

SYNTHESIS AND MAGNETIC PROPERTIES OF CARBON NANOTUBE-IRON OXIDE NANOPARTICLE COMPOSITES FOR HYPERTHERMIA: A REVIEW

W. Zhang, X. D. Zuo and C. W. Wu

State Key Laboratory of Structural Analysis for Industrial Equipment,
Faculty of Vehicle Engineering and Mechanics, Dalian University of Technology, Dalian 116024, P. R. China

Received: July 30, 2015

Abstract. Magnetic inducing hyperthermia (MIH) is gaining great popularity due to its good targeted therapy and less side effects. Magnetic agents play a crucial role in this technique. As novel candidates, recently, carbon nanotubes/iron oxide nanoparticles composites have demonstrated great potential in MIH by combining the unique characteristics of carbon nanotubes with the excellent magnetic properties of iron oxides. In this article, we review the recent advances in the synthesis of these composites. The formation mechanisms of composites by methods such as co-precipitation, thermal decomposition, solvothermal method, in situ growth, electron beam evaporation and microwave plasma torch etc. are discussed and, with the emphases on the coercivity and saturation magnetization, the magnetic properties of composites are also summarized. Then the main challenges facing the clinic applications of these composites are addressed. It is likely that this summary can provide referential information for the synthesis of carbon nanotubes/iron oxide nanoparticles composites with improved magnetic property for MIH.

1. INTRODUCTION

Hyperthermia is a newly developed method for the treatment of malignant tumor. The use of magnetic particles in association with external alternating magnetic field to generate heat is one popular method. Actually, this concept can be traced back to as early as 1950's [1]. Since then there have been numerous publications in this field [2-4], and, in particular, the past decade has witnessed the proliferation. Basically, the magnetic media was introduced to tumor area by implantation or intervention. And then on the application of alternating magnetic field, heat will be generated, leading to the increase of temperature locally. As a consequence, the tumor cells can be killed selectively without affecting the adjacent normal tissue, i.e. a targeted therapy can be achieved [5]. Meanwhile, owing to

thermal diffusion, the subclinical lesions around will undergo apoptosis and active immunization can be incurred. A combination of these effects ensures that the tumor cells can be killed efficiently. Compared with other ways of treating malignant tumor, magnetic inducing hyperthermia may overcome the deficiencies of current hyperthermia techniques and heat the cancer tissue to an effective temperature of treating precisely [6]. Its great potential of treating cancer has attracted people's interest, and as a matter of fact, in recent years, many magnetic hyperthermia experiments have been conducted in animals and clinical trials and have achieved exciting results [7,8]. So far, the most popular magnetic agents used are Fe_3O_4 and Fe_2O_3 nanoparticles. This is largely because these two iron oxides have been proved nontoxic in human body and their syntheses are relatively simple and convenient.

Corresponding author: C.W. Wu, e-mail: cwwu@dlut.edu.cn

Carbon nanotubes (CNTs) are well ordered, hollow graphitic materials with high aspect ratio [9-15]. Their fascinating one-dimensional tubular structures, high surface areas, high stability and unique electronic, mechanical, chemical properties make them novel nanomaterials for various biomedical applications [16-18]. In particular, after functionalization, CNTs may easily come across the membrane into the cell via endocytosis and diffusion [19-23]. This means CNTs can serve as drug carriers that deliver drug molecules for chemical therapy to the target cells. The large surface area of CNTs, together with their hollow structure, enables them to be loaded with a large quantity of drug molecules [24,25]. The attachment of drug molecules to CNTs can also effectively prolong the circulation time of drug molecules in blood and thus enhance cellular uptake of the drug by cancer cells [26,27]. As specific antibodies or ligands can also be grafted onto CNTs, targeted drug delivery can be achieved, reducing the side-effects of drug molecules [28]. In addition, CNTs are able to absorb light in the near infrared region, resulting heating of CNTs. This unique property of CNTs has been exploited as a method to kill cancer cells via thermal effects [29,30]. Owing to the characteristics of Raman scattering, CNTs can be used as tracer to monitor the distribution of drug molecules in human body as well [31,32]. Apparently, CNTs can take a multiple role in malignant tumor therapy, for instance, drug carrier, light-inducing heat treating agent, and drug molecule tracer.

As such, researchers have recently attempted to combine the merits of iron oxide nanoparticles with CNTs by making CNT/iron oxide composites and developed novel agents for multimodality therapy. Indeed, these composites have demonstrated great potential in the therapy of malignant tumor [33-35]. Focusing on magnetic inducing hyperthermia, in this communication, we summarize the recent advances in preparation of CNTs/iron oxide composites with the specific emphasis on their magnetic properties. The challenges are then addressed and future working directions are also discussed.

2. SYNTHESSES AND PROPERTIES OF CNT/IRON OXIDE NANOPARTICLE COMPOSITES

Various technologies such as co-precipitation, thermal decomposition, and solvothermal method, in-suit growth, electron beam evaporation, microwave plasma torch, etc., have been attempted to synthesize CNTs/magnetic composites.

2.1. Co-precipitation

Co-precipitation is a simple and convenient method for the synthesis of CNTs/magnetic nanoparticle composites [36-38]. At room temperature or elevated temperature, the metal precursors are mixed at given molar ratios and then the pre-treated CNTs were introduced, yielding the CNTs/magnetic nanoparticles composites.

Fan et al. prepared Fe_3O_4 nanoparticles using $\text{FeCl}_2 \cdot 4\text{H}_2\text{O}$ and $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$ as iron precursors [39]. The obtained nanoparticles were then attached to CNTs, which was first functionalized by nitric acid oxidation. The saturation magnetization (M_s) of the composites with the diameter of Fe_3O_4 being 6 nm and 10 nm is 6.5 emu g^{-1} and 7.52 emu g^{-1} , respectively. In contrast, the M_s of the corresponding pure Fe_3O_4 nanoparticles is $69.257 \text{ emu g}^{-1}$ and $101.24 \text{ emu g}^{-1}$ respectively. The drop in M_s may be ascribed to the negligible contribution of CNTs to the magnetization. Similarly, Cao et al. reported that both the coercivity (H_c) and M_s of the CNTs/ $\gamma\text{-Fe}_2\text{O}_3/\text{Fe}_3\text{O}_4$ are smaller than individual iron oxides nanoparticles ($\gamma\text{-Fe}_2\text{O}_3$ and Fe_3O_4), but higher than pure CNTs [40].

However, Correa-Duarte et al. observed that the M_s of CNTs/ $\text{Fe}_3\text{O}_4/\gamma\text{-Fe}_2\text{O}_3$ increases by 17% with respect to the corresponding $\text{Fe}_3\text{O}_4/\gamma\text{-Fe}_2\text{O}_3$ particle powder [33], see Fig. 1. They suspected that either the adsorption of iron oxide powder onto CNTs changes the particle magnetization, or the applied MWCNTs carry an intrinsic magnetization due to the presence of remaining Ni, which is used as catalyst for the growth of CNTs. Chen et al. observed the similar trend and the M_s is increased by 40% in comparison with the initial Fe_3O_4 nanoparticles. They ascribed the origin of the magnetization to the agglomeration of Fe_3O_4 nanoparticles on the CNTs surface [41].

In addition, the content of magnetic nanoparticles in the composites may also influence the magnetic properties of the composites. Zhou et al. [42] reported the M_s of CNTs/ Fe_3O_4 nanoparticles is 47 emu g^{-1} , which is higher than that of CNTs/ Fe_3O_4 nanocomposites (35 emu g^{-1}) reported by Chen et al. [41] in a similar way. Zhou explained that the reason is the content of Fe_3O_4 in nanocomposites of his research (about 55 wt.%) is much higher than that of Chen's research (about 16 wt.%). Apart from iron oxides, magnetic particles such as TiO_2 coated Fe_3O_4 and Fe-Co have also been suggested to prepare magnetic particles/CNTs composites [43,44]. The resultant composites showed excellent result in magnetic thermal test

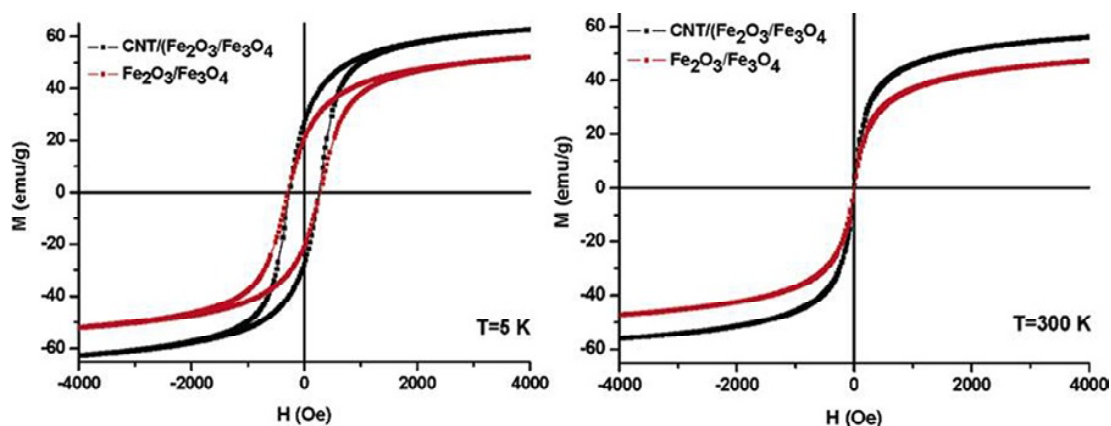


Fig. 1. The magnetization curve of CNT/ $\text{Fe}_2\text{O}_3/\text{Fe}_3\text{O}_4$ and $\text{Fe}_2\text{O}_3/\text{Fe}_3\text{O}_4$ at different temperature, reprinted with permission from M. A. Correa-Duarte, M. Grzelczak and V. Salgueirífo-Maceira // *J. Phys. Chem. B.* **109** (2005) 19060, © 2005 American Chemical Society.

and good prospects on magnetic thermal therapy as well.

The formation mechanism of CNTs/magnetic nanoparticles is another concern of investigation. Typically, there are two kinds of interactions between magnetic nanoparticles and CNTs. The first one is covalent bonding. Zhou grafted poly acrylic acid (PAA) groups onto acid functionalized CNTs by the condensation of carboxylic groups in PAA with hydroxyl group on CNTs [42]. And then Fe_3O_4 nanoparticles were attached covalently onto the surface of PAA-g-CNTs through amidation, see Fig. 2. Owing to the grafting of PAA oligomers, more

reactive sites can be introduced onto CNT's surface and accommodate more Fe_3O_4 nanoparticles.

The other typical interaction is electrostatic attraction. This interaction is widely adopted due to its efficiency and convenience. Depending on the manner by which the electrostatic charges are endowed onto CNTs, two popular methods have been proposed. Stoffelbach et al. demonstrated the carboxyl, hydroxyl or carbonyl groups could be grafted onto CNTs' surfaces through acid oxidation, and then the negative charged magnetic nanoparticles were adsorbed onto CNT's surfaces by electrostatic interaction [45]. Another popular way is so-called

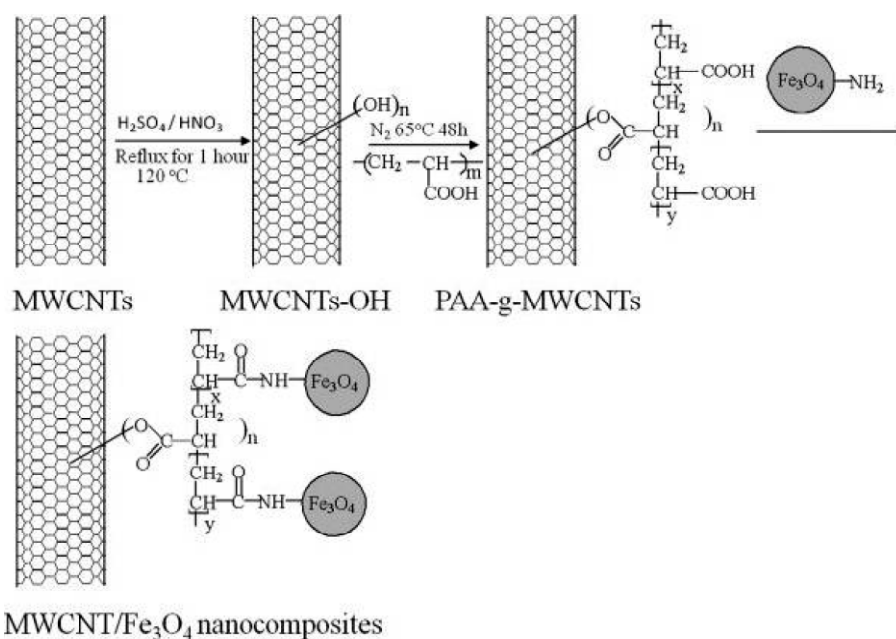


Fig. 2. The process of preparing CNTs/magnetic nanoparticles with covalent binding, reprinted with permission from H. Zhou, C. Zhang and H. Li // *J. Polym. Sci. Pol. Chem.* **48** (2010) 4697, © 2010 John Wiley & Sons, Inc.

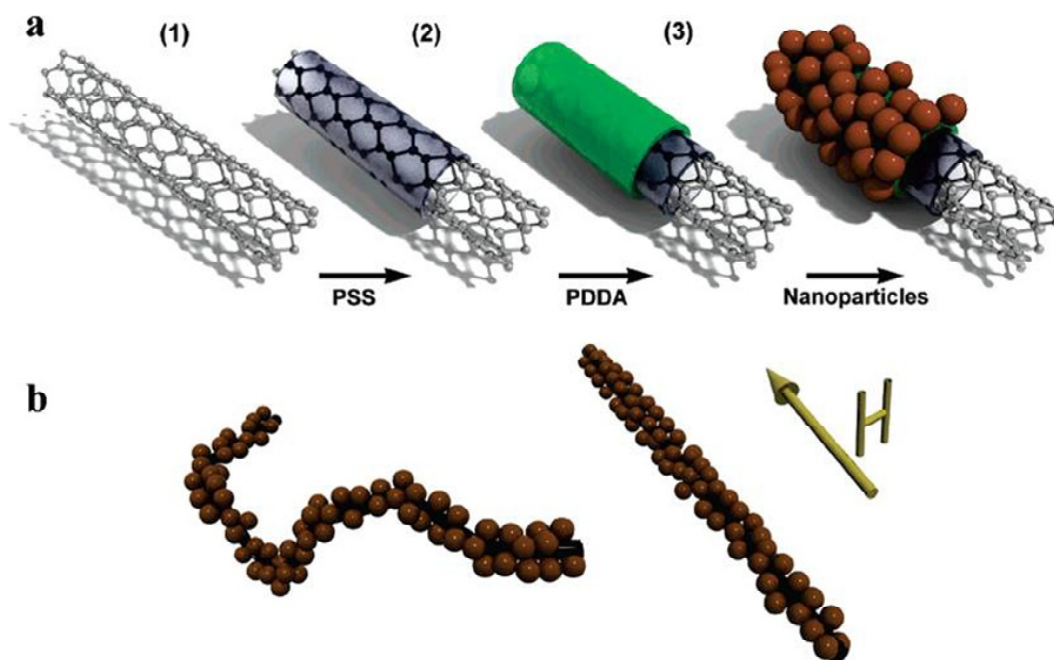


Fig. 3. The process of preparing CNTs/magnetic nanoparticles by LBL technique, , reprinted with permission from M. A. Correa-Duarte, M. Grzelczak and V. Salgueiriño-Maceira // *J. Phys. Chem. B.* **109** (2005) 19060, © 2005 American Chemical Society.

layer-by-layer technique. Poly (sodium 4-styrene sulfonate) (PSS) was used as a dispersing agent to provide remarkable stable aqueous dispersions of CNTs, and then cationic poly(dimethyldiallylammonium chloride) (PDDA) was assembled through the electro-static interaction with sulfonate groups in PSS, which in turn provides a homogeneous distribution of positive charges. These positive charges ensure the efficient adsorption of negatively charged magnetic nanoparticles onto the surface of CNTs by means of electrostatic interactions, see Fig. 3 [33].

The principle and procedure of co-deposition are simple and readily applicable to prepare CNTs/magnetic nanoparticles. In general, the content of the magnetic particles in the composites determines the magnetic properties of the products. For CNTs/magnetic nanoparticles prepared by co-precipitation, iron particles are usually dispersed evenly on CNTs' surface and the size and shape of particles can be controlled by simply modifying the molar ratio of the reactants. However, the monodispersion of the pure magnetic particles is hard to achieve and consequently the properties of the products is not easy to control [46].

The magnetic property and formation mechanism of CNTs/magnetic nanoparticles prepared by co-precipitation are summarized in Table 1.

2.2. Thermal decomposition and solvothermal method

Thermal decomposition and solvothermal method are the ways of synthesizing CNTs/magnetic nanoparticles at elevated temperatures. The process of thermal decomposition is first to mix CNTs with organic metal solution at elevated temperature. And then the decomposition of organic metal solution followed by oxidation can lead to the generation of high-quality monodispersed nanoparticles. In solvothermal synthesis, metal salt precursors are mixed with CNTs in a sealed container. And the reaction usually takes place at high temperature (generally in the range from 130 to 250 °C) and high pressure (typically in the range from 0.3 to 4 MPa). Quite often, the magnetic nanoparticles synthesized by this way are highly crystallized [46,47].

The reaction conditions such as temperature, solvent, and reactant ratio usually have important effects on the magnetic properties of products. Sun et al. synthesized CNTs/magnetic nanoparticles by the thermal decomposition of ferrocene at 350, 425, and 500 °C [48]. The resulting products at different temperatures have different sizes and magnetic properties, see Table 2 for details. They also found that the maghemite in CNT-maghemite composites obtained at 500 °C are sheathed with amorphous carbon based materials. The TEM observations in-

Table 1. Magnetic property of CNTs/magnetic nanoparticles prepared by co-precipitation.

Iron precursors and their molar ratio (unless specified)	Iron oxide and its diameter(nm)	Hc(Oe)	Ms(emu/g)	Formation mechanism (functional groups of interaction)	Ref.
$\text{FeCl}_2 \cdot 4\text{H}_2\text{O} : \text{FeCl}_3 \cdot 6\text{H}_2\text{O} = 1:2$	Fe_3O_4 , 10, 6	0*	7.52, 16.5	Electrostatic attraction (-OH, -COOH.)	39
$\text{FeCl}_2 : \text{FeCl}_3 = 1:2$	Fe_3O_4 , 9.5	0	47	Covalent binding(-NH-)	42
$\text{Fe}(\text{NO}_3)_3$	$\text{Fe}_3\text{O}_4/\text{g-Fe}_2\text{O}_3$, 25-80	163.44	20.07	Electrostatic attraction(SO_4^{2-} I).	40
$\text{FeCl}_3 \cdot 6\text{H}_2\text{O} : \text{FeSO}_4 \cdot 7\text{H}_2\text{O} = 3:2$	Fe_3O_4 , 5-8	3.9	57	Electrostatic attraction (>C=C, >C=O, -CH ₂ , -OH)	36
$(\text{NH}_4)_2\text{Fe}(\text{SO}_4)_2 \cdot 6\text{H}_2\text{O} : \text{NH}_4\text{Fe}(\text{SO}_4)_2 \cdot 6\text{H}_2\text{O} = 9:2$ (mass ratio)	Fe_3O_4 , 30-50	-	-	Electrostatic attraction(-COOH)	37
$\text{FeCl}_3 : \text{FeCl}_2 = 1:2$	Fe_3O_4 , 5	-	-	Electrostatic attraction (C(CH ₃)(CN)CH ₂ CH ₂ COO-)	45
$\text{Fe}(\text{NO}_3)_3 \cdot 9\text{H}_2\text{O} : \text{MWCNTs}$ (mass ratio)=2:1	Fe_2O_3 , 7.9-8.4	500 °C:4.8 600 °C:6.3	0.3 0.2	Electrostatic attraction (Dodecyl benzenesulfonate)	38
$\text{Fe}(\text{NO}_3)_3 \cdot 9\text{H}_2\text{O} : \text{MWCNTs}$ (mass ratio)=4:1	Fe_2O_3 , 10.1-10.8	500 °C:2.8 600 °C:9.6	2.0 1.4		
$\text{FeCl}_3 : \text{FeSO}_4 = 1:2$	$\gamma\text{-Fe}_2\text{O}_3/\text{Fe}_3\text{O}_4$, 6-10	0	57	Electrostatic attraction (PSS, PDDA)	33
FeSO_4 (6.44 g/L), CoSO_4 (7.12 g/L)	FeCo , 2-9	-	4.2	-	43

*Hc value of zero means the composites are in the superparamagnetic state.

Table 2. Magnetic property of CNTs/magnetic nanoparticles prepared by thermal treatment.

Reactants and their quantities (weight ratio unless specified)	Solvent	Temperature(°C)	Hc(Oe)	Ms(emu/g)	Iron oxides attached on CNTs and their size(nm)	Ref.
Fe(CO) ₅ (10 ml), MWCNTs(0.15 g)	Vacuum	180	32.09	12.93	γ-Fe ₂ O ₃ 11nm	53
MWCNTs(0.15 g)						
FeCl ₃ :CNTs=1	Diethylene glycol	200	-	-	Fe ₃ O ₄	51
FeCl ₃ :CNTs=2	Diethylene glycol	200	0*	31.34	Fe ₃ O ₄	51
FeCl ₃ :CNTs=0.25	Diethylene glycol	200	0	12.15	Fe ₃ O ₄	51
Fe(NO ₃) ₃ :CNTs=1:1	Methanol	240	298	-	Fe ₂ O ₃ , 15	56
Fe(acac) ₃ :MWCNTs=4:1	Triethylene glycol	278	0	29.35	Fe ₃ O ₄ , 6	50
Fe(acac) ₃ :MWCNTs=1:1	Triethylene glycol	278	0	2.05	Fe ₃ O ₄ , 9	50
Fe(C ₂ H ₅) ₂ (30 ml), CNTs (15 mg)	Benzene	500	110	32.5	Fe ₃ O ₄ , 14	49
Fe(CO) ₅ , MWCNTs	N,N-dimethylformamide	180	538.5	43.6	Fe, 13-35	54
MWCNTs (15 mg), FeCl ₃ ·6H ₂ O (6 mmol)	Polyethylene glycol	200	83	61.8	Fe ₃ O ₄ , 50-200	55
Ferrocene:CNTs=1:1	Air	500	59	10.4	γ-Fe ₂ O ₃ , 12±2	48
	Air	425	0	-	γ-Fe ₂ O ₃ /Fe ₃ O ₄ , 8±2	48
	Air	350	0	-	γ-Fe ₂ O ₃ /Fe ₃ O ₄ , 5±2	48

*Hc value of zero means the composites are in the superparamagnetic state.

indicated that the produced maghemite particles not only decorate the external walls of CNTs but also are encapsulated within CNTs. Wang et al. also prepared CNTs/Fe₃O₄ composites by the decomposition of ferrocene [49]. The difference is they used benzene as solvent, but no solvent involved were in Sun's experiments. At 500 °C, they obtained the composites with the Hc and Ms being 110 Oe and 32.5 emu g⁻¹, respectively.

The ratio of reactants affects the size and magnetic properties of products as well. Wan et al. suggested to modify the magnetic properties of the products by changing the ratio between Fe(acac)₃ (iron (III) acetylacetonate) and CNTs. When Fe(acac)₃:CNTs is 4:1, the Ms equals 29.35 emu g⁻¹; whereas Fe(acac)₃:CNTs is equal to 1:1, the Ms is 2.05 emu g⁻¹ [50]. Wang heated the mixture of FeCl₃ and CNTs in diethylene glycol and the diameter of the obtained Fe₃O₄ in CNTs/Fe₃O₄ nanoparticles is around 6 nm [51]. They found that the magnetization curve could be modified by changing the ratio between FeCl₃ and CNTs as well. By the thermal decomposition of Fe[(NH₂)₂CO]₆(NO₃)₃, Jiang et al. investigated the influence of reactant ratio, reaction temperature and time on phase composition of magnetic products, see Table 3 for details [52]. Tan used Fe(CO)₅ as the metal precursor for thermal decomposition and oxidation in vacuum [53]. The product was CNTs/g-Fe₂O₃ in the diameter of 6-12 nm. By thermal decomposition of Fe(CO)₅, Shen et al. prepared CNTs/polycrystalline

iron nanoparticles [54]. It is interesting that the resulting composites display good potential for microwave absorption in high-frequency electromagnetic testaments. This characteristic may pave some way to a new mechanism of hyperthermia.

Several proposals have been put forward with respect to the formation mechanism. Based on the analyses of FTIR spectra, Wang et al. concluded that the CNTs/Fe₃O₄ composites hardly contain –COOH or –OH groups [49] and the unique atomic structure sp² of CNTs has not been damaged. Thus, CNTs and the magnetic nanoparticles may adsorb each other by electrostatic attraction. Zhang et al. claimed that the formation mechanism of solvothermal method is the interaction and electrostatic attraction among functional groups, for instance, amino-groups, hydroxyl groups [55]. Wang observed the intermediate product of the composites by TEM at 200 °C and proposed a possible mechanism as follows [51]. FeCl₃ was partly reduced by diethylene glycol into very fine magnetite particles at elevated temperatures, and these tiny particles have high surface energy and are preferentially attached onto the surface of CNTs from polyol solution automatically. The tiny particles will then serve as the nuclei for growth of magnetite nanoparticles. Wan et al. explained the mechanism of thermal decomposition in a similar way [50]. At elevated temperature, Fe(acac)₃ was reduced to magnetic nanoparticles with high surface energy by triethylene glycol and can be attached on CNTs

Table 3. The iron oxides attached on CNTs under various reaction conditions, [52].

Fe[(NH ₂) ₂ CO] ₆ (NO ₃) ₃ :CNTs weight ratio	Solvent	Temperature (°C)	Time (h)	Iron oxides attached on CNTs
0:1	C ₂ H ₈ N ₂	100	50	unreacted precursor
0:1	C ₂ H ₈ N ₂	150	50	α-Fe ₂ O ₃ +unreacted precursor (trace)
10:1	C ₂ H ₈ N ₂	200	10	α-Fe ₂ O ₃ +Fe ₃ O ₄
10:1	C ₂ H ₈ N ₂	200	25	α-Fe ₂ O ₃ (trace)+Fe ₃ O ₄
10:1	C ₂ H ₈ N ₂	200	50	Fe ₃ O ₄
Without CNTs	C ₂ H ₈ N ₂	200	50	α-Fe ₂ O ₃ (trace)+Fe ₃ O ₄ (without CNTs)
20:1	C ₂ H ₈ N ₂	200	50	Fe ₃ O ₄
5:1	C ₂ H ₈ N ₂	200	50	α-Fe ₂ O ₃ (trace)+Fe ₃ O ₄
2:1	C ₂ H ₈ N ₂	200	50	α-Fe ₂ O ₃ (trace)+Fe ₃ O ₄
1:1	C ₂ H ₈ N ₂	200	50	α-Fe ₂ O ₃ +Fe ₃ O ₄
10:1	C ₂ H ₅ OH	200	50	α-Fe ₂ O ₃
10:1	H ₂ O	200	50	α-Fe ₂ O ₃
10:1 (baked CNTs)	C ₂ H ₈ N ₂	200	10	α-Fe ₂ O ₃ +Fe ₃ O ₄
10:1 (baked CNTs)	C ₂ H ₈ N ₂	200	25	α-Fe ₂ O ₃ +Fe ₃ O ₄
10:1 (baked CNTs)	C ₂ H ₈ N ₂	200	50	α-Fe ₂ O ₃ (trace)+Fe ₃ O ₄

surface. And then the particles grew up by adsorbing other particles nearby via Vander Waals forces. And he also observed the intermediate products of magnetic CNTs by TEM. In many researchers' explanations, the solvent used plays a vital role in the formation of magnetic CNTs. The role of solvent is not only for common solvent, but also as reducing agent and stabilizer. In Huang's research, CNTs pretreated by nitric acid would obtain functional groups such as $-\text{COOH}$, $-\text{OH}$ or $-\text{C}=\text{O}$ on the surface, and these functional groups are the nucleation sites of magnetic CNTs [56]. When methanol is used as the solvent, more functional groups for example CH_3O^- or H^+ would appear and thus the composites would have higher nucleation density. Wang also pointed out that oxygen-containing solvent is not favorable for the formation of magnetite nanoparticles and their assembly on CNTs [49]. Sun et al. gave an explanation to the formation of magnetic CNTs by the decomposition of ferrocene [48]. Ferrocene sublimated to gas when the temperature reached a certain value. And then most part of ferrocene molecules exist outside of the CNTs and simultaneously some molecules diffused into the interior cavity of CNTs. The ferrocene molecules started to decompose into iron atoms and the corresponding hydrocarbon molecules when temperature increased to a certain value. Then the iron atoms reacted with oxygen in the vessel to form iron oxides, deposited on the CNTs, and grew into small particles through nucleation and growth of particles, resulting in magnetic CNTs composites.

In thermal decomposition and solvothermal methods, the reaction takes place at high temperature and sometimes high pressure. As stated above, the reaction conditions have great effects on the magnetic properties of the final products. However, the exact links between the reaction variables such as temperature, solvent, reactant ratio, reaction time and magnetic properties such as M_s , H_c , and size, shape, morphology of the final products are still unclear [57]. The magnetic nanoparticles (iron oxide) synthesized by thermal decomposition are usually monodisperse and have narrow size distribution, and the magnetic nanoparticles synthesized by solvothermal method is often crystallized [46,47].

Table 2 lists the magnetic properties of CNTs/magnetic nanoparticles prepared by thermal treatment.

2.3. In situ growth

In this method, magnetic nanoparticles or metal ions are introduced when CNTs are grown in a template

by chemical vapor deposition (CVD). The template is then dissolved using acid and magnetic CNTs with magnetic nanoparticles embedded in the inner wall can be achieved. The resulting composites are promising for high capacity drug loading given that the magnetic functionalization did not block any of the active sites available for drug attachment, either from the CNT internal void or on the internal and external surfaces. This is in contrast to typical approaches of loading CNTs with particles that proceed through surface attachment or capillary filling of the tube interior. The fact that the magnetic functionality is provided from 'inside the walls' can allow for multimode functionalization of the graphitic surfaces makes the composites promising for targeted therapeutic applications.

By this method, Jang et al. synthesized the inner diameter controllable CNTs/ Fe_2O_3 composites [58]. They dropped FeCl_3 /poly(amic acid)/N-methyl pyrrolidone solution onto the AAO(anodic aluminum oxide) surface and then the solution migrated into the AAO pores by capillary force. After carbonization, iron embedded CNTs formed in the channels of AAO and the CNTs/ Fe_2O_3 composites can be obtained by dissolving AAO using hydrochloric acid. The coercivity and remanence of the magnetic CNTs is 226.17 Oe and 0.86 emu g^{-1} , respectively. Open-ended CNTs with magnetic nanoparticles encapsulated within their graphitic walls were fabricated by a combined action of template growth and a ferrofluid catalyst/carbon precursor, as demonstrated by Vermisoglou et al [59]. The authors also attached the amino benzothiazine onto CNTs as the drug in magnetic field induced drug delivery and found that the treatment effect increased significantly. D Mattia [60] also tried to use this method to synthesize magnetic CNTs with the magnetic nanoparticles attached to the inner wall, but the XRD patterns only showed the presence of Fe_3C and Fe. The authors explained that the Fe_3O_4 nanoparticles were reduced to Fe by hydrogen, then after carburizing, some Fe becomes Fe_3C .

In terms of formation mechanism, two proposals have been discussed [60,61]. The first one is the tip-growth mechanism, *i.e.* with particles lifted from the membrane pore wall due to the formation of a metal carbide particle and further dissolution of carbon in the carbide with subsequent lift of the particle (Fig. 4a). The appearance of Fe_3C signal in XRD patterns partly supports this mechanism. The second mechanism can be described as follows. Carbon starts to deposit on the uncovered alumina template pore wall, and further expands along the pore wall (Fig. 4b). Once the carbon growing along

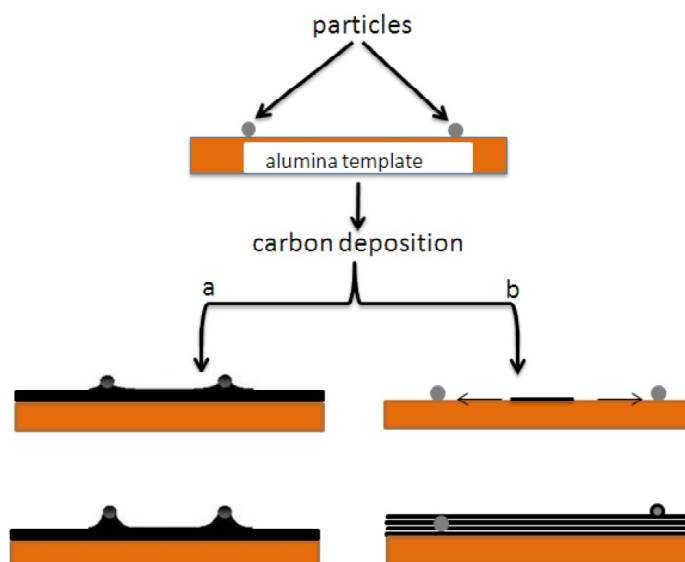


Fig. 4. The formation mechanism of CNTs/metal particles synthesized by growth method.

the pore wall reaches a particle, it begins to lift it off from the substrate. The process continues, with the simultaneous formation of an equally thick layer of carbon on the nanoparticles that are still exposed in the cavity of the tubes.

In in-suit growth, the inner and outer diameters of the CNTs can be controlled. Compared with the co-deposition and thermal treatment, this method is also distinguishable in that magnetic nanoparticles can be attached to the inner wall of CNTs. As the nanoparticles can be well protected from pH environment by CNTs shell, the composites have great potential in drug delivery applications. However, it should be pointed out the reduction in Ms may happen due to the replacement of iron oxide by iron carbide. Ms of the latter is three orders of magnitude smaller than iron and two orders of magnitude smaller than Fe_3O_4 .

2.4. Other methods

In addition to the methods discussed above, methods such as electron beam evaporation and microwave plasma torch have also been used to prepare magnetic CNTs composites.

2.4.1. Electron beam evaporation

Coating of various metals such as Ni and Fe on suspended CNTs has been carried out by Zhang et al. using electron-beam evaporation [62]. TEM studies reveal that Ni coating on the suspended tubes are continuous and quasi-continuous, resulting in nanotube-supported metal nanowire structures. In sharp contrast, Fe coatings on the suspended CNTs only form isolated discrete particles on the

nanotubes. This is interpreted in terms of difference in the interactions between the deposited atoms and CNTs. Ni interacts strongly with the sidewall of CNTs and the interactions are likely to be partially associated with covalent bonding between the metals and carbon atoms. In terms of Fe, the interactions are relatively weak.

2.4.2. Microwave plasma torch

Lenka et al. synthesized magnetic CNTs composites by microwave plasma torch [63]. The experiments were carried out at atmospheric pressure operating at the frequency of 2.45 GHz in the mixture of $\text{CH}_4/\text{H}_2/\text{Ar}$ with added $\text{Fe}(\text{CO})_5$ vapors. They found that, when the power of microwave was at 360 W, most of the particles (Fe_3O_4 , $\gamma\text{-Fe}_2\text{O}_3$) self-assembled into long chains by magnetic interaction and they had hexagonal, crystalline form. At higher power of 440-460 W, the deposit contained significant amount of CNTs covered by iron oxide nanoparticles. The nanoparticles were a mixture of various iron oxides, namely Fe_3O_4 and $\alpha\text{-Fe}_2\text{O}_3$, and they had a spherical shape with the core of iron oxide covered by thin layer of carbon.

3. CHALLENGES FACING CLINIC APPLICATION

3.1. Efficiency of heat generation

Generally speaking, the growth rate of tumor cell will be inhibited at 41-45 °C and to kill the cell, the temperature needs to reach 45-47 °C [64,65]. For safety reasons, on the other hand, the frequency and intensity of magnetic field that can be applied

to human body are constrained; the former should fall in the range of 50-1000 kHz and the latter should be below 30 kA/m [66,67]. It is therefore not surprising that one of the biggest challenges facing hyperthermia is to prepare suitable magnetic media, which can generate heat efficiently on the application of alternating magnetic field with low frequency and intensity.

The heat generated by CNTs/iron oxide nanoparticles in magnetic field mainly relies on the magnetic nanoparticles. As the diameter of magnetic iron nanoparticles that attached onto CNTs ranges from a few nanometers to several hundred nanometers, the prevailing mechanisms of heat generation are hysteresis loss and Neel relaxation, *i.e.* the rotation of particles and magnetic moment [68]. Hence, the heat generation efficiency is highly dependent on particle size, but not in a monotonous manner. Theoretically, there exists a critical size region where coercivity is higher and thus the specific energy absorption rate is much higher than that of superparamagnetic and multi-domain particles [69-71]. In experimental, however, it is hard to prepare such critical-sized particles, since in many cases the produced particles are with a wide distribution of particle size. In parallel, experimental techniques that can be easily adopted to differentiate and characterize superparamagnetic, single-domain and multi-domain structures are also desired.

3.2. CNT biocompatibility

The biocompatibility of CNTs is another concern in practical application. The toxicity of CNTs may arise from the formation of CNT agglomerates and the presence of residual metal catalysts such as Ni and Co. The quantity of CNTs used also affects its toxicity [72-74]. To implant water soluble groups onto CNTs' surface or wrapping CNTs with polymer and bio-molecules can effectively enhance the solubility of CNTs and consequently reduce their toxicity [75-77]. It was also found that CNTs can be metabolized in liver and eliminated through kidneys and bile systems, making less concern about the persistence residence of them in bodies [78]. In addition, the dose differences exist between the pharmacological and toxicological effects of CNTs, which means it is possible to alleviate the toxicological effect by controlling the dose [79]. However, further pathological experiments are still necessary to ascertain the bio-compatibility of CNTs.

4. SUMMARY

In this article we have reviewed the magnetic properties and formation mechanism of CNTs/iron oxide nanoparticles synthesized by various methods. It's obvious that the unique properties of CNTs/magnetic nanoparticles composites have great potential in the therapy of malignant tumor. Using the iron oxide as the heating agents, magnetic inducing hyperthermia can be achieved. With the fascinating one-dimensional tubular structures, meanwhile, the CNTs provided a good opportunity to combine magnetic inducing hyperthermia with targeted drug delivery, photothermal therapy, and monitoring of drug distribution to develop multimodality therapy. Although it is still too early to establish CNT/iron oxide nanoparticles composites for clinic use, these novel materials are undoubtedly interesting and deserve further investigation, in particular, with the advance in the synthesis theory and method and the ascertainment of biocompatibility of CNTs

ACKNOWLEDGEMENT

The National Natural Science Foundation of China (51105051), the Fundamental Research Funds for the Central Universities of China (DUT14LK36) and the Scientific Research Foundation for the Returned Overseas Chinese Scholars (State Education Ministry) were acknowledged for the financial support.

REFERENCES

- [1] R. K. Gilchrist, R. Medal and W. D. Shorey // *Ann. Surg.* **146** (1957) 596.
- [2] A. Jordan, R. Scholz and P. Wust // *J. Magn. Mater.* **201** (1999) 413.
- [3] I. Hilger, K. Frühauf and W. Andrä // *Acad. Radiol.* **9** (2002) 198.
- [4] H. Saito, K. Mitobe and A. Ito // *Cancer. Sci.* **99** (2008) 805.
- [5] J. T. Tang, *Magnetic Induction Hyperthermia for cancer* (People's Medical Publishing House, Beijing, 2009).
- [6] Q. A. Pankhurst, J. Connolly and S. K. Jones // *J. Phys. D. Appl. Phys.* **36** (2003) 167.
- [7] S. Wada, L. Yue and K. Tazawa // *Oral. Dis.* **7** (2001) 192.
- [8] C. Xu, J. Xie and N. Kohler // *Chem. Asian.* **3** (2008) 548.
- [9] W. Yang, P. Thordarson and J. J. Gooding // *Nanotechnology* **18** (2007) 412001.
- [10] S. Iijima // *Nature* **354** (1991) 56.

- [11] L. Dai and A. W. H. Mau // *Adv. Mater.* **13** (2001) 899.
- [12] S. Niyogi, M. A. Hamon and H. Hu // *Accounts. Chem. Res.* **35** (2002) 1105.
- [13] E. Hernandez, V. Meunier and B. W. Smith // *Nano. Lett.* **3** (2003) 103.
- [14] A. Bianco, K. Kostarelos and M. Prato // *Curr. Opin. Chem. Biol.* **9** (2005) 674.
- [15] R. H. Baughman, A. A. Zakhidov and W. A. de Heer // *Science* **297** (2002) 787.
- [16] J. E. Podesta, K. T. Al Jamal and M. A. Herrero // *Small* **5** (2009) 1176.
- [17] Z. Liu, W. Cai and L. He // *Nat. Nanotech.* **2** (2006) 47.
- [18] S. Vardharajula, S. Z. Ali, P. M. Tiwari, E. Eroğlu, K. Vig, V. A. Dennis and S. R. Singh // *Int. J. Nanomedicine* **7** (2012) 5361.
- [19] N. W. Shi Kam, T. C. Jessop and P. A. Wender // *J. Am. Chem. Soc.* **126** (2004) 6850.
- [20] D. Pantarotto, J. P. Briand and M. Prato // *Chem. Commun.* **1** (2004) 16.
- [21] M. M. Rasenick, M. Watanabe and M. B. Lazarevic // *J. Biol. Chem.* **269** (1994) 21519.
- [22] A. E. Porter, M. Gass and K. Muller // *Nat. Nanotechnol.* **2** (2007) 713.
- [23] D. Pantarotto, R. Singh and D. McCarthy // *Angew. Chem. Int. Ed.* **116** (2004) 5354.
- [24] Z. Liu, K. Chen, and C. Davis // *Cancer. Res.* **68** (2008) 6652.
- [25] A. Bianco, K. Kostarelos and C. D. Partidos // *Chem. Comm.* **5** (2005) 571.
- [26] A. M. A. Elhissi, W. Ahmed, I. U. Hassan, V. R. Dhanak and A. D'Emanule // *J. Drug. Deliv.* **2011** (2012) 837327.
- [27] Z. Liu, K. Chen and C. Davis // *Cancer. Res.* (2008) **68** 6652.
- [28] L. J. Meng, X. K. Zhang and Q. H. Lu // *Biomaterials.* **33** (2012) 1689.
- [29] P. Chakravarty, R. Marches, N. S. Zimmerman, A. D. E. Swafford, P. Bajaj, I. H. Musselman, P. Pantano and R. K. Draper // *Proc. Nat. Acad. Sci.* **105** (2008) 8697.
- [30] X. Liu, H. Tao and K. Yang // *Biomaterials.* **32** (2011) 144-.
- [31] A. S. Biris, E. I. Galanzha and Z. R. Li // *J. Biomed. Opt.* **14** (2009) 021006.
- [32] Z. A. Nima, M. W. Mahmood and A. Karmakar // *J. Biomed. Opt.* **18** (2013) 055003.
- [33] M. A. Correa-Duarte, M. Grzelczak and V. Salgueiriño-Maceira // *J. Phys. Chem. B.* **109** (2005) 19060.
- [34] D. Yang, F. Yang and J. Hu // *Chem. Comm.* **29** (2009) 4447.
- [35] C. Gao, W. Li and H. Morimoto // *J. Phys. Chem. B.* **110** (2006) 721.
- [36] A. K. Mishra and S. Ramaprabhu // *J. Phys. Chem. C.* **114** (2010) 2583.
- [37] C. K. Dong and X. Li // *Chem. Res. Chin. Univ.* **25** (2009) 936.
- [38] T. K. Il and T. Rina, *Electrical Properties of Carbon Nanotubes* (InTech, 2011).
- [39] X. J. Fan and X. Li // *New Carbon Mater.* **2** (2012) 111.
- [40] H. Q. Cao, M. F. Zhu and Y. G. Li // *J. Solid. State. Chem.* **179** (2006) 120.
- [41] C. Qin, J. Shen and Y. Hu // *Compos. Sci. Technol.* **69** (2009) 427.
- [42] H. Zhou, C. Zhang and H. Li // *J. Polym. Sci. Pol. Chem.* **48** (2010) 4697.
- [43] L. Wilson, E. E. Kalu and L. Martin // *J. Mater. Chem.* **22** (2012) 595.
- [44] H. F. Zhou and C. Zhang // *Synthetic. Met.* **161** (2011) 2199.
- [45] F. Stoffelbach, A. Aqil and C. Jérôme // *Chem. Commun.* **36** (2005) 4532.
- [46] W. Wu, Q. He and C. Jiang // *ChemInform.* **40** (2009) 397.
- [47] S. Laurent, D. Forge and M. Port // *Chem. Rev.* **108** (2008) 2064.
- [48] Z. Sun, Z. Liu and Y. Wang // *J. Mater. Chem.* **15** (2005) 4497.
- [49] X. Z. Wang and Z. B. Zhao // *J. Phys. Chem. Solids.* **71** (2010) 673.
- [50] J. Wan, W. Cai and J. Feng // *J. Mater. Chem.* **17** (2007) 1188.
- [51] H. Wang, L. Cao and S. Yan // *Mat. Sci. Eng. B. Solid.* **164** (2009) 191.
- [52] L. Jiang and L. Gao // *Chem. Mater.* **15** (2003) 2848.
- [53] F. Tan, X. Fan and G. Zhang // *Mater. Lett.* **61** (2007) 1805.
- [54] X. Shen, R. Z. Gong and Y. Nie // *J. Magn. Magn. Mater.* **288** (2005) 397.
- [55] Q. Zhang, M. Zhu and Q. Zhang // *Compos. Sci. Technol.* **69** (2009) 633.
- [56] Y. Huang, J. Lin and X. X. Ding // *Mater. Lett.* **61** (2007) 697.
- [57] A. H. Lu, E. L. Salabas and F. Schüth // *Angew. Chem. Int. Edit.* **46** (2007) 1222.
- [58] K. JináLee // *Chem. Commun.* **30** (2005) 3847.
- [59] E. C. Vermisoglou, G. Pilatos and G. E. Romanos // *Nanotechnology* **22** (2011) 355602.

- [60] D. Mattia, G. Korneva and A. Sabur // *Nanotechnology* **18** (2007) 155305.
- [61] K. L. Yu, J. J. Zou, Y. H. Ben, Y. P. Zhang and C. J. Liu // *Diamond. Relat. Mater.* **15** (2006) 1217.
- [62] Y. Zhang, N. W. Franklin and R. J. Chen // *Chem. Phys. Lett.* **331** (2000) 35.
- [63] L. Zajýckova, P. Synek, O. Jasek, M. Elias, B. David, J. Bursik, N. Pizurova, R. Hanzlýkova and L. Lazar // *Appl. Surf. Sci.* **255** (2009) 5421.
- [64] S. Karen // *Nanomedicine. Nanotechnology* **7** (2012) 497.
- [65] K. Maier-Hauff, R. Rothe and R. Scholz // *Neuro-oncol.* **81** (2007) 53.
- [66] C. C. Berry and A. S. G. Curtis // *J. Phys. D. Appl. Phys.* **36** (2003) R198.
- [67] P. Moroz, S. K. Jones and B. N. Gray // *Int. J. Hyperther.* **18** (2002) 267.
- [68] J. P. Fortin, C. Wilhelm and J. Servais // *J. Am. Chem. Soc.* **129** (2007) 2628.
- [69] F. E. Luborsky // *J. Appl. Phys.* **32** (1961) 171.
- [70] M. Ma, Y. Wu and J. Zhou // *Magn. Magn. Mater.* **268** (2004) 33.
- [71] A. Tomitaka, H. Kobayashi and T. Yamada // *In. Journal of Physics: Conference Series* **200** (2010) 122010.
- [72] D. X. Cui, F. R. Tian and C. S. Ozkan // *Toxicol. Lett.* **155** (2005) 73.
- [73] S. K. Smart, A. I. Cassady and G. Q. Lu // *Carbon* **44** (2006) 1034.
- [74] M. L. Becker, J. A. Fagan and N. D. Gallant // *Adv. Mater.* **19** (2007) 939.
- [75] M. Adeli, N. Mirab and M. S. Alavidjeh // *Polymer* **50** (2009) 3528.
- [76] K. Medepalli, B. Alphenaar and A. Raj // *Nanomedicine* **7** (2011) 983.
- [77] A. Demming // *Nanotechnology* **22** (2011) 260201.
- [78] Z. Liu, C. Davis and W. Cai // *Proc. Natl. Acad. Sci. USA.* **105** (2008) 1410.
- [79] G. Jia, H. Wang, L. Yan, X. Wang, R. Pei, T. Yan, Y. Zhao and X. Gu // *Environ. Sci. Technol.* **39** (2005) 1378.