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Stereolithographic and molding fabrications of hydroxyapatite-polymer gels applicable to bone regeneration materials

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ABSTRACT

A bone regeneration material was fabricated from hydroxyapatite-poly(dimethyl acrylamide) (HAp–PDMAAm) composite through stereolithographic 3D printing technique, and additionally, a material from HAp–agarose composite was also prepared inside a mold. Then the tensile strength and morphology of both bone regeneration materials were compared. The HAp–PDMAAm composite xerogel from 0.17 weight ratio of HAp content can resist a tensile stress of 30.2 MPa, whereas 26.2 MPa was observed in case of agarose bone composite 0.5 weight ratio of HAp content. The achieved mechanical strengths indicate that the products can be applicable as bone regenerative medicine and the utilized fabrication technique plays a significant role toward patient-specific bioprinting technology.

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1. Introduction

Currently bone regeneration medicine may be dependent on fabrication of appropriate bone matrix which can serve as a formwork for the re-growth of natural bone cells. Thus, the regenerated bone will maintain the shape of the desired structure under treatment. Hence an effective bone tissue should have considerable mechanical strength, porosity, biocompatibility and osteoconductivity [1–3]. Many researches on bone tissue engineering are concerned to search an appropriate polymeric hydrogel binder that can provide a porous structure, and an inorganic substance with preferable mechanical strength and improved osteoconductivity. Hydroxyapatite (HAp) is a known inorganic substance and one of the main components of the natural bone tissue together with collagen. Then synthesized HAp can be utilized as a raw material in the preparation of bone regeneration materials from its biocompatibility and formability of porous structures [4–10]; it regenerates the mineral component of a natural bone. On the other hand, biopolymers such as agarose [11–13], alginate [14] and collagen [15–18] are preferable as a binder of mineral components due to their availability, biocompatibility and non-toxicity unlike synthesized organic polymers [19–25]. The property of the fabricated bone regeneration materials depends on the type of binder used, preparation technique employed and composition ratio between the mineral and binder.

Sintering of the HAp particles at high temperature or using high power laser is one of 3D printing technologies to prepare a desired shape and properties of the bone regeneration materials. The fabricated product maintains the shape of a given template, although the technique demands more energy and is difficult on handling [26,27]. It is known that stereolithographic 3D printing technique enables to print the object with the higher resolution in the range of 50–200 μm compared with other commercialized 3D printers. This is advantageous to control the fine structure of the various shaped materials with the desired structural and mechanical properties [28]. For instance, an advanced on-demand 3D printing technology was reported based on stereolithographic photopolymerization of liquid organic monomers to prepare a networked polymer structure that act as a matrix substrate so that it will glue HAp particles together through layer-by-layer polymerization of the entire 3D structure [7,29]. However, in most of the cases, the shape of the final product is usually restricted on the shape of positive or negative molds that are used during the fabrication process. This shape limitation might be a problem to fabricate a

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bone scaffold for the treatment of randomly fractured bone damages [23].

Thus, in this work, we have reported facile synthesis of xerogels from composite hydrogel of agarose and N,N-dimethyl acrylamide (DMAAm)-based polymer (PDMAAm) as reinforcing matrices for HAp nanoparticle powder which can be usable as materials in bone regeneration medicine. Both agarose and PDMAAm hydrogels can retain large amount of water in the infinite gel network, and such unique characteristics make them a good candidate as an entrapping matrix of HAp filler [24,30]. Moreover, it is possible to manipulate the desired shape of these composite gels depending on the preparation. Therefore, HAp–agarose composites were prepared through temperature-dependent gel formation of agarose and their xerogels were fabricated in specific mold. In contrast, HAp–PDMAAm composite xerogels were prepared by free radical polymerization of precursor monomer mixed with HAp by using stereolithographic 3D printing technique. Subsequently, as-prepared xerogels of composites were assessed by their mechanical strength and morphology and discussed in comparison with natural bones.

2. Experimental

2.1. Materials and characterization

Hydroxyapatite powder (95%+) and DMAAm monomer were purchased respectively from JUNSEI, Japan, and TCI, Japan, while N,N'-methylene-bis(acrylamide) (MBA) and benzophenone (BPO) were bought from Wako (Japan). All chemicals were used as received.

The mechanical strength test was performed by STA-1150 (ORIENTEC, Japan) for dumbbell-shaped specimens of HAp–PDMAAm composites and by dynamic mechanical analysis (QC-508M2, Cometech, Taiwan) for rectangular specimens of HAp–agarose composites. The xerogels were sectioned perpendicularly with stainless steel knife to get the cross section for SEM observation by using a scanning electron microscope (SEM, JEOL JSM-6390LV, Japan). Moisture analyzer (MS-70, A&D Co. LTD, Japan) was also used to measure water content in hydrogels.

2.2. Preparation of HAp–PDMAAm composite hydrogels/xerogels

DMAAm monomer was polymerized in the presence of MBA cross linker by partly modifying the known free radical polymerization method [24,31]. Briefly, an aqueous solution of monomer (21.45 M, 22 ml), cross linker MBA (0.1 mol%), and initiator BPO (0.15 mol%) were mixed. The mole percent (mol%) was calculated relative to mole of the monomer.

The mixed solution was transferred into a silicone frame (inner size: length × width × thickness = 8 × 8 × 0.2 cm) covered by polyethylene terephthalate sheet and glass plate, sequentially. On polymerization process, a laser beam (355 nm, 100–200 mW, continuous light) from optical fiber equipped with the printer (Easy Realizer of Soft and Wet Materials (SWIM-ER)) was allowed to move over horizontally placed mold according to the computer design data of the desired 3D shape which is needed to be printed. So, only the irradiated portion of the solution was polymerized. Here, the laser scanning speed was 0.5 mm/sec and the distance between top of the most upper glass surface and laser source was 2.3 mm.

For the preparation of HAp–PDMAAm composite hydrogel, HAp was added in the mixed solution of monomer, MBA and BPO, and then the mixture was stirred for three days at room temperature to get a pre-polymer composite solution. Polymerization of this solution was done in the same way as the preparation of PDMAAm described above. The composite hydrogel products were labeled as 0-HP, 0.17-HP and 0.5-HP, based on different weight ratios (0, 0.17 and 0.5) of HAp to the monomer. These hydrogels were preheated in oven at 70 °C for two days and then heated at 160 °C up to a constant weight of xerogels. Furthermore, a finger-shaped composite was fabricated based on our previous report by using the pre-polymer solution of 0.17-HP after preparing the corresponding computer model of the desired shape [29].

2.3. Preparation of HAp–Agarose composite hydrogels/xerogels

Agarose (0.4 g) was dissolved in water (10 ml) with stirring and heating at 85 °C for 20 min, and then HAp was added in agarose solution at 85 °C and further stirred for 30 min to completely mix. The mixture was immediately poured into a rectangular plastic mold (5 × 2 × 0.3 cm) and dried in air at room temperature. Then the dried gel was sandwiched with plastic plates and put in an oven (45 °C) to completely dry. The content of HAp in the composite was altered to be 0, 0.5, 1 and 2.5 weight ratio of HAp to agarose and labeled as 0-HA, 0.5-HA, 1-HA and 2.5-HA.

3. Results and discussion

3.1. HAp–PDMAAm composites

The PDMAAm was synthesized from DMAAm monomer in the existence of initiator and cross linker and its property was assessed. From moisture analysis, both PDMAAm polymers obtained from 0.1 and 0.15 mol DMAAm monomer contained 44 and 67 wt% of water respectively. Meanwhile, as observed in the tensile stress measurement (Fig. 1A), the high monomer concentration provided strong stress for the hydrogel, since the stress value of 0.15 mol DMAAm was 0.07 MPa, and 0.1 mol DMAAm exhibited 0.04 MPa stress. Incidentally, the strain was improved up to threefold (from 1.0 to 3.0 mm/mm) by increasing the monomer amount from 0.1 to 0.15 mol. Although the elasticity may be inversely proportional to the water content, the present result is not such a case and the elasticity was high for swollen gel. In the present case, the elasticity can be determined by the ratio of crosslinking agent and monomer and, thus, the swollen gel had a higher deformation rate before breaking.

Complete evaporation of water from PDMAAm hydrogels produced the corresponding xerogels but the dehydration affected the gel size due to the shrinking of polymer chain distance. The size of xerogels was decreased 28% for 0.1 mol DMAAm hydrogel and only 15% for another polymer gel. Fig. 1B shows that the tensile strength of xerogels was significantly improved up to 33.8 MPa for higher monomer content, and the latter gave 16.6 MPa. This enhancement was attributed to the increased dipolar interaction between shrank polymer molecules [32] and may be due to the formation of multiple cross linking points. However, the decreased strain values (0.072 and 0.040 (mm/mm)) for both xerogels compared to their corresponding hydrogels indicate that they exhibited less elastic property. The higher the concentration of DMAAm, the stronger the polymer network in both hydrogel and xerogel of PDMAAm. Finally, the xerogel from 0.15 mol monomer was considered as pristine (0-HP) to compare with composites.

PDMAAm composite hydrogels containing HAp as a filler were also soft, flexible and elastic. However, the tensile stress data seen in Fig. 2A revealed that addition of HAp particles increased the stress and strain values of the composite than pristine PDMAAm hydrogel. For example, the stress value of 0.5-HP hydrogel was 0.61 MPa which is almost 10 times greater than that of 0-HP hydrogel. This is attributed to the electrostatic interactions between polar polymer molecules and ionic surface of the HAp particles [33]. The result also seems to depict a role of HAp as a

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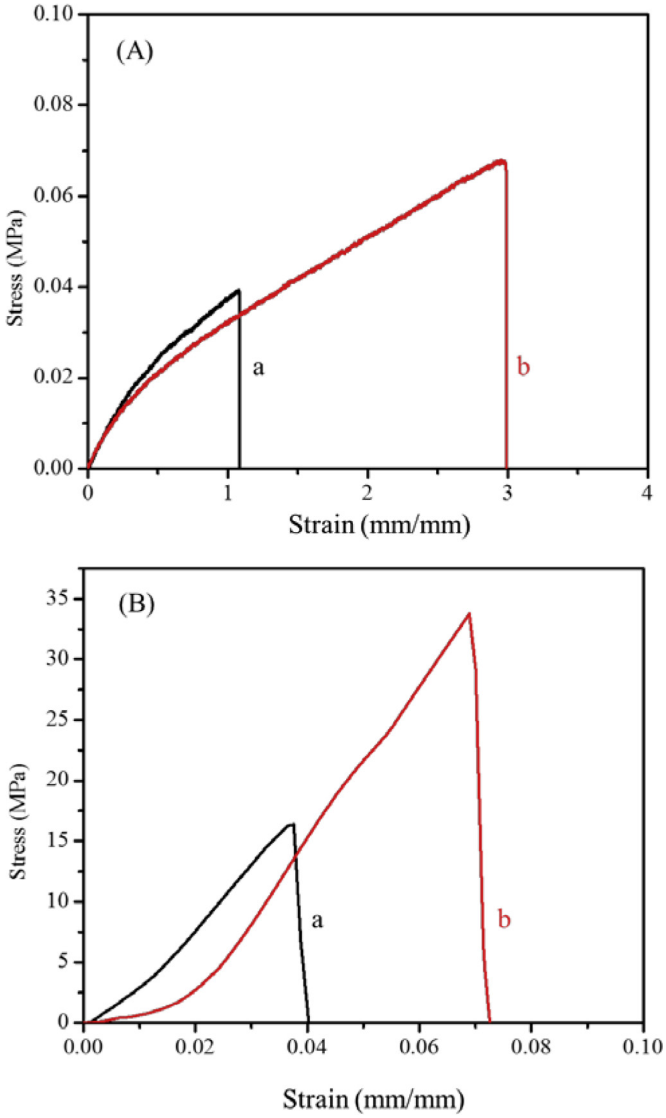

Fig. 1. Tensile stress data of PDMAAm (A) hydrogels and (B) xerogels prepared from (a) 0.1 mol and (b) 0.15 mol DMAAm monomer.

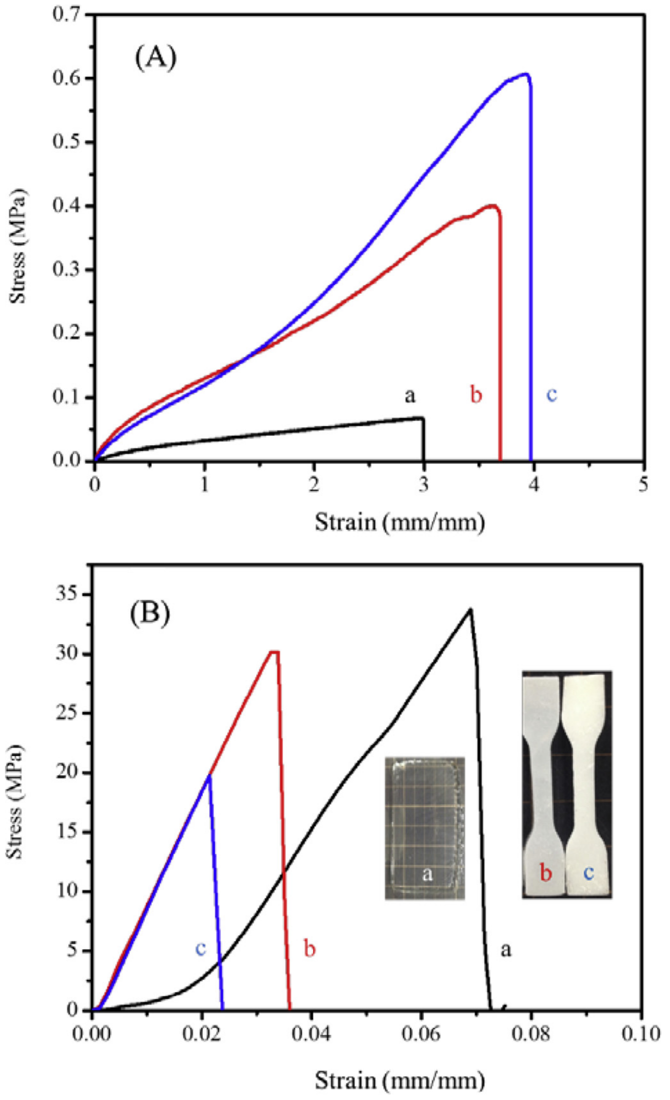

Fig. 2. Tensile stress data of PDMAAm-HAp composite (A) hydrogels and (B) xerogels with different HAp weight ratios; (a) 0-HAP, (b) 0.17-HP, (c) 0.5-HP. Inset is photographs of xerogels.

filler that effects hardening of PDMAAm resulted in ductile hydrogel composites with applicable mechanical strength. The strength of produced composite is comparable to the other already reported bonding stress of HAp-containing double network hydrogels (0.61 MPa) [24,30,34].

For dried composites (xerogels), breaking stresses of 30.2 and 19.6 MPa were achieved for 0.17-HP and 0.5-HP xerogels, respectively (Fig. 2B), while 0-HP xerogel breaks at 33.8 MPa. The results indicate that the addition of HAp did not preferably influence on the mechanical strength of pristine xerogel. This phenomenon may be due to the quantitative decrease of PDMAAm against HAp in the composite. Otherwise, the light irradiated on the surface has lost due to scattering on excess HAp particles that resulted insufficient polymerization. Regardless of the composites exhibited lower tensile strength than pristine polymer, the adequate amount (0.17 weight ratio) of HAp in the composite (0.17-HP) shows tensile strength, which might be comparable to natural femur bone of females with the age of 50–70 years having stress value of 30 MPa [35]. Moreover, the morphological study from cross-sectional SEM images (Fig. 3) of composite xerogels showed the rough morphology that will be important for strong attachment with natural bone that will enhance efficient flow of nutrients through it during bone regeneration process [24], whereas 0-HP without HAp displayed the smoother cross-section.

Moreover, 3D structures of hydrogels (Fig. 4(inset)) were designed from 0-HP and 0.17-HP pre-polymer composite solutions. The compression stress test (Fig. 4a) also revealed that while 0-HP hydrogel exhibited the compression stress of 3.7 MPa, the composite (0.17-HP) showed 2.0 MPa (Fig. 4b). The effect of HAp on compression stress was consistent with that on tensile stress for thin film-like structures described above. The printed composite hydrogel product (0.17-HP) did not break apart even after application of 500 N load but the deformed shape was rather restored after 8.0 mm/mm strain, revealing the elastic nature of wet hybrid gels.

Uniform distribution of HAp was not observed in entire structure of 0.17-HP hydrogel but HAp was condensed in the bottom, different from a homogeneous transparent hydrogel of 0-HP. However, when carboxylmethylcelluose (CMC) as a dispersant was added in a 0.17-HP pre-polymer composite solution, a stable dispersion was obtained and a uniformly HAp-dispersed hydrogel was achieved (see Fig. 4(inset)). The interaction between anionic portion of CMC and ionic surface of HAp particles helps to disperse HAp in an aqueous medium of HP pre-polymer composite with

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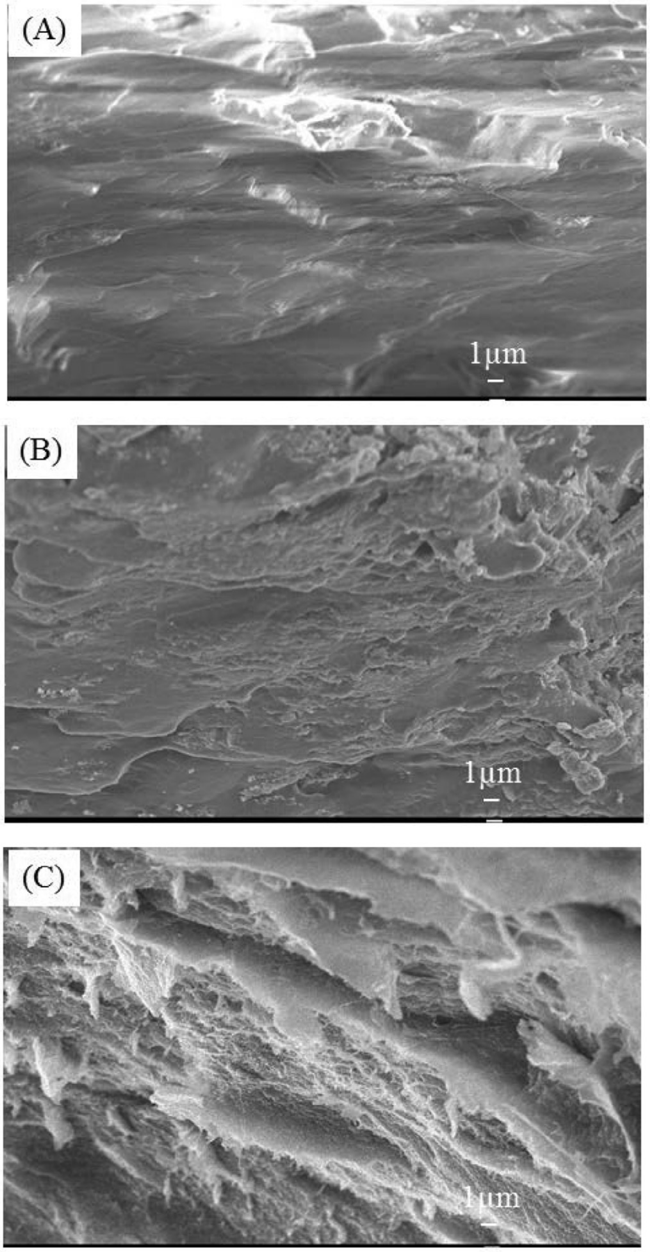

Fig. 3. Cross-section SEM images of xerogels (A) 0-HP, (B) 0.17-HP and (C) 0.5-HA.

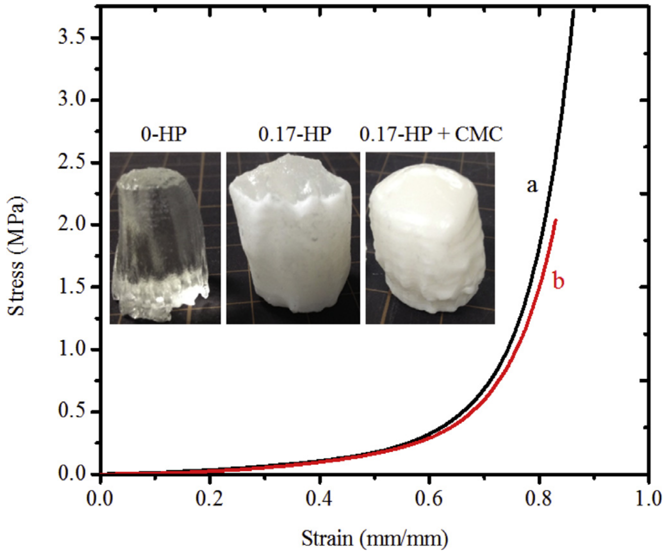

Fig. 4. Compression stress data of as-prepared 3D printed hydrogels from (a) 0-HP and (b) 0.17-HP. Inset photograph images are for as-prepared hydrogels from 0-HP, 0.17-HP and 0.17-HP with CMC.

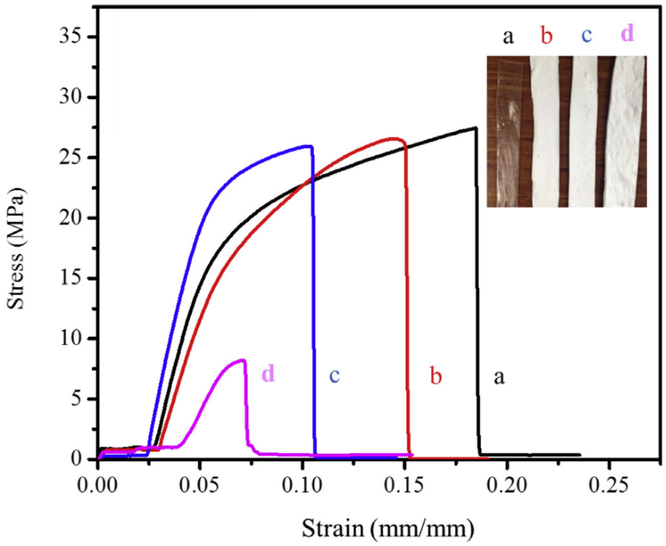

Fig. 5. Tensile stress data of HAp–agarose composite xerogels; (a) 0-HA, (b) 0.5-HA, (c) 1.0-HA and (d) 2.5-HA. The inset photographs are for corresponding xerogels.

added CMC [36]. As a result, a 3D networked, strong and elastic hydrogel was fabricated from a HAp/DMAAm/CMC (0.17:1:0.1 weight ratio) composites. Hence, this technique is much easier to develop osteon-like structures that are usually prepared by assembling sequentially synthesized rings obtained from photo-induced crosslinking by using multiply sized photomasks [23].

3.2. HAp–Agarose composites and their comparison with HAp–PDMAAm composites

When agarose is served as a matrix of HAp, the dipole–dipole interaction between hydroxyl functionality of the matrix and HAp surface enables to produce a homogeneous composite with a considerable mechanical strength for practical application. As the tensile stress data (Fig. 5) indicated that the 0.5-HA xerogel has exhibited the breaking stress of 27 MPa with elongation of about 1.5 mm/mm. However, weaker mechanical strength was observed in case of 2.5-HA. This result is attributed to the presence of excess amount of HAp that may cause insufficient gluing by agarose in the entire composite network. The achieved comparable tensile strengths of the prepared composite xerogel is considered as an advantage of agarose to be a promising candidate toward tissue regeneration treatment of damaged natural bones such as femur bones of females with the age of 50–70 years [35].

Regardless of the achieved tensile strengths exhibited by both composites from different binder, there was major difference between two polymer binders that was analyzed from their respective stress-strain data, that is, the observed shape difference of the stress-strain curves for PDMAAm and agarose composites indicated that the two composites have exhibited different mechanical characteristics *i.e.* the former showed elastic property until the final breaking stress point, whereas the agarose composite exhibited additional yield stress curve because of internal cracking before the material breaks up. This indicates that agarose might be a more

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Table 1
Summary of data from mechanical strength measurements.

		Hydrogel		Xerogel	
Composite	Sample	Tensile stress (MPa)	Strain (mm/mm)	Tensile stress (MPa)	Strain (mm/mm)
HAp–PDMAAm	0-HP	0.07	3.00	33.8	0.07
	0.17-HP	0.40	3.69	30.2	0.03
	0.5-HP	0.61	3.95	19.6	0.02
HAp–Agarose	0-HA	–	–	27.6	0.18
	0.5-HA	–	–	26.2	0.15
	1.0-HA	–	–	25.7	0.10
	2.5-HA	–	–	8.1	0.07

preferable binder than PDMAAm to prepare HAp composite. All the tensile strength data is presented in Table 1.

4. Conclusions

Two types of polymer matrices, namely PDMAAm and agarose, were employed for the preparation of HAp–polymer composite gels. For the first case, hydrogel network was synthesized through photo-polymerization of DMAAm monomer in the presence of HAp as a filler by using a stereolithographic 3D printer, and the desired bone structure was produced based on computer-assisted 3D printing. The result shows that a bone material having the desired shape and structure can be successfully printed without using any mold. Unlike HAp–PDMAAm composite, a mold was used to prepare the desired film of a composite xerogels by means of HAp–agarose composite. Although HAp–agarose composite has exhibited better mechanical strength than the HAp–PDMAAm composite, an easy, applicable and promising on-demand 3D printing should be successful to fabricate bone regeneration materials from HAp–polymer composite.

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