

A review: Synthetic strategy control of magnetite nanoparticles production

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Abstract. Iron oxide nanoparticles excite researcher interest in biomedical applications due to their low cost, biocompatibility and superparamagnetism properties. Magnetic iron oxide especially magnetite (Fe₃O₄) possessed a superparamagnetic behaviour at certain nanosize which beneficial for drug and gene delivery, diagnosis and imaging. The properties of nanoparticles mainly depend on their synthesis procedure. There has been a massive effort in developing the best synthetic strategies to yield appropriate physico-chemical properties namely co-precipitation, thermal decomposition, microemulsions, hydrothermal and sol-gel. In this review, it is discovered that magnetite nanoparticles are best yielded by co-precipitation method owing to their simplicity and large production. However, its magnetic saturation is within range of 70-80 emu/g which is lower than thermal decomposition and hydrothermal methods (80-90 emu/g) at 100 nm. Dimension wise, less than 100 nm is produced by co-precipitation method at 70°C-80°C while thermal decomposition and hydrothermal methods could produce less than 50 nm but at very high temperature ranging between 200°C and 300°C. Thus, co-precipitation is the optimum method for pre-compliance magnetite nanoparticles preparation (e.g., 100 nm is fit enough for biomedical applications) since thermal decomposition and hydrothermal required more sophisticated facilities.

Keywords: nano-medicine; chemical synthesis; nano-particles; nanobiotechnology

1. Introduction

Recent years have witnessed unprecedented expansion of research and applications in the area of nanotechnology. Even though, nanotechnology that deals with nanoscale particles began to emerge some 20 years ago (Hodes 2007), nano applications are already showing up across many discipline as diverse as military (Dong *et al.* 2010), pharmaceutical (Liu *et al.* 2008), engineering (Chang and Li 2007), resources (Hajjari *et al.* 2014) and water remediation (de Souza *et al.* 2006). Nanotechnology surely will make our lives more secure, improve healthcare, optimize the usage of unrenewable resources and provide a better environment.

In the recent development of nanotechnology, various nanoparticles (NPs) have gained increasing attention for use in biomedical applications. The application of nanoparticle in medical specifically in diagnosis, imaging, transfection and drug delivery application is set to growing exponentially. Traditionally, some chronic diseases such as cancer are treated with surgery,

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radiation and chemotherapy. However, these approaches have several drawbacks such as lack of sufficient enrichment of therapeutic agents in the tumour area, large tendency of killing normal cells and fatally damaging healthy tissues (Kievit and Zhang 2011, Tietze *et al.* 2015). Hence, nanoparticles has become a promising platform by creating a nanoagent that can stealthy deliver the biological agent or drugs into the targeted tissue and at the same breath limit the cardiotoxicity, cytotoxicity, neurotoxicity, nephrotoxicity and ototoxicity effect.

Nanoparticles possessed a very small size dimension behaviour that simultaneously provide large surface area which give them a superior advantage *in vitro* and *in vivo* drug and gene transport. Nanosize property of nanoparticles offer a great possibility to bind or encapsulate the poorly soluble drugs (Deng *et al.* 2012, Prabaharan *et al.* 2009), protect the therapeutic molecules from physiological barrier (Whitehead *et al.* 2009) and enhance tissue distribution (Gao *et al.* 2004). The physiological barrier such as blood, liver and spleen, kidneys, blood brain barrier and tumour vasculature are very sensitive with the foreign substance that comes to human body. The size of therapeutic agent must remain small to move inside the body without disrupting normal functions of human body system and enhance the efficacy of delivering the payloads into the target tissue (Estelrich *et al.* 2015). For instance, many studies have reported that the majority of injected nanoparticles are taken up by the reticuloendothelial system (RES) which readily response to the materials larger than 100 nm (Kievit and Zhang 2011). In other parts, the basal lamina of the kidneys consists of approximately 10 nm pores, thus the nanoparticles lower than ~100 nm and larger than ~10 nm will not be secreted out from the blood circulation too fast (Kievit and Zhang 2011).

In these times, various nanoparticles are studied as biological application particularly iron oxide nanoparticles (IONPs). IONPs possess a great interest as drug or gene delivery due to their superparamagnetic activity, biocompatibility and very low cost (Ahmed *et al.* 2012). Furthermore, iron oxide is biodegradable and the iron from degraded IONPs enters the body's natural iron store such as haemoglobin in red blood cell (Sun *et al.* 2010). Unique magnetism feature exhibit by IONPs give an extra advantage where IONPs can magnetically drag into the targeted site. Particles size dominates the magnetic behaviour of individual magnetic nanoparticles. At some limit size, the nanoparticles will experienced superparamagnetism behaviour where the size of the particle form a single domain. Domains are the regions where all the atomic moments points in the same direction so that within each domain the magnetization is at maximum values (Owens and Poole 2008). However, the particles will show no longer magnetic interaction when the external field was removed (Lim *et al.* 2011). Superparamagnetism characteristics occurs for nanoparticles where the diameter is usually between 3-50 nm depending on the materials (Dormann *et al.* 1980) and according to D.J. Dunlop, the superparamagnetic size of magnetite IONPs is ~35 nm in diameter (Dunlop 1973). However, some reported that the nanosized of magnetite must be smaller than 20 nm in order to obtain a single domain and exhibit a superparamagnetic property (Sheng-Nan *et al.* 2014).

Iron oxide exists in a rich variety of structure. Anyhow, magnetite (Fe_3O_4) are one of the most magnetic nanoparticles that widely used in the nanomedical application. Nonetheless, it is a technological challenge to control size, shape, surface characteristics, magnetic properties and dispersibility of magnetite in desired solvent (Wu *et al.* 2008). Moreover, bare magnetite possessed two problems where bare magnetite have a tendency to oxidised in air to form maghemite ($\gamma\text{-Fe}_2\text{O}_3$) and consequently the synthesised magnetite will lose their magnetism and dispersibility properties (Lu *et al.* 2007). Another problem is bare magnetite are prone to agglomerate due to van der Waals forces and magnetic interaction among the particles and

correspondingly lower the catalytic and selectivity of the magnetite (Balazs *et al.* 2006). These problems can be encountered by employment an appropriate preparation of magnetite nanoparticles.

2. Synthesis approaches

Numerous researches have been reported to achieve proper control of particle size, well-shaped controlled, colloiddally stable, high magnetic properties and monodisperse magnetite. This such properly designed nanoparticles enhance the ability for localisation of cargo inside the targeted site, by either passive or active targeting (Shapira *et al.* 2011). Fig. 1 present the three most important different routes on the synthesis of magnetite nanoparticles (Mahmoudi *et al.* 2010). However, for our discussion here, we will focus on several chemical synthesis techniques of magnetite nanoparticles especially for nanomedical usage with domain dimensions below 100 nm. Some modifications towards existing techniques such as application of microwave assisted, bioinspired and continuous preparation of magnetite are also addressed.

2.1 Co-precipitation

Well established and the infamous conventional method for obtaining magnetite nanoparticle is

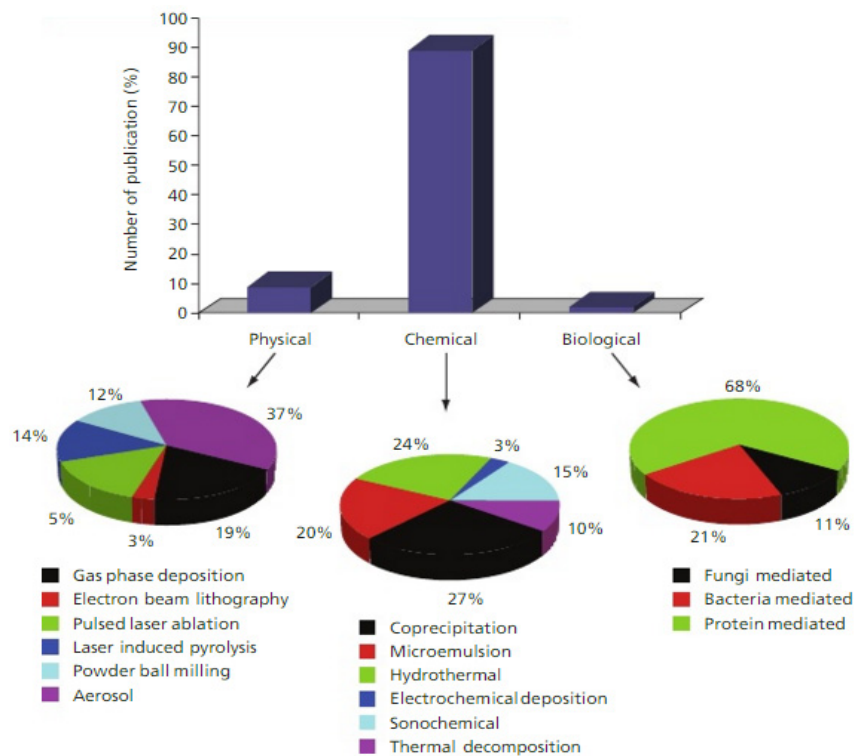
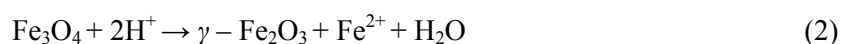


Fig. 1 Numerous publication on the synthesis of IONPs by three different routes. Sources: Institutes of Scientific Information (Mahmoudi *et al.* 2010)

by co-precipitation. This method allows the preparation of magnetic nanoparticles with a rigorous control in size and shape in a convenient way (Wani *et al.* 2014). In general this method consist of mixing ferric (Fe^{2+}) and ferrous (Fe^{3+}) ions in a molar ratio of 1:2 in basic solution and left to react either at room temperature or elevated temperature (Eq. (1)) (Laurent *et al.* 2008).



The presence of oxygen in the mixture lead the magnetite transformed into maghemite (Eq. (2)) and accordingly lower the magnetic properties. Also, smaller increment in size was observed from the original magnetite due to the reduction of Ostwald ripening process for larger nanoparticles (Sun *et al.* 2004). Thus, the reaction are performed under bubbling nitrogen or argon gas to create an oxygen-free environment.



The size, shape and magnetic properties of magnetite nanoparticles depend on the type of salts used, molar ratio of ferric and ferrous ions, pH value, stirring rate, reaction temperature and other parameters (Laurent *et al.* 2008). These factors need to be carefully controlled to ensure that the synthesis nanoparticles fall within the target range. A study by Ahn *et al.* (2012) reported that the formation pathways of magnetite by this method are highly complex and potential to transforms to other different composition of iron (oxyhydroxide) species (Lenders *et al.* 2014). Principally, the composition and also the size of magnetite is strongly depended on Fe^{2+} and Fe^{3+} molar ratio. Small values of $x = \text{Fe}^{2+}/\text{Fe}^{3+}$ ratio which is x lower than 0.1 lead to the goethite [$\text{FeO}(\text{OH})$] formation. For $x = 0.2$ and $x = 0.3$, distinct phase of oxyhydroxide and variable size of nonstoichiometric magnetite was formed (Jolivet *et al.* 1992, 1997). However, the best and well known molar ratio used is $x = 0.5$ producing a homogenous in size and composition nanoparticles (Jolivet *et al.* 1992). Increasing the x ratio value will increase the mean size of nanoparticles which is not suitable for *in vivo* medical application (Merk *et al.* 2014, Yao *et al.* 2014). Laurent *et al.* (2008) suggested that the x ratio between 0.4 to 0.6 is the best range to get the well shape and monodisperse magnetite nanoparticles.

Normally, black precipitate of magnetite nanoparticles formed at pH greater than 8. Higher pH and ionic strength will give smaller particle size and large distribution size due to the lower surface tension of the particles (Malyutin *et al.* 2015). However, the decrement of magnetite size was stopped at pH 11 and kept increasing again when the pH is greater than that (Wang *et al.* 2013, Mahdavi *et al.* 2013a, b). Besides that, good polydispersity and shape anisotropy of magnetite formed when the NaOH solution was added into the mixture at constant rate (50 ml/min) instead of adding NaOH solution all at once (Šutka *et al.* 2015). Meanwhile, the measured magnetite size did not reveal a large difference when the concentration of 2.5 M NaOH or 5 M NaOH was used (Šutka *et al.* 2015).

Size distribution of magnetite also can be tailored by the reaction temperature. Mostly, preparation of magnetite nanoparticles are done at ambient temperature rather than at elevated temperature since the crystallite size are larger at elevated temperature (Wang *et al.* 2013). Such phenomena are already studied where the crystallite size of magnetite are reduced when 25°C to 45°C initial reaction temperature was used. Even so, the crystallite size increase when the initial reaction temperature increase from 45°C to 85°C (Mahdavi *et al.* 2013a, b). The growth of magnetite nucleus is easier to happen when higher temperature was selected due to the energy

possessed by the particles resulting a greater number of collision between the particles (Mahdavi *et al.* 2011, 2013a, b). Reduction in size and sphere shape production also can be manipulated by stirring rate. At high stirring rate, the energy transferred to the suspension medium is increased and the reaction solution can be dispersed into smaller droplets resulting a reduction in size (Sun *et al.* 2007). However, such phenomena only experienced up to 800 rpm (Mahdavi *et al.* 2013a, b).

Instead of using two iron precursor, one can start only an aqueous Fe^{3+} salt solution. The procedure consist of mixing iron chloride (FeCl_3) with potassium iodide aqueous solution with a 3:1 molar ratio. Potassium iodide reduce the iron salt and the mixture was hydrolysed with 25% ammonia to get the black precipitate of magnetite. Accordingly, magnetite nanocrystals with diameter 7.84 ± 0.05 nm and nanorods with diameter 6.3 ± 0.2 nm and length 46.2 ± 0.9 nm was formed (Khalil 2015). Besides that, some reported that superparamagnetic magnetite nanoparticles with a high saturation magnetisation (M_s) can also be synthesized in oxygen-rich environment. In air medium, oxygen potential to transform Fe^{2+} to Fe^{3+} and reduce the initial ratio (Karaagac *et al.* 2010). Thus, 8.77 nm nanoparticles was formed using preferred ratio of $x = 0.667$ instead of $x = 0.5$ (Karaagac *et al.* 2010, Khalafalla and Reimers 1980).

Thermal energy absolutely will increase the molecular kinetics and festinate the molecular reactions. Thus, the energy created by microwaves also can affect the reaction rate by altering the integrity of noncovalent secondary bonding (Leong *et al.* 2010). Bhattacharya *et al.* (2011) used microwave irradiation (MI) instead of conventional heating method to produce a better superparamagnetic magnetite properties. Under TEM, the chemical co-precipitation method of iron salts in poly (vinyl) alcohol produce slightly larger magnetite size under MI (11.5 nm) compared to the magnetite without MI (8.5 nm). But the magnetic saturation (M_s) of MI magnetite (~ 27 emu/g) was more than double than without MI magnetite (~ 12 emu/g) which is more suitable to use in magnetic responsive *in vivo* application (Bhattacharya *et al.* 2011).

Most synthetic magnetite is produced by current fast co-precipitation method and yield poor control of particle dimension and morphology (Ahn *et al.* 2012). Lenders *et al.* proposed a new simple protocol that involve slow co-precipitation using magnetotactic bacteria. Magnetotactic bacteria presence of a ferrihydrite precursor inside the magnetosome vesicle (Baumgartner *et al.* 2013, Fdez-Gubieda *et al.* 2013). Through this method, the local formation of ferrihydrite are produced at low pH and converted to magnetite at high pH ($\text{pH} > 8$) by reaction with Fe^{2+} . The crystal size are controlled through the ammonia influx and the Fe^{2+} concentration (Lenders *et al.* 2014). Another development of reliable and eco-friendly processes was done by Mahdavi *et al.* where magnetite nanoparticles were synthesized using reduction of ferric chloride solution with brown seaweed (BS, *Sargassum muticum*). BS extract containing sulphated polysaccharides that cause the reduction of Fe^{3+} and subsequently achieve to harvest 18 ± 4 nm superparamagnetic cubic magnetite (Fig. 2) (Mahdavi *et al.* 2013a, b).

2.2 Thermal decomposition

Another synthetic strategy is using very high heat energy to break down the chemical bonds of iron precursor prior another reaction occur to form the magnetite nanoparticle. Such pathways is called as thermal decomposition or thermolysis. In theory, monodispersed magnetite are synthesized using organometallic precursor such as iron (III) acetylacetonates [$\text{Fe}(\text{acac})_3$], iron (III) cupferronates (FeCup_3) or iron carbonyl compound in high boiling organic solvents that contain surfactant. Fatty acids, hexadecylamine, oleylamine or oleic acid are the common used surfactants.

Morphology and size of magnetite nanoparticles can be manipulated by various parameters

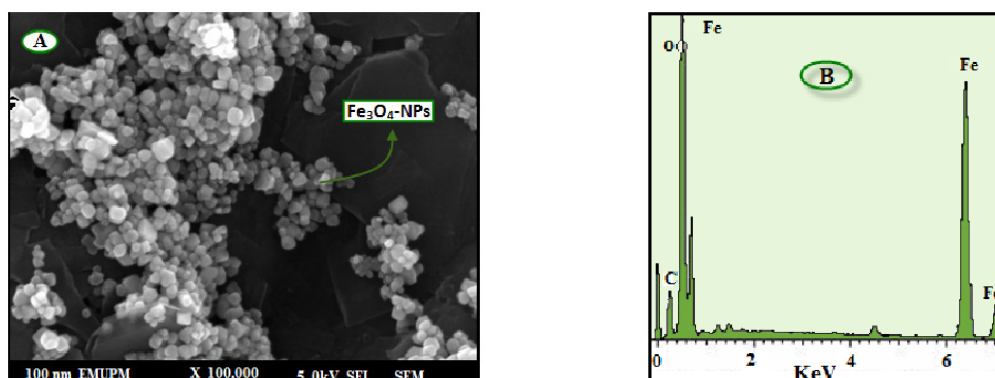


Fig. 2 FESEM image of cubic magnetite nanoparticle (A) and energy dispersive X-ray fluorescence spectrometry spectra of cubic magnetite nanoparticles synthesized using BS extract (B) (Mahdavi *et al.* 2013a, b)

including ratio of starting reagent, type of solvent or surfactant used, stirring, reaction temperature, reaction time and also aging period. Salas *et al.* (2012) studied the effect of varying the surfactant concentration which is oleic acid under extensive heating of $\text{Fe}(\text{acac})_3$ at 315°C . In this case, constant volume of solvent 1-octadecene and constant reaction time was used throughout of the experiment. The result show that, the as-synthesized nanoparticle size decrease when the amount of oleic acid was kept increasing. The reaction rate of growth process will be faster with low oleic acid concentration that lead to larger particles. However, the growth process is slower at high oleic acid concentration producing smaller nanoparticles (Salas *et al.* 2012). Besides that, Salas *et al.* also studied about the effect of stirring and without stirring mixture using the same reagent and parameters. Larger nanoparticles are obtained for non-stirring mixture with broad size distribution. Non stirring mixture causes the reaction mixture form a highly heterogeneous from the beginning of reaction which makes it difficult to control the size and shape of magnetite (Salas *et al.* 2012). It is found that the cubic and spherical shape can be manipulated using the same reagent. Spherical magnetite was formed through $\text{Fe}(\text{acac})_3$, oleic acid and 1-octadecene reaction mixture while cubic nanoparticle was formed by employed similar method with absent of oleic acid. Both nanoparticles has almost same size (spherical = 8.5 nm in diameter, cubic = 8.0 nm in side length) and possessed magnetic coercivity near zero value that confirm that their superparamagnetic nature (Fig. 3). However, spherical magnetite exhibit lower M_s due to either crystalline defect structure (smaller magnetic domain) or their greater of oxidation and nonmagnetic iron oxide content (Zhen *et al.* 2011). Furthermore, the as-synthesized cubic magnetite also show great promise for use in biomedical imaging by proving higher T_2 relaxivity, higher degree crystallinity and good magnetic properties under analytical equipment (Zhen *et al.* 2011).

Alternatively, $\text{Fe}(\text{acac})_3$ was also reported to produce cubic magnetite nanoparticle using different surfactant and solvent. Cubic shaped magnetite with size range from 5 nm to 30 nm can be controlled by modifying the molar ratio of $\text{Fe}(\text{acac})_3$ -to-decanoic acid in dibenzyl ether solvent. By lowering the amount of decanoic acid may promote faster growth of the particle and created unstable system which give broadening of the particle size distribution. Previously synthesized magnetite was heated up to 200°C and then they further their study by using higher synthesis temperature which is 265°C and 275°C . But the nanoparticles give a broader size distribution, more irregular shape and bigger size (Guardia *et al.* 2010). This phenomena was confirmed by

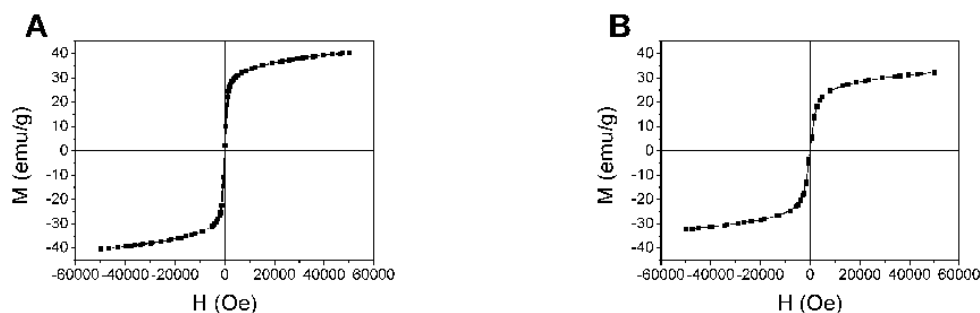


Fig. 3 Magnetization, M (emu/g) vs magnetic field, H (Oe) for comparison of cubic (A) and spherical (B) magnetite nanoparticle at 293 K (Zhen *et al.* 2011)

another research group (Belaid *et al.* 2013, Kim *et al.* 2009, Wang *et al.* 2015).

Presence of solvent in the reaction mixture can limit the thermal decomposition temperature by the boiling temperature of the solvent (Maity *et al.* 2009). Thus, Maity *et al.* (2009) come with a new approach by developing the thermal decomposition of $\text{Fe}(\text{acac})_3$ in the presence of stabilizing surfactant only. The thermal decomposition temperature and reaction time can be varied easily in a free-solvent mixture so that the size and crystallinity of magnetite can be tailored effectively. As a result, the nanoparticles obtained exhibit larger size and M_s when the synthesis temperature and reaction time increase (Maity *et al.* 2009).

Particle size can be tuned from 7 nm to 25 nm by using another type of iron precursor such as iron pentacarbonyl [$\text{Fe}(\text{CO})_5$]. Here, octyl ether acted as solvent while oleic acid as a surfactant. The synthesis includes reflux procedure and then the oxidation into iron oxide nanoparticles. Under constant ratio, the superparamagnetic nanoparticle size increases with the aging time (Zhu *et al.* 2011). Magnetite nanoparticles can also be prepared by using ferrous oxalate dihydrate [$\text{Fe}(\text{C}_2\text{O}_4)_2 \cdot 2\text{H}_2\text{O}$] precursor. Thermal decomposition of the oxalates at sufficiently low oxygen partial pressure managed to synthesize 35 nm to 55 nm magnetite size (Angermann and Töpfer 2008). In addition, using iron chloride ($\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$) precursor can lead to production of monodisperse magnetite nanoparticles as well. The presence of halogen ion (Cl^- or Br^-) in the reaction mixture assists in stabilizing (Dogan *et al.* 2004) facets of magnetic iron oxides and influences the shape control of nanocubes magnetite. By using such precursor, the morphologies of iron oxide nanoparticles were similar and no remarkable difference in size or shape was observed when different heating rates were used (Fig. 4). Similar observations are seen in another publication where greater size and crystallization are obtained when the reaction temperature was increased (Xu *et al.* 2010).

2.3 Hydrothermal

Magnetite nanoparticles with controlled size and shape have been synthesized by heating various iron precursors at high temperature. The reaction can be performed either in aqueous medium in reactors or autoclaves under high pressure (generally in the range of 0.3 to 4 MPa) and high temperature (generally in the range of 130°C to 250°C) (Wu *et al.* 2008). Typically, Fe^{3+} salt was used as precursor in the solvent (urea, sodium citrate or acetate). Synthesis parameters such as type of iron precursor used, ratio of precursor to solvent, reaction time and reaction temperature must be strictly monitored in order to get well shape and good crystallinity of magnetite nanoparticles.

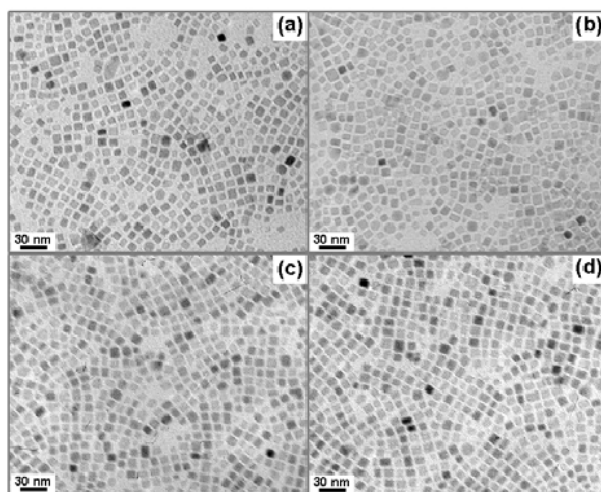


Fig. 4 The TEM images of cubic iron oxide nanocrystals synthesized at different heat rates: (a) 1.5; (b) 10; (c) 20; and (d) 30 K/min (Xu *et al.* 2010)

The magnetite nanoparticles with highly crystalline and the tuneable diameter using $\text{FeCl}_2 \cdot 4\text{H}_2\text{O}$ as iron source are governed by various reaction conditions. Preceding oxidation of $\text{FeCl}_2 \cdot 4\text{H}_2\text{O}$ before autoclave at 134°C with gauge pressure of 2 bar managed to produce superparamagnetic magnetite size in the range of 15 nm to 31 nm. With the amount of $\text{FeCl}_2 \cdot 4\text{H}_2\text{O}$ increase from 0.25 g to 1.25 g, the output magnetite size was decreased. This behaviour are due to the large concentration of Fe^{2+} ions that will form a large number of seed nuclei (Hui *et al.* 2008, Shevchenko *et al.* 2002). The effect of using same amount of two solvents which are water and ethanol instead of water only producing lower magnetite size. The hydroxyl group on the surface of magnetite can absorb ethanol molecule through the hydrogen bond formation. Subsequently, attached ethanol will inhibited the successive growth and aggregation of the particles (Ge *et al.* 2009). Instead of using ethanol, Li *et al.* use nontoxic tartaric acid (TA) as modulators and reducing agent. In absent of TA in the reaction mixture, 150 nm of cubic nanoparticles are obtained and the products only consists of hematite nanoparticles (Fe_2O_3). Then, as the amount of TA increase, more gradual structure are formed where magnetite composition increase indicating that Fe^{3+} ions are reduced by TA. It can be deduced that high TA can produce more nucleus sites for magnetite nanocrystalline. This is proven by XRD as the smallest size obtained which is 13.5 nm on average. Interestingly, the as-synthesized magnetite nanoparticles will not be oxidised to maghemite after being stored in air for 1 year, revealing that their potential applications in biomedicine (Yan *et al.* 2009).

The presence of Cl^- ion or other ion that comes from the iron precursor can easily contaminated the solution. Washing step to get clear magnetite nanoparticles are impeded by strong adsorption of ions on the nanoparticle surface (Burugapalli *et al.* 2004). Besides that, iron sulfate precursor also was not a best choice owing to potentially to form oxysulfates that cannot be eliminated easily. While, iron nitrate precursor have a tendency to oxidise in air (Hu *et al.* 2011). Therefore, some researcher use environmental precursor such as iron acetylacetonate, $[\text{Fe}(\text{acac})_3]$ for hydrothermally produce magnetite nanoparticle (Gao *et al.* 2010, Yang *et al.* 2012). Yang *et al.* (2012) synthesis the magnetite nanoparticles by using $\text{Fe}(\text{acac})_3$ precursor while poly(acrylic acid)

(PAA) was chosen as the stabilizer and at the same time acts as a coating material to increase the stability and biocompatibility of nanoparticles. Effect of different solvent, reaction time, and the amount of the stabilizer towards the size are studied (Table 1). The reaction temperature is related to the boiling point of the solvent and thus giving a late growth process for higher boiling point solvent. Thus, poor shape and dispersion are formed due to the decrease of reduction of solvent. Thus, Yang *et al.* used ethylene glycol (EG) for another parameters study (Yang *et al.* 2012).

In spite of preparation and surface modification of magnetite in batch mode, some group comes out with a new idea in order to allow large scale of magnetite production by continuous hydrothermal process (Liang *et al.* 2010, Maurizi *et al.* 2011, Xu and Teja 2008). Maurizi *et al.* (2011) managed to obtain 40 nm of citrate coating magnetite nanoparticle. Iron salt, citrate solution and NaOH counter currently introduced with the preheated distilled water in a reactor leading to rapid heating and subsequent precipitation reaction (Maurizi *et al.* 2011).

Microwave assisted significantly reduce the processing time and energy cost of the reaction (Kharisov *et al.* 2012). Hu *et al.* (2011) synthesis 3 different iron oxide nanoparticle by using specially designed laboratory microwave autoclave reactor. Using FeCl₃ as the single precursor led to the production of pure hematite only. While, magnetite and maghemite nanoparticle are formed when single FeCl₂ precursor was used (Hu *et al.* 2011). Conventional heating hydrothermal method requires a long time to complete the synthesis process. Conversely, magnetite samples that

Table 1 Experimental detail and parameters of the controlled clinical trials (Yang *et al.* 2012)

Batch	Fe(acac) ₃ (mmol)	Solvent (40mL)	PAA (wt%)	Stirring	Temperature (°C)	Time (h)	Average particle size of primary NP (nm)	Average particle size of secondary NP (nm)
1	1.5	EG ^a	1.00	Ultrasonic (30 min)	200	16	9.3	120
	1.5	DEG ^b	1.00		250	16	8	-
	1.5	TREG ^c	1.00		280	16	7	-
2	1.5	EG	1.00	Ultrasonic (30 min)	200	5	20	-
	1.5	EG	1.00		200	8	7	90
	1.5	EG	1.00		200	12	10	126
	1.5	EG	1.00		200	16	6	50
	1.5	EG	1.00		200	24	5	137
	1.5	EG	1.00		200	32	5	130
3	1.5	EG	0.00	Ultrasonic (30 min)	200	16	8	75
	1.5	EG	0.25		200	16	8	150
	1.5	EG	0.50		200	16	5	137
	1.5	EG	0.75		200	16	5	120
	1.5	EG	1.00		200	16	-	-
	1.5	EG	2.00		200	16	-	-
4	1.5	EG	1.00	Agitation (30 min)	200	16	6	120
	1.5	EG	2.00		200	16	6	110
	1.5	EG	3.00		200	16	6	100

^a Ethylene glycol; ^b Diethylene glycol; ^c Triethylene glycol

processed under microwave-assisted for 8 and 15 minutes at 100°C managed to produce ~25 nm of cubic nanoparticle. Interestingly, XRD measurement revealed that no impurity phases were observed instead of cubic magnetite only (Xavier *et al.* 2014).

2.4 Microemulsion

Under microemulsions or the reverse micelles methods, a broad range of nanoparticles can be formed. This synthetic technique use of a biphasic heterogeneous solution of water-in-oil (w/o) where iron precursors are stirred (Lam *et al.* 2013). Aqueous phases are essential to use as nucleation sites for the formation of nanoparticles, usually in the presence of surfactant molecules in order to form micelles. The magnetite precipitation process start within the contained micelle when two identical w/o microemulsions containing the desired reactant are mix together (Fig. 5) (Gupta and Gupta 2005, Patel *et al.* 2013). Thus, the nanosized of water pool behave as intelligent nanoreactor. The size and polydispersity of the nanoparticles inside the micelles can be tuned by control of stirring speed, bulk temperature, type of solvent used, the surfactant and co-surfactant employed, addition of electrolyte, reagent concentration and molar ratio $w = [\text{water}]/[\text{surfactant}]$ (Mahmoudi *et al.* 2011, Maleki *et al.* 2012, Patel *et al.* 2013).

Every single micelle in the mix up mixture are continuously move and collide each other due to the Brownian motion (López-Quintela *et al.* 2004). In each collision, interchange of material took place which is known as intermicellar exchange. Efficiency of the intermicellar exchange are strongly depend on the elasticity of the surfactant film (Candau *et al.* 1999). Surfactant molecules form a single layer at the interface between the oil and water phase owing to the hydrophobic-hydrophilic interaction. Lu *et al.* (2013) using different kind of surfactants to synthesized nanosized magnetite particles (Lu *et al.* 2013). The difference of crystal defect is predominantly controlled by the charge of the polar headgroup. The lattice perfection of magnetite decreased when anionic surfactant was used compare to neutral and cationic surfactant. In anionic surfactant such as sodium dodecyl sulphate (SDS) microemulsions, the positive iron ions of Fe^{2+} and Fe^{3+} were attracted with the anionic headgroup SO_4^- and OH^- . The electrostatic attraction between

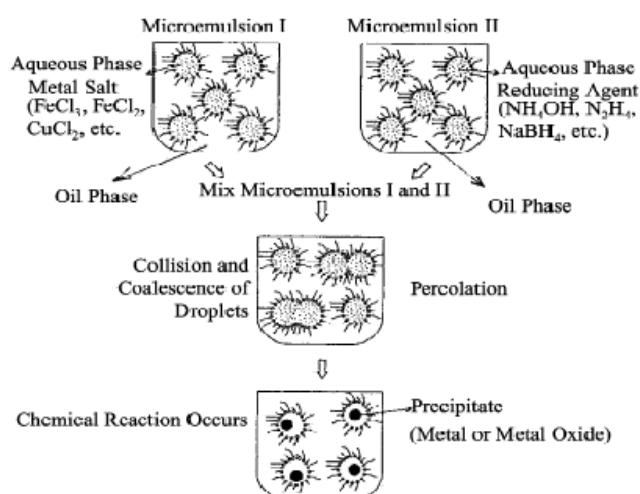


Fig. 5 Mechanism for the formation of metal particles by water-in-oil microemulsions (Patel *et al.* 2013)

surfactant and reactant lower down the sufficient collisions for material exchange and subsequently give poor perfection of the particles. Oppositely, cationic surfactant speed up the material exchange since existence of electrostatic repulsion between head group and iron ions (Lu *et al.* 2013). Besides that, bigger surfactant headgroup spacing enhanced the magnetite crystallization process by controlling the flexibility of the surfactant film. Larger headgroup produce loose arrangement among the surfactant molecule resulting flexible film instead of rigid film on the interface. Therefore, efficient intermicellar exchange was attained (López-Quintela *et al.* 2004). The length of the hydrophobic tail can manipulate the duration of the micellar lifetime. Lengthy micellar lifetime was possessed when longer hydrophobic tail was used and subsequently affects the process of nanodroplets motion-collision exchange and thus the growth rate of the nanoparticles (Aniansson *et al.* 1976, Lu *et al.* 2013).

Surfactant covered water pools offer a confined environment for the nucleation and controlled growth of the nanoparticles where the amount of surfactant to water will determine the last size of the nanoparticle. Under constant surfactant concentration, the size of the water pools increase proportionally to the amount of the added water phase (Caruntu *et al.* 2005). Concurrently, nanoparticle has a capacity to grow larger as compared to small water pool (Maleki *et al.* 2012). The shape of the nanoparticle also affect by the water-to-surfactant ratio where decreasing the ratio value will changed the spherical shape to cylindrical and lamellar shapes (Loo *et al.* 2008). At higher concentration of Fe salts but at constant $[Fe^{2+}/Fe^{3+}] = 0.5$ favour a higher nucleation rate resulting larger nanoparticles size (Maleki *et al.* 2012). Such behaviours are developed due to the overlapping nucleation and growth process (Karlsson *et al.* 2008). On the other hand, no obvious variation of the particle size was observed when the synthesized temperature was regulated from 50°C to 70°C except the crystal defect was decreased (Loo *et al.* 2008). The Brownian force of microemulsions systems become active at higher temperature and thus increase the effective collision for the material exchange and favour a faster nucleation and growth process (Lu *et al.* 2013).

In principle, type, concentration and strength of the reduction agent can manipulate the speed of reaction and then favours more perfect nanoparticles characteristics. At lower concentration of NH_4OH , better crystallinity and higher M_s was obtained. Meanwhile, insignificant effect was observed on the size of the magnetite nanoparticles when the concentration of NH_4OH was changed in the range of 25%-30% v/v (Maleki *et al.* 2012). Park *et al.* reported that nanoparticles prepared by using ammonium hydroxide leads to the formation of $Fe(OH)_3$ that later can lower the crystallinity of nanoparticles. Thus, they employed ammonium acetate as reduction and precipitating agent which give better crystallinity (Park *et al.* 2001).

Superparamagnetic magnetite nanoparticles were found to have average diameters between 6.9 to 7.9 nm by employed bicontinuous microemulsions rather than using normal reverse micelle microemulsions. Bicontinuous microemulsion offered a higher capacities of aqueous phase by forming a nanoscale interconnected aqueous channels structure instead of nanodroplets aqueous phase (Candau *et al.* 1999, Esquivel *et al.* 2007). One reported that the formation of bicontinuous microemulsions structure only occurs when the content of aqueous phase is higher than 20 % (Eicke *et al.* 1989). Under controlled aforesaid amount of aqueous phase, Loo *et al.* revealed that increment of surfactant concentration caused a diminution in the diameter of the nanoparticles due to the smaller interconnected aqueous channel form (Loo *et al.* 2008).

Even though bicontinuous microemulsions able to obtain particles up to 1.16 g of product per 100 g of total mixture (Esquivel *et al.* 2007) which is about 92% of increment as compared to normal reverse microemulsion (Gobe *et al.* 1983, Lee *et al.* 1992), the yields is still consider low if

correlated with co-precipitation and thermal decomposition method. Plus, large amount of solvent are required to synthesize appreciable amounts of particles where it is not applicable for large scale application (Lu *et al.* 2007).

2.5 Sol gel and polyols

The sol-gel process is a versatile chemical approach for the synthesis of nanoparticles with precise shapes and size. Sol-gel synthetic strategy makes use of a gelling agent to form a homogeneous gel where a metal salt is stirred (Lam *et al.* 2013). This process basically undergo the hydroxylation and condensation of metal precursors in solution to form a colloid.

Sol-gel method provide a wide range of synthesis temperature, for instance, Cui *et al.* managed to obtain nearly monodispersed α -Fe₂O₃, γ -Fe₂O₃ and Fe₃O₄ with same procedure and same starting reagent through a medium temperature sol-gel route. Uniquely, the formation of different final iron oxide structures are only depended on the drying process (Fig. 6). The size displayed by TEM revealed that 4.9 nm of Fe₃O₄ nanoparticles are obtained by the centrifugation of sol. While, slight increment in size of γ -Fe₂O₃ was formed when xerogel was heated at 150°C. Yet, directly drying of wet Fe₃O₄ gel at 150°C without the formation of xerogel first allowed phase transformation to 10.1 nm α -Fe₂O₃ (Cui *et al.* 2013).

The sizes of obtained magnetite nanoparticles are readily tailored by longer annealing temperature range under vacuum environment. The magnetic behaviour, particle size and crystallinity of magnetite nanoparticles is very sensitive to the annealing temperature where these physico-chemical properties increase as annealing temperature was adjusted from 200°C to 400°C (Xu *et al.* 2007). Combination of microwave heating with this route provide a fast and energy efficient synthesis methodology to metal oxide nanoparticles (Bilecka *et al.* 2009). The reaction mixture of Fe(acec)₃ that dissolved in benzyl alcohol was heated at 170°C by exposed to microwave radiation for 12 min and accomplished to yield 5-6 nm of nanoparticles (Bilecka *et al.* 2011).

Liquid polyols offer a high dielectric constant which provides a better solvent to dissolve inorganic compound (Laurent *et al.* 2008). Besides that, polyols often served as high boiling point solvent, reducing agent and also as stabilizer agent to control the particles growth and prevent the

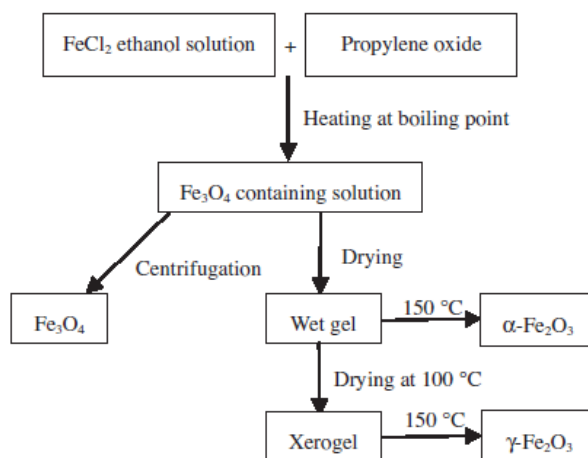


Fig. 6 Scheme flow for the preparation of α -Fe₂O₃, γ -Fe₂O₃ and Fe₃O₄ nanoparticles (Cui *et al.* 2013)

Table 2 Summary of the synthetic methods

Method	Difficulty	Reaction temperature (°C)	Reaction period	Size distribution	Shape control	Yield
Co-precipitation	Very simple, ambient or inert condition	20-90	Min-hours	Relatively narrow	Mode rate	Very high
Thermal decomposition	Complicated, inert atmosphere	100-320	Hours-days	Very narrow	Very good	Very high
Microemulsions	Complicated, ambient condition	20-50	Hours	Relatively narrow	Good	Low
Hydrothermal	Simple, high pressure and temperature	> 220	Hours	Very narrow	Very good	Medium
Sol-gel	Moderate	> 40	Min-hours	Narrow	Good	High

aggregation (Cai and Wan 2007). Seeing of these special characters, Cai and Wan (2007) successfully synthesized magnetite nanoparticles in liquid polyols at elevated temperature. Four types of polyols including ethylene glycol (EG), diethylene glycol (DEG), triethylene glycol (TREG) and tetraethylene glycol (TEG) have been explored to study the formation of magnetite nanoparticles by using $\text{Fe}(\text{acac})_3$ as iron precursor. Anyhow, only TREG leads to non-aggregated and narrow size distribution of magnetite nanoparticles. Meanwhile, no magnetite structure was formed under EG and employment of DEG and TEG as a solvent leads to poor stability magnetite nanoparticles (Cai and Wan 2007). Non-aggregated quasi-spherical shape also can be produced by applying sol-gel method followed by a supercritical drying in ethyl alcohol. Computation from XRD and Mössbauer measurement discovered that the obtained product is of pure magnetite phase with 8 nm size (Lemine *et al.* 2012).

3. Conclusions

The chosen of the methods that meet the certain properties are actually depended on the personnel or research group choice. Roughly, in terms of simplicity and fast preparation technique, co-precipitation is the preferred method. But required a careful pH adjustment and tendency to form a large size distribution. Concerning the size and morphology control, thermal decomposition implied a great potential to develop. However, employment of very high temperature and time consuming reaction hindered the advantages. Hydrothermal synthesis offers similar benefits, but also the synthesized period completed in few days plus poor dispersity as compared to thermal decomposition route makes it not a promising choice. Monodispersed nanoparticles can be obtained by microemulsions technique. Withal, this technique is not relevant to use in large scale production since large amount of solvent are involved. Despite the sol-gel route manage to produce well shape and size of magnetite nanoparticles up to 60 g in a single reaction (Cui *et al.* 2013), such technique is relatively little explored method and the product form have a possibility to contaminate from the by-products (Teja and Koh 2009). Up to now, magnetic nanoparticles are mostly prepared from co-precipitation and thermal decomposition for various application notably in nanobiomedicine. The advantages and disadvantages of the five aforementioned synthetic technique are briefly tabulated in Table 2.

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