Materials Letters 170 (2016) 93–96

Contents lists available at ScienceDirect

Materials Letters

journal homepage: www.elsevier.com/locate/matlet

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

Bo Chen [a,1], Yang Li [a,1], Xiquan Zhang [b], Fei Liu [b], Yanlong Liu [b], Min ji [a], Fei Xiong [a], Ning Gu [a,*]

[a] State Key Laboratory of Bioelectronics, Jiangsu Key Laboratory for Biomaterials and Devices, School of Biological Science and Medical Engineering, Southeast University, Nanjing 210096, PR China
[b] Research Institute of Chia Tai Tianqing Pharmaceutical Group Limited by Share Ltd., Xuanwu Avenue 699, Nanjing 210000, PR China

ARTICLE INFO

Article history:
Received 30 September 2015
Received in revised form
1 February 2016
Accepted 3 February 2016
Available online 5 February 2016

Keywords:
Ferumoxytol
Alternating-current magnetic field
Magnetic materials
Nanoparticles
Chemical co-precipitation synthesis

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.

© 2016 Elsevier B.V. All rights reserved.

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 carboxymethyether (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 administrated 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 earlist 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

$FeCl_3 \cdot 6H_2O$ and $FeCl_2 \cdot 4H_2O$ were from Aladdin Chemical Reagent Company (Shanghai, China), 28% aqueous ammonia was

* Corresponding author.
E-mail address: guning@seu.edu.cn (N. Gu).
[1] These authors contribute equally to this work.

http://dx.doi.org/10.1016/j.matlet.2016.02.006
0167-577X/© 2016 Elsevier B.V. All rights reserved.

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, $FeCl_3 \cdot 6H_2O$ (300 mg) and $FeCl_2 \cdot 4H_2O$ (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 diffusion 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 (Ms) 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 (T2) 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/T2) as the longitudinal coordinates, whose the slope is r2 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 $mM^{-1}\,s^{-1}$, slightly higher than that of Feraheme™ (95.5 $mM^{-1}\,s^{-1}$). 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

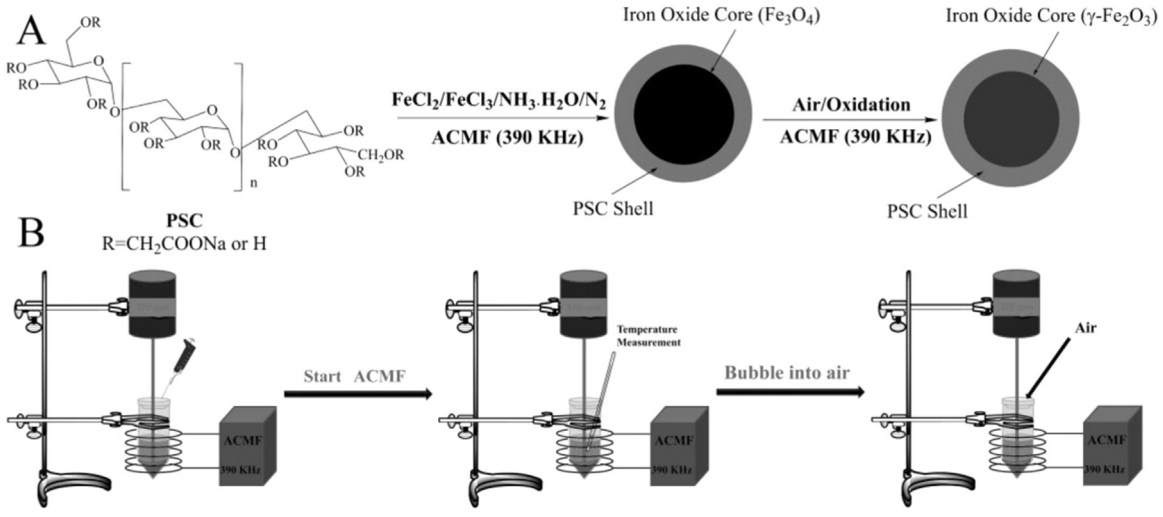

Fig. 1. (A) Synthetic procedure for ferumoxytol induced by alternating-current magnetic field. (B) Schematic illustration of ferumoxytol preparation induced by alternating-current magnetic field.

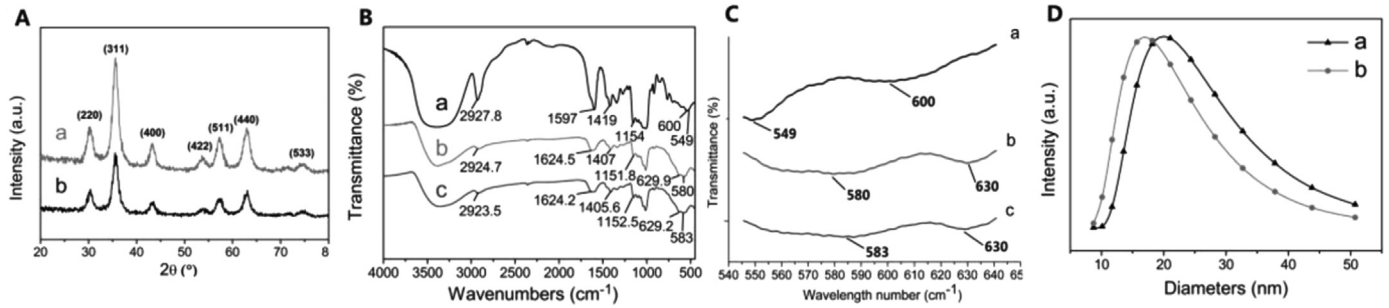

Fig. 2. (A) The X-ray diffraction spectrogram of (a) as-synthesized ferumoxytol and (b) Feraheme™. (B) The fourier transform infrared spectra of (a) PSC, (b) Feraheme™ and (c) as-synthesized ferumoxytol. (C) The enlarged spectra of Fig. 2B from 540 cm^{-1} to 650 cm^{-1}. (D) The hydrodynamic size distribution of (a) Feraheme™ and (b) as-synthesized ferumoxytol.

Table 1
Main parameters differences between as-synthesized ferumoxytol and Feraheme™.

Product name	Hydrodynamic size (nm)	Polydispersity index	Saturation magnetization (emu/g)	T_2 relaxation constant ($mM^{-1}\,s^{-1}$)	SAR (w/g)
Feraheme™	31.91	0.219	56	95.5	60
As-synthesized ferumoxytol	30.15	0.158	77	97.8	76

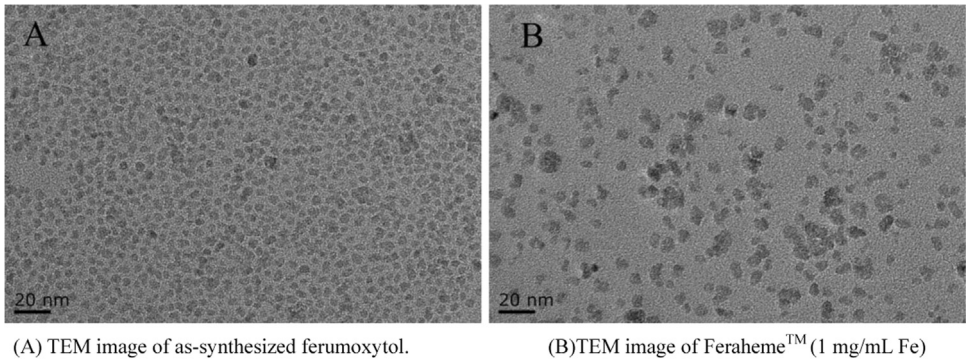

Fig. 3. (A) TEM image of as-synthesized ferumoxytol. (B)TEM image of Feraheme™ (1 mg/mL Fe).

ability of MNPs when an ACMF magnetic field is applied (390 kHz, 12 A) [7]. SAR of as-synthesized ferumoxytol was 76 w/g while Feraheme™ was 60 w/g. The data manifested that as-synthesized ferumoxytol owned the better magnetically-induced heating efficiency in ACMF than Feraheme™.

Compared with the classic chemical co-precipitation, this novel alternating-current magnetic field synthesis strategy could produce ferumoxytol with better magnetism and narrower size distribution (see Table 1), and we speculated that the reason is that in this ACMF the heat could be offered more uniformly and the temperature could be regulated more sensitively.

4. Conclusions

In this study, taking advantage of heat induced by alternating-current magnetic field, ferumoxytol was easily synthesized. As-prepared ferumoxytol were characterized with TEM, VSM, FT-IR, XRD, particle size analyzer and heating measurement in ACMF. The results implied that as-synthesized ferumoxytol displayed more uniform particle size distribution, more regular morphology, better magnetism and crystallinity. In summary, this novel heating mode has a great potential to be applied in synthesis of ferumoxytol and other MNPs.

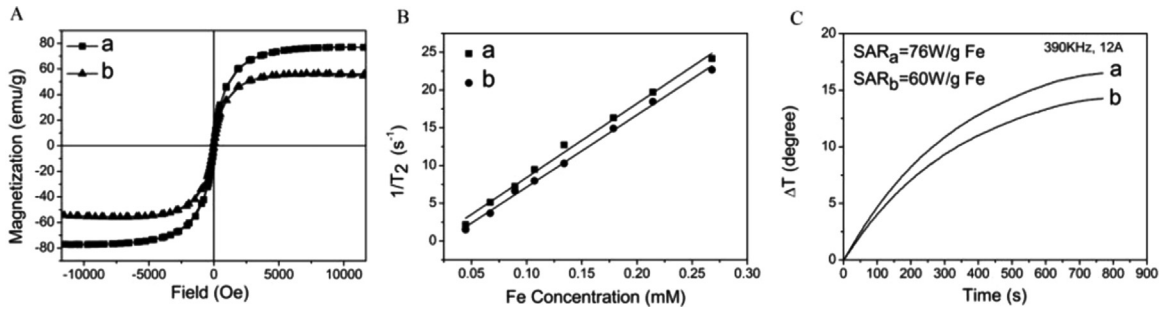

Fig. 4. (A) The overlap magnetic hysteresis loop of (a) as-synthesized ferumoxytol and (b) Feraheme™. (B) Dependency of relaxation time of (a) as-synthesized ferumoxytol and (b) Feraheme™ upon iron concentration measured by a 1.5 T NMR scanner. (C) Time-temperature curves of (a) as-synthesized ferumoxytol and (b) Feraheme™ in aqueous phase (6 mg of Fe/ml) under ACMF (390 KHz, 12 A).

Acknowledgements

The authors gratefully acknowledge financial support from National Key Basic Research Program of China (2011CB933503, 2013CB733804), National Natural Science Foundation of China for Key Project of International Cooperation (61420106012), as well as National Natural Science Foundation of China (81473160). The authors also thank Professor Fang Yang, Professor Yu Zhang and Professor Jianfei Sun for helpful discussion. Thanks for the support from Collaborative Innovation Center of Suzhou Nano Science and Technology.

References

[1] M.H. Rosner, M. Auerbach, Ferumoxytol for the treatment of iron deficiency, Expert Rev. Hematol. 4 (2011) 399–406.
[2] M.R. Bashir, L. Bhatti, D. Marin, R.C. Nelson, Emerging applications for ferumoxytol as a contrast agent in MRI, J. Magn. Reson. Imaging 41 (2015) 884–898.
[3] S. Laurent, D. Forge, M. Port, A. Roch, C. Robic, L.V. Elst, et al., Magnetic iron oxide nanoparticles: synthesis, stabilization, vectorization, physicochemical characterizations, and biological applications, Chem. Rev. 108 (2008) 2064–2110.
[4] T. Kobayashi, Cancer hyperthermia using magnetic nanoparticles, Biotechnol. J. 6 (2011) 1342–1347.
[5] K.G. Paul, T.B. Frigo, J.Y. Groman, E.V. Groman, Synthesis of ultrasmall superparamagnetic iron oxides using reduced polysaccharides, Bioconjug. Chem. 15 (2004) 394–401.
[6] S. Yu, G.M. Chow, Carboxyl group (–CO_2H) functionalized ferrimagnetic iron oxide nanoparticles for potential bio-applications, J. Mater. Chem. 14 (2004) 2781–2786.
[7] J. Xie, Y. Zhang, C. Yan, L. Song, S. Wen, F. Zang, et al., High-performance PE-Gylated Mn-Zn ferrite nanocrystals as a passive-targeted agent for magnetically induced Cancer theranostics, Biomaterials 35 (2014) 9126–9136.