Continuous synthesis of iron oxide (Fe₃O₄) nanoparticles via thermal decomposition

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Abstract Iron oxide nanoparticles have become of great interest in the medical field for their potential uses in areas such as biomagnetic imaging and hypothermia cancer treatment. Traditionally, particles for these applications are produced through batch-based methodologies. Herein, we demonstrate an alternative continuous flow production method for the synthesis of Fe₃O₄ iron oxide nanoparticles. Advantages of continuous flow over the batch method include consistent formation of uniformly spherical particles, thorough mixing of reactants, and capacity for high-volume particle production. In this study, a continuous flow reaction mechanism was proposed in which stoichiometric control of reactants had the potential to control final particle size. The project was conducted under the supposition that the iron oleate/ligand ratio in the precursor was the greatest size control factor, with a higher ratio resulting in smaller particles. The resulting particles produced by this continuous method were characterized by high-resolution transmission electron microscopy, X-ray diffraction, and magnetometry.

Keywords: Continuous flow; Iron oxide; Magnetite; Synthesis

1 Introduction

Magnetic nanoparticles have become an important focus for biomedical research because of their potential for multiple biological applications (Gonzales-Weimuller, Zeisberger, & Krishnan, 2009; Ito, Shinkai, Honda, & Kobayashi, 2005; Yu, Huang, Yousaf, Hou, & Gao, 2013; Laurent et al., 2008; Ma et al., 2004; Pankhurst, Connolly, Jones, & Dobson, 2003; Park et al., 2007; Veiseh, Gunn, & Zhang, 2010). Their small size, biological compatibility, and responsiveness to magnetic fields make them great materials to be used in the magnetic separation of cells and other biological materials, cell targeted drug delivery, magnetic

hyperthermia, and improved bioimaging as contrast agents. There are several routes for synthesizing iron oxide nanoparticles. Particles can be formed through coprecipitation using a solution of Fe(II) and Fe(III) salts and an alkali metal hydroxide (Dresco, Zaitsev, Gambino, & Chu, 1999; Massart, 1981). However, higher-quality particles (i.e., with more narrow size distribution) are most commonly made using thermal decomposition of an iron precursor. A common method is the decomposition of iron acetylacetonate in a high-boiling point organic solvent, with a surfactant or reagent (Sun & Zeng, 2002; Xu, Shen, Hou, Gao, & Sun, 2009). Alternatively, what is referred to as Park's synthesis uses a mixture of iron oleate, oleic acid, and 1-octadecene and is another well-known batch method for the production of iron oxide nanocrystals (Park et al., 2004). Traditionally, such batch methods are used for the vast majority of magnetic nanoparticle synthesis. Unfortunately, they are often limited to smaller-scale reactions, as the batch method is difficult to scale up because of the importance of thermal control during the reaction (Park et al., 2004). The rate of heating, the final temperature of the reaction, and the annealing time are all very important to both the size and size distribution of the nanoparticles (Park et al., 2004; Sun et al., 2004). The larger the batch becomes, the more difficult it is to control the temperature throughout the reaction, and the particles produced are less consistent. Continuous flow can potentially avoid these limitations.

One proposed method to continuously produce nanoparticles is by means of a flow microreactor (Chang, Paul, Remcho, Atre, & Hutchison, 2008). For example, a continuous flow process was used to produce silver nanoparticles (Table 1A) with a narrow size distribution ($8.6 \text{ nm} \pm 1.0 \text{ nm}$ by TEM) (Lin, Terepka, & Yang, 2004). In this process, particle aggregation along the walls of the reactor was an issue. This was counteracted by the addition of more oleylamine in the system, which also resulted in higher polydispersity (Lin et al., 2004). Gold nanoparticles and nanorods have been produced with distinct control over particle shape and size in a continuous flow reactor (Table 1B and 1C) (Boleininger, Kurz, Reuss, & Sönnichsen, 2006; Wagner & Köhler, 2005). An issue with the gold nanoparticles microreactor was along the walls, leaving a thin film. To prevent fouling of the reactor, the inside walls were given a protective coat to prevent the deposition of the metal (Wagner & Köhler, 2005). Proper control of the pH was another way to decrease the effects of fouling, but the mean diameter of the resulting particles tended to increase with increasing pH. Control of the shape was demonstrated in gold nanorod synthesis, in that nanorods with higher growth temperatures tended to exhibit an extinction maximum shifted to lower wavelengths, which corresponded to rods with smaller aspect ratios (Boleininger et al, 2006). Titania nanoparticles were produced using a continuous flow through a same-axle dual pipe (Table 1D) (Takagi, Maki, Miyahara, & Mae, 2004). The resulting particles had an average size of 100 nm with a narrow size distribution. The corresponding batch method produced particles with a random size distribution (Takagi et al., 2004).

Table 1

Currently, there are several microreactor designs for the large-scale synthesis of iron oxide nanoparticles. Several of these methods use the co-precipitation route for continuous or large-scale nanoparticle production. One proposed design uses a millimetric coaxial flow device operating under laminar flow (Table 1E) (Abou Hassan, Sandre, Cabuil, & Tabeling, 2008). Basically, fluid flowing in an uninterrupted streamline containing ferrous and ferric salts with a base are mixed using separate tubes that connect to form a microreactor. In this microreactor, the flow rates of the iron salts and base can be controlled individually to produce stable particles. A similar method uses separate feeding channels for the iron salts and base, but the mixing is further controlled using droplet-sized tube diameters (Table 1F) (Frenz et al., 2008). Maximum control of mixing is achieved because the flow rate of each element in the reaction can be set to the drop. Another method used controlled feed jets to create a thin fluid film of an iron salt solution over a spinning, grooved disc in the presence of ammonia; the particles produced using this methods were small (7 and 10 nm, respectively), but do not appear to be monodisperse or uniform in shape (Table 1G) (Chin, Iyer, Raston, & Saunders, 2008).

A continuous flow system has the ability to surpass the batch process in terms of efficiency and throughput (Jahn et al., 2008; Lin et al., 2004). The design of a continuous flow reactor can largely dictate the properties of the particles produced. For example, continuous flow reactors with a syringe pump to produce gold and silver nanoparticles can lead to a broad dispersion of residence times of the growth solutions because of the inhomogeneous profile of pressure-driven flow (Boleininger et al., 2006). The pattern of the tubing, e.g., the bends and turns, aids in the mixing of the flowing solution (Jahn et al., 2008; Lin et al., 2004). In a different example, uniformity of produced particles has been demonstrated to be directly related to flow rate. Because the walls of a flow reactor serve as nucleation sites, slower flow rates allow a particle to remain attached to the wall and grow. Higher flow rates exert greater shear forces on the walls, effectively reducing wall nucleation and growth and producing more homogeneous particles (Jahn et al., 2008; Lin et al., 2004; Takagi et al., 2004; Wagner & Köhler, 2005; Ying, Chen, Zhao, Li, & Yuan, 2008). Smaller reactor systems can be easily manipulated for exact execution of variable changes (temperature, concentration, flow) and generally use less volume, proving to be cost-effective while the reaction is perfected (Jahn et al., 2008; Takagi et al., 2004; Wagner & Köhler, 2005). Smaller reactors experience larger area-to-volume ratios inside the reactor and thus a better heat transfer rates than larger batch reactors. It should be noted that an instantaneous leap from room temperature to the reaction temperature (around 300 °C) can lead to polydisperse nanoparticles. To increase the effectiveness of the reaction, the solution may be allowed to be heated at a temperature slightly below the reaction temperature. Similarly, a lower temperature gradient through the use of step-up baths could lead to the production of more monodisperse nanoparticles (Sun et al., 2004). In summary, microreactors, and in a similar sense, small scale reactors, exert finite control over system variables, allowing for precise execution of different reaction conditions and facilitating control over and production of homogeneous nanoparticles (Ying et al., 2008; Zhao, He, Qiao, & Middelberg, 2011).

In this article, the novel production of iron oxide nanoparticles via thermal decomposition in continuous flow is demonstrated. This was accomplished by constructing a high-temperature continuous flow reactor, where factors such as flow rate, temperature, and precursor composition could be controlled, modifying the resulting nanoparticles. This work demonstrates the feasibility of large-scale continuous production of iron oxide nanoparticles.

2 Material and methods

2.1 Materials

Sodium oleate (97%) was purchased from Pfaltz & Bauer (Waterbury, CT, USA). Iron chloride hexahydrate (97%) and oleic acid (90%) were purchased from Alfa Aesar (Haverhill, MA, USA). Hexane (HPLC grade) and ethanol (95%) were purchased from Fisher Scientific (Waltham, MA). Trioctylamine (98%) was purchased from Sigma-Aldrich (St. Louis, MO, USA). All reagents were used without additional purification.

2.2 Preparation of precursor solution

Iron oleate was produced following a procedure used by Park et al. (2004). Briefly, 36.5 g of sodium oleate, 10.8 g of iron chloride hexahydrate, 80 mL of ethanol, 140 mL of hexane, and 60 mL of de-ionized water (DIW) were mixed together in a three-necked flask. The solution was mixed at room temperature on a stir plate for 30 min then heated to 70 °C, while maintaining stirring, and kept at that temperature for 4 h. Once the solution cooled, it was washed three times with DIW using a separatory funnel. The resulting solution was concentrated via rotary evaporator (90 rpm at 90 °C) until the remaining solvent was boiled off and a waxy solid was obtained. The iron oleate was placed uncovered in a vacuum oven (room temperature) overnight to further remove any remaining solvent.

The precursor solution was prepared from iron oleate, oleic acid, and trioctylamine. The amount of trioctylamine was held consistent for all reactions at 23.45 g (67 mmol). The amounts of each were varied based on molar ratio to modify the size and stability of produced particles (see Results and Discussion). The precursor batch was stored in a sealed flask under a flow of nitrogen. It should be noted that the reactions were created from two different iron oleate batches, but the effects were not investigated in this study.

Thermo gravimetric analysis (TGA) was enacted on a solution of iron oleate using a Hi-Res TGA 2950 thermogravimetric analyzer from TA Instruments (New Castle, DE) to determine the optimal reaction temperature for the full degradation of the compound during reaction. The iron oleate was found to most rapidly decompose around near 300 °C in a nitrogen atmosphere, consistent with Park et al (2004). Therefore,

the reaction temperature was set around near or above this temperature to ensure full decomposition.

2.3 Continuous synthesis of Fe₃O₄ nanoparticles

The continuous flow reactor is a simplistic design consisting of five main components: a pump, reactor coil, salt bath, hot plate, and thermocouple (Fig. 1). Precursor solution was pumped into the coil by a metering pump. The coil (length: 50 ft. (15.24 m), diameter: 0.085 in. (2.16 mm) stainless steel tubing) was submerged in a salt bath heated using a hot plate. The flow rate was kept at an average rate of 0.175 mL/min with an average reaction time of 86 min. A thermocouple was used to determine the temperature in the salt bath. The coil exited the salt bath and solution flowed from the end. Two back flow regulators were located on the coil, before entering the salt bath and after exiting, to restrict the flow of precursor to one direction.

Fig. 1

In preparation for reaction, the salt bath was raised to the desired temperature using a hotplate. While heating, the reactor coil was purged with 20 mL of trioctylamine to flush out any pockets of air or other impurities and ensure a smooth flow. After the initial purge, trioctylamine was periodically pumped during heating to prevent air from entering the coil. Once a stable reaction temperature was reached (5 min of steady temperature), the precursor solution was extracted from the sealed flask using a syringe and placed into a beaker. The metering pump was turned on, precursor solution pumped into the coil, and exiting solution was collected in labelled vials. Once all of the precursor solution had entered the reactor, pure trioctylamine was used to flush the reactor coil at the same flow rate. Finally, once all precursor solution had completely been run through the reactor (clear trioctylamine began exiting the coil), the coil was flushed with trioctylamine at a high flow rate. Any material flushed out by the high flow rate was collected for analysis and deemed particle wall growth.

The reacted solutions were placed into centrifuge tubes with approximately 25 mL of ethanol added to precipitate out particles. The solutions were centrifuged for 10 min at 6000 rpm in a VWR Clinical 200 centrifuge (Radnor, PA). The solvent was decanted off, and the particles were redispersed in hexane. This procedure was repeated three times. If deemed necessary, acetone was used in place of ethanol in an attempt to improve the particle wash.

3 Characterization

Transmission electron microscopy (TEM) was the primary method of determining the size and morphology of the nanoparticles produced by the continuous flow reactor. TEM photographs were obtained using a Hitachi H-7600 and H-9500 (Japan). The TEM images obtained were analyzed using the Fovea Pro

program in Photoshop to determine average (mean) size and size distribution. Two hundred particles were deemed a sufficient number of points for quality size analysis. High-resolution TEM was also used to confirm the crystallinity of a nanoparticle produced in the continuous flow reactor.

Powder X-ray diffraction (XRD) was performed on a sample of continuous flow particles by drop casting a nanoparticle suspension on a silicon substrate and letting the solvent evaporate. Diffractograms were collected using a Rigaku X-ray diffractometer (Japan) with Smart Lab Guidance control for automation and data acquisition. Cu-K α radiation was used in conjunction with a scintillation detector and diffracted beam monochromator. Data analysis was done using PDXL software in combination with the ICDD (International Centre for Diffraction Data) PDF2 database.

Hysteresis loops for continuous flow nanoparticles were obtained using a vibrating sample magnetometer (VSM), (Quantum Design, San Diego, CA). The parameters for the measurement were 300 K from ± 398 kA/m ($\pm 5,000$ Oe). The nanoparticles were mounted on a cotton swab, fully dried, and placed under vacuum for measurement. After the measurement, the sample was digested by heating to 600 °C to burn off the organic content. The residual iron was dissolved in concentrated hydrochloric acid and complexed with 1,10-phenanthroline. UV–Vis was then performed on the residual to determine total iron concentration (ASTM International, 2009).

4 Results and discussion

The synthesis of iron oleate was the first step in the continuous flow production process and resulted in a waxy solid of a dark reddish black color. The iron oleate was washed and dried using a rotary evaporator to remove hexane and other organic solvents. To produce particles, the solution was then diluted with trioctylamine and oleic acid in specified amounts and placed under a nitrogen flow prior to reaction. The precursor was pumped into the heated coil, where nanoparticle nucleation and growth commenced. The resulting particle solution was washed and the particles were characterized as discussed below.

The selection of the lower limit reaction temperature was based on the TGA of the iron oleate precursor (Fig. 2). The authors speculate that the first curve on the plot is indicative of the loss of two oleic acid chains from the primary iron atom, and the second peak is representative of the loss of the final chain from the iron atom. The residual char, approximately 7%, is to be expected from the percentage of weight contributed by the remaining iron. The lower limit for the reaction temperature was determined to be at the onset of the second degradation curve, at approximately 300 °C (Fig. 2). An upper limit for the reaction temperature was set at 360 °C, the approximate boiling point of trioctylamine. Therefore, 310 °C and 320 °C and 340 °C were selected as sufficient reaction temperatures for the continuous flow particle syntheses presented in this manuscript.

Fig. 2

The precursor flow rate was also varied to obtain the best results. It was hypothesized that the flow in the coil during a reaction was turbulent in nature, providing an advantage over the batch method. Turbulent flow would cause even mixing in the reactor, resulting in uniform growth and a narrow particle size distribution. Though it was difficult to confirm if the flow was turbulent or laminar, the process was found to form relatively uniform, spherical particles in all reactions that maintained continuous flow, as observed through TEM imaging (Fig. 3). Consistent flow was the determining factor in the selected flow rate (which corresponded to an optimum setting on the Eldex pump). As seen in other research, blockages in a nanoparticle microreactor were an issue (Wagner & Köhler, 2005). The solution we employed was simply to use a high enough flow rate to prevent these blockages.

Fig. 3

The highest volume precursor that was run through the continuous flow reactor was approximately 60 mL. This in itself is a sufficiently high volume to demonstrate the high throughput ability of the continuous flow reactor. Higher quality, more durable materials in the construction of the continuous flow reactor (i.e., coil, heat bath) than implemented in this research would allow one to far exceed this volume and continuously produce particles of a uniform size and shape until a desired amount of particles is obtained.

The proposed continuous flow reaction mechanism is based on an established mechanism consisting of two primary steps: nucleation and growth. The reaction begins with the initial formation of nucleates. Nucleation takes place nearly instantaneously as the precursor comes into contact with the heated section of the coil, where the tubing entered the salt bath. The number of nucleates is primarily dependent on iron oleate concentration and taken as a primary factor in final particle size (see the following paragraph for further discussion). In the subsequent growth step, nucleates utilize the surrounding iron oleate and grow into larger particles. During this step, larger particles grow at the expense of smaller particles in the process known as Ostwald ripening. Once the particle growth/reduction reaches equilibrium, reaction conditions being held constant, no other major size changes take place. It was concluded that nucleates (1–2 nm particles) observed in all reacted solutions are part of the particle system equilibrium.

Micrograph size analysis The continuous flow research was intended to align with the research of Qi et al. (2013) on batch nanoparticle production. Qi et al. (2013) observed that lower precursor/ligand ratios produced larger sizes of iron oxide nanoparticles in a batch method utilizing iron acetylacetonate instead of iron oleate. Though they used a different organometallic in the precursor, the principle behind concentration's effect on particle size was the same as that held for continuous flow. In the current research, several reactions were run in a series of increasing iron oleate/oleic acid ratios with the goal of demonstrating control of particle size

through precursor composition (Figs. 3 and 4; Table 2). The iron oleate to ligand (oleic acid) ratio in the precursor was considered a primary factor in particle size, with relatively low iron oleate concentrations (<5 wt% of the total solution) producing larger mean particle diameter (Table 2). The reasoning was that lower iron oleate/oleic acid ratios caused the formation of less initial nucleates, leading to larger amounts of iron oleate available to each nucleate, and resulting in larger final particles sizes (Fig. 5). Conversely, higher iron oleate/oleic acid ratios were thought to result in smaller mean particle diameters (Table 2). Unfortunately, the results from the reaction series were inconclusive as to a concise trend between composition and particle size (Fig. 4). It should be noted that nucleates observable in every particle solution had an effect on the TEM particle size analysis.

Figs. 4 & 5, Table2

High resolution transmission electron microscopy Crystallinity of particles produced in this study was investigated using high-resolution transmission electron microscopy (HR-TEM) of nanoparticles produced in the continuous flow reactor. Fig. 6(a) shows the image of an iron oxide nanoparticle, in which one can discern atomic lattice planes. Furthermore, in Fig. 6(b), the HR-TEM diffraction pattern of the same sample displays diffraction spots, confirming the crystalline nature of the continuous flow particles. It is currently not known if the crystalline particles are either magnetite or maghemite, but we suspect both are present.

Fig. 6

X-ray diffraction X-ray diffraction was conducted on a sample to obtain structural information on iron oxide particles produced using the continuous flow reactor (Fig. 7). Several specific lattice planes are seen in the XRD readout, thereby further confirming the crystalline nature of the particles. Powder XRD shows primarily a face-centered cubic (FCC) crystal system in the particles. This indicates little presence of hematite, a hexagonally close packed (HCP) structure, and a possible by-product of the nanoparticle synthesis. Although this is true, it is virtually impossible to distinguish the Fe_3O_4 (magnetite) phase from the $\text{Fe}_2\text{O}_3/\gamma\text{-Fe}_2\text{O}_3$ (maghemite) phase using purely X-ray powder diffraction.

Fig. 7

Vibrating sample magnetometry The M vs. H curve obtained from vibrating sample magnetometry (VSM) illustrates the superparamagnetic nature of the particles at room temperature (Fig. 8). The small amount of hysteresis can be explained by the polydispersity of the particles as well as the limited accuracy of the instrument at low fields. Although superparamagnetism is evident from the curve shape, when normalized for mass, the saturation magnetization is much lower than has been previously reported in literature. This may be explained by a large amount of unreacted precursor being present in the final sample, which would contribute

greatly to the amount of iron but not to the magnetic properties of the sample. These results can be improved by obtaining a higher reaction yield through further investigation and optimization of reaction parameters (i.e., time, temperature) and purification techniques.

Fig. 8

5 Conclusions

We have demonstrated the first successful continuous flow method for the production of iron oxide nanoparticles via thermal decomposition. In this study, the continuous flow reactor has been shown as a practical method for the synthesis of uniform iron oxide particles. Furthermore, the particles produced in the continuous flow reactor were confirmed as crystalline. A workable reaction mechanism was devised, in which the iron oleate/oleic acid molar ratio was the largest deciding factor in particle size. The future of this research will focus on the following: (1) determining the identity of the particles; (2) confirming control of the particles produced through precursor composition and reaction temperature; (3) investigating the repeatability of high-volume continuous flow reactions; and (4) implementing large-scale production of particles for use in research.

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Figure captions:

Fig. 1. Diagram of the continuous flow reactor.

Fig. 2. Readout from the TGA analysis of a sample of iron oleate produced in the lab.

Fig. 3. TEM images and size histograms of continuous flow Fe₃O₄ nanoparticles synthesized at different oleate/oleic acid molar ratios to demonstrate particle size dependence on the precursor composition. Table 2 shows the precursor composition and average particle diameters for this series of syntheses.

Fig. 4. Results of continuous flow synthesis at varying temperatures.

Fig. 5. Environment of nucleates for high and low iron oleate concentrations in the continuous flow reaction.

Fig. 6. HR-TEM image of an iron oxide particle in which the atomic lattice can be observed (a), and the TEM diffraction pattern of the same nanoparticle sample (b).

Fig. 7. XRD analysis of iron oxide nanoparticles produced in the continuous flow reactor with several diffraction peaks indicated.

Fig. 8. Mass normalized M vs. H loop of iron oxide nanoparticles produced in the continuous flow reactor with an inset showing small hysteresis.

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Tables

Table 1 Various continuous flow reactors with the material synthesized.

	Technique	Materials produced	References
A	Syringe pump and hot oil bath	Silver nanoparticles	Lin et al., 2004
B	IPHT microreactor – lab on a chip	Gold nanoparticles	Wagner et al., 2005
C	Seed and growth solutions injected with independent flow rates into single reactor tube	Rod shaped gold/silver nanocrystals	Boleininger et al., 2006
D	Same-axle dual pipe reactor	Titania nanoparticles	Takagi et al., 2004
E	Coaxial flow device operating under a laminar regime	Iron oxide nanoparticles	Abou Hassan et al., 2008
F	Pairing module: Two aqueous phases injected (droplet size) by channels into a central oil channel in which the reactants are emulsified	Iron oxide nanoparticles	Frenz et al., 2008
G	Spinning disk reactor which mixes reactants through turbidity created on disk	Iron oxide nanoparticles	Jahn et al., 2008

Table 2 Reaction data for five high-volume reactions

Reaction	Temperature (°C)	Iron oleate/Oleic acid ^a (molar ratio)	Diameter (nm)	Stan dev (nm)
1	320	2.00	6.97	2.34
2	320	1.00	9.97	4.50
3	320	0.67	7.93	3.95
4	320	0.50	10.85	6.02
5	320	0.40	9.29	6.21

^a Total mass of iron oleate and oleic acid comprises <5 wt % of precursor solution