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Microwave-assisted fabrication of carbon nanotubes decorated polymeric nano-medical platforms for simultaneous drug delivery and magnetic resonance imaging†

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A facile microwave method to enable biopolymer particles to get functionalized by iron–enriched carbon nanotubes (CNT–Fe), serving as drug carriers and MRI agents. For example, multifunctional CNT–Fe coated poly(lactic-*co*-glycolic acid) (PLGA) (CNT–Fe–PLGA) particles (CFPP) are comprised of a PLGA core to carry cancer drugs, and CNT–Fe coating to provide a magnetic resonance (MR) signal. The process also gives the particles a unique brush-like, nanostructured surface morphology to enable a variety of biological and chemical activities.

Polymeric particle carriers, including micro and nanoparticles, possess considerable potential for the diagnosis and treatment of human diseases. Poly(lactic-*co*-glycolic acid) (PLGA) is one of the few polymers approved for human use.[1–4] Several different types of therapeutic agents can be encapsulated into PLGA particles for protected delivery; these include small molecule drugs, nucleic acids (siRNA), imaging agents, and nutrients.[5–10] There is great interest in developing particles that can deliver drug, and generate MR signal for imaging (MRI). MRI contrast agents such as super paramagnetic iron oxide (SPIO) and gadolinium(III) diethylenetriaminepentaacetic acid (Gd-DTPA) have been co-encapsulated with drugs in the PLGA matrix or coated on the surface of PLGA particles through covalent modification.[11–13] However, these methods have limitations; (i) it is difficult to develop a method that is optimal for encapsulating for multiple payloads, (ii) covalent surface modification is a multi-step synthesis conducted in aqueous solutions, the type of conditions which often lead to drug release from the particles, (iii) the low availability of functional groups on particle surfaces and the reaction yield of conjugation of MRI contrast agent to particles may negatively impact the particles in MR imaging.

Herein, we report on CNT decorated PLGA multifunctional carriers (CNT–Fe–PLGA particles) (CFPPs) for simultaneous drug delivery and MR imaging. These CFPPs were fabricated by catalyzing the growth of CNTs onto drug-loaded PLGA particles using short bursts of microwave. The approach makes use of conducting polymer (CP) and an organometallic precursor, endowing the particles with the ability of providing an MR signal. The microwave technology[14] induces very little damage or chemical alteration on the bio-substrates due to its ultrafast nature.

The synthetic procedure of CFPPs is represented in Fig. 1. Paclitaxel (PTX)-loaded PLGA particles were prepared by using an oil-in-water (O/W) emulsion and a subsequent solvent evaporation method.[15] Three steps are needed to grow CNTs on PTX-loaded PLGA particles using the microwave technology: (i) a layer of conducting polymer (CP) was *in situ* deposited on the surface of the PLGA particles during the polymerization reaction; (ii) the resultant CP coated particles were mixed well with ferrocene in solid state by a speed mixer at three thousand rpm; and (iii) upon microwave irradiation, the CP layer will absorb the microwave irradiation, and the temperature will rise very quickly to a level high enough to decompose ferrocene to iron nanoparticles and cyclopentadienyl groups. Iron nanoparticles will serve as the catalyst; and the carbon atoms pyrolyzed from cyclopentadienyl ligands will serve as the carbon source.

Following the microwave catalyzed process, PTX-loaded PLGA micro particles (Fig. 2A), were found to have an extensive CNT matrix deposited on their surface (Fig. 2B). The spaghetti-

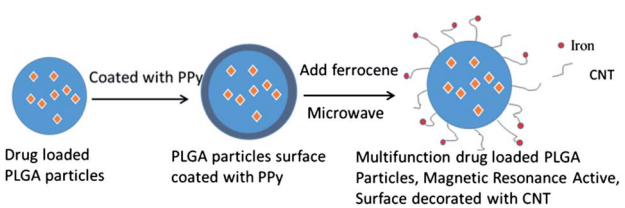

Fig. 1 Illustration of the synthetic procedure for the CNT–Fe–PLGA particles.

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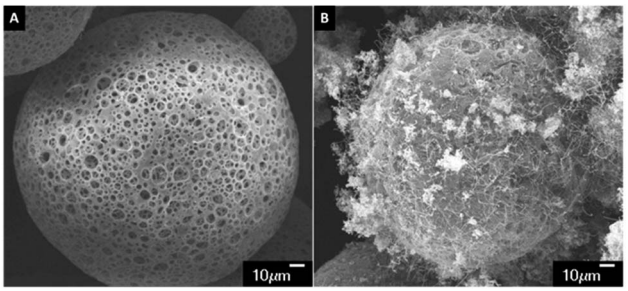

Fig. 2 SEM images of (A) PTX-loaded PLGA micro particles before and (B) after microwave-catalyzed deposition (or growth) of CNTs.

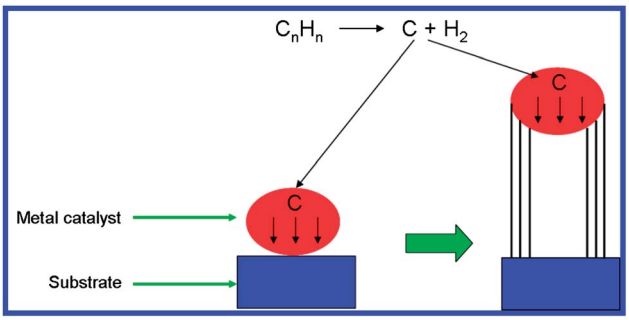

Fig. 4 Illustration of the tip-growth mechanism of CNTs.

like, hollow CNTs were observed with TEM (Fig. 3A) showing that they have outer diameters in the range of ~50 nm. Although some of the catalyst iron nanoparticles were trapped in the middle of the CNTs, more were found to be capped at the outer tip of the tubular structures, which were exhibited as the brighter dots in SEM images (Fig. 2B). Recently, Zhu *et al.* also conducted a similar microwave-assisted pyrolysis study and was able to successfully obtain nanoparticles composed of magnetic cores and carbon shells with different morphologies including CNTs, carbon nanoflakes and amorphous carbon.[16] High resolution TEM (HR-TEM) and energy-dispersive X-ray spectroscopy (EDX) were also conducted to investigate the morphology of the CNTs and the nature of the catalyst (Fig. 3). As revealed by these results, the catalyst iron particles are mainly trapped in CNTs, which are multi-walled (MWCNT) in nature, with around 30 layers of coaxial graphitic carbon lattices. By reviewing HR-TEM images, we found the catalyst particles are located at the tip or middle part of the MWCNTs, indicating that those MWCNTs are formed through the tip-growth mode (Fig. 4) instead of the base-growth mode.[17] The C_nH_n was actually originated from the decomposition of ferrocene, which generated Fe catalyst as well. The reason for a tip growth while not base-growth could be due to the weak interactions between the iron catalyst and the CP layer, *e.g.*, conducting polypyrrole (PPy) coating. Moreover, the tip-growth mode would minimize the damage on the polymeric particles, since the iron catalyst nanoparticles were not penetrating deep into the surface of the substrate micro particles.

A major concern about the biocompatibility of CNTs is their anticipated hydrophobic nature. In order to disperse CNTs in aqueous solutions, a high-power probe sonication is usually required, which may have negative effects on biomolecules such as peptide, proteins or even the drug delivery carrier itself. Interestingly, even though they were coated with a layer of CNTs, the CFPPs were readily dispersed in water with only mild vortexing. The CFPP did not have any major difference in terms of being dispersed in aqueous solution when compared to bare PLGA particles. Fig. 5 presents a CFPP dispersion before and after vortex, showing a homogeneous dispersion of CFPPs after a 10 s vortex. The microwave process had little impact on the PTX loaded inside the CFFPs, as shown in the UV spectra (Fig. 6A). We also found that the PTX could still be released when dispersed in PBS at 37 °C (Fig. 6B), but had a slower initial burst release compared to the bare PTX-loaded PLGA particles. The simplest interpretation of this finding is that the slower initial burst release of PTX from CFPPs was mainly caused by the CNT coating. Therefore, one can envision that the CNT-coating could be used to control and optimize the release rate of a drug by adjusting the length and thickness of CNT coverage.

The as-synthesized CFPPs could also be used as MRI contrast agents. Iron nanoparticles within CFPPs were magnetically

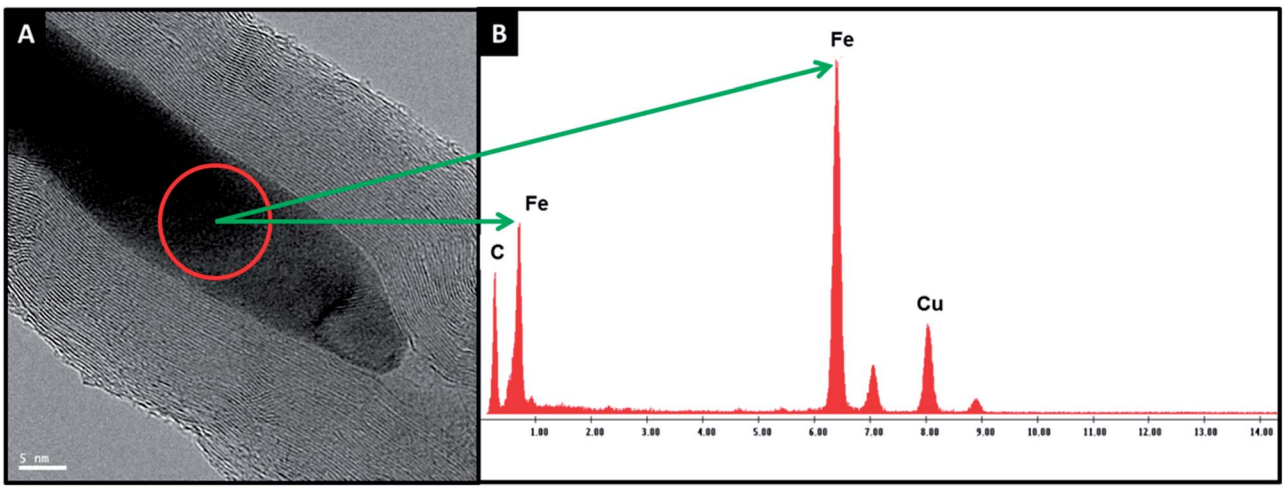

Fig. 3 (A) HRTEM image of the as-produced CNTs and (B) EDX pattern of the selected area.

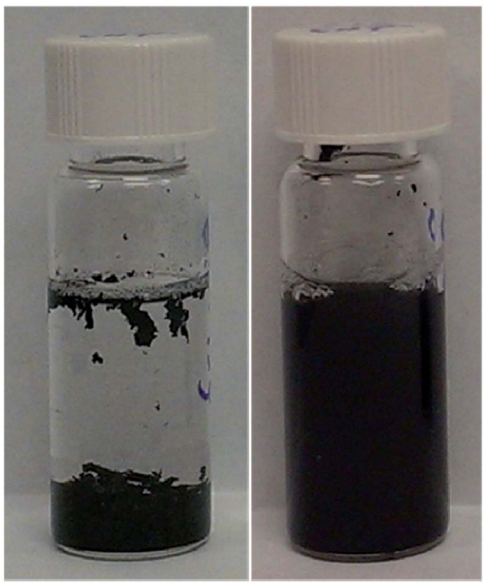

Fig. 5 CFPP dispersion before (left) and after (right) vortex. A homogeneous black solution was obtained after 10 seconds vortex.

active and visible in T2-weighted (T2-w) MRI as a hypo intense signal in comparison to the control using 11.7 T BioSpec (Bruker, Billerica, MA) (Fig. 7). The T2 value of the sample was measured to be at 40–46 ms, which indicates its potential as a good T2-w MR contrast agent for *in vivo* analysis.

As one of the few Food and Drug Administration (FDA) approved biocompatible polymers, PLGA has been extensively used to fabricate particular drug carriers. There are many different methods of fabricating solid polymeric PGLA particles including gas flow focusing,[18] electrospray,[19,20] solvent-based methods such as interfacial polymerization,[21] the evaporation of emulsions,[22] and nanoprecipitation.[23]

Although it is easier to develop and optimize a method to encapsulate a specific payload, it is very difficult to develop a method that can be optimized for the encapsulation or coating of additional payloads. This is a considerable technical

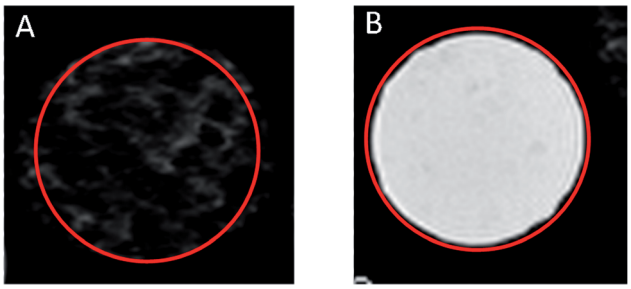

Fig. 7 T2-weighted MR images of; (A) CNT–Fe–PLGA nanoparticles in 0.4% agarose gel giving rise to hypo intense signal due to T2-shortening effect of iron in CNT–Fe–PLGA, and (B) control nanoparticles that were not coated with CNT–Fe in 0.4% agarose gel. MSME; TR/TE = 3000 ms/12 ms.

challenge, especially with MRI agents, due to their compatibility issues. For example, a water-in-oil-in-oil double emulsion solvent evaporation technique has been developed to add Gd-DTPA into PLGA platform for MRI purposes,[11] but the use of mineral oil and hexane in such techniques induces toxic organic solvent and complicates the purification of PLGA particles. Our strategy of building CNT–Fe–PLGA platform can avoid such dilemma. Here, one payload can be encapsulated into PLGA particles using any of the established methods to achieve maximum loading without concern for the addition of second payload or functional group. Instead, the iron catalysts used in the microwave process can directly serve as the MRI agent. Another added benefit of this method is that the CNT coating can be used to control the release of the drug. It should also be noted that the brush-like surface morphology of the CFPP resembles PEGylated nanoparticles which can play a very important role in extending the circulation of the particles *in vivo*. CNTs have been widely examined as potential drug delivery agents because of their nanostructure, as well as their intrinsic stability and structural flexibility. It has also been reported that peptides,[24] drugs,[25–28] protein,[29] DNA,[30] siRNA,[31,32] and RNA[33] can be covalently attached to CNTs. Consequently, CFPPs have the potential of carrying such molecules on their external CNT matrices.

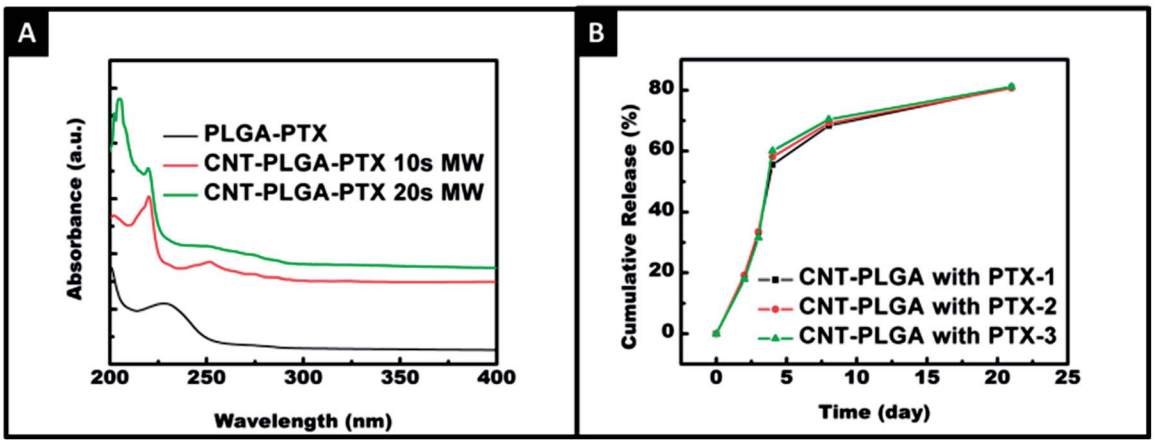

Fig. 6 UV-Vis spectra of PTX loaded PLGA particles before and after microwave process (A). Cumulative release profiles of CFPPs in PBS at 37 °C (B).

In summary, we developed a novel microwave method to fabricate a biocompatible multifunctional nano-carriers based on traditional PLGA drug delivery system. The nano-carrier can, not only carry and release the drug, but also possess MR property at the same time. The brush-like morphology provided by CNT coating is very similar to the surface morphology of PEGylated solid polymeric particles, and affects the release profile of PTX, however, it has little impact on the affinity to aqueous solutions.

In the future, more research will focus on the impact of the CNT coating on the release profile of the drug, and study the effects of brush-like surface morphology on *in vivo* applications and compare it to PEGylated particles, and explore of the potential of attaching functional molecules to the external CNT matrix.

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