Highly compressible hydrogel reinforced with cellulose nanocrystals for ultrasound scanning via microwave-assisted synthesis

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Abstract In this study, a rapid fabrication method was developed to prepare hydrogel structures with high mechanical strength and low attenuation coefficient for ultrasound scanning. Poly acrylic acid (PAA) hydrogel was first prepared via a free radical polymerization approach. To shorten the process time (~30 min in water bath), microwave heating was applied to facilitate the reaction and reduce the reaction time down to 80 s. The produced hydrogels showed excellent elasticity but had a low compressive strength of 100 kPa. To further enhance the mechanical strengths of PAA hydrogels, cellulose nanocrystals (CNCs) were added to the precursor solution. After the microwave assisted crosslinking process, the compressive strength of the hydrogel increased to 350 kPa. Moreover, the ultimate compressive strain was enhanced from 60 to 80% with great recoverability. The PAA/CNC hydrogel has a great ultrasound transmission for high-quality ultrasound images comparable to conventional liquid hydrogels. To demonstrate the feasibility of the PAA/CNC hydrogel in ultrasonic medical applications, a customized ultrasound probe coat was created with a 3D printed mold and practically used in the ultrasound scanning process.
Graphical abstract

Keywords  Cellulose nanocrystal · PAA hydrogel · Microwave · Ultrasound transmitting

Introduction

Ultrasound scanning is a widely used medical examination technology. The scanning technology can help detect objects in human body by converting the sonic reflections into images to investigate organ conditions or to perform physical checkup. During the scanning process, a lubricating gel is usually needed to allow ultrasound probes to move smoothly and more importantly to ensure continuous contact on skin. Without using lubricating gels, scanning errors might be induced due to air gaps between the probe and skin (Carovac et al. 2011). The application of liquid gels allows good ultrasound penetrations for distinct image formation, but also causes inconvenience as the gel needs to be cleaned after therapy. To avoid this inconvenience, ultrasound transmitting coats have been proposed (Aoyagi and Hiraguri 2017): the ultrasound probe can be wrapped with a silicone coat or a plastic bag filled with water to perform ultrasound analyses without smearing liquid gels over human body. Among various materials, hydrogels catch widespread attention due to their great ultrasound transmittance and bio-compatibility. By forming hydrogen bonds between molecules, the polymeric network in hydrogels can absorb large amount of water, which allows good ultrasound transmission, and also provides good elasticity and mechanical strengths (Ahmed 2015; Chai et al. 2017) at the same time. Moreover, with special nano-structure designs, hydrogels can be also stretchable and responsive to environments (Xia et al. 2013) for various smart biomedical applications.

To obtain good ultrasonic scanning signals, the compressive motion of the probe requires a hydrogel coating with high mechanical strength and compressive recoverability (Oyen 2014; Vedadghavami et al. 2017). Among various hydrogel polymers, poly acrylic acid (PAA) is a commonly used water absorbing polymer (Lim et al. 2015), and has been widely used as a gel coupling medium for ultrasonic scanning (Jahan et al. 2020). However, PAA hydrogels regularly exhibit low mechanical endurance for compressive or shear stresses. Fortunately, the recent research shows that addition of cellulose nanocrystals (CNCs), a notable hydrophilic crystalline nanomaterial, can bridge between PAA polymer chains to form interpenetration networks and thus enhance the mechanical strength of hydrogels (Lim et al. 2017, 2014; Wan Ishak et al. 2020; Rosli and Ahmad 2019). CNC, as a derivative from natural cellulose, is an environmental friendly material and compatible to human bodies. The nanoscale size and high crystallinity provide CNCs distinctive chemical characteristics with great mechanical properties. First, CNCs exhibit great hydrophilicity due to vast hydroxyl groups on the surface. These functional groups also allow good affinity and compatibility with hydrophilic polymers, such
as PAA. Moreover, the hydroxyl groups on CNCs also provide active sites for chemical reactions. As proposed in the literature (Lim et al. 2014), CNCs can react with the carboxylic groups on PAA chains to proceed an esterification reaction, facilitating the formation of crosslinking hydrogel network for stronger mechanical strengths.

Apart from mechanical property enhancement of hydrogels, the manufacture procedure is also of critical importance. Regularly, PAA hydrogels are produced by crosslinking monomers in water at elevated temperatures. Traditionally, aqueous precursor samples are thermally heated in water or oil bath to produce hydrogel. Due to the thermal conductive limits, it usually takes hours for the samples to reach required temperature for complete crosslinking reaction. During the heating process, the non-uniform temperature profiles in the samples might also lead to defects in the thermally crosslinked samples. Thus, to increase the heating uniformity and reaction efficiency, microwave-assisted process is commonly adopted in the literature. Microwave heating make use of electromagnetic rotation or vibration of polar molecules for heat generation. Because of its radiative nature, microwave heating can efficiently deliver thermal energy uniformly inside aqueous samples, and reduce the heating time from hours to minutes with guaranteed product quality (Zhong et al. 2019; Głowniak et al. 2021).

In this study, a fast formulation method is developed to prepare PAA hydrogel with customized shapes. With high water content, microwave heating, a rapid and uniform heating process can be directly applied to complete the crosslinking reaction quickly within minutes for hydrogel formation. With proper CNC and crosslinker addition, the mechanical strengths will be optimized to fulfill the compression requirements for ultrasonic scanning probe coats, which allow ultrasound scanning without the need of rubbing ultrasonic grease over human body. The ultrasonic transmittance and biocompatibility of the prepared hydrogels will also be investigated. Finally, three-dimensional structures made from the hydrogel will be demonstrated to show the simplicity for customized geometries formation and the feasibility for potential ultrasound applications.

Materials and methods

Materials

Acrylic acid (AA) was purchased from Emperor Chemical CO., LTD. Cellulose nanocrystals (CNCs) were provided by The University of Maine. N, N’-methylenebisacrylamide (MBA) was purchased from Sigma-Aldrich. Ammonium persulfate (APS) was purchased from GE Healthcare Life Sciences. All chemicals were used as received without further purification.

Hydrogel synthesis

1.2 g of AA monomer was first added with 0.07 g CNC and diluted with 8.7 g DI water and well mixed in an ultrasonic bath for 5 min. After mixing, 0.02 g of MBA was added as the crosslinking agent and 0.01 g of APS was mixed in as the reaction initiator. To ensure that the solution was completely mixed without bubbles, the solution was mixed (2000 rpm for 1 min) and deaerated (2200 rpm for 2 min) with a planetary centrifugal mixer (THINKY, ARE-310). The above experimental steps are all operated under room temperature. The prepared solution was then put into a microwave oven for gelation (Fig. 1a). The oscillating frequency and the energy output of the microwave was 2450 MHz and 800 W, respectively. The solution temperature was heated to 70 °C at around 80 s of heating. AA monomer and MBA were initiated by APS. The radicals then propagated and formed PAA chains or PAA hydrogel networks crosslinked by MBA. Hydroxyl groups on CNCs reacted with the carboxyl groups on PAA chains and form more rigid networks. The illustration of the mechanisms is depicted in Fig. 1b.

Characterizations

The rheological properties of the precursor solutions or hydrogels were measured by using a rheometer (TA, HR2, Thermal). The prepared hydrogels are cylindrical samples with 2.5 cm in diameter and 2 mm in thickness. The rheometer is equipped with a cone-plate with a diameter of 40 mm and a cone angle of 3.5949°. The mechanical strength of hydrogel was
Fig. 1  
(a) Schematic diagram of experimental procedure. 
(b) Mechanism of AA monomer radical polymerization and crosslinking of PAA/CNC
examined by using a dynamic mechanical analyzer (JSV-H1000, ALGOL instrument CO., LTD.). A strain rate of 20%/min is used for the measurement of ultimate compressive strength. The hydrogel samples used in the compressive measurements were cylindrical samples with 2.5 cm in diameter and 1 cm in height; hydrogel samples used in the tensile measurements were bone-shaped with 1 cm in length. The ultrasound attenuation coefficient was examined by using a water tank test. The morphology of the samples was observed by a scanning electron microscope (SEM, Nova NanoSEM 230) and an optical microscope (MICROTECH D5-SWD). Samples prepared for SEM were freeze-dried hydrogels after thermal crosslinking as described in the former section.

Results and discussion

Gel preparation method

First, the gelation temperature of the PAA precursor is determined for hydrogel preparation. The viscosity of an aqueous precursor mixture containing AA, MBA, and APS is measured with increasing temperature (Fig. 2). Initially, the viscosity of the precursor solution remains constant at 0.04 Pa.s and slightly increases with temperature. As the temperature reaches 70 °C, the viscosity elevates dramatically and climbs to 1000 Pa.s at 75 °C, indicating a gelation temperature at ~70–75 °C, which is consistent with literature reports (Umar et al. 2014). To prepare the hydrogel, a water bath of 75 °C can be used to heat the precursor solution (Fig. 3a). Because the thermal energy is transferred mainly by conduction through the vial, the temperature increases the required temperature of 75 °C in 1200 s with a time constant of 582 s, following the typical lump capacitance model (Lachi et al. 1997). The crosslinking reaction can be much facilitated by microwave heating compared with traditional water bath (Jovanovic and Adnadjevic 2010). In contrast to hot water bath, in the microwave heating process (Fig. 3b), the temperature increases linearly with time due to the radiation nature of the heating mechanism. In particular, because of the large water content, the precursor solution absorbs emitted

| Mechanical strength | Water bath | Microwave |
|---------------------|------------|-----------|
| Compressive strength (kPa) | 313.27 ± 38.12 | 353.67 ± 35.70 |
| Tensile strength (kPa) | 11.30 ± 1.56 | 10.54 ± 0.93 |
microwave energy quickly in ~ 60 s, 20 times faster than the water bath, to reach the gelation temperature. The mechanical properties of the hydrogels prepared by water bath and microwave heating are tested to check the differences between the preparation process. As summarized in Table 1, the hydrogels prepared by the two heating method do not show significant differences in tensile or compressive strengths, indicating that the hydrogels from both heating processes have nearly the same microstructures after thermal crosslinking. For the sake of heating efficiency, the microwave heating method are used in the following section for hydrogel preparation.

Preparation of PAA hydrogel

The crosslinking degree of hydrogel strongly affects the elasticity (Weber et al. 2009), and can be adjusted by changing the crosslinker/precursor ratio. To determine the optimum crosslinker/precursor ratio, samples with different crosslinker/AA ratios are prepared and crosslinked via microwave heating. Rheological properties of these samples are examined to investigate the gelling condition of the prepared hydrogels (Bromberg 1998; Epstein-Barash et al. 2010; Tian et al. 2016). Regularly, damping factor (tan δ), which is the ratio between storage and loss modulus, is commonly used as an index for gel elasticity evaluation. When tan δ value is much less than 1, the sample is expected to be elastic and presents solid nature. With a crosslinker/AA ratio of 1/120, the tan δ value is less than 1 at low frequencies but gradually increases beyond unity at frequencies higher than 10 rad/s. This partial fluidity at high frequencies suggests that crosslinking points of the sample are insufficient for rigid gel formation. As the crosslinker/AA ratio increases to 1/60 or beyond, the tan δ values remains ~ 0.1 at all frequencies, indicating sufficient crosslinking points for gel formation. Hence, to produce hydrogels with stable viscoelasticity, a crosslinker/AA ratio of 1/60 is used in the following sections (Fig. 4a).

To further ensure sufficient hydrogel formation, the rheological properties of crosslinked samples at different AA concentration are also investigated. As shown in Fig. 4b, with 10 wt% AA content, the tan δ value increases with frequency and exceeds 1 at frequencies higher than 60 rad/s, indicating the liquid nature of the sample at high frequency. When the AA concentration is more than or equal to 12 wt%, the sample is able to remain its hydrogel structure with significant elasticity with tan δ values at ~ 0.2. Despite high water contents of these samples (Fig. 5) for ultrasonic transmitting efficiencies, the compressive strengths of these PAA hydrogels are less than 140 kPa, lower than the required compressive stress.
of 200 kPa on the probes in ultrasonic scanning processes. Therefore, further enhancement of mechanical strength is needed.

Addition of cellulose nanocrystals (CNCs).

To improve the compressive strength at high water content, CNCs are introduced to the precursor solution for hydrogel formation. The CNCs used in this study has a stick shape with a diameter of ~10 nm and a length of ~120 nm (Fig. 6a). The viscosity changes along with temperature rise after CNC addition is shown in Fig. 6b. The viscosity increases abruptly at 80 °C, higher than the gelation temperature of pristine PAA, indicating a different crosslinking mechanism. From literature (Spoljaric et al. 2013; Lim et al. 2017), with CNC addition, esterification reaction usually occurs between the PAA chain and CNC, and results in a higher gelation temperature. To further verify the esterification, FTIR spectra of PAA, CNC, and PAA/CNC hydrogels are compared in Fig. 6c. The peak at 1720 cm⁻¹, representing the carboxylate group (COOH) in PAA, disappears after CNC addition. Instead, a peak at 1221 cm⁻¹, representing an ester group (COOC) (Chen et al. 2015), is observed in the PAA/CNC hydrogel.

The esterified PAA/CNC composites show a great improvement in mechanical strength. As shown in...
Fig. 7a, compared to pristine PAA hydrogel, addition of only 0.7 wt% CNCs can significantly augment the compressive strength from 100 to 350 kPa, indicating a more durable molecular structure after the esterification between PAA and CNC (Spoljaric et al. 2013). Further addition of CNCs, however, cannot increase the ultimate compressive strength, possibly because of the limited esterified linkages between

Fig. 8  a Recoverability of PAA/CNC hydrogel (12 wt% AA with 0.7 wt% CNCs) after 10 compression cycles. A PAA hydrogel (12 wt% AA) is compared but breaks around 100 kPa. A strain rate of 20%/min is used. b Tensile strength test for PAA and PAA/CNC hydrogels. A strain rate of 20%/min is used. c Comparison of shear strengths between PAA and PAA/CNC hydrogels. An angular frequency of 1 rad/s is used

Fig. 9  a 3D structures made of the PAA/CNC hydrogel from molding. The CAD files are compared to show the accurate detailed geometries. b Demonstrative gel structures using multi-step molding process. The precursor solution was dyed with red and blue to differentiate first and second molding process

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CNC and PAA. These evidences suggest that a fully percolative network of CNC is built in the hydrogel after 0.7 wt% with a maximal compressive strength. Yet, because of the diversity of PAA chain lengths and the CNC sizes, the crosslinking density of the hydrogel networks cannot be well controlled right at the percolation threshold of 0.7 wt% CNC, thus leading to slightly larger error bars around 0.7 wt%. After the CNC concentration reaches 2.0 wt%, the amount of CNC fillers is excessive for crosslinking network formation, and result in smaller error bars. To further investigate the morphological changes, SEM analysis (Fig. 7b) shows that the hydrogel pore size decreases from ~25 to ~10 µm after CNC addition. This porous hydrogel structure with smaller pore size and more uniform pore distribution thus results in higher compressibility (Xia et al. 2013; Lim et al. 2014; Wang et al. 2013).

To ensure the durability of the PAA/CNC hydrogel during ultrasound scanning procedure, the recoverability of the hydrogels under repeatedly compression are also evaluated. A compression cycle (0–70% strain) at a strain rate of 0.2 min⁻¹ is used to test the recoverability of PAA/CNC hydrogel. From the results (Fig. 8a), the stress/strain curve of the first and tenth cycles nearly overlap each other, indicating the great elasticity and recoverability of the PAA/CNC hydrogel. The tensile strength is also greatly enhanced after CNC addition. As shown in Fig. 8b, the pristine PAA hydrogel is quite fragile and breaks at ~2% tensile strain. After CNC addition, the PAA/CNC hydrogel can remain elastic with a tensile strain up to 70%. Besides the enhanced mechanical strengths, the PAA/CNC hydrogel also possesses a higher shear strength of 6000 Pa than its PAA counterpart (3500 Pa). This enhanced shear strength can thus fulfill the shear requirement for the inevitably rubbing process in ultrasound scanning (Fig. 8c).

Creation of complex structures

To showcase the convenience of this microwave assisted hydrogel formation method, several specific structures with complicated geometries are created with molds. As shown in Fig. 9a, all the prepared hydrogel structures show good shape definition in details. In addition, if the structure designs are too complicated to complete with a single mold, multiple molds can be used in sequence to perform shape combination. A piece of hydrogel structure is first created and merged in another mold to construct a more complex geometry without an apparent boundary (Fig. 9b). These examples demonstrate the capability of this microwave approach to create hydrogel structures quickly at ease.

Ultrasound scanning performance

Ultrasound attenuation coefficients are first evaluated to verify the ultrasound transmittance through the hydrogel for scanning signal translation. Several widely used reagent in ultrasonic therapies are tested and the results are listed in Table 2 (Kim et al. 2018; Ginzel et al. 1994; Menikou and Damianou 2017), where the attenuation coefficient of a commercially available transmitting grease is also provided. Main parts in human body, including blood, soft tissue, and fat, have low attenuation coefficients at 0.15, 0.75, 0.63 dB/cm/MHz, respectively (Shankar et al. 2011). As the transmitting gel is applied, it is

| Material | Attenuation Coefficient (dB/cm/MHz) | References |
|----------|-----------------------------------|------------|
| Personalized gelatin couplant pad | 0.05 | Kim et al. (2018) |
| Synthesized elastomer | 0.56 | Ginzel et al. (1994) |
| Poly(acrylamide) hydrogel | 0.08–0.14 | Prokop et al. (2003) |
| Polyvinyl alcohol cryogel (PVAC) | 0.075–0.28 | Menikou and Damianou (2017) |
| Ultrasound Grease (Commercially available) | 0.05 | Provided by manufacturer |
| PDMS | 0.3645 | Measured |
| Silicone | 0.1711 | Measured |
| PAA | 0.0158 | Measured |
| PAA/CNC | 0.0156 (this work) | Measured |
necessary to have lower attenuation coefficients than human bodies in order to gain good ultrasonic image quality. Among all tested materials, the PAA/CNC hydrogel has the minimal attenuation coefficient (0.0156 dB/cm/MHz) for ultrasound, i.e. a great ultrasound transmission due to its high water content. The value of the attenuation coefficient is also close to that of PAA hydrogel, indicating that CNC addition to PAA hydrogel has little impact on ultrasound transmitting ability.

To further demonstrate the possibility to apply hydrogel in ultrasound scanning, an ultrasound scanning coat is created (Fig. 10a). An ultrasound scanning probe is first 3D scanned to create a CAD file, which is used to generate a 3D printed mold. After filled with precursor solution and heated by microwave, the prepared coat can fit well on the probe.
for ultrasound scanning. The scanning image using the PAA/CNC gel coat shows little signal noises (Fig. 10b), and the scanning results are exactly the same as those from using a commercial pad, indicating the great transmissive effects of the PAA/CNC gel coat. To test the biocompatibility for biomedical applications, cell viability of the PAA/CNC gel are also evaluated. By using a direct contact method (Fig. 11a), the population of live cells (green dots) is approximately the same in all samples, and nearly no dead cells (red dots) are observed. The results indicate that PAA and CNC have high biocompatibility and low toxicity. In addition, the cells spread nicely over the PAA/CNC hydrogel with irregular protrusions (Fig. 11b), showing the effective bio-adhesion (Liao et al. 2012). Therefore, the PAA/CNC hydrogel coat is confirmed to be secure when applied in medical procedures.

Conclusion

The hydrogel synthesis developed in this study provides a time-saving and convenient procedure with the assistance of microwave heating. Compared with regular hydrogel preparation process (~30 min in water bath), the microwave assisted process facilitates the reaction extent and reduces the reaction time down to 80 s. To fulfill the requirements of high mechanical strength and low attenuation coefficient for ultrasound scanning, cellulose nanoparticles (CNCs) are added to the precursor solution to enhance the mechanical strengths of PAA hydrogels. The compressive strength of the hydrogel increases from 100 to 350 kPa after the CNC addition, and the ultimate compressive strain is enhanced from 60 to 80% with great recoverability. The PAA/CNC hydrogel shows good biocompatibility and is highly transmissive to ultrasound. To demonstrate the feasibility of using the PAA/CNC hydrogel in ultrasonic medical applications, a customized ultrasound probe coat is created with a 3D printed mold. The coat is practically used in the ultrasound scanning process to yield high-quality ultrasound images comparable to those from conventional liquid hydrogels. These results show the capability of this microwave assisted approach to quickly prepare hydrogel structures for biomedical uses and can be further extended to other hydrogel applications.

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Declarations

Competing interests The authors have not disclosed any competing interests.

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