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Letter

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Injectable Materials with Magnetically Controlled Anisotropic Porosity

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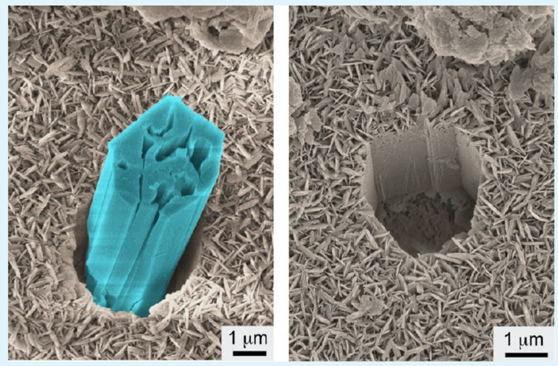
Supporting Information

ABSTRACT: We propose a method to create aligned porosity in injectable materials by using magnetically responsive microrods as pore forming sacrificial templates. Rod alignment occurs through the application of an external magnetic field after injecting the material into the desired end location. Removal of the sacrificial templates through dissolution or resorption generates porosity in deliberately tuned orientations after injection, offering a powerful method to design the porous architecture of injectable materials.



KEYWORDS: *macroporous materials, magnetic alignment, anisotropy, cement, sacrificial template*

Anisotropic porous materials are widely used as filters, heat exchangers, bioscaffolds, and catalytic supports.[1−5] Oriented porosity can be created via infiltration of natural or synthetic anisotropic sacrificial templates,[5−9] unidirectional solidification of suspensions or melts,[10−13] unidirectional gas generation,[14] ionotropic gelation,[15] extrusion,[16] anodic oxidation,[16] metal-assisted etching processes,[17] or rapid prototyping.[18,19] Despite the broad variety of microstructures developed,[5] these methods are not applicable to injectable materials because of the lack of tools to control their microstructure after injection into the desired end location. Anisotropic sacrificial templates for example do not lead to deliberately oriented porosity in such materials because their alignment is difficult to control under the complex shear forces developed during injection. Techniques that would allow for the creation of deliberately oriented pores in systems that are injected or cast into complex shapes would open new possibilities in several applications. Injectable cements for bone regeneration for instance could have their pores aligned with the bone's main loading axis to accelerate cell in-growth and osseointegration while minimizing the deleterious effect of porosity on the mechanical stability.[20−22] Also, aligned pores could be incorporated in refractory linings to provide microstructural openings that accelerate their drying process and thus avoid explosive spalling with minimum added porosity.[23,24]

In this letter, we report a method to create oriented porosity in injectable materials by using magnetic fields to align magnetically responsive sacrificial templates after the material has been placed into a specific location. Pores are formed upon removal of the sacrificial templates, as schematically shown in Figure 1. The formation of oriented porosity using this approach requires the preparation of magnetically responsive sacrificial templates, the alignment of such templates using magnetic fields, the consolidation of the surrounding continuous phase after injection/shaping, and the eventual removal of the sacrificial template. Here we present possible routes to fulfill these requirements using magnetically orientable calcium sulfate rods or chained droplets/microparticles as examples of anisotropic sacrificial templates and calcium aluminate and calcium phosphate cements as a model injectable materials.

To make nonmagnetic calcium sulfate rods respond to magnetic fields, we coat the surface of the rods with superparamagnetic iron oxide particles (SPIONs).[25] The magnetic field required for orientational control is minimized by choosing a synthetic procedure that typically leads to calcium sulfate rods with length in the order of tens of micrometers. Rods of this size and density exhibit an ultrahigh magnetic response (UHMR), because they are too large to be significantly affected by Brownian motion while being too small to be dominated by gravity.[25] Following this design rule for obtaining UHMR particles, sacrificial rods were synthesized by heating calcium sulfate dihydrate particles (Sigma, Switzerland) in a 40 wt % $CaCl_2$ aqueous solution at 105 °C for 30 min. The resulting precipitate was washed with boiling water and with acetone using a Büchner filter, following the procedure described by Wang et al.[26] Rods with length between 10 and 70 μm and average aspect ratio of 10.6 were obtained using this synthetic route. Larger calcium sulfate rods with lengths up to

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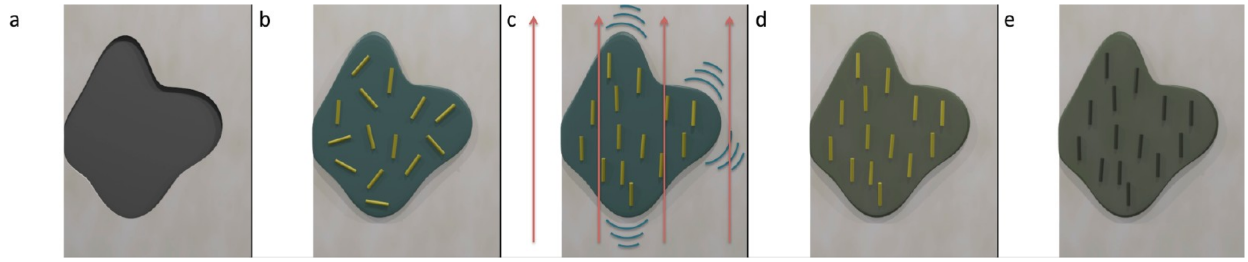

Figure 1. Schematics illustrating the method proposed for the creation of anisotropic pores in injectable/castable materials. (a, b) Material loaded with magnetically responsive, sacrificial templates is injected into a cavity of arbitrary shape. (c) The anisotropic templates are aligned in any desired direction by applying an external magnetic field combined with mechanical vibration. (d, e) The aligned sacrificial templates are dissolved away or resorbed to generate oriented porosity.

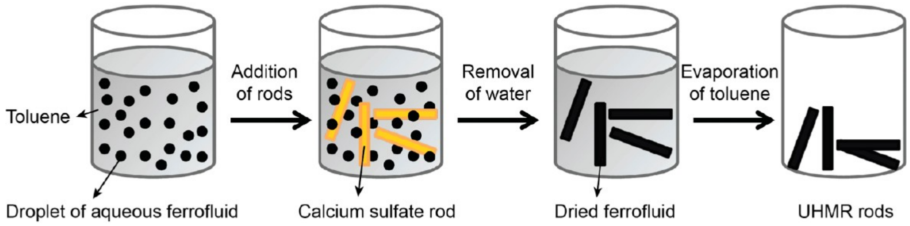

Figure 2. Schematics showing one of the procedures used to coat the calcium sulfate rods with superparamagnetic iron oxide nanoparticles.

500 μm were also synthesized to evaluate the versatility of the proposed method (see synthetic procedure in the Supporting Information).

Coating of the calcium sulfate rods with SPIONs was accomplished using one of two possible approaches. In one method, 10 μL of cationic aqueous ferrofluid were added to 4 mL of an aqueous solution containing 20 mg of calcium sulfate rods and saturated with calcium sulfate ions to avoid dissolution of the rods. The pH of 10 of the resulting suspension leads to opposite charges on the surface of the calcium sulfate rods and the iron oxide nanoparticles. This leads to the electrostatic adsorption of the SPIONs on the surface of the microrods, as described in our previous studies.[25] In an alternative method, rods were added to an emulsion consisting of ferrofluid aqueous droplets in a toluene continuous phase, as schematically depicted in Figure 2. In this procedure, 100 μL of cationic aqueous ferrofluid (EMG605, Ferrotec, Germany) were first emulsified in 10 mL of toluene (≥99.7%, Fluka Analytics, Switzerland) through vigorous stirring. One g of calcium sulfate rods was then added to the emulsion and the mixture was left stirring for 10 min to allow for the adsorption of the ferrofluid droplets on the rods. Because of the hydrophilic nature of the calcium sulfate surface, the aqueous droplets containing SPIONs readily adsorbed on the surface of the rods. Water from the droplets was then gradually removed by diffusion due to its slight solubility in the continuous toluene phase. UHMR calcium sulfate rods were finally obtained by completely evaporating the toluene at 90 °C.

The magnetic response of the obtained calcium sulfate rods was verified by suspending the sacrificial particles in an aqueous solution and imposing a magnetic field using a solenoid with computer-controlled field strength. An aqueous solution saturated with calcium sulfate ions was used to prevent dissolution of the suspended rods. Figure 3a−c shows that the rods could be easily aligned at deliberate orientations using low magnetic field strengths on the order of only 1 milliTesla.

The alignment control enabled by the UHMR calcium sulfate rods was exploited to generate injectable anisotropic porous

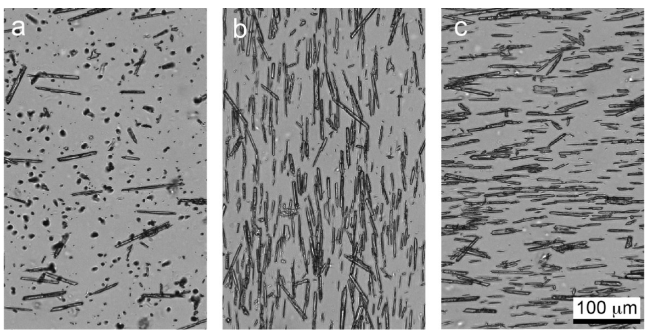

Figure 3. UHMR calcium sulfate rods suspended in a saturated aqueous solution in the presence of (a) out-of-plane and (b, c) in-plane fields in two different directions.

materials. For that purpose, we first investigate a dimethacrylate-based resin as the continuous phase to enable easy visualization of the enclosed sacrificial templates. The dimethacrylate monomer was combined with a two component photoinitiator to allow for consolidation upon UV-initiated polymerization. Typically, 253 mg of UHMR calcium sulfate rods were blended into a mixture consisting of 2 mL of triethylene glycol dimethacrylate (Aldrich, Switzerland) with 10.2 mg of camphorquinone (97%, Aldrich, Switzerland) and 11.6 mg of ethyl 4-dimethylaminobenzoate (99+ %, Aldrich, Switzerland) as photoinitiators. Samples of cylindrical shape were obtained by injecting the suspension into a polymer mold, followed by the removal of entrapped air under vacuum for 15 min and exposure to a magnetic field. A solenoid, which exhibits a low gradient in magnetic field strength, was chosen to prevent concentration of the rods near the magnetic source. Polymerization was performed using a blue light source (Bluephase 20i, Ivoclar Vivadent) at maximum intensity for 2 min. Microscopic analysis of a fractured surface of the acrylate specimens (Figure 4a,d) showed that the UHMR calcium sulfate rods were successfully oriented in the direction of the applied magnetic field, confirming that the alignment in the

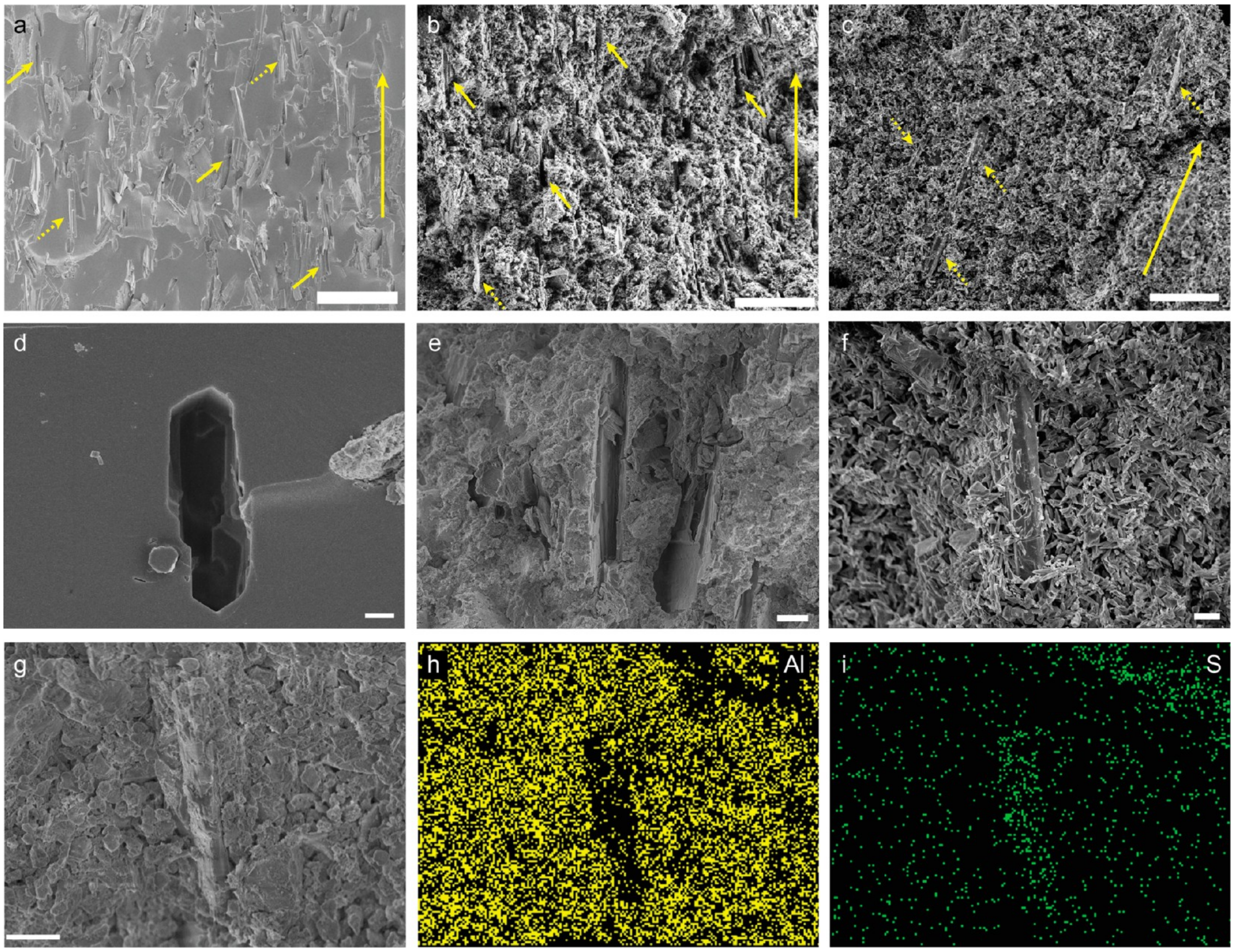

Figure 4. (a−c) Fracture surfaces of consolidated specimens containing UHMR calcium sulfate rods that were aligned under an external magnetic field in (a) a triethylene glycol dimethacrylate resin, (b) an injectable calcium aluminate cement paste, and (c) an injectable calcium phosphate cement. The fracture surfaces were prepared before removal of the templating rods and correspond to a cross-section of the sample parallel to the alignment direction. The alignment direction is indicated by the big yellow arrows. Some of the calcium sulfate rods were detached from the surface during fracture and appear as aligned anisotropic pores. The small yellow arrows indicate some of the aligned rods (dashed arrows) and pores (full arrows). (d−f) Detailed view of a calcium sulfate rod or a pore generated after removal of the calcium sulfate rod within the (d) methacrylate, (e) calcium aluminate and (f) calcium phosphate matrices. (h,i) EDX mapping of (h) Al and (i) S elements in a region of the fracture surface containing (g) an aligned calcium sulfate rod in the calcium aluminate matrix. Scale bars: (a, b) 100, (c) 20, (d) 2, (f) 3, and (e, g) 10 μm.

fluid state can be effectively preserved during consolidation of the continuous phase.

Creating an injectable material with anisotropic porosity requires not only a curable matrix containing magnetically responsive sacrificial templates but also a matrix that is sufficiently fluid to enable alignment before consolidation takes place and permeable enough to allow for dissolution of the template after alignment and consolidation. Suspensions of calcium aluminate cement in water were used as first example of an injectable system that exhibits appropriate rheological properties in the fluid state and leads to a water-permeable matrix after setting. Specimens were prepared by first mixing UHMR calcium sulfate rods with calcium aluminate cement powder in the dry state. A predefined amount of dispersing agent and $CaSO_4$-saturated water was added to the dry mixture to obtain a moldable cement paste that can be used to fill defects of any kind and shape. In a typical formulation, 121 mg of UHMR rods were mixed with 1.57 g of cement (CA270, Almatis, Germany), 500 mg of water saturated with $CaSO_4$, and 15.7 mg of poly(acrylic acid) sodium salt as dispersant (M_w 2100 g/mol, Aldrich, Switzerland). The $CaSO_4$−saturated aqueous solution was prepared by adding calcium sulfate powder to ultrapure water beyond its solubility limit. 31.4 mg of citric acid monohydrate (Merck, Switzerland) was also added to the formulation to retard the cement setting reaction.

The resulting calcium aluminate cement paste exhibited a finite yield stress and a strong shear thinning behavior within the first minutes after mixing (Figure 5a). Thus, alignment of the calcium sulfate rods in this system required the application of mechanical vibration to fluidize the paste during its exposure to the external magnetic field. In addition to the shear-thinning effect, mechanical vibration also provides the rods with enough kinetic energy to reach their most energetically favorable configuration.

Cylindrical specimens of calcium aluminate cement containing 5 vol% of calcium sulfate rods aligned parallel to the cylinder axis were prepared by injecting the cement pastes into a polymer mold and placing the mold on top of a regular vibrating table (Fritsch analysette 03.502, Fritsch, Switzerland) whereas a magnetic field in the range 7−50 milliTesla was applied using a hand-held magnet.[27] The vibration and the magnetic field were applied for a total of 10 min, after which

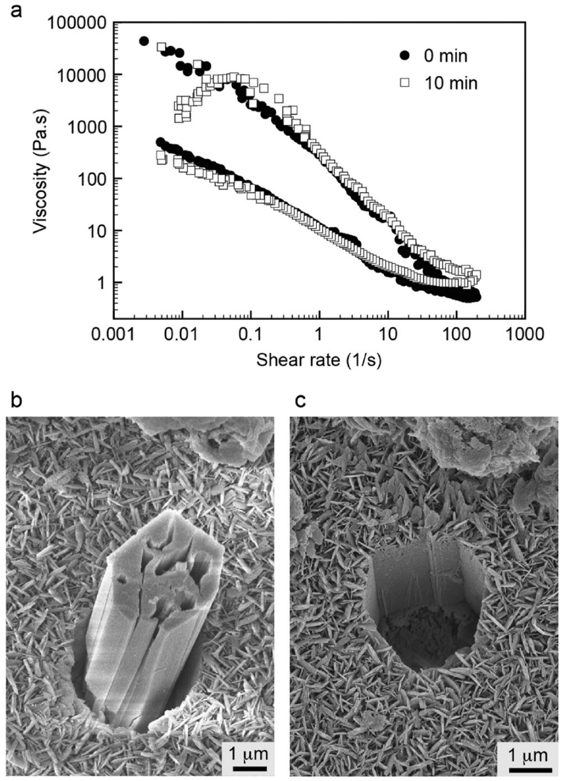

Figure 5. (a) Rheological behavior of the calcium aluminate cement paste measured immediately (0 min) and 10 min after mixing. (b, c) Dissolution of the calcium sulfate rods from a calcium aluminate cement matrix: (a) undissolved rod and (b) pore generated after removal of the rod template.

the samples were placed in a climate chamber at 50 °C and 95% relative humidity to allow for curing of the cement for 24 h. The cylinders had diameter and length of 4 and 8 mm, respectively. Fracture surfaces of the obtained samples show that this procedure leads to good alignment of the sacrificial rods with the applied magnetic field (Figure 4b,e,g–i). Although the low contrast in electron density between the two inorganic phases makes the visualization of individual rods difficult, a clear vertically aligned texture is evident in Figure 4b.

The possibility of removing the aligned sacrificial rods by permeating water through the consolidated cement phase was evaluated by immersing cured specimens in ultrapure water for at least 72 h. Because of the high microporosity and water permeability of cured cement, the water-soluble calcium sulfate rods could indeed be dissolved from the sample without damaging the surrounding cement structure. The SEM images of Figure 5 reveal the effective removal of the rods following this simple procedure. Complete dissolution was also confirmed by measuring the local concentration of sulfur in the sample, which was found to be low within the aligned macropores. Upon removal of the template, the microstructure of the injected material exhibited macropores well aligned in the direction of the magnetic field applied during casting.

The choice of the sacrificial template material and the continuous phase depends on the specific application. Because of its high solubility in water and fast resorbability in the human body,[28] calcium sulfate would be an interesting template to be used in injectable scaffolds for bone tissue regeneration. In combination with a slowly resorbable calcium phosphate cement as continuous matrix, the calcium sulfate rods would be resorbed at a faster rate by the host tissue[28] to enable rapid in-growth of new bone within the calcium phosphate matrix. Because the calcium phosphate cement is also resorbable, bone in-growth would be facilitated even in cases where the aligned templating rods do not form a percolating network throughout the cement matrix. This strategy could lead to a fully resorbable injectable material that facilitates tissue in-growth with minimum adverse effect to the mechanical properties.

To evaluate the feasibility of creating oriented porosity in a slowly resorbable injectable material like calcium phosphate cement, we incorporated magnetically responsive calcium sulfate rods to a two-component calcium phosphate system and exposed the resulting paste to a magnetic field of approximately 100 milliTesla combined with mechanical vibration (see details in the Supporting Information). The microstructure of the consolidated specimen revealed an effective alignment of the sacrificial rods within the calcium phosphate matrix, as indicated by the fracture surfaces shown in Figure 4c, f. Although an iron oxide concentration of 1 vol% (with respect to the rod volume) was used in this experiment, the proposed method has been shown to be applicable also with iron oxide contents as low as 0.01 vol %.[25] Thus, the amount of iron oxide required for rod alignment can potentially be lowered to levels 6-fold below the dosage of 175 μg Fe/mL approved by regulatory agencies for magnetic resonance imaging of organs and tissues in the abdomen.[29] According to our previous study,[25] magnetic fields on the order of 0.1 T together with mechanical vibration would be sufficient to align anisotropic microrods containing this minimum amount of iron oxide particles. In practice, magnetic fields in the range of 0.5–3 T can be supplied by state-of-the-art magnetic resonance imaging equipment, whereas earlier reports also showed that the required mechanical vibration has already been suggested as a means to aid the insertion of hip joint replacements in surgical procedures.[30,31]

Since the calcium sulfate rods prepared in this work might be too small to generate the porosity required for cell in-growth, one can potentially also use droplets as sacrificial templates that can be chained and aligned in a magnetic field to create anisotropic porosity at length scales covering a much broader size range, from 10 μm to 1 mm.[5] To illustrate the potential use of droplets to obtain anisotropic features at larger length scales, we prepared magnetically responsive droplets by emulsifying an oil-based ferrofluid (Supermagnete, Switzerland) in the monomer triethylene glycol dimethacrylate through simple hand agitation. Indeed, the resulting droplets form fully aligned chains upon application of an external magnetic field, as shown in Figure 6. Because of the more pronounced effect of gravity in these larger systems, it is important to match the density of the droplet with that of the continuous phase to avoid creaming or sedimentation. In the example shown in Figure 6 this was accomplished by mixing 89% of the as-received ferrofluid with 11% of hexadecane. In injectable calcium phosphate pastes, density matching could be achieved by loading the magnetized droplets shown here with small calcium sulfate particles. Alternatively, such droplets can be converted into magnetically controllable dense or hollow calcium sulfate/iron oxide microparticles by removing their liquid phase through the continuous phase of the emulsion, as described in one of our previous studies.[32] This route was used here to prepare calcium sulfate/iron oxide microparticles, which could be effectively aligned when exposed to magnetic fields in the range of 10–20 milliTesla (Figures 6b, c). In applications where polydispersity

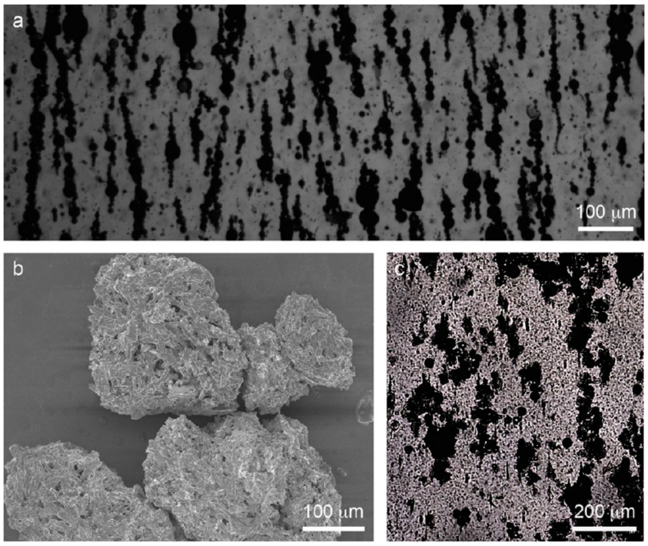

Figure 6. Alignment of droplets and templating microparticles under external magnetic fields. (a) Magnetically driven chaining and alignment of droplets of oil ferrofluid in triethylene glycol dimethacrylate. (b) Calcium sulfate/iron oxide microparticles obtained by drying water droplets loaded with gypsum and iron oxide particles. (c) Alignment of the calcium sulfate/iron oxide microparticles (in black) under an external magnetic field in the range of 10−20 milliTesla.

is undesired, monodisperse magnetically responsive droplets can also be produced by emulsifying the above formulation using a microfluidic device.[33]

The effective alignment of calcium sulfate rods with diameter of 5−20 μm and length of 10−500 μm as well as ferrofluid droplets and calcium sulfate microparticles with sizes up to hundreds of micrometers shows that the method is applicable to sacrificial templates spanning over a broad size range. The flexibility of the approach used here to magnetize the templating particles and the minimum amounts of iron oxide nanoparticles needed to achieve magnetic response makes this a versatile route that can be applied to a variety of different chemistries.

In summary, we demonstrate a method to create injectable materials with anisotropic porosity by using magnetically responsive sacrificial templates, whose orientation can be controlled with external magnetic fields after injecting the material into its end location. Deliberately aligned pores are created by removing the templating particles in a dissolving or resorbing medium. Using calcium sulfate rods or microparticles as templating particles soluble in water and calcium aluminate or calcium phosphate cements as injectable materials, we show the successful alignment of anisotropic templates using magnetic fields in the range 7−100 milliTesla. The application of mechanical vibration was found to be important to enable shear thinning of the cement paste and to provide enough kinetic energy to the rods to align with the externally applied field. This versatile approach offers a unique way to create injectable materials with anisotropic porous microstructures of potential interest in tissue regeneration and structural applications.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental procedure describing the preparation of large calcium sulfate rods, magnetically responsive calcium sulfate microparticles, injectable material based on calcium phosphate cement, cement rheology, and bulk materials with magnetically aligned sacrificial templates after injection. This material is available free of charge via the Internet at http://pubs.acs.org/.

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) Scheffler, M.; Colombo, P., *Cellular Ceramics: Structure, Manufacturing, Properties and Applications*; Wiley-VCH: Weinheim, Germany, 2005; p 645.
(2) Fu, Q. A.; Saiz, E.; Tomsia, A. P. *Adv. Funct. Mater.* **2011**, *21*, 1058−1063.
(3) Greil, P. *J. Eur. Ceram. Soc.* **2001**, *21*, 105−118.
(4) Soon, Y. M.; Shin, K. H.; Koh, Y. H.; Lee, J. H.; Kim, H. E. *Mater. Lett.* **2009**, *63*, 1548−1550.
(5) Studart, A. R.; Gonzenbach, U. T.; Tervoort, E.; Gauckler, L. J. *J. Am. Ceram. Soc.* **2006**, *89*, 1771−1789.
(6) Greil, P.; Lifka, T.; Kaindl, A. *J. Eur. Ceram. Soc.* **1998**, *18*, 1961−1973.
(7) Sieber, H.; Hoffmann, C.; Kaindl, A.; Greil, P. *Adv. Eng. Mater.* **2000**, *2*, 105−109.
(8) Richman, E. K.; Brezesinski, T.; Tolbert, S. H. *Nat. Mater.* **2008**, *7*, 712−717.
(9) Piazza, D.; Capiani, C.; Galassi, C. *J. Eur. Ceram. Soc.* **2005**, *25*, 3075−3078.
(10) Deville, S.; Saiz, E.; Nalla, R. K.; Tomsia, A. P. *Science* **2006**, *311*, 515−518.
(11) Fukasawa, T.; Deng, Z. Y.; Ando, M.; Ohji, T.; Goto, Y. *J. Mater. Sci.* **2001**, *36*, 2523−2527.
(12) Hyun, S. K.; Murakami, K.; Nakajima, H. *Mater. Sci. Eng., A* **2001**, *299*, 241−248.
(13) Davidenko, N.; Gibb, T.; Schuster, C.; Best, S. M.; Campbell, J. J.; Watson, C. J.; Cameron, R. E. *Acta Biomater.* **2012**, *8*, 667−676.
(14) Ding, X. J.; Zhang, J. Z.; Wang, R. D.; Feng, C. D. *J. Eur. Ceram. Soc.* **2002**, *22*, 411−414.
(15) Dittrich, R.; Tomandl, G.; Despang, F.; Bernhardt, A.; Hanke, T.; Pompe, W.; Gelinsky, M. *J. Am. Ceram. Soc.* **2007**, *90*, 1703−1708.
(16) Okada, K.; Isobe, T.; Katsumata, K.; Kameshima, Y.; Nakajima, A.; MacKenzie, K. J. D. *Sci. Technol. Adv. Mater.* **2011**, 12.
(17) Chartier, C.; Bastide, S.; Levy-Clement, C. *Electrochim. Acta* **2008**, *53*, 5509−5516.
(18) Hutmacher, D. W.; Sittinger, M.; Risbud, M. V. *Trends Biotechnol.* **2004**, *22*, 354−362.
(19) Zein, I.; Hutmacher, D. W.; Tan, K. C.; Teoh, S. H. *Biomaterials* **2002**, *23*, 1169−1185.
(20) Jones, J. R.; Hench, L. L. *Curr. Opin. Solid State Mater. Sci.* **2003**, *7*, 301−307.

dx.doi.org/10.1021/am301500z | *ACS Appl. Mater. Interfaces* 2012, 4, 5086−5091

(21) Schmitz, J. P.; Hollinger, J. O.; Milam, S. B. *J. Oral Maxillofac. Surg.* **1999**, *57*, 1122−1126.
(22) Bohner, M.; Baroud, G. *Biomaterials* **2005**, *26*, 1553−1563.
(23) Innocentini, M. D. M.; Ribeiro, C.; Salomao, R.; Pandolfelli, V. C.; Bittencourt, L. R. M. *J. Am. Ceram. Soc.* **2002**, *85*, 2110−2112.
(24) Salomao, R.; Pandolfelli, V. C. *Int. J. Appl. Ceram. Technol.* **2007**, *4*, 496−502.
(25) Erb, R. M.; Libanori, R.; Rothfuchs, N.; Studart, A. R. *Science* **2012**, *335*, 199−204.
(26) Wang, P.; Lee, E. J.; Park, C. S.; Yoon, B. H.; Shin, D. S.; Kim, H. E.; Koh, Y. H.; Park, S. H. *J. Am. Ceram. Soc.* **2008**, *91*, 2039−2042.
(27) Erb, R. M.; Segmehl, J.; Charilaou, M.; Löffler, J. F.; Studart, A. R. *Soft Matter* **2012**, DOI: 10.1039/C2SM25650A.
(28) Thomas, M. V.; Puleo, D. A. *J. Biomed. Mater. Res., Part B: Appl. Biomater* **2009**, *88B*, 597−610.
(29) U.S. Food and Drug Administration, http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/EnforcementActivitiesbyFDA/WarningLettersandNoticeofViolationLetterstoPharmaceuticalCompanies/UCM231350.pdf. (accessed Sept 13 2012).
(30) Thomas, A. M. C.; Dunn, J. W.; Luo, D. Z. *Lancet* **1988**, *1*, 116−117.
(31) Drew, T.; Talih, S.; Thaker, E.; Henderson, S. *J. Bone Joint Surg. Br.* **2009**, *91-B no. supp II*, 294.
(32) Sander, J. S.; Studart, A. R. *Langmuir* **2011**, *27*, 3301−3307.
(33) Sander, J. S.; Erb, R. M.; Denier, C.; Studart, A. R. *Adv. Mater.* **2012**, *24*, 2582−2587.