonding and to gel formation. The photochemical reaction (as a crosslinking method) has been attracting a lot of attention in the field of gel preparation.[6,7] To date, various photocrosslinked hydrogels have been investigated as materials that can be used as drug-delivery systems and tissue engineering. These hydrogels were prepared via a photochemical reaction using mono-, di-, or multifunctional vinylated monomers or macromers, including HEMA,[8–10] poly(ethylene glycol) dimethacrylate,[7,11–14] poly(ethylene glycol) diacrylate,[15] methacrylated sebacic acid,[16] azide and lactose moieties introduced in chitosan,[17–19] and styrenated gelatin.[20–22]

The photochemical reaction provides many benefits over gelation. First, the reaction enables the conversion of an aqueous solution of the polymer into a hydrogel within a very short time under physiological conditions.[22,23] In addition, the crosslinking density of the hydrogel can be set at a lower level than that generated by ionic bond crosslinking because covalent crosslinking is stronger than ionic bond crosslinking; this allows the hydrogels to retain a much larger amount of water while maintaining sufficient mechanical strength.[4] Moreover, the reaction enables a high degree of spatial and temporal control of the crosslinked structure of the hydrogel.[6,7,12] In previous studies, various formulation factors (e.g., polymer concentration, degree of modification of the polymer with HEMA, and initiator amount) affected the gelation significantly,[3,4] and the physical properties of the resulting hydrogel were changed over a wide range by changing the factors. However, the mechanisms of action of these factors are diverse and complex; thus, further knowledge about their contribution to the gel properties is required to design a desirable hydrogel that can be used in dermatological patching.

This study focused on the physical state and molecular mobility of water in hydrogels. Several studies have addressed this issue using different hydrogels.[24–28] Because water is the dominant component of the hydrogel, there is a good possibility that the gel properties are controlled by the state of the water. In this study, first we investigated the water state in hydrogels that were generated using different preparation combinations. To evaluate the water state in the hydrogels, we used the

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magnetic resonance (MR) parameters of the hydrogel: the T_1 relaxation time and the diffusion coefficient (D). We also evaluated various gel properties, including gel fraction, swelling behavior, gel strength, and water-retention ability, followed by the analysis of the observations using Bayesian networks (BNs). The results of this study allowed us to characterize the relationships between the state of water in the hydrogel and formulation, process factors, and gel properties.

MATERIALS AND METHODS

Materials

Polyacrylic acid with various molecular weights (MWs; 5, 250, and 1000 K) and 2,2-dimethoxy-2-phenylacetophenone (DMPA) were purchased from Wako Pure Chemical Industries (Osaka, Japan). HEMA and 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride (EDAC) were purchased from Sigma–Aldrich (St. Louis, Missouri). All other reagents were of analytical grade.

Sample Preparation

To prepare PAA–HEMA hydrogels, the photoreactive PAA–HEMA polymer was first synthesized according to our previous studies.[3–5] The degree of modification of PAA with HEMA was 5 and 20 mol %. Briefly, HEMA was added to PAA dissolved in purified water, and the mixture was stirred. The designated amount of EDAC (equivalent to 5 or 20 mol % of carboxyl groups in PAA) dissolved in purified water was added to the mixture, which was then stirred for 4 h at room temperature, to complete the reaction. The reaction mixture was freeze-dried after dialyzing in purified water using a seamless cellulose tube (size 36; Union Carbide, Houston, Texas). Consequently, a white cotton-like photoreactive PAA–HEMA polymer was obtained. It was stored at room temperature until use in the experiments.

The model formulations are listed in Table 1. The formulation and process factors used in this investigation were assigned according to an L16 orthogonal experimental design. For the preparation of the model formulations, the designated amounts of the photoreactive PAA–HEMA were dissolved in phosphate-buffered saline (PBS, pH 7.4), and an appropriate amount of DMPA dissolved in ethanol was added to the polymer solution, as a reaction initiator. These reaction solutions (0.5 g) were placed in a tube. Subsequently, exposure of the reaction mixture to UV light was carried out using a UV curing system (Aicure ANUP5204; Matsushita Electric Works, Tokyo, Japan). The light intensity measured at 365 nm using a photometer (UIT-150; Ushio, Tokyo, Japan) was 28 mW/cm^2.

In addition to the PAA–HEMA hydrogel, this study prepared PAA aqueous solutions with different concentrations and MWs of the polymer. PAA–25K was dissolved at concentrations ranging from 5% to 15%, whereas PAA with different MWs (5–1000 K) was dissolved at a concentration of 10%.

MR Parameters

The T_1 and D of water in the hydrogels were determined using a Varian NMR system at 9.4 T at room temperature. The T_1 of water in the samples was measured using the inversion-recovery (IR) sequence ($180^\circ - t - 90^\circ$ acquisition) and a spin-echo (SE) sequence. Such IR–SE mixed sequences are used frequently for T_1 measurements.[29–31] The D of water was determined by the pulse sequence superimposition of a pair of square-shaped gradient field pulses (the so-called motion-probing gradients) using a stimulated echo acquisition mode (STEAM). The gradient pulse factor, b-value, ranged from 0 to 1010 s/mm^2.

To visualize the water state in hydrogels, T_1 mapping and apparent diffusion coefficient (ADC) mapping were carried out. T_1 maps were acquired using a gradient-echo pulse sequence with a TE of 3.20 ms, seven different TIs (50, 100, 300, 500, 1000, 4000, and 8000 ms), a flip angle of 10°, an FOV of 30 × 30 mm^2, a matrix size of 128 × 128, and a slice thickness of

Table 1. Experimental Values of MR Parameters and Gel Properties of PAA–HEMA Hydrogels

Formulation Number	Conditions for Hydrogel Preparation ($A/B/C/D$)[a]	T_1 (s)	D ($\times 10^{-10}$ m^2/s)	Gel Fraction (%)	Swelling Ratio	Gel Strength [Log (Pa)]	Removed Fluid (%)
1	10/5/1/0.1	2.26 ± 0.02	20.91 ± 1.98	82.1 ± 3.2	114.3 ± 8.4	0.00 ± 0.00	9.01 ± 0.28
2	10/5/1/1.0	2.20 ± 0.13	18.84 ± 0.37	91.6 ± 0.7	147.1 ± 87.0	2.79 ± 0.21	5.83 ± 1.86
3	10/5/5/0.1	2.12 ± 0.09	17.82 ± 0.27	82.9 ± 5.2	493.9 ± 87.0	2.96 ± 0.07	9.17 ± 0.33
4	10/5/5/1.0	2.17 ± 0.03	16.89 ± 0.62	97.6 ± 4.6	566.2 ± 37.0	3.23 ± 0.04	6.25 ± 0.61
5	10/20/1/0.1	2.20 ± 0.01	17.64 ± 0.42	57.7 ± 15.5	333.3 ± 57.8	3.28 ± 0.24	5.82 ± 0.48
6	10/20/1/1.0	2.17 ± 0.15	17.21 ± 0.53	77.9 ± 3.4	299.4 ± 9.0	3.60 ± 0.14	4.71 ± 0.16
7	10/20/5/0.1	2.13 ± 0.10	17.95 ± 0.51	62.1 ± 1.4	274.7 ± 36.4	3.79 ± 0.03	5.6 ± 0.16
8	10/20/5/1.0	2.13 ± 0.10	19.45 ± 0.84	79.8 ± 1.5	293.9 ± 5.1	4.27 ± 0.05	4.87 ± 0.72
9	15/20/1/0.1	1.80 ± 0.11	15.72 ± 1.15	62.4 ± 10.8	152.9 ± 6.6	4.32 ± 0.16	3.41 ± 0.51
10	15/20/1/1.0	1.87 ± 0.04	15.9 ± 1.47	84.4 ± 2.4	157.2 ± 3.1	4.33 ± 0.13	3.04 ± 0.28
11	15/20/5/0.1	1.84 ± 0.11	15.82 ± 1.3	79.7 ± 2.2	110.5 ± 2.2	4.87 ± 0.02	2.81 ± 0.35
12	15/20/5/1.0	1.85 ± 0.12	15.14 ± 0.54	90.3 ± 0.4	127.3 ± 8.8	5.20 ± 0.04	3.37 ± 0.57
13	15/5/1/0.1	1.96 ± 0.08	16.32 ± 0.87	82.1 ± 10.7	301.9 ± 65.9	2.65 ± 0.13	5.44 ± 0.2
14	15/5/1/1.0	1.93 ± 0.07	16.01 ± 0.69	86.7 ± 5.4	263 ± 17.2	3.21 ± 0.07	4.46 ± 0.54
15	15/5/5/0.1	1.93 ± 0.07	14.39 ± 0.62	74.7 ± 3.0	298.8 ± 25.2	3.57 ± 0.02	4.85 ± 0.39
16	15/5/5/1.0	1.89 ± 0.12	15.6 ± 0.33	92.6 ± 3.9	388.6 ± 24.9	3.86 ± 0.06	3.52 ± 0.46

[a] Model formulations were prepared under different conditions of formulation factors. The conditions were assigned according to an L16 orthogonal experimental design. The formulation factors were as follows: A, polymer concentration (%); B, degree of modification with HEMA relative to the carboxyl group of the parent PAA (mol %); C, UV-exposure time (min); and D, initiator concentration (wt % of polymer amount). Each experimental value represents the mean ± SD of three determinations.