



An efficient synthesis of ferumoxytol induced by alternating-current magnetic field



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ABSTRACT

Ferumoxytol (Feraheme™), as one kind of magnetic nanoparticles (MNPs), was approved for clinical application in USA and widely used as magnetic resonance imaging (MRI) agent in tumor and inflammation for preclinical diagnosis research. In this study, we explored a novel synthesis of ferumoxytol induced by alternating-current magnetic field (ACMF). As-prepared ferumoxytol was characterized by transmission electron microscopy (TEM), particle size analyzer, fourier transform infrared spectrometer (FT-IR), X-ray diffraction (XRD), vibrating sample magnetometer (VSM) and heating measurement in ACMF. Relative characterizations proved that as-synthesized ferumoxytol demonstrated better quality than Feraheme™ that was prepared by ordinary chemical co-precipitation on particle size distribution, crystallinity and magnetism. Above all, this ACMF induced synthesis may offer a better strategy for ferumoxytol preparation.

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1. Introduction

Feraheme™ (ferumoxytol injection for intravenous use, AMAG) is one kind of superparamagnetic iron oxide nanomedicine, composing of two parts: a superparamagnetic iron oxide core and a polyglucose sorbitol carboxymethylether (PSC) shell, which was approved by USA Food and Drug Administration (FDA) for treatment of iron deficiency in patients with CKD stages I–V or end stage renal disease on 30 June 2009 [1]. Ferumoxytol can be administered rapidly at 1 mL per second of 17 mL totally for intravenous iron supplement, and can replenish as much as 510 mg iron once. Supplying such an extremely large dose of iron in such a short time gives a strong evidence of exceedingly high security on clinical application of ferumoxytol. In comparison to other intravenous iron injection, there is fewest adverse reactions occurred and most efficacious for iron supplement on ferumoxytol [1]. As one kind of nanomedicine, in addition to the treatment of iron deficiency anemia, ferumoxytol can simultaneously be applied as MRI contrast agent for vascular lesions, tumors, and lymphnodes [2]. Consequently, ferumoxytol has a great potential for research in biomedical field.

Numerous methods for preparing iron oxide magnetic

nanoparticles have been developed, including chemical co-precipitation, hydrothermal and high-temperature reactions, sol-gel reactions and so on [3]. Among these methods, chemical co-precipitation synthesis is established earliest and the exclusive method to be adopted in industrial scale production. Feraheme™ is also prepared by this classic chemical co-precipitation.

As we all know, super-paramagnetic iron oxide nanoparticles (SPIONs) can produce efficient heat induction in the ACMF mainly by Neel Relaxation and Brown Relaxation for cancer hyperthermia [4]. However, to the best of our knowledge, few reports focus on synthesis of SPIONs including Feraheme™ based on this heat but exogenous heating mode such as water bath or oil bath in chemical co-precipitation [5]. Nevertheless, there are several inevitable drawbacks for the exogenous heating mode, containing insensitive temperature control and preparation of particle in irregular shape. Our work aims at a preferable ferumoxytol preparation induced by ACMF through the innovative heat mode. Finally we achieved a facile and efficient synthesis method and after characterization we can observe that the product owned better properties than Feraheme™.

2. Experimental

$\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$ and $\text{FeCl}_2 \cdot 4\text{H}_2\text{O}$ were from Aladdin Chemical Reagent Company (Shanghai, China), 28% aqueous ammonia was

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from Lingfeng Chemical Reagent Company (Shanghai, China), Feraheme™ (ferumoxytol injection) was purchased from AMAG Pharmaceuticals (Lexington, MA, USA). Polydextrose sorbitol carboxymethyl ether (PSC) was prepared from Jiangsu Key Laboratory for Biomaterials and Devices. All the chemical reagents were AR grade.

In order to eliminate irrelevant heat generated by magnetic materials in the ACMF, the reaction instruments which were exposed in the ACMF such as stirring paddle and reaction container were chosen to be made of polytetrafluoroethylene that makes negative response to the ACMF and can tolerate high temperature around 80 °C.

In our experiment, firstly, PSC (450 mg) was dissolved completely with 3.5 mL ultrapure water in the round bottom plastic tube immobilized in the ACMF induction coil. Secondly, $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$ (300 mg) and $\text{FeCl}_2 \cdot 4\text{H}_2\text{O}$ (150 mg) were dissolved totally in 2.5 mL ultrapure water then mixed into the PSC aqueous solution under vigorous mechanical stirring (IKA RW20, 370 rpm, Germany) with nitrogen bubbling. In succession, ammonium hydroxide (1.5 mL) was added in the mixture. Then the moderate radio frequency heating machine (Shuangping SPF-06-II, 390 KHz, 14 A, China) was carried out immediately to start AC magnetic field for driving the solution to produce heat. The colloidal mixture was heated to 80 °C and maintained this temperature for 1 h by regulating magnetic field intensity. Afterwards, bubble air instead of nitrogen into the solution to oxidize the iron oxide core for another 4 h. Lastly, the deep-red mixture was allowed to cool to room temperature and as-prepared ferumoxytol was obtained by dialysis and ultrafiltration (Fig. 1).

3. Results and discussion

To confirm that as-synthesized ferumoxytol displayed superior properties than Feraheme™, quite a few characterizations were performed immediately including the morphology, particle size, the structure of iron oxide nanoparticle crystals, the magnetism, nuclear magnetic relaxation properties, magnetically-induced heating efficiency in ACMF.

Fig. 2A shows the X-ray diffraction (XRD) pattern of as-prepared sample (a) and Feraheme™ (b). The result suggested that all the X-ray diffraction peaks of as-synthesized ferumoxytol were corresponded to those of Feraheme™, indexed to the cubic maghemite (JCPDC: 39-1346). Fig. 2B depicts FT-IR spectra of PSC (a),

as-prepared ferumoxytol (b) and Feraheme™ (c). Both MNPs had the common IR absorption band, meaning that ferumoxytol iron oxide nanoparticles have been successfully obtained by the ACMF. Furthermore, although the peak position of 630 cm^{-1} and 580 cm^{-1} in PSC spectra are extremely similar to those in other two spectra, the peak at 630 and 580 cm^{-1} in PSC spectra is weak and cannot be distinguished clearly, while those in other two spectra is sharp and clear in Fig. 2C. So the characteristic peak of confirmed that both MNPs were maghemite [6], consistent with the XRD result.

In Fig. 2D, the hydrodynamic diameters of these two particles were presented, the peak value of curve stands for the mean hydrodynamic diameters, apparently, as-synthesized ferumoxytol has a identical diameter with Feraheme™. However, in Table 1 we can observe that PDI of Feraheme™ is 0.219 and that of as-synthesized ferumoxytol is 0.158. Because as the value of PDI decreases, the particles presented a narrower dispersion, we can infer that as-synthesized ferumoxytol distributed more concentrated compared to Feraheme™. Moreover, TEM images gave us a more intuitive understanding on particle distribution. In Fig. 3B, the iron core of Feraheme™ displayed irregular shape, poor crystallinity and a broad size distribution ranging from 3 nm to 12 nm, while those of as-synthesized ferumoxytol dispersed more homogeneously around 7 nm, basically in round shape and a superior crystallinity.

The overlap magnetic hysteresis loop of the two MNPs is demonstrated in Fig. 4A, which indicates that they are both superparamagnetic. However, as-synthesized product showed a more excellent magnetism in saturation magnetization (M_s) of 77 emu/g than 56 emu/g of ferumoxytol. T_2 relaxation curve is shown in Fig. 4B. After detecting the value of transverse relaxation time (T_2) and the concentration of iron in the nanoparticle solution, we established a linear equation setting iron concentration as horizontal coordinates and reciprocal of spin relaxation time ($1/T_2$) as the longitudinal coordinates, whose the slope is r_2 value. It is obviously observed that the trend of the two curves was similar, but r_2 value of as-synthesized product is $97.8\text{ mM}^{-1}\text{ s}^{-1}$, slightly higher than that of Feraheme™ ($95.5\text{ mM}^{-1}\text{ s}^{-1}$). Accordingly, as-prepared ferumoxytol displayed a more extraordinary magnetism. The temperature rising curves for the two MNPs in ACMF (390 KHz, 12 A) were presented in Fig. 4C and the values of specific absorption rate (SAR) were calculated from the curves. SAR was defined as the amount of heat generated per unit gram of magnetic material per unit time, and highly determines the heating

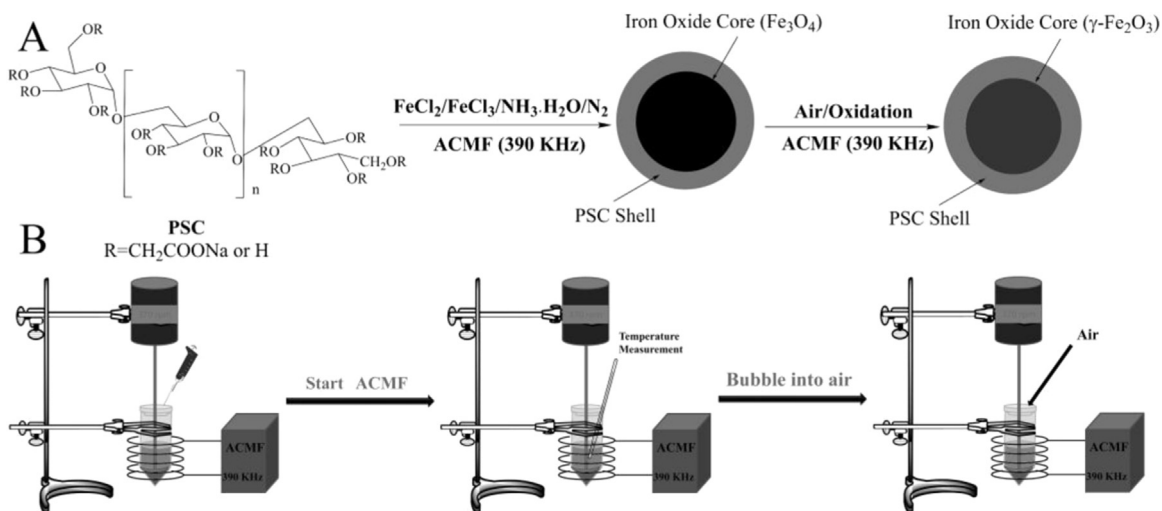


Fig. 1. (A) Synthetic procedure for ferumoxytol induced by alternating-current magnetic field. (B) Schematic illustration of ferumoxytol preparation induced by alternating-current magnetic field.

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