



Nanocomposite scaffold fabrication by incorporating gold nanoparticles into biodegradable polymer matrix: Synthesis, characterization, and photothermal effect



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ABSTRACT

Nanoparticle incorporation into scaffold materials is a valuable route to deliver various therapeutic agents, such as drug molecules or large biomolecules, proteins (e.g. DNA or RNA) into their targets. In particular, gold nanoparticles (Au NPs) with their low inherent toxicity, tunable stability and high surface area provide unique attributes facilitating new delivery strategies. A biodegradable, photocurable polymer resin, polypropylene fumarate (PPF) along with Au NPs were utilized to synthesize a hybrid nanocomposite resin, directly exploitable in stereolithography (SL) processes. To increase the particles' colloidal stability, the Au NP nanofillers were coated with polyvinyl pyrrolidone (PVP). The resulting resin was used to fabricate a new type of composite scaffold via mask projection excimer laser stereolithography. The thermal properties of the nanocomposite scaffolds were found to be sensitive to the concentration of NPs. The mechanical properties were augmented by the NPs up to 0.16 μM , though further increase in the concentration led to a gradual decrease. Au NP incorporation rendered the biopolymer scaffolds photosensitive, i.e. the presence of Au NPs enhanced the optical absorption of the scaffolds as well, leading to possible localized temperature rise when irradiated with 532 nm laser, known as the photothermal effect.

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1. Introduction

Inorganic–organic hybrid nanocomposites have attracted great attention since their discovery due to their wide variety of properties. Depending on the possible components, multiple applications have arisen, for instance, in OLED technology/flexible electronics [1,2] or medicine.

Regarding biological applications, as a polymeric matrix for such hybrid nanocomposites (NCs), research has focused on biodegradable polymers, mainly due to their flexible chemistry, environmentally friendly design and versatility within various fields, such as agriculture, packaging, or biomedical devices. Their impact on medicine has been particularly high for their capability to degrade without leaving any toxic residues behind, making them ideal for tissue engineering (TE) purposes [3–5]. These polymers are usually exploited for TE in the form of scaffolds, i.e., microenvironments capable of supporting tissue growth [6]. Such scaffolds, apart from providing a mimicking environment for cell growth, may also be used as drug delivery systems, where the speed-adjusting factor for the delivery is the polymer's long-lasting, and sometimes, tunable degradation process. Obviously,

for such process to be viable, the drug carriers need to be homogeneously dispersed inside the scaffold's material.

Easy synthesis, simple surface functionalization [7], biocompatibility, and suitable optical absorption make gold nanoparticles (Au NPs) ideal for drug delivery and other biomedical applications [8]. Several protocols have already been investigated for Au NP synthesis, including wet chemical [9,10] and photochemical methods [11], and laser ablation [12]. Since all of these protocols involve synthesis in aqueous media, the particles require surface modifications to be well dispersed in any organic medium directly compatible with any polymeric matrix. Polyvinyl pyrrolidone (PVP) is a good candidate for such purpose, since its interaction with Au NPs has already been thoroughly investigated leading to a stable colloidal of coated Au NPs in various organic solvents, e.g. butanol [13]. Furthermore, such PVP-coated Au NPs could still be suitable platforms for drug delivery after further functionalization by biomolecules with poor water solubility [14].

In this work, the chemically synthesized and PVP-capped Au NPs were homogeneously dispersed in diethyl fumarate (DEF), then mixed with a poly-propylene fumarate (PPF) liquid resin prior to the photocross-linking process conducted within a mask projected excimer stereolithography (MPExSL) system [15]. The dispersion of the NPs in DEF and PPF was monitored by UV–vis absorption and transmission electron microscopy imaging. We assume that the method used for the dispersion of the NPs inside the liquid resin could potentially be

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extended to other particles as well, such as carbon nanotubes or nanooxions, silver, or iron-oxide particles. It is also important to note that in principle all UV-curable materials (organically-modified ceramics (ORMOCERs) and acrylated bio-polymers, like collagen-based gelatin methacrylate (GelMA), poly(ethylene glycol) diacrylate (PEGDA), Methacrylated Glycol Chitosan (MGC)) can be used for 3D scaffold fabrication, however Au NP incorporation into those materials needs to be investigated in detail to achieve good homogeneity distributions.

The incorporation of NPs into the polymer had a considerable effect on the behavior of the fabricated hybrid nanocomposite scaffolds, such as increased stiffness, thermal stability, catalytic activity, and enhanced optical properties. 2D and 3D scaffolds were fabricated from the PPF:DEF-Au NP hybrid resin using different NP concentrations.

In this study, PPF:DEF scaffolds were thoroughly investigated as follows: the interaction between the Au NPs and the PPF was mapped by chemical and distribution concepts using Fourier-transmission infrared spectroscopy (FT-IR) and field emission scanning electron microscopy, respectively. The synergy of the various particle concentrations with the polymer and its impact on the overall physical properties of the scaffolds was evaluated by the variations in thermal and mechanical properties using thermogravimetric analysis (TGA) and nanoindentation.

The surface plasmon resonance (peak at around 520 nm) of spherical Au NP has already been used in photothermal therapies of surface type tumors by using visible cw [16] or pulsed lasers [17]. Such prompt photothermal behavior of the embedded Au NPs could be exploited within our fabricated constructs. This photothermal capability with the lengthy degradation process could make our PPF:DEF-Au NP composite scaffolds ideal for the localized target delivery during tissue regeneration as well as cancer treatment.

2. Materials and methods

2.1. Au NP synthesis and surface coating; preparation of PPF:DEF-Au NP nanocomposites

All chemicals were used as received unless otherwise stated. Au NPs (with a diameter of 13 ± 1 nm, 85%) were prepared by a standard citrate reduction protocol [18]. A solution of hydrogen tetrachloroaurate trihydrates ($\text{HAuCl}_4 \cdot 3\text{H}_2\text{O}$, Alfa Aesar 99.9% (metal base) Au 49% min) 1 mM was boiled, then 3 ml of 30 mM trisodium citrate (Sigma Aldrich) aqueous solution were injected under vigorous stirring for 20 min. After the solution was cooled down, the nanoparticles were separated by centrifugation. During the three centrifugation cycles, the supernatant was replaced by Milli-Q water of 18.2 M Ω resistance every time, resulting in NPs dispersion in water. The particles' concentration, optical absorption, and size were determined by inductively coupled plasma optical emission spectrometry (ICP-OES), spectrophotometry, and electron microscope, respectively.

90 mg of PVP (Sigma Aldrich, MW 10 KDa) were added to the Au NP dispersion. The final concentration of PVP was adjusted to be 3 mg/ml. The reaction solution was stirred overnight. Finally, the coated nanoparticles were collected and cleaned from excess PVP by three cycles of centrifugation with the supernatant exchanged with Milli-Q water (18.2 M Ω) each time. The coating process was repeated twice. In the end, the coated NPs were dispersed in ethanol prior to any further processing.

This ethanol colloidal of PVP-coated Au NPs was mixed to DEF (Aldrich) by means of sonication (30 min) and stirring (24 h). With the identified particle size, the final concentration of the Au NPs in the DEF was detected to be 18.4 μM by means of ICP-OES. Using the NP-embedded DEF, a series of PPF:DEF-Au NP nanocomposite resins were prepared for MPExSL: first the DEF-Au NP was mixed with pristine DEF and stirred for 1 h, then added to the PPF. The photoinitiator was added to this reaction mixture. For all PPF:DEF-Au NP nanocomposite resins, the percentage of BaPO and the total added amount of

DEF was 1% and 30%, respectively. The Au NPs themselves have been incorporated into the resin in different concentrations in order to map their effects on the fabricated scaffolds. The quantities of the nanocomposite components are described in Table 1.

2.2. Mask projection excimer laser stereolithography (MPExSL) and the resin

MPExSL is a stereolithography process developed in our laboratory [OMEX paper], relying on excimer laser irradiation of a liquid photocrosslinkable resin. The geometry of the fabricated scaffolds is defined by a set of interchangeable masks and various laser and resin parameters [15], e.g., the photoinitiator concentration [19,20], the number of pulses [19,20], or the pulse fluence [21].

PPF prepolymer was prepared and purified as previously mentioned [21]. The liquid resin itself is a blend of PPF and DEF with a weight ratio of 7:3. The PPF blending with DEF is necessary to decrease the viscosity for the smooth and faster fabrication process. One percent bis(acyl) phosphine oxide (BaPO) as a photoinitiator was added to the resin in all samples.

Following a previous work [19–21], the laser parameters have been adjusted to achieve a uniform layer thickness with the SL process. Any change in the resin absorption, and therefore the 308 nm laser penetration depth in the resin, is directly related to the increased nanoparticle concentration in the blend. Thus, it was compensated by increasing the number of pulses. Pulse fluence has been a constant 20 mJ/cm². 2D samples have been fabricated for spectroscopic characterizations, while 2-mm diameter, poreless, 25-layer thick, 3D blocks were built for the mechanical tests and the thermogravimetric analysis (TGA).

2.3. Characterization techniques

Fourier-Transformed Infrared spectroscopy measurements were performed by a Bruker Vertex 70v FT-IR instrument in transmission mode. The spectra were collected under vacuum in the range 500–4000 cm⁻¹ at a resolution of 4 cm⁻¹ using DTGS detector. Plasma optical emission spectrometry (ICP-OES) was conducted in a Thermo Fisher ICP-ICAP 6300 DUO scientific inductively coupled plasma optical emission spectrometer. Spectrophotometric analysis was carried out by a Varian Cary 6000i UV-vis-NIR spectrophotometer. For transmission electron microscope (TEM) imaging Jeol JEM 1011 operating at 100 kV was used. Stiffness measurements on the scaffolds were performed by means of nanoindentation. The indenter was a Micro Materials Ltd. NanoTest, using a Berkovich tip with a maximum load of 0.6 mN, a dwell time at maximum load of 30 s, loading and unloading periods of 30 s and 15 s, respectively. Young's modulus was acquired by using the Oliver and Pharr method. Thermogravimetric analysis (TGA) was conducted in a TGA Q500 from TA Instruments. The sample was placed in a platinum pan with an equilibrating step at 30 °C. The heating went to 800 °C with a 10 °C/min rate and the Nitrogen flow was 50 ml/min. High resolution field emission HRSEM (Jeol-JSM 7500 F) was used to characterize the cross-linked nanocomposites scaffolds. Heat detection for the photothermal effect was performed using a Fluke Ti300 Infrared Camera using a laser intensity of 1–20 mW/mm².

Table 1
Components of the PPF:DEF-Au NP composite resins.

Nanocomposite number	PPF %	DEF %	Vol. of Au NPs/DEF (ml)	Vol. of DEF (ml)	Conc. of Au NPs (μM)
1	70	30	0	3	0
2	70	30	0.03	2.97	0.0552
3	70	30	0.09	2.91	0.1656
4	70	30	0.21	2.79	0.3864
5	70	30	0.3	2.7	0.552
6	70	30	0.75	2.25	1.38
7	70	30	0	3	5.52

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