GOLD NANOPARTICLE-BASED HYDROGEL CONTRAST AGENT PARTICLES WITH TUNABLE ELASTICITY FOR X-RAY COMPUTED TOMOGRAPHY IMAGING

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ABSTRACT

This paper reports a novel method of fabricating gold nanoparticle-based hydrogel microparticles for use as contrast agents for X-ray computed tomography (CT) imaging. In contradistinction to the current clinically available iodine-based CT contrast agents, as well as recently developed CT contrast agents including gold or tantalum oxide nanoparticles, the approach presented herein yields an engineering flexibility to the design of contrast agents. The capability to precisely fabricate particles of varying shape, size, and elasticity offers myriad advantages for biomedical imaging and sensing applications, when compared to currently available agents.

KEYWORDS

Contrast agents, Computed tomography, Microfabrication, Gold nanoparticle

INTRODUCTION

Contrast agents are substances used to enhance the contrast of structures or fluids within the body. The use of these agents in X-ray computed tomography (CT) serves to potentiate and deliver the full potential of CT imaging for biomedical imaging. The CT contrast agents which are currently commercially available in the clinic are typically in the form of water soluble organic iodine compounds [1]. However, this class of contrast agents has many drawbacks, including the relatively short blood circulation time secondary to rapid renal excretion, the suboptimal attenuation of iodine in the range of X-ray energies appropriate for CT imaging, and the lack of specificity for any particular disease process. Recently, nanoparticles, including gold and tantalum oxide nanoparticles, have been developed to mitigate several of the limitations of iodinated contrast agents [2-4]. Fundamental limitations of gold nanoparticles (GNPs) include the significant cost considerations of gold nanoparticles for clinical imaging. In addition, the bottom-up approach to nanoparticle synthesis lacks the capability to precisely tune particle size and shape, both of which are critical determinants of *in vivo*, biological behavior.

This paper reports a novel method of fabricating GNP-based hydrogel microparticles for use as contrast agents for X-ray computed tomography (CT) imaging. By employing top-down fabrication, the approach presented herein yields an engineering flexibility to the design of contrast agents of precisely defined and tunable shape, size, and elasticity. In addition, the use of a nanoparticulate material as the X-ray attenuating payload addresses the potential limitations of particle stability identified with iodinated hydrogel particles [5].

EXPERIMENTS

Gold nanoparticles (GNPs) have many applications in chemical and biological systems, such as drug and gene delivery vehicles, thermal therapy, and sensing agents, among others [6]. Hydrogels have been widely used as a biocompatible, environmentally responsive material for myriad biomedical applications [7]. We sought to leverage the properties of GNPs and hydrogels to fabricate CT contrast agents. To this end, we employed a novel transparent film transfer technology to yield GNP-based hydrogel particles which affords precise control of particle size, shape, and elasticity, designed to meet the requirements of a next generation contrast agent, given the increasing realization of the effects of these particle properties on *in vivo* behavior [8].

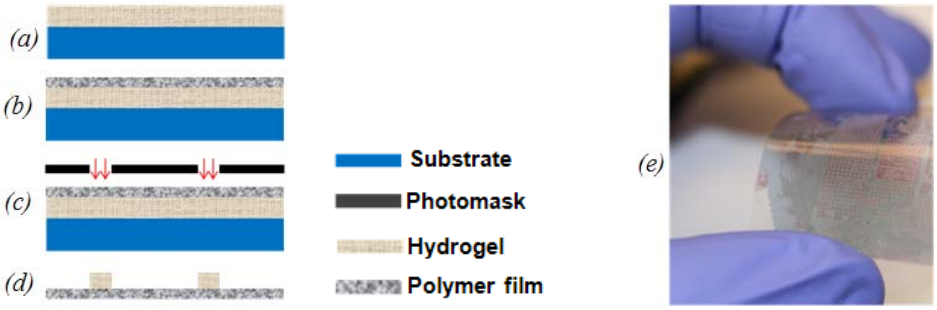

Figure 1: Microfabrication process flow for hydrogel particles: (a) drop-coating of hydrogel precursor on the wafer; (b) placement of transparent polymer film on the hydrogel layer; (c) photolithography through a photomask; (d) release of hydrogel layer from wafer; (e) photo showing microfabricated hydrogel patterns on flexible PET film.

The fabrication process is shown in Fig.1. Firstly, macromers comprised of poly(ethylene glycol) diacrylate (PEGDA) (average M_n 575, Aldrich) and a GNPs solution (Accurate™, Nanopartz Inc.) were drop-coated on silicon

wafers. These hydrogel presolutions were prepared in deionized water and also included 1.5% 2-hydroxy-2-methylpropiophenone as a photoinitiator. Subsequently, a transparent polymer film was placed on the hydrogel layer in order to serve as a supporting substrate for hydrogel particles. We selected the polyethylene terephthalate (PET) film as the transparent polymer given its adhesion with the hydrogel particles. Next, the macromers were exposed to UV light through a photomask to yield polymerization of the hydrogel. Finally, the PET film with the adherent hydrogel pattern was readily separated from silicon substrate.

Fig.2 demonstrates several nonspherical hydrogel particle arrays with different shapes and sizes fabricated using this simple method. A surgical blade was employed to mechanically peel away hydrogel particles from polyethylene terephthalate (PET) film and harvest them for subsequent use as shown in Fig.3.

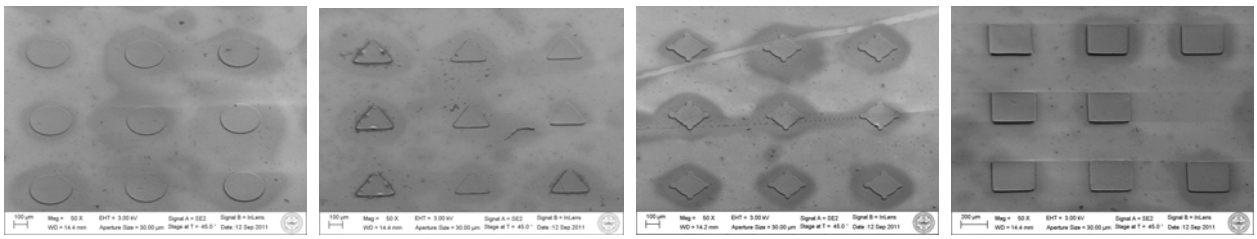

Figure 2. SEM of hydrogel particles on the PET film demonstrating variation in size and shape.

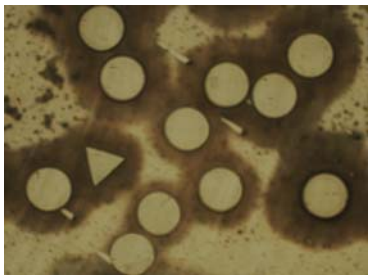

Figure 3. Optical microscopy image showing circular and triangular hydrogel particles peeled away from the PET film.

RESULTS AND DISCUSSION

The nanoindentation method from contact mechanics was used to measure the elasticity of hydrogel sample. Herein, we employed a quasistatic punch testing with the cylindrical flat tip to obtain the load-deflection relationship curve and elasticity of hydrogel samples as shown in Fig.4. The elastic module of hydrogel particle can be readily adjusted from 0.1MPa to 1.7MPa by changing the PEGDA volume concentration in the hydrogel precursor. This tunability yields an additional degree of freedom over contrast agent design and is an important feature in optimizing contrast agent design.

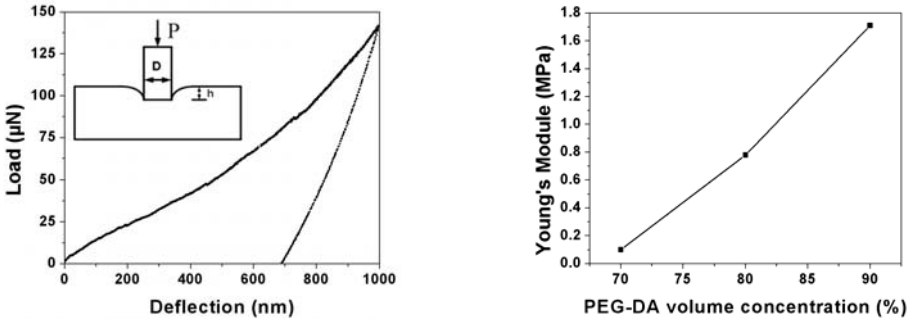

Figure 4: (a) Quasistatic load-deflection relationship in nanoindentation; (b) Elastic module of hydrogel with different PEDGA volume concentrations.

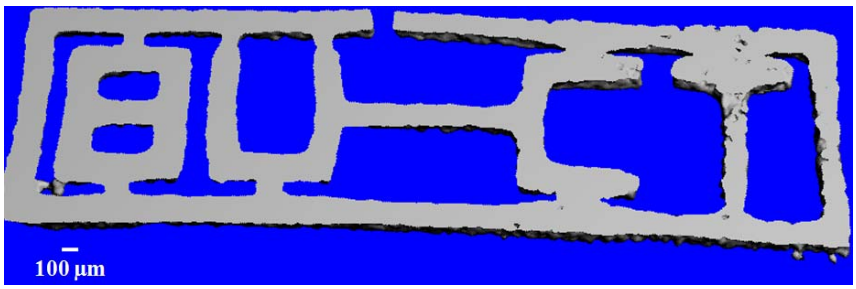

Figure 5. 3D CT image demonstrating X-ray attenuation of the GNPs-based hydrogel structures.

The GNP-based hydrogel sample with 10mg/mL GNPs concentration was tested using 70 kVp and 113 μA of X-ray energy in a microCT instrument. The CT image of a GNPs-based hydrogel microstructure is shown in Fig.5 (structured in the shape of letters "BU-CT"), demonstrating very good X-ray attenuation of the fabricated hydrogel structures. Finally, we used a clinical CT scanner to evaluate the rate of leakage of the GNPs from a hydrogel immersed in the water. Compared with iodinated hydrogel particles [5], it can be seen that there is no detectable leakage by 32 hours based on Fig.6, supporting its further development as a long circulating contrast agent.

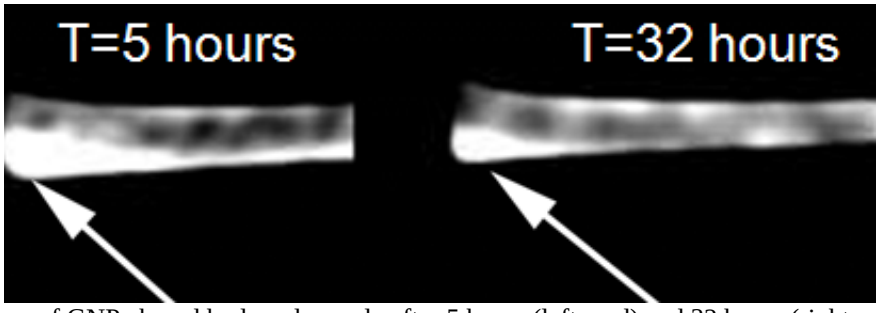

Figure 6. CT image of GNPs-based hydrogel sample after 5 hours (leftward) and 32 hours (rightward) immersion in water. The white arrows point to hydrogel sample, the attenuation of which remained stable throughout this time.

CONCLUSIONS

The CT contrast agent presented herein, to the best of our knowledge, represents the first top-down fabrication approach to next-generation CT contrast agent design employing a gold nanoparticle payload. The fabrication methodology presented herein allows for precise control over critical particle parameters, including size, shape and elasticity. This approach has the potential to significantly increase vascular circulation times, improve sensitivity and disease specificity for certain imaging applications such as cancer, afford multiplexing capability through the incorporation of materials beyond gold, and has the potential for functional imaging and sensing with the use of environmentally responsive hydrogel structures.

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