METHOD OF SYNTHESIS OF AMPHIPHILIC MAGNETIC COMPOSITE PARTICLES

Inventors: Pei Li, Hong Kong (CN); Kin Man Ho, Hong Kong (CN)

Assignee: Hong Kong Polytechnic University, Kowloon, Hong Kong (CN)

Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 821 days.

Appl. No.: 12/359,393
Filed: Jan. 26, 2009

Prior Publication Data

Int. Cl.
B03B 15/02 (2006.01)
B05D 7/02 (2006.01)
C08K 9/00 (2006.01)

U.S. Cl. ................. 428/407; 428/402.24; 428/403; 428/404; 428/405; 427/222; 523/201; 523/209; 523/210

Field of Classification Search ................. 427/222, 427/127, 132, 128; 428/403, 212, 405, 407, 428/694, 695, 900; 523/201; 430/106.6, 430/107, 138, 98, 124, 108

See application file for complete search history.

References Cited
U.S. PATENT DOCUMENTS
6,209,033 B1 3/2001 Müller-Schulte
6,255,477 B1 7/2001 Kleiber et al.
6,514,688 B2 2/2003 Müller-Schulte

FOREIGN PATENT DOCUMENTS
JP 08-176461 * 7/1996

OTHER PUBLICATIONS

Primary Examiner — James J Seidleck
Assistant Examiner — S. Camilla Pourbohloul
Attorney, Agent, or Firm — Leydig, Voit & Mayer, Ltd.

ABSTRACT
Amphiphilic, magnetic composite particles are comprised of cores and shells. The core contains both hydrophobic vinyl graft copolymer, hydrophobic vinyl homopolymer and magnetic nanoparticles, and the shell to which the hydrophobic vinyl polymer is grafted is a hydrophilic, nitrogen-containing polymer. Typically, the composite particles are made by a process which involves generating radicals on nitrogen atoms of the water-soluble polymer, and then initiating free-radical copolymerization of said vinyl monomer(s) and vinyl-coated magnetic nanoparticles, whereby vinyl polymer(s) undergo(s) phase separation and the vinyl coated magnetic nanoparticles are encapsulated within the vinyl polymer to form a composite latex.
OTHER PUBLICATIONS


* cited by examiner
Figure 1

\[
\begin{align*}
\text{FeCl}_2 + 2\text{FeCl}_3 + \text{NH}_2\text{OH} & \quad \text{pH 11-12} \\
& \rightarrow \gamma-\text{Fe}_2\text{O}_3 \\
& \rightarrow \text{c-Fe}_2\text{O}_3 \\
& \text{(Trisodium Citrate)}
\end{align*}
\]

Figure 2

\[
\begin{align*}
\text{c-Fe}_2\text{O}_3 + \text{NH}_2\text{OH, TEOS} \quad \text{Methanol}:\text{H}_2\text{O (4:1 v/v)} & \rightarrow \text{MPS-Fe}_2\text{O}_3
\end{align*}
\]

Figure 3

\[
\begin{align*}
\text{n} = 0.74 + \text{MMA} + \text{MPS-Fe}_2\text{O}_3 & \quad \text{TBHP (0.1 mM)} \\
& \rightarrow \text{Acetic acid solution (0.6 v/v\%)} \\
& \rightarrow \text{MCS particles}
\end{align*}
\]
Figure 5

Figure 6
Figure 7

Figure 8
Figure 9(a)

Figure 9(b)

$D_p = 202$ nm

$D_n = 185$ nm

$D_p/D_n = 1.09$
Figure 12

Figure 13
METHOD OF SYNTHESIS OF AMPHIPHILIC MAGNETIC COMPOSITE PARTICLES

FIELD OF THE INVENTION

The present invention relates to amphiphilic magnetic composite particles, and to a process of making amphiphilic magnetic composite particles.

BACKGROUND TO THE INVENTION

There is an increasing interest in magnetic particles because of their wide application in such fields as biotechnology, biomedical, electromagnetics, magnetic storage and coating to name just a few. Various approaches to the preparation of magnetic particles have been investigated including co-precipitation of ferrous and ferric salts under alkaline conditions in the presence of either polymers or surfactants, crosslinking of functional polymer in an emulsifier-stabilized magnetic nanoparticle dispersion and layer-by-layer (LBL) self-assembly of alternating layers of polyelectrolytes and magnetic nanoparticles onto colloidal templates. Despite of the success of these, and other, approaches in preparing the magnetic particles, there are still some major drawbacks with respect to the methods and the properties of the particles produced. For example, synthesis involves tedious multiple step reactions and the use of large amounts of toxic solvent agents, emulsifiers and surfactants. Leaching of magnetic nanoparticles from the polymeric particles and nanoparticle dissolution in acidic medium are still serious concerns. In addition, magnetic polymeric particles produced through these approaches generally have broad size distributions and usually lack of surface functional groups, which are highly desirable for further chemical modifications.

SUMMARY OF THE INVENTION

The present invention provides amphiphilic, magnetic composite particles comprising a core and shell. The core contains both hydrophobic vinylly graft copolymer, hydrophobic vinylly homopolymer and vinylly coated magnetic nanoparticles, and the shell to which the hydrophobic vinylly polymer is grafted is a hydrophilic, nitrogen-containing polymer.

The present invention further provides a method of making magnetic composite particles comprising the generation of radicals on nitrogen atoms of the water-soluble polymer, and initiation of free-radical copolymerization of vinyllic monomer(s) and vinylly-coated magnetic nanoparticles, whereby vinyllic polymer(s) undergo(es) phase separation and the vinylly coated magnetic nanoparticles are encapsulated within the vinyllic polymer to form a composite latex. The method does not use any surfactants, emulsifiers or toxic solvent agents. The method also provides for the making of magnetic composite particles with different polymer cores, such as hard, soft or temperature sensitive.

BRIEF DESCRIPTION OF THE DRAWINGS

The invention will now be described by way of example only and with reference to the accompanying drawings in which:

FIG. 1 illustrates a magnetic composite particle according to the invention,

FIG. 2 illustrates a first of three preferred steps in making amphiphilic magnetic composite particles according to the invention,

FIG. 3 illustrates the second preferred step in making the vinylly coated magnetic nanoparticles,

FIG. 4 illustrates the third, and final, preferred step in making the magnetic composite particles,

FIG. 5 shows the infrared (IR) spectrum of magnetic composite particles, wherein the hydrophobic core contains poly(methyl methacrylate) (PMMA) and vinylly coated gamma-phase iron oxide (MPS-Fe₃O₄) nanoparticles.

FIG. 6 shows the IR spectra of (a) isolated magnetic, PMMA graft copolymer composites using chloroform as a solvent in Soxhlet extraction and (b) isolated PMMA after extraction.

FIG. 7 shows the IR spectra of (a) isolated magnetic, chitosan grafted copolymer composites using a 1v/w% of acetic acid solution as a solvent in Soxhlet extraction and (b) isolated chitosan after extraction.

FIG. 8 shows the thermogravimetry analysis (TGA) thermograms of (a) PMMA/chitosan core-shell particles without encapsulated magnetic nanoparticles, and b) magnetic composite particles (containing 8.4 w/w% of γ-Fe₂O₃).

FIG. 9(a) is a transmission electron micrograph of a magnetic composite particle according to the invention and FIG. 9(b) is a graph of particle size distribution of magnetic composite particles according to the invention, wherein the hydrophobic core contains PMMA and vinylly coated gamma-phase iron oxide nanoparticles.

FIG. 10 shows pH dependence of zeta-potential of the magnetic composite particles.

FIG. 11 shows the room temperature magnetization measurement of the magnetic composite particles with a 8 w/w% of γ-Fe₂O₃ content.

FIG. 12 shows the images of film formation of magnetic composite particle through annealing the magnetic composite particle dispersion at 155°C. (a) is a surface topographic image (5 μm×5 μm) and (b) is a top view of magnetic force microscopy image (5 μm×5 μm).

FIG. 13 shows transmission electron microscopy images of the magnetic composite particles with different core components: (a) hard (PMMA) (b) soft (a mixture of PBA and PMMA) and (c) temperature sensitive (PNIPAM with 10% crosslinking), according to the invention, and

DETAILED DESCRIPTION OF THE INVENTION

FIG. 1 illustrates a preferred amphiphilic magnetic composite particle according to the invention. The particle contains a shell 101 and a core 102.

The shell 101 is a hydrophilic, nitrogen containing compound, such as a polymer, which can be natural or synthetic. The nitrogen can be present as an amino group. Primary amine (—NH₂), secondary amine (—NR₁) and tertiary amine (—NR₂) are examples of functional groups for this reaction. Structurally, the amino-containing polymers may be in the form of cyclic alicyclic or linear or aromatic amine. The amino function may be located in the polymer main chain or in the side chain. Examples of the nitrogen-containing compounds include natural amino polymers such as N-acetyl sugars such as chitosan, or proteins such as casein, gelatin, bovine serum albumin, and cellulose, and synthetic amino polymers such as polyethyleneimine, poly(vinyl amine)-co-poly(vinyl alcohol)-co-poly(vinyl amine)-co-poly(acrylonitrile), etc. In the preferred embodiment, the nitrogen containing compound used in the shell is made of chitosan.

The core 102 is composed of a graft copolymer of the hydrophobic vinylly monomers, and homopolymer of a hydrophobic vinylly monomer or a mixture of two or more hydrophobic vinylly monomers or hydrophobic temperature sensi-
tive polymers of a hydrophilic monomer, and encapsulated vinylic coated magnetic nanoparticles. The vinylic polymer is prepared using a vinylic monomer. The monomer can be, for example, a vinylic monomer, an acrylate monomer, an acrylamide monomer, polymerizable nitrite, acetate, chloride monomers, a styrene monomer, N-substituted acrylamide monomers. Examples of vinylic monomers include those of formula \( R_1^1 R_2 = \text{H}_2 \), where \( R_1^1 \) is hydrogen or alkyl, and where \( R_2^2 \) is alkyl, aryl, heteroaryl, halogen, cyano, or other suitable hydrophobic group. Groups for \( R_1^1 \) can include hydrogen and methyl. Group for \( R_2^2 \) include \( C_1-C_8 \) alkyl, phenyl, monocyclic heteroaryl with 4 to 8 ring atoms, more preferably 5 or 6 ring atoms, and with 1, 2, or 3 ring heteratoms, preferably 1 or 2, preferably 1 ring atom, selected from nitrogen, oxygen, or sulfur; chloro; and cyano. Examples of acrylate monomers include those of formula \( CH_2 = CR^2 \text{COOR}^1 \), where \( R^1 \) is hydrogen or alkyl, and where \( R^2 \) is alkyl or substituted alkyl, or other suitable hydrophobic group. Groups for \( R^1 \) include hydrogen and methyl. Group for \( R^2 \) include \( C_1-C_8 \) alkyl which may be straight-chain or branched, and such groups substituted with one or more substituents chosen from unsubstituted amino, monosubstituted amino or substituted amino, hydroxy, carboxy, or other usual acrylate substituent. Acrylate monomers may contain ethyl(eth)methacrylate, isopropyl(meth) acrylate, n-butyl(methyl)acrylate, etc. Examples of acrylamide monomers include those of formula \( CH_2 = CR^2 \text{COONR}^1 \), where \( R^1 \) is hydrogen or alkyl, and where \( R^2 \) is hydrogen or alkyl or substituted alkyl or another suitable hydrophobic group. Examples of encapsulated magnetic nanoparticles includes those of formula \( MO.\text{Fe}_3\text{O}_4 \), where \( M \) is iron, nickel, cobalt, manganese, copper and platinum. In preferred embodiment, the core is composed of poly(methyl methacrylate) and vinyl coated magnetite nanoparticles.

The magnetic composite particles according to the invention are made by first preparing the magnetic nanoparticles. Secondly coating the surface of the nanoparticles with a vinyl surface coating. And thirdly, the vinyl surface coated magnetic nanoparticles are encapsulated via the peroxide-induced graft copolymerization of vinylic monomers(s) from water soluble polymer containing amino groups in the presence of vinyl coated magnetic nanoparticles.

The first step of preparing the magnetic nanoparticles is achieved as follows. Two metal salts are dissolved in deionized water, the resulting solution is mixed with an alkaline solution under vigorous stirring, and the solution is allowed to react for 1 hour at room temperature, and reflux for another 1 hour to form magnetic nanoparticles. In one embodiment, iron(II) chloride and iron(II) chloride are dissolved in de-ionized water. The metal salts comprise ferromagnetic elements selected from the group consisting of ferrites that have formula \( MO.\text{Fe}_3\text{O}_4 \), where \( M \) is iron, nickel, cobalt, manganese, copper and platinum. The surface of magnetic nanoparticles is coated with carboxylic acid to form acid modified magnetic nanoparticles. Adding a carboxylic acid can include for example trisodium citrate, gluconic acid sodium salt, sodium oleate, and lauric acid. In one embodiment, trisodium citrate in a 0.2 molar concentration of total volume is added.

A preferred example of this first step shown in FIG. 2. \( \text{FeCl}_2 \text{H}_2 \text{O} \) (1.99 g) and anhydrous \( \text{FeCl}_3 \) (3.25 g) are dissolved in water (20 mL) separately, and mixed under vigorous stirring. A \( \text{NH}_4 \text{OH} \) solution (0.6 M, 200 mL) is then added to the stirring mixture at room temperature, immediately followed by the addition of a concentrated \( \text{NH}_4 \text{OH} \) solution (25 w/w %, 50 mL) to maintain the reaction pH between 11 and 12.

The resulting black dispersion is continuously stirred for 1 hour at room temperature and then heated to reflux for 1 hour to yield a brown dispersion. The magnetic nanoparticles are then purified by a repeated centrifugation (3000-6000 rpm for 20 min), deionization, and redispersibility cycle for 3 times until a stable brown magnetic dispersion is obtained. A total of 100 mL of the \( \gamma-\text{Fe}_2\text{O}_3 \) nanoparticle dispersion (2.42 w/w %) prepared as stated previously was acidified with a \( \text{HNO}_3 \) solution (4 M, 100 mL) and then centrifuged at 3000 rpm for 20 min to collect the magnetic nanoparticles. The collected magnetic nanoparticles were dispersed in water (200 mL), and the dispersion was heated to reflux. Trisodium citrate dihydrate (11.7 g) was then added, followed by heating the mixture for 1 hour under reflux to produce citrate-coated iron oxide nanoparticles. The brown dispersion was purified by being placed into a dialysis tube (10 kDa molecular weight cutoff, Sigma-Aldrich) and dialyzed against water for 8 days with a daily change of water until the conductivity of water was comparable to that of purified \( \text{H}_2\text{O} \) used.

The second step of coating the surface of the nanoparticles with a vinyl surface coating is achieved as follows. The acid modified magnetic nanoparticles are treated with an alkaline solution and mixed with silanol precursor; the resulting solution is allowed to react at 40°C for 24 h. Adding a silanol precursor can include tetraethyl orthosilicate (TMOS), tetraethyl orthosilicate (TEOS), tetrapropyl orthosilicate, (TPOS), tetrabutyl orthosilicate (TBOS), methyl polysilicate, ethyl polysilicate, etc. In one embodiment, tetraethyl orthosilicate in a molar concentration from 0.02 to 0.16 M is added. The resulting mixture is subsequently mixed with a silane coupling agent containing vinyl groups in a alcohol/water mixture, preferably 4 to 1 volume ratio, and the mixture is allowed to react at 40°C for 24 h to form vinyl coated magnetic nanoparticles. The silane coupling agent comprises (3-triethoxysilyl)propyl methacrylate (MPS), (3-methacryloxy)propyl methacrylate, (3-triethoxysilyl)propyl methacrylate, (triethoxysilyl)methyl methacrylate, (triethoxysilyl)methyl methacrylate, etc. In one embodiment, 3-(triethoxysilyl)propyl methacrylate in a molar concentration from 0.2 to 0.8 M is added.

A preferred example of this second step shown in FIG. 3. The \( \gamma-\text{Fe}_2\text{O}_3 \) nanoparticles were first obtained as described with reference to FIG. 2. A layer of a silanol precursor is coated on the surface of the \( \gamma-\text{Fe}_2\text{O}_3 \) nanoparticles by premixing a dispersion of the purified citrate-coated nanoparticles (8.5 w/w %, 20 mL) with methanol (80 mL) for 1 hour at 40°C. Concentrated ammonia solution (25 w/w %, 1.8 mL) is added and the resulting mixture is stirred at 40°C for 30 min. Subsequently, tetraethyl orthosilicate (TEOS, 1.0 mL) is charged to the reaction vessel and the mixture is continuously stirred at 40°C for 24 hours. Finally, 3-(trimethoxysilyl)propyl methacrylate (MPS, 5.3 mL) is added and the mixture is allowed to react at 40°C for 24 hours to give vinyl-coated \( \gamma-\text{Fe}_2\text{O}_3 \) nanoparticles. The vinylic-coated nanoparticles were collected by placing a permanent magnet (4 Tesla) next to the container wall, followed by discarding the solution. The collected magnetic nanoparticles were dispersed in ethanol (20 mL) and the dispersion was transferred into a dialysis tube (10 kDa molecular weight cutoff, Sigma-Aldrich) and dialyzed against ethanol for 7 week with a daily change of ethanol to remove the unreacted MPS, TEOS, and \( \text{NH}_3 \). The amounts of unreacted MPS molecules removed through the dialysis were monitored with ultraviolet (UV) measurements using a PerkinElmer UV-vis spectrophotometer (Lambda 35) at 203.5 nm. Finally, the purified dispersion was concentrated to a 10.0 w/w % solid content for subsequent reactions.
The third step of encapsulating the vinyl surface coated nanoparticles is achieved as follows. A nitrogen containing compound is dissolved in an aqueous medium, the resulting solution is then mixed with the vinyl coated magnetic nanoparticles and a vinyl monomer or a mixture of two or more monomers. A catalyst is added, and the solution is allowed to react at 80°C for 2 h. The nitrogen containing compound can be dissolved in an aqueous medium such as water, acid or other appropriate system chosen to suit the polymer or protein, such as having an appropriate pH and temperature. In one embodiment, chitosan is dissolved in a 1% acetic acid solution.

The resulting solution can be mixed with vinyl coated magnetic nanoparticles, and vinyl monomer or a mixture of monomers in a weight ratio of monomer to vinyl coated magnetic nanoparticles to nitrogen containing compound of 4:1:2.5 to 8:1:2.5, preferably 4:1:2.5 to 6:1:2.5. In one embodiment, there is 63% vinyl monomer, 11% vinyl coated magnetic nanoparticles and 26% nitrogen containing compound.

Adding a catalyst can include adding for example, alkyl hydroperoxide, and hydrogen peroxide.

Alkyl hydroperoxides such as t-butyl hydroperoxide (TBHP), cumene hydroperoxide, p-isopropyl cumene hydroperoxide, p-methane hydroperoxide and pinane hydroperoxide are suitable initiating agents to induce the graft copolymerization of a vinyl monomer from the water-soluble polymers. Hydrogen peroxide (H₂O₂) is also suitable initiating agents to induce the graft copolymerization of a vinyl monomer from the water-soluble polymers. Grafting efficiency of chitosan graft initiated by H₂O₂ is comparable to that initiated by TBHP.

Radical initiators such as tert-butyl hydroperoxide and hydrogen peroxide have been carefully investigated for the graft copolymerization of, for example, methyl methacrylate (MMA), a hydrophobic monomer from chitosan in the presence of vinyl coated magnetic nanoparticles. Results are listed in Table 1.

### Table 1

<table>
<thead>
<tr>
<th>Initiator</th>
<th>Coating nanoparticles</th>
<th>Conv. %</th>
<th>Dv</th>
<th>Dv/Dw</th>
<th>Chitosan graft %</th>
<th>γ-Fe₃O₄ %</th>
</tr>
</thead>
<tbody>
<tr>
<td>TBHP</td>
<td>2:5:6:1</td>
<td>92</td>
<td>194</td>
<td>1.13</td>
<td>33</td>
<td>7</td>
</tr>
<tr>
<td>H₂O₂</td>
<td>2:5:6:1</td>
<td>78</td>
<td>202</td>
<td>1.09</td>
<td>40</td>
<td>8</td>
</tr>
</tbody>
</table>

Conv. % represents monomer conversion; Dv represents volume average hydrodynamic diameter; Dw represents number average hydrodynamic diameter; Chitosan graft % is determined by extraction of crude product using 1% acetic acid as a solvent in a Soxhlet extraction; γ-Fe₃O₄ % is determined by thermogravimetry analysis.

A preferred example of this third step is shown in FIG. 3. For a total of 25 mL of solution, 1 mL of vinyl coated grama-phase iron oxide nanoparticle dispersion (10 w/w % in ethanol) was mixed with ethanol and then with 22 mL of chitosan solution containing 0.25 g of chitosan and 0.6 w/w % acetic acid (99 w/w %) using a homogenizer (Sonics VC130P, output wattage 6 W), giving a final volume ratio of H₂O/ethanol of 12.5:1. The dispersion was homogenized for another 10 min and then transferred into a water-jacketed flask equipped with a thermometer, a condenser, a magnetic stirrer, and a nitrogen inlet. The dispersion was purged with nitrogen for 20 min and stirred at 80°C prior to the addition of MMA (0.6 g) and TBHP (final concentration was 0.1 mM). The resulting mixture was continuously stirred at 80°C for 2 hours under nitrogen. After the reaction, the particle dispersion was filtered to remove precipitates (if any) generated during the polymerization. The MMA conversion (conv %) was determined gravimetrically. The particle dispersion was purified by a repeated centrifugation (13,000 rpm), decantation, and redispersion cycle until the conductivity of the supernatant was close to that of distilled water used.

In order to determine the chemical composition of the magnetic composite particles, the purified particles was dried, and then identified with Fourier-transform infrared (IR) spectroscopy. The results are graphically illustrated in FIG. 5. IR spectrum of the purified magnetic composite particles shows a broad N—H peak of chitosan at 3400 cm⁻¹, a strong carbonyl peak (C=O) of PMMA at 1735 cm⁻¹, N—H bending peaks of the chitosan between 1550 and 1600 cm⁻¹, ester peaks (—C—O—) of PMMA between 1247 and 1272 cm⁻¹, and γ-Fe₃O₄ absorption peaks between 400 and 600 cm⁻¹. The IR spectrum clearly verifies that the purified magnetic composite particles are composed of chitosan, PMMA and γ-Fe₃O₄.

To confirm the formation of both magnetic, PMMA graft composites and PMMA homopolymers and to determine their compositions, the dispersion of magnetic composite particles is freeze-dried. The resulting brown solids are then subjected to the chloroform extraction for 48 h. PMMA homopolymer dissolved in chloroform is separated from the insoluble magnetic, PMMA graft copolymer that remained inside the thimble. The amounts of both PMMA dissolved in chloroform and insoluble polymer composites are determined gravimetrically. The PMMA homopolymer and the PMMA graft were 12% and 88%, respectively. Such a high percentage of the PMMA graft is may be attributed to the presence of reactive methacrylate groups of the vinyl coated grama-phase iron oxide nanoparticles. Since these reactive groups are close to chitosan due to the interaction between the vinyl coated nanoparticles and chitosan, their copolymerization with MMA enhances the chance of grafting from/onto
the chitosan chains. The isolated magnetic, chitosan/PMMMA
graft composites are further identified with IR analyses. The
results are graphically illustrated in FIG. 6. The spectrum
clearly illustrates the characteristic peaks of PMMMA such as
the carbonyl peak at 1755 cm\(^{-1}\) and the ester peaks between
1247 and 1272 cm\(^{-1}\).

To separate both magnetic, grafted chitosan copolymers and
un-grafted chitosan in the copolymer composites and
determine their compositions, the freeze-dried magnetic
copolymeric particles were extracted with a 1 v/v % of acetic
acid solution for 48 h. Un-grafted chitosan dissolved in an
acetic acid solution, is separated from the insoluble magnetic
copolymer composites which remained in the thimble.
The actual amounts of chitosan dissolved in an acetic acid
solution and those that are insoluble are determined
graphically. The un-grafted chitosan and grafted chitosan were
62% and 38%, respectively. In other words, there is 62% of
charged chitosan, which do not take part in the grafting
reaction. It is either dissolved in solution or is adsorbed on the
resulting particles. The isolated magnetic, grafted chitosan
copolymer composites are further characterized with IR
analyses. The results are graphically illustrated in FIG. 7,
which shows the characteristic peaks of chitosan, which are
the amine peak of chitosan at 1400 cm\(^{-1}\) and the N–H bende
of chitosan between 1550 and 1600 cm\(^{-1}\). This result
indicates that chitosan is grafted onto the copolymer
composites.

In order to characterize the weight percentage of the mag
netic nanoparticles, a Thermogravimetric Analyzer (TGA)
employed to measure the weight and to monitor the weight change
of the magnetic composite particles as a function of de
composition temperature. FIG. 8 shows the TGA thermogram
of PMMMA/chitosan core-shell particles, showing a complete
weight loss at above 500° C. For the magnetic composite
particles, the thermogram shows that there is 85% weight loss
from 380 to 500° C, which is due to the loss of polymers.
However, there is 8.4% weight remained at 900° C, which is
probably attributed to the presence of γ-Fe\(_{2}\)O\(_{3}\)
nanoparticles, since magnetic nanoparticles have a high thermal stability
below 1000° C. [ref.]

Based on the monomer conversion, the Soxhlet extraction
of un-grafted chitosan and the TGA of encapsulated γ-Fe\(_{2}\)O\(_{3}\),
the compositions of the magnetic composite particles were
determined. The magnetic core-shell particles contained 65
w/w % of PMMMA cores, 27 w/w % of chitosan, and 8 w/w %
of γ-Fe\(_{2}\)O\(_{3}\), respectively.

FIG. 9(a) displays a transmission electron microscope
(TEM) image of a representative magnetic composite particle
wherein poly(methyl methacrylate) (PMMA) is the hyd
phobic polymer core synthesized using the typical recipe. The
magnetic composite particles comprise core and shell,
wherein the hydrophobic PMMA core contained magnetic
nanoparticles and coated with chitosan as a shell. Particle size
measurement indicated that an average particle diameter \(D\)_
\(\text{p}\) of 185 nm with \(D/\text{p}\) of 1.03 is formed (FIG. 9(b)).

The presence of chitosan shells was verified by \(\zeta\)-potential
measurements as a function of pH in a 1 mM NaCl solution at
25° C. FIG. 10 shows that the positive \(\zeta\)-potential of MCS
particles decreases from +50 to 0 mV as the pH increases
from pH 3.0 to 8.0. This effect is probably due to the de
protonation of quaternary ammonium ions of chitosan.

FIG. 11 shows the magnetic property of the particles mea
sured by applying external magnetic fields from 0 to 5 KA/m
using a VSM. Results indicated that the MCS particles exhib
ited superparamagnetic properties at room temperature since
the data from both scans were completely overlapped without
a hysteresis loop. The \(M\)_\(s\) value was 2.7 emu/g, which is
comparable to magnetic polymeric particles produced by
other encapsulation methods such as seeded precipitation
and microemulsion polymerization (1-3 emu/g latexes).

The film-forming properties of the magnetic composite
particles on a glass substrate were evaluated by AFM. Since
PMMA has a glass transition temperature (Tg) of 105° C,
the film-forming process is expected to occur at annealing
temperatures higher than its Tg. Examination of different annealing
temperatures from 130 to 155° C for film formation of the
composite particles suggested that the best film formed at
155° C. The AFM topographic image of the film in FIG. 12(a)
clearly illustrates that there were no individual magnetic
composite particles, suggesting that particle deformation
occurred at 155° C. Statistical analyses of the topographic
image indicated that the average height of the film was 45±28
nm. FIG. 12(b) shows the MFM image of the film. The out
of-plane spheres corresponding to the position of the particles
in the topographic image are the magnetic signals. These
signals are evenly distributed throughout the film, suggesting
that the core-shell particles are able to prevent magnetic
nanoparticles from aggregation during the film-forming process.
This property may have promising potential for various appli
cations.

Multi-functional particles that are able to alter their physical
and chemical properties in response to environmental stimuli,
such as pH, temperature, and magnetic field, are
attractive candidates for many potential applications, including
drug delivery, biosensor, affinity separation, enzyme
immobilization, and soft actuators. To demonstrate the versatil
ity of the invention for the preparation of multi-functional
core-shell particles, two types of vinyl monomers such as
n-butyl acrylate (BA) and N-isopropyl acrylamide (NIPAM)
were examined (FIG. 13).

The present method is very efficient for the encapsulation
of magnetic nanoparticles into the PMMMA/chitosan particles.
The following is a list of important features with respect to the
synthetic method and particle properties:

1. The synthesis is carried out in water. Stable magnetic
composite particles are produced in the absence of surf
actants and toxic solvent agents. Thus, it is an environmen
tally benign method.

2. The diameters of MCS particles ranging from 100 nm to
400 nm can be easily tailored by varying monomer
concentration.

3. The particles are biocompatible, and contain a consider
able amount of surface amino groups which can be
easily modified to other functionalities.

4. The magnetic composite particles possess a good film
forming ability. A smooth and uniform magnetic thin
film with a thickness around 5 μm coated on a glass
substrate can be easily produced by thermal annealing
the magnetic composite particles. Magnetic nanoparticles
with sizes between 60 and 80 nm were found to
evenly distribute within the polymer matrix. In other
words, the amphiphilic structure of the composite
particles is able to prevent magnetic nanoparticles from
aggregation during film forming process, which is a long
standing problem.

5. The synthetic method is a versatile route to a variety of
magnetic composite particles which have different core
properties such as hard (PMMA), soft poly(n-butyl acry
late) (PBA) or temperature-sensitive poly(N-isopropyl
acrylamide) (PNIPAm). Thus, tailor-made of the com
posite particles with different core compositions and
properties can be prepared for specific applications.
What is claimed is:

1. A process for making amphiphilic magnetic composite particles, the process comprising, sequentially:
   - forming magnetic nanoparticles from a solution of metal salts and coating the nanoparticles with a carboxylic acid to produce acid-modified magnetic nanoparticles;
   - coating the acid-modified magnetic nanoparticles with a silanol precursor in an alkaline solution to produce precursor-coated magnetic nanoparticles;
   - adding a silane coupling agent including a vinyl group to a dispersion of the precursor-coated magnetic nanoparticles and coating the precursor-coated magnetic nanoparticles to form vinyl-coated magnetic nanoparticles; and
   - encapsulating the vinyl-coated magnetic nanoparticles by homogenizing a dispersion of the vinyl-coated magnetic nanoparticles with an aqueous solution of a water-soluble polymer containing amino groups, a peroxide, and a monomer, graft copolymerizing the monomer to encapsulate the vinyl-coated magnetic nanoparticles in cores, and shells covering the cores, thereby forming the amphiphilic magnetic composite particles.

2. The process of claim 1, wherein the water-soluble polymer is a natural or synthetic water-soluble polymer containing amino groups.

3. The process of claim 1, wherein weight of the monomer is from 25% to 95% of total weight of the magnetic composite particles.

4. The process of claim 1 further comprising generating radicals on nitrogen atoms of the water-soluble polymer, and
   - initiating free-radical copolymerization of the monomer and the vinyl-coated magnetic nanoparticles, whereby the vinyl-coated magnetic nanoparticles are encapsulated in cores inside polymer shells.

5. The process of claim 1, wherein the monomer is hydrophobic and is selected from the group consisting of a hydrophobic vinyl monomer, an acrylate monomer, an acrylamide monomer, polymerizable nitrile, acrylate, chloride monomers, and a styrenic monomer.

6. The process of claim 1, wherein the monomer has the formula R1CH=CHR2, where R1 is hydrogen or alkyl, and R2 is alkyl, aryl, heteroaryl, substituted aryl, halo, or cyano.

7. The process of claim 1, wherein the monomer has the formula CH2=CR2COOR4, where R2 is hydrogen or alkyl, and R4 is alkyl or substituted alkyl.

8. The process of claim 1, wherein the monomer has the formula CH2=CR2COONHR4, where R2 is hydrogen or alkyl, and R4 is alkyl or substituted alkyl and the monomer is water insoluble.

9. The process of claim 1, wherein the monomer has the formula CH2=CR2CONR4, where R2 is hydrogen or alkyl, and R4 is alkyl or substituted alkyl or a hydrophobic group.

10. The process of claim 1, wherein the monomer has the formula CH2=CR2CONR4, where R2 is hydrogen or alkyl, and R4 is alkyl or substituted alkyl or a hydrophobic group.

11. The process of claim 1, wherein the carboxylic acid comprises trisodium citrate.

12. The process of claim 1, wherein the monomer is chosen from the group consisting of 3-(trimethoxysilyl)propylmethacrylate, (3-methyldiethoxysilyl)propylmethacrylate, (3-triethoxysilyl)propyl 2-propenoate, (3-triethoxysilyl)methyl methacrylate, and (triethoxydimethyl)methyl methacrylate.

13. The process of claim 1, wherein weight of the magnetic nanoparticles is from 5% to 30% of total weight of the magnetic composite particles.

14. The process of claim 1, wherein the water-soluble polymer is present in an amount between 5% and 20%, based on total weight of magnetic composite particles.

15. The process of claim 1, wherein the peroxide is an alkyl hydroperoxide or hydrogen peroxide.

16. The process of claim 1, wherein molar ratio of the monomer to the peroxide is more than 1000:1.

17. The process of claim 1 including graft copolymerizing in the absence of a surfactant.

18. The process of claim 1, wherein the silanol precursor is chosen from the group consisting of tetramethyl orthosilicate, tetraethyl orthosilicate, tetrapropyl orthosilicate, tetraethyl orthosilicate, methyl polysilicate, and ethyl polysilicate.

19. The process of claim 1, wherein the water-soluble polymer containing amino groups is chitosan.

* * * * *