Nanomedicine and Nanotoxicology

Surender Kumar Sharma
Yasir Javed *Editors*

Magnetic Nanoheterostructures

Diagnostic, Imaging and Treatment

Springer

Nanomedicine and Nanotoxicology

Series Editor

V. Zucolotto, Institute of Physics São Carlos, University of São Paulo, São Carlos, São Paulo, Brazil

More information about this series at http://www.springer.com/series/10620

Surender Kumar Sharma · Yasir Javed
Editors

Magnetic Nanoheterostructures

Diagnostic, Imaging and Treatment

Springer

Editors
Surender Kumar Sharma
Department of Physics
Faculty of Science and Technology
The University of the West Indies
St. Augustine, Trinidad and Tobago

Yasir Javed
Department of Physics
University of Agriculture Faisalabad
Faisalabad, Pakistan

ISSN 2194-0452 ISSN 2194-0460 (electronic)
Nanomedicine and Nanotoxicology
ISBN 978-3-030-39922-1 ISBN 978-3-030-39923-8 (eBook)
https://doi.org/10.1007/978-3-030-39923-8

This Springer imprint is published by the registered company Springer Nature Switzerland AG
The registered company address is: Gewerbestrasse 11, 6330 Cham, Switzerland

Preface

Nanohybrid systems have raised considerable interest in basic research as well as potential applications due to their broad range of novel and enhanced physical properties. As an important family of materials, nanoheterostructured e.g., core-shell, dumbbell, or dimer architectures have attracted increasing attention. This is due to their unique functionalities, arising from the synergetic combination of interesting physical properties in the same nano-entity, which leads to appealing biomedical applications especially cancer. Early cancer detection is one of the major limitations of currently available techniques, magnetic nanohybrids as contrast agents provide higher relaxation rates and increase the visibility of a portion of the biological systems. There are many reviews available where different magnetic nanoparticles and their applications for magnetic resonance imaging (MRI) and treatment have been discussed in a scattered manner. However, comprehensive data, where different types of magnetic nanohybrids, their structures, magnetism and use for diagnosis, imagining and treatment, is missing.

This book is aimed at highlighting the complexity of the nanoheterostructured especially magnetic metal oxides, ferrites and doped magnetic nanomaterials and their prospective applications for early detection, imaging and treatment of cancer. It will serve as an overview for a wide audience: from beginners and graduate-level students up to advanced specialists in both academic and industrial sectors.

St. Augustine, Trinidad and Tobago — Surender Kumar Sharma

Contents

Chapter 1
Liquid-Phase Synthesis of Multifunctional Nanomaterials: A Recent Update

Gopal Niraula, Navadeep Shrivastava, Kanwal Akhtar, Yasir Javed, J. A. H. Coaquira and S. K. Sharma

Abstract The design of novel materials is a fundamental focal point of material science research. Nanomaterials less than 100 nm in size have attracted significant interest over several decades due to their unique properties led by surface effect and finite size effect. Colloidal chemistry plays a key role in the controlled production of different classes of nanoparticles, thus being a subject of growing interest in several fields of materials, inorganic, physical chemistry, biophysics, and biomedical. Therefore, in this chapter, we sought to present an introductory outline of liquid-phase synthesis, nucleation, and growth mechanism of nanomaterials focusing on the magnetic nanoparticles. As per the broadness of this book, special attention was devoted to nanoparticles based on iron oxide and rare earth compounds, due to their rapid flourishing importance in biomedical field. Therefore, the work presents ideas involved in the most commonly applied methodologies for the liquid-phase synthesis of nanoparticles, such as co-precipitations and hydro/solvothermal techniques, as well as precipitations into nanoreactors based on reverse microemulsions, with a brief survey of the main advances in these fields in recent years. We have thoroughly presented the synthesis routes of several hybrid nanostructures such as magnetic silica/carbon, magnetic luminescence, magneto-plasmonics, and others. At last, the importance of surface modification and further bio-conjugation has been discussed.

G. Niraula
Department of Physics, Federal University of Maranhao, Sao Luis 65080-805, Brazil

N. Shrivastava (✉)
Institute of Physics, Federal University of Goias, Goiânia 74690-900, Brazil
e-mail: enavadeep@gmail.com

K. Akhtar · Y. Javed
Department of Physics, Magnetic Materials Laboratory, University of Agriculture Faisalabad, University Main Rd, Faisalabad 38000, Pakistan

J. A. H. Coaquira
Laboratory of Magnetic Materials, NFA, Institute of Physics, University of Brasilia, Brasilia, DF 70910 900, Brazil

S. K. Sharma (✉)
Department of Physics, the Faculty of Science and Technology, The University of West Indies, St. Augustine, Trinidad and Tobago
e-mail: surender.sharma@sta.uwi.edu; surender76@gmail.com

S. K. Sharma and Y. Javed (eds.), *Magnetic Nanoheterostructures*, Nanomedicine and Nanotoxicology, https://doi.org/10.1007/978-3-030-39923-8_1

Keywords Liquid-phase synthesis · Multifunctional nanoparticles · Nucleation and growth · Post-synthesis chemistry

Introduction

One of the great promises of nanotechnology is the application to biology and medicine. Nanometer-size protein particles called 'self-assembling peptide nanofiber scaffold' were used for the regeneration of axonal tissue of a hamster with severe optic tract. Also, it is used for site-specific or targeted drug delivery applications (Matson et al. 2011; Ellis-Behnke et al. 2006). Nanoparticles (NPs) selectively coated with biodegradable polymer can carry the drug in vivo to the desired location such as tumor cells or around inflammation sites as the polymer degrades. Superparamagnetic magnetite particles coated with dextran are used as image enhancement agents to detect small lymph-node metastases of prostate cancer in magnetic resonance imaging (Sun et al. 2008). Certain nanoparticles integrated on chips, 'laboratory-on-a-chip,' to work as tags or labels are used as biological tests measuring the presence or activity of selected substances become quicker, more sensitive, and more flexible (Jain 2003; Alharbi and Al-sheikh 2014).

Recently, magnetic NPs are an emerging field of study and have gained much attention among researchers due to their widespread applications in various fields including catalysis, data storage, environmental remediation, magnetic fluids, electronic communication, and biomedicine, etc. (Karatutlu and Sapelkin 2018; Alivisatos 1996). Among different types of magnetic NPs (MNPs), iron oxide NPs (IONPs) are the most popular and widely used in the field of biomedicine due to their ease of surface modification, synthesis, and low toxicity. Current studies and literature have confirmed that magnetic IONPs are frequently used in the treatment of hyperthermia or as drug carriers in cancer treatment, magnetic resonance imaging (MRI) agents, bioseparation, gene delivery, biosensors, protein purification, immunoassays, and cell labeling (Hurley et al. 2016; Ho et al. 2011; Lee et al. 2011; Mazumder et al. 2009; Sun et al. 2010).

Due to the unique properties like superparamagnetism, high coercivity, low Curie temperature, and high magnetic susceptibility, magnetic iron oxide NPs have a great importance for the researchers in a broad range of disciplines, including magnetic fluids, data storage, and catalysis to bio-applications (Hergt et al. 2008; Bertotti 1998; Dias et al. 2017; Aivazoglou et al. 2018). Especially, iron oxide NPs with appropriate surface chemistry have numerous in vivo applications in biomedical area such as magnetic resonance imaging (MRI) (Ho et al. 2011; Bae et al. 2012; Zhang et al. 2017), the deterioration of cancer cells via hyperthermia treatment (Hurley et al. 2016; Hergt et al. 2006; Yang et al. 2015; Carrey et al. 2011), tissue repair, immunoassay (Mattoussi et al. 2000), detoxification of biological fluids, drug delivery, and cell separation (Lee et al. 2011; Gao et al. 2004; Kim et al. 2008; Louie et al. 2000; Zhu et al. 2010). In this sense, an accurate choice of the nanomaterial with

adjustable physical and chemical properties plays an important role for such kinds of applications. In this consideration, magnetic NPs became the strong candidates.

The emergence of improved characterization techniques (such as the advances made to transmission electron microscopy) has allowed researchers to probe the precise nature of nanomaterials, enabling the relationships between size, shape, elemental composition, and physical properties of a material to be investigated. As such, the ability to develop 'tunable' nanomaterial syntheses (which can produce a high-quality nanomaterial product with properties pre-determined for a particular application) has emerged as a major research goal for scientists. Within nanoscale research, a number of distinct research branches have emerged, each relating to the study of a particular type of nanomaterial and its applications. It is therefore important to understand the synthesis methods with biocompatibility, coating nucleation and growth of NPs. Many efficient synthetic routes have been developed to produce shape-controlled, highly stable, and monodisperse magnetic NPs. Techniques such as co-precipitation (Salavati-Niasari et al. 2012; Pereira et al. 2012), thermal decomposition (Zhang et al. 2017; Salavati-Niasari et al. 2008; López-Ortega et al. 2015), reverse micelle synthesis (Vestal and Zhang 2003), hydrothermal synthesis (Karatutlu and Sapelkin 2018; Hayashi and Hakuta 2010; Brown et al. 1994), laser pyrolysis (Majidi et al. 2016; Reau et al. 2007), and microwave-assisted synthesis (Karatutlu and Sapelkin 2018; Russo et al. 2012; Tsuji et al. 2005; Bano et al. 2016) have been used to produce high-quality magnetic NPs.

This chapter deals mainly with the synthesis processes of magnetic NPs (and magnetic hybrid NPs) in detail for the sake of the entire book and coating methodologies of such NPs, in view of biomedical applications, along with several illustrative examples. Further, the physics of nucleation and growth of NPs have been provided with few selected illustrations.

Synthesis Methodologies: Role of Chemistry

There are two general approaches to fabricating nanomaterials, commonly known as the 'top-down' and 'bottom-up' methods. The top-down approach uses physical methods and is so-called as it arrives at a nanoscale product by breaking up a bulk material into smaller, nanosized parts. Conversely, the bottom-up approach 'builds' a nanomaterial from atomic or molecular precursors and is considered the chemical approach.

Top-Down Approach

A common top-down approaches to fabricating nanomaterials involve using a high-energy beam to 'etch' nanoscale features and patterns onto a substrate. This etching is achieved using a beam of high-energy particles (photons, ions, or electrons) to achieve

accurate site-specific sputtering and milling of a sample. Patterning of substrates is used extensively by the semiconductor industry when fabricating circuits. This technique is suitable for introducing fine detail onto a surface at the sub-micrometer level, though cannot produce discrete nanomaterial (Stanford et al. 2017; Wang and Xia 2004). Another commonly used top-down technique is ball milling. In ball milling, a powder of bulk material is continually circulated in a cylindrical chamber in the presence of a mixing agent (usually steel or stone balls) which grinds up the powder to produce fine particles. High-energy ball milling has been used to produce NPs with sizes as low as ~9 nm, though the disadvantage of this process is that there is very little control over the final particle shape and size (Prasad Yadav et al. 2012; Piras et al. 2019).

Bottom-Up Approach

The bottom-up approach involves building a nanomaterial in a step-by-step, atomic approach, fueled by the decomposition of a molecular precursor or the generation of atomic species. For example, in the pulsed laser decomposition (PLD) method a target material is irradiated by a laser beam, causing the material to vaporize. The vaporized material can be deposited on a nearby substrate, leading to thin-film growth. PLD allows precise control over the composition and thickness of a thin film, though the PLD apparatus is expensive and not suitable for producing large quantities of material. The solution-based synthesis of nanomaterials has been the subject of significant research interest in recent years, as this approach has the ability to produce a range of nanomaterial products with a high level of size and shape control (Wang and Xia 2004; Charitidis et al. 2014).

Liquid-Phase Synthesis

Over two decades, myriad breakthroughs have emerged following the advent of nanomaterial research in natural sciences and engineering, due to their unique properties depending upon shape and size. It is well known that reducing the size of materials down to microscale to nanoscale leads to produce nanomaterials with profound and significant changes in its physical, i.e., electrical, magnetic, and thermal properties, and hence could be good candidates in different application, i.e., optoelectronics, magnetic storage memory devices, and biomedical (Karatutlu and Sapelkin 2018; Alivisatos 1996). The designer of such nanomaterial in nanoscale varying with shape and size, depending upon application, is very complex and thus needs proper understanding of their architecture to synthesis. Usually, bottom-up approach, also referred as solution-phase chemistry that consists of liquid-phase synthesis (LPS hereafter), is used to prepare materials, rather than top-down approach in which bulk materials

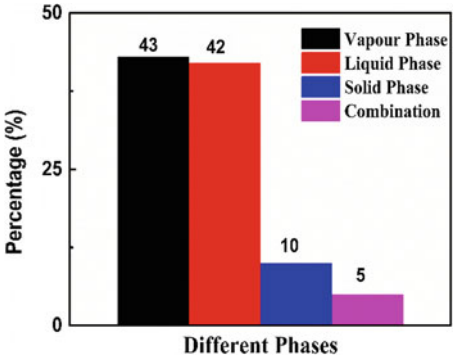

Fig. 1.1 Different methods to prepare nanomaterials. Reprinted with permission from Charitidis et al. (2014). Copyright 2014 Manufacturing Review

are etched in an aqueous solution for producing NPs or nanostructures, for example, electrochemical etching and mechanical grinding. LPS methods have several advantages over other gas-phase and solid-phase synthesis methods; for instance, LPS helps to controlled size and shape of NMs at low temperature within a short time from minutes to hours, reasonably low cost particularly compared to solid-phase synthesis methods, simple with high mass yield, and surface modifications with functionalization can be achieved in situ, even post-synthesis with respect to the application field (Charitidis et al. 2014; Gutsch et al. 2004; Feng et al. 2015).

Figure 1.1 shows that different ways of preparing nanomaterials and prepared nanomaterial in percentage until date through these ways (Charitidis et al. 2014). NPs obtained by liquid-phase synthesis methods can remain in liquid suspension for further/future use or may be collected by filtering or by spray drying to produce a dry powder. Liquid-phase synthesis methods from a solution of chemical compounds include chemical stain etching, colloidal methods, co-precipitation, electrochemical deposition, direct precipitation, sol–gel processing, microemulsion method, reverse micelle synthesis, hydrothermal synthesis, template methods, polyol method, and laser ablation. Here, we attempt to explain the methods of the most common liquid-phase synthesis as follows.

Precipitation

Co-precipitation was widely studied to prepare magnetic NPs due to its extraordinary advantages, such as gram-scale production and facility. Co-precipitation method based on the hydrolysis of a mixture of Fe^{2+} and Fe^{3+} ions is used to fix the A to B molar ratio in the inverse spinel structure during the preparation of magnetite. Usually, the reaction is performed under an inert (N_2 or Ar) atmosphere using degassed solutions to avoid uncontrollable oxidation of Fe^{2+} into Fe^{3+} (Bandhu et al. 2009), as shown in Fig. 1.2a. In this method, Fe^{2+} and Fe^{3+} ions are generally precipitated in alkaline solutions, such as ammonium hydroxide, potassium hydroxide, or sodium hydroxide. In most cases, the syntheses are performed at 70–80 °C (Ozkaya et al.

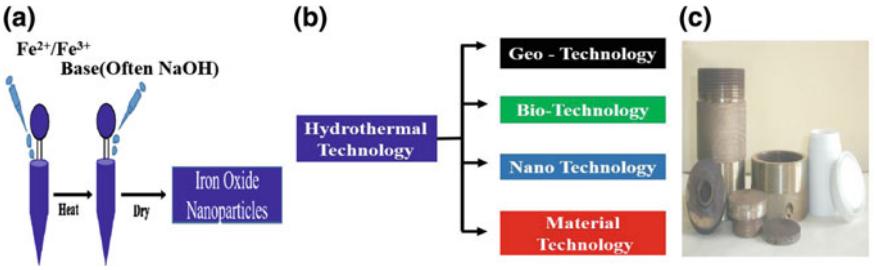

Fig. 1.2 **a** Co-precipitation method of synthesis, **b** application of hydrothermal technology, and **c** most uses autoclave for hydrothermal synthesis. Reprinted with permission from Byrappa and Adschiri (2007), Copyright 2007 Elsevier Ltd. All rights reserved

2009) or higher temperatures. The effects of mixing methods, stirring rate (Valenzuela et al. 2009), digestion time (Gnanaprakash et al. 2007), initial pH, and the presence or absence of a magnetic field (Hu et al. 2009; Vereda et al. 2007) on particle size, morphology, and resulting magnetic properties should take an account as an important factor. Co-precipitation methods performed under various precipitation conditions. For example, when only Fe^{2+} was used for precipitation, then H_2O_2 (Hu et al. 2009; Mizukoshi et al. 2009) or $NaNO_2$ (Nedkov et al. 2006) were adopted to partially oxidize Fe^{2+} into Fe^{3+} in the precipitated product. When only Fe^{3+} was used for precipitation, then Na_2SO_3 (Qu et al. 1999) partially reduces ferric to ferrous ion in the precipitation product. Some co-precipitation methods are performed in the presence of polymers (Pardoe et al. 2001), including polyvinyl alcohol (PVA) and dextran to prevent both agglomeration and/or oxidation of the NPs. All these co-precipitation methods are comparatively complex and require strict control of precipitation conditions.

Recently, several modified co-precipitation methods have been developed; for example, Wu et al. (2011) have synthesized magnetic NPsFe_3O_4 nanopowders with an average diameter of 15 nm by ultrasonic-assisted chemical co-precipitation utilizing high purity iron separated from iron ore tailings by an acidic leaching method. The present synthesis method of Fe_3O_4 NPs easily yields SPIONPs without a protecting gas. Pereira et al. (2012) prepared superparamagnetic Fe_3O_4 NPs with sizes of 4.9–6.3 nm, by a one-step aqueous co-precipitation route based on the use of alkanol-amines as the base; the reported methodology provides a simple, versatile, and cost-effective route for the high-yield synthesis of IONPs featuring improved magnetic properties and small particle sizes (Pereira et al. 2012). Currently, the problems of aggregation and biocompatibility of IONPs perhaps hinder the applications in biomedical fields. Therefore, many surfactants and biomolecules have been introduced directly in the co-precipitation process. For instance, Salavati-Niasari et al. (2012) have reported Fe_3O_4 NPs with a size range of 25 nm that were prepared by a facile chemical co-precipitation method; the surfactant octanoic acid was present in the reaction system to improve the dispersity. Liu et al. (2011) have prepared magnetic chitosan-coated Fe_3O_4 NPs by the co-precipitation method under 0.45 T static

magnetic fields, which assisted the glutaraldehyde cross-linking reaction; the water was replaced by 2% chitosan in an acetic acid solution during the reaction process. The resulting NPs were used to immobilize lipase.

Hydro/Solvothermal Synthesis

The word 'hydrothermal' is self-defined, made by hydro plus thermal whose meanings are water plus heat, respectively. Since the last two decades, researchers/technologists of different fields have been attracted toward it to synthesize the NPs. The nanomaterials prepared via this method in the diverse field are shown in Fig. 1.2b.

Several definitions about hydrothermal preparation of materials using autoclave and reagents in solutions at constant pressure and temperature have been mentioned in the past. In conclusion of such several approaches can be summarizing as chemical reactions in solvents contained in sealed vessels in which solvent temperature can be brought to around their critical points (coexistence point of critical temperature and critical pressure) through heating. The process is called 'hydrothermal' synthesis method when water is used as the solvent, whereas the term 'solvothermal process' is used when organics are used as solvents (Byrappa and Adschiri 2007; Rabenau 1985; Morey and Niggli 1913; Byrappa and Yoshimura 2013). Hydrothermal synthesis in supercritical water has advantages for the synthesis of multi-metal-oxide compounds because the reaction rate is enhanced more than 10^3 times that under the conventional hydrothermal conditions owing to the low dielectric constant ($<10^3$) as well as products with high crystallinity (Hayashi and Hakuta 2010; Adschiri et al. 2000). The particle size of metal oxide depends on the hydrolysis rate and solubility of the metal oxide. To achieve the control of the solvent field during nucleation and crystallization of particles, hydrothermal conditions of temperature and pressure can be varied in subcritical and supercritical water. Hydrothermal methods for preparing fine metal-oxide particles in subcritical and supercritical water have been developed using batch reaction and flow reaction systems (Yahya et al. 2001; Hakuta et al. 2004; Sue et al. 2006).

In recent year, the hydro/solvothermal process has gained great success in manufacturing nanomaterials with crystallinity, crystal phase, morphology, and size control, due to its outstanding advantages (Higgins et al. 1998; Maslar et al. 2001). This method is environment friendly and far away from high-cost instrumentation, energy, and precursors than others. Besides for processing nanomaterials, the hydrothermal technique offers special advantages because of the highly controlled diffusivity in a strong solvent media in a closed system. Nanomaterials require control over their physicochemical characteristics, if they are supposed to be used as functional materials. As the size reduced toward the nanometer range, the materials exhibit peculiar and interesting mechanical and physical properties: increased mechanical strength, enhanced diffusivity, higher specific heat, and electrical resistivity compared to their conventional coarse-grained counter-parts due to a quantization effect (Gleiter 1989).

Also, due to mild hydrothermal reaction, temperature (<300 °C) helps to overcome the several encountered found in high-temperature reaction, i.e., poor stoichiometric control due to volatilization of components in other synthesis methods. Moreover, nanomaterials prepared through hydrothermal method help to improve the luminescent properties due to the absence of Schottky defects, mostly present in materials prepared by other high-temperature reactions, for instance Sr, Ta, etc. Thus, varieties of size and morphology have been appeared in NPs synthesized by hydrothermal method. The possibility of hybridization with other synthesis process is another advantage to enhance the kinetics of reaction and to wax the ability to make new material. However, this method includes the need for expensive autoclaves and the impossibility of observing the crystal as it grows if a steel tube is used. The different autoclave for different synthesis is essential as per the interest of nanomaterials. An autoclave that uses at the material laboratory, mostly, is shown in Fig. 1.2c. The laboratory with facility of reliable pressure and temperature is another challenge (Byrappa and Adschiri 2007; Hamann 1981; Song et al. 2016; Cho et al. 1995). The corrosion resistance is major factor to choose the autoclaves because most of the nanomaterials under hydrothermal is prepared by corrosive salt. So autoclave must have the capacity to sustain in highly corrosive solvent at high temperature and pressure for longer time, i.e., hours to several days. The most successful autoclaves using by researcher are stainless steel whose inside is coated with non-reactive material having larger coefficient thermal expansion, called Teflon (also called The Liners), helps to avoid the corrosion (Song et al. 2016; Gogotsi and Yoshimura 1995).

Effect of Time and Temperature on the Size of NPs

There are only some studies about the effect of parameters such as reaction temperature and time on the growth of the NPs. Taniguchi et al. (2009) reported that the average crystalline diameter of sodium oleate-coated iron oxide NPs increased from 8.3 to 10.8 nm with the increase of reaction temperature from 100 to 230 °C under the hydrothermal process. Later, to investigate the effect of the reaction time and temperature on the nanoparticle size, Ozel et al. (2015) prepared the iron oxide NPs with the reaction time 12 h, average size of particles from 14 to 17 nm were obtained, and with increasing reaction time from 12 to 24 h at 150 °C, the size of NPs increased from 16 to 23 nm, respectively. After this, they have studied the effect of increasing temperature at 60 °C, 100 °C, 150 °C, and 180 °C for 12 h and found the size of iron oxide NPs are 12 nm, 14 nm, 16 nm, and 21 nm, respectively. Thus, we can conclude that from above discussion, the size of NPs is time and temperature dependent. Moreover, the magnetic properties such as magnetization and coercivity depend upon the size of NPs; it means that variation of time and temperature on the NPs directly influences to its structural and magnetic properties.

Synthesis of Magnetic NPs by Hydrothermal Method

Several workers have prepared the α-Fe_2O_3 (hematite) phase as NPs under hydrothermal conditions (using both aqueous and non-aqueous solvents) with or without surfactants (Li et al. 2002; Jing and Wu 2004; Zheng et al. 2005). These hematite particles find extensive applications such as catalysts, pigments, recording medium, and sensors. Surfactants like sodium dodecyl sulfonate (SDS), sodium dodecyl benzene sulfonate (DBS), cetyltrimethylammonium bromide (CTAB), and hexadecylpyridinium chloride (HPC) have been used. $Fecl_2$, $Fecl_3$, $FeSO_4$, $Fe(NO_3)_3{\cdot}9H_2O$, or FeC_2O_4, etc., were used as the source of iron. NaOH or *N,N*-dimethylformamide (DMF) was used as a solvent. The experimental temperature ranges from 180 to 250 °C in most of the cases. The typical size of the products varies from 20 to 200 nm depending upon the starting materials (reagents and solvents) and the experimental temperature. Iron oxides of spinel and magnetic structures are very important for their unique magnetic properties, which can be varied systematically through dopants like Co, Ni, Zn, Mn, etc. Cote et al. (2003) have prepared $CoFe_2O_4$ NPs through hydrothermal means within a temperature range 200–400 °C and pressure 25 MPa. A complete mechanism of formation of $CoFe_2O_4$ has been discussed in (Cote et al. 2002). It was found necessary to control the pH and experimental temperature to obtain the desired phase with a size of 100 nm. Wu et al. (2005) have synthesized nanowire arrays of Co-doped magnetite under hydrothermal conditions at 200 °C using ferrous chloride, cobalt chloride, and sodium hydroxide. These nanowires are believed to possess a single magnetic domain which can be regarded as small-wire like magnets. A soft template-assisted hydrothermal route used to prepare single-crystal Fe_3O_4 nanorods with an average diameter of 25 nm and length of 200 nm at 120 °C in 20 h. The formation of these Fe_3O_4 nanorods has been ascribed to ethylenediamine, which plays a crucial role not only as a base source but also as a soft template to form single-crystal Fe_3O_4 nanorods (Byrappa and Yoshimura 2013).

Sattar et al. (2015) have synthesized the $CoFe_2O_4$@$NiFe_2O_4$ core–shell NPs by hydrothermal synthesis method with core diameter of ~18 nm and shell thickness 3 nm as observed by TEM. They found that $CoFe_2O_4$@$NiFe_2O_4$ core–shell nanocomposite is in well-crystalline nature using different techniques. The magnetic properties of this core–shell have been studied via hysteresis loop. The magnetization saturation, coercivity, and retentivity of these NPs are 28.13 emu/g, 867.9 Oe, and 10.77 emu/g; these values were between the magnetic properties of the core ($CoFe_2O_4$) and shell ($NiFe_2O_4$) materials. Both of the saturation magnetization and coercive field are decreased compared with $CoFe_2O_4$. The decreases in the saturation magnetization and coercive field can be explained in terms of the existence of $NiFe_2O_4$ on the surface of $CoFe_2O_4$ NPs (Kolhatkar et al. 2013). Sun et al. (2018a) synthesized of Fe_3O_4@E-SiO_2 core–shell nanostructure with a rough surface. Superparamagnetic Fe_3O_4 nanosphere was first obtained with a hydrothermal process. It was found that $\sim 200 \pm 10$ nm in diameter and composed of aggregated Fe_3O_4 NPs. The hysteresis loops with zero remanence and zero coercivity demonstrated that Fe_3O_4 core had a superparamagnetic behavior with the saturation magnetization value of ~72.4 emu/g which could be attributed to its smaller grain size of aggregated Fe_3O_4 NPs than the

critical size for superparamagnetic Fe_3O_4 at ~25 nm (Zhang et al. 2008). After coating by SiO_2, the diameter of the nanosphere increased to ~400 nm with an ~100 nm silica shell. They heated the obtained Fe_3O_4@SiO_2 core–shell NPs with polyvinylpyrrolidone (PVP) for 1 h where PVP was adsorbed by the surface of Fe_3O_4@SiO_2 with the preservation of morphology of core–shell. This PVP on the surface acts as protecting agent during etching that could be diffuse with pores of SiO_2 shell and become porous. The etched sample had a much larger specific surface area of ~217.8 m^2/g, and its total pore volume increased to ~0.175 cm^3/g which also indicated that the etched sample had a rough surface. Sheng et al. (2014) have developed one-step approach to prepare superparamagnetic NPs with silk fibroin (SF) as the template and coating material, providing a simpler and more feasible way for core–shell Fe_3O_4@SF nanoparticle fabrication by hydrothermal method. The synthesized pure Fe_3O_4 NPs showed irregular morphologies with a size of about 20 nm. However, the increase of SF in the reaction system and the Fe_3O_4 NPs became more regular and finally transformed into nanospheres when the concentration of SF was above 7%. They observed no evident differences in pure Fe_3O_4 and Fe_3O_4@SF NPs, suggesting that the crystalline structure of the NPs was not affected by the SF coating. The Fe_3O_4/SF NPs showed insignificant coercivity, suggesting the superparamagnetic nature of the particles. The potential of Fe_3O_4@SF NPs as a contrast agent was examined by using a 3T MR scanner. An obvious darkening of T_2-weighted MRI was observed with the increasing concentration of Fe, showing a transverse relaxivity (r_2) of 40 mM^{-1} s^{-1}. Thus, their results suggested that SF could be used to control the morphology and size of Fe_3O_4 microspheres. The biocompatibility and transverse relaxivity of the Fe_3O_4@SF core–shell nanomaterial, as well as its easy coupling ability with antibodies, suggest its future in different biomedical applications.

Thermal Decomposition

Thermal decomposition is simple, easier, convenient, and an innovative method to synthesize stable monodispersed NP product. In principle, synthesis strategies can be subdivided into hot-injection approaches, where the precursors are injected into a hot reaction mixture and conventional reaction strategies where a reaction mixture is prepared at room temperature and then heated in a closed or open reaction vessel. Above room temperature, higher monodisperse, narrow size distribution, and highly crystalline magnetic IONPs are obtained from high-temperature thermal decomposition of organometallic or coordinated iron precursors in organic solvents, which display superior properties to those obtained by co-precipitation. It means thermal decomposition helps to overcome some conventional method, for instance co-precipitation (Li et al. 2008; Sun and Zeng 2002). As similar to other method of synthesis, time of reaction, temperature, concentrations of the reactants, stabilizers, capping agents (surfactants), and types of surfactants are factors to be considered to obtain controlled nanometric size (Kino et al. 2008). To date, the thermal decomposition method is mostly used to prepare iron oxide NPs with different shapes as per

application required, such as nanocrystals, nanocubes, and nanospheres, etc. Usually, it is recommended to use of various organic molecules including oleic acid, 1-octadecene, 1-tetradecene, and oleylamine in the reaction process as stabilizers to get monodisperse iron oxide NPs that can slow down the nucleation process and it affects the adsorption of additives on the nuclei and the growing nanocrystals, which may inhibit the growth of the IONPs and favor the formation of small IONPs often below 30 nm. However, the nucleation of IONPs in thermal decomposition involves boiling the solvents, so the accurate shape of the IONPs is not fully reproducible (Lynch et al. 2011). Amara et al. (2012) have offered novel single-step thermal decomposition method to synthesized Fe_3O_4 nanocubes and nanospheres with mixtures of ferrocene and PVP without solvent. Sun and Zeng (2002) have prepared Fe_3O_4 NPs of narrow size distribution which have been synthesized by thermal decomposition of $Fe(acac)_3$ in phenyl ether in the presence of stearyl alcohol, oleic acid, and oleylamine. Park et al. (2005) prepared monodisperse γ-Fe_2O_3 NPs with average diameters from 4 to 16 nm with controlling the molar ratio of metal precursor to surfactant [$Fe(CO)_5$], and oleic acid, respectively. The overall synthetic procedure is similar to seed-mediated growth. These monodisperse NPs were obtained directly without a size-selection process, and the synthetic procedure is highly reproducible. Subsequent chemical oxidation produced monodisperse and highly crystalline iron oxide nanocrystals. This concept of continuous growth without additional nucleation could be applicable to other materials for the incremental, 1-nm size-controlled synthesis of monodisperse NPs. Since several experiments have shown $Fe(CO)_5$ is very expensive and toxic, it is suggested to replace $Fe(CO)_5$ with iron chloride ($FeCl_3$) and iron acetylacetonate [$Fe(acac)_3$]. A growth scheme has been provided in Fig. 1.3.

Kovalenko et al. (2007) reported at first the synthesis of nanocubes by decomposing an iron oleate precursor using a sodium oleate (NaOl) salt along with oleic acid (OA) as ligands. It is well known that oleic acid is one of the most widely employed surfactants for the synthesis of various nanomaterials from metals, semiconductors, and metal oxides. The presence of a carboxylic group with significant affinity to various surfaces together with a nonpolar tail group for sterical hindering is the base for the excellent stabilizing function of this ligand. Commonly used approaches to further tailor the ligand performance of carboxylic acids are those based on the modifications of length or structure of the nonpolar group. They have concluded their synthesis result with various oleic acid salts acting as stabilizers for the size- and shape-controlled synthesis of iron oxide NPs. Their novel shapes for

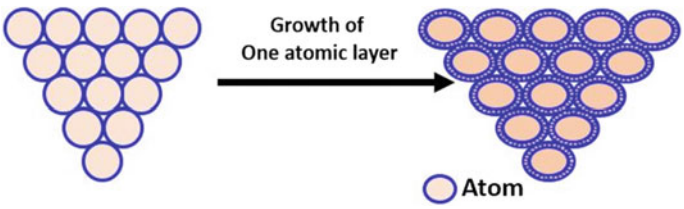

Fig. 1.3 Growth scheme: direct- and atomic-scale controlled synthesis of monodisperse NPs

superparamagnetic iron oxide nanocrystals, such as cubes and bipyramids with different magnetization properties at low temperatures, were demonstrated, enlarging the family of well-defined NP shapes for inverse spinel iron oxides. These results suggest the general applicability of oleic acid salts as stabilizers in well-controlled NP syntheses.

Microwave-Assisted Hydrothermal Method

In the recent years, researcher/scientist have attracted toward microwave-assisted synthesis method and have been successfully applied in various laboratories of nanomaterial synthesis (Nadagouda et al. 2011; Kou and Varma 2012), solid-state chemistry, nanotechnology (Virkutyte and Varma 2011), and organic synthesis (Polshettiwar et al. 2009a), etc., and many more applications, shown in Fig. 1.4a. Recent time has witnessed that the microwave heating technology is emerging as an alternative heat source for rapid volumetric heating with shorter reaction time and higher reaction rate, selectivity, and yield as compared to the conventional heating methods, providing fast chemical reactions and quick material preparation in very short span of time, usually in minutes/seconds, instead of hours or even days usually required by the conventional heating methods, leading to relatively low cost, energy saving, and high efficiency for material production (Galema 1997; Bilecka and Niederberger 2010; Kappe 2004). Beside, having large numbers of advantages of microwave-assisted synthesis, the limitation of such synthesis is rapid heating that requires a reaction component with a large loss tangent, denoted by tan δ (such as water, ethylene glycol) than their corresponding reaction media/solvent, phenomena is called selective heating (Baghbanzadeh et al. 2011). So it is always beneficial to use those solvent having high microwave absorbing capacity to get high heating rates, water, and alcohol for example. Also, the poor solubility of organic reactants in aqueous media is another limitation for organic synthesis in water, which usually results in immiscible or biphasic reaction mixtures. However, there were several attempts to

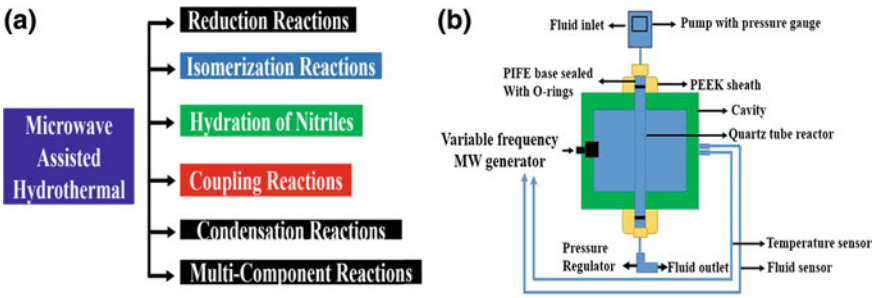

Fig. 1.4 **a** Application of microwave-assisted method, and **b** experimental setup of the present MW-assisted flow reactor system with MW cavity part

Table 1 Loss tangent (tan δ) values at 2.45 GHz and 20 °C and boiling points of different solvents (Gawande et al. 2014)

Solvent	Boiling point	Tan δ
Ethylene glycol	198	1.350
Ethanol	78	0.941
2-propanol	82	0.799
Methanol	65	0.659
1,2 dichlorobenzene	180.5	0.280
N-methyl 2-pyrrolidone	202	0.275
Acetic acid	118	0.174
N,N-dimethylformamide	153	0.161
1,2-dichloroethane	84	0.127
Water	100	0.123
Chlorobenzene	131	0.101
Acetone	57	0.054
Tetrahydrofuran	66	0.047
Toulene	111	0.040
Hexane	68–69	0.020

overcome this problem by using surfactants, mixing with co-solvents, heating of the reaction mixture, or grinding of reactants. Thus, in spite of those limitations, it has great promise in microwave-assisted organic synthesis (MAOS) and in MW-assisted nanomaterial synthesis (Bilecka and Niederberger 2010; Gawande et al. 2014).

Microwave-assisted chemical reactions depend on the ability of the reaction mixture to efficiently absorb MW energy, which often depends on the choice of solvents for the reaction. The ability of a specific solvent or material to convert MW energy into heat is determined by the so-called loss tangent (δ). The concept of dielectric loss tangent was introduced to compare heating efficiencies of microwave in materials with similar characteristics using, which is given by, $\tan \delta = \frac{\varepsilon''}{\varepsilon'}$, where ε'' is the imaginary component of the dielectric and represents the microwave radiation absorption and conversion to heat and ε' is the real component, which signifies the ability of the material to reflect or store an electric field (Baghbanzadeh et al. 2011; Mingos and Baghurst 1991). The solvents used in microwave heating can be classified on the basis of their loss tangent (tan δ): high (tan $\delta > 0.5$), medium (tan $\delta \approx$ 0.1–0.5), and low (tan $\delta < 0.1$) (Kappe 2004). The value of the loss tangent (tan δ) according to solvent is different and briefly tabulated in Table 1.

Microwave Heat Generation and Mechanism

Simply, microwave heating is a process of transferring of electromagnetic energy to thermal energy rather than transfer of heat. The basic principles of microwave chemistry have been discussed in several review papers (Tsuji et al. 2005; Galema

1997; Baghbanzadeh et al. 2011; Mingos and Baghurst 1991; Nüchter et al. 2004; Gabriel et al. 1998). As an example, Gabriel et al. (1998) have provided the theory of the microwave dielectric heating, which consists of two main mechanisms namely dipolar polarization and ionic conduction. Microwaves generally heat any material containing mobile electric charges such as polar molecules or conducting ions in a solvent or in a solid. During the microwave heating, polar molecules such as water molecules strive to orientate with the rapidly changing alternating electric field; thus, heat is induced by the rotation, friction, and collision of molecules (known as dipolar polarization mechanism). Ions also move with the oscillating field, colliding, and generating heat. These collisions of ions with other species in solution generate much more heat than dipolar polarization. The studies on the mechanisms of microwave heating are even complicated by the fact that the rate enhancements of chemical reactions are dependent on many complex factors. Gedye et al. (1988) found the effects of several factors, such as sample volume, solvent, homogeneous and heterogeneous reactions, size of reaction vessel, and power level, on rate enhancements in microwave-assisted organic synthesis. In addition, higher pressure and temperature attained rapidly in MW-assisted processes may help increase the rate of reactions via enhanced homogeneous mixing of the reactants (in water) and decreasing the hydrophobic effects (on water). They proposed that the rate enhancements were caused predominantly by the rapid superheating of the solvent by microwaves. Moreover, they found that the microwave heating rate increased due to the presence of ions in the reaction mixture. In addition to these thermal heating effects, de la Hoz et al.(2005) added the role of 'non-thermal microwave effects' also called 'specific microwave effects' which is arises due to interaction of microwaves with materials in the reaction medium and hence conclude that irradiation on microwave is due to both thermal and non-thermal effects. So it is convoluted to separate discussion in regard to the mechanism of heating factor in microwave.

The reported 'non-thermal microwave effects' include varied activation energy, increased collision efficiency by mutual orientation of polar molecules and possible excitement of rotational or vibrational transitions (Galema 1997; de la Hoz et al. 2005; Perreux and Loupy 2001; Stass et al. 2000). Single-mode microwave reactors, also referred as monomode reactors, having only one reactor vessel can be irradiated, a highly homogenous energy field of high-power intensity is provided, resulting in fast heating rates (Dąbrowska et al. 2018). The simple experimental/instrumental outlook of single-mode microwave reactors is shown in Fig. 1.4b. Such microwave reactor was used for continuous flow reactions, wherein the power was controlled by a temperature feedback module and resonance frequency auto-tracking function (Nishioka et al. 2013; Öhrngren et al. 2012). The continuous flow reactor is capable of operating in a genuine high-temperature/high-pressure process window (310 °C/60 bar) under MW irradiation conditions. The faster heating rate, small reactor volumes, and rapid change in reaction temperature in real time are some of the salient features of this continuous flow MW-assisted organic synthesis (CF-MAOS) system, which aims to be a unique laboratory tool for safe and fast optimization of

reaction conditions and scale-out synthesis. Thus, the fusion of MW and a flow reactor system does offer unique features that can be adapted to organic and inorganic material syntheses (Morschhäuser et al. 2012).

Microwave-Assisted Synthesis of NPs

MW-assisted synthesis of inorganic nanomaterials and the use of nanocatalysts are growing rapidly. Inorganic nanomaterials include diverse classes of functional materials, namely metals, metal oxides, sulfides, phosphates, and halides. Some important examples of NPs are in brief below with the versatility of the MW-assisted approach for accessing a variety of nanomaterials.

α-Fe_2O_3 was synthesized using hydrothermal technique by simply heating the $K_4[Fe(CN)_6]$ in water under MW irradiation condition at 150 °C for three hours. The morphology of these particles appeared like a pine tree and hence the term micropine particle. TEM and ESEM images of the synthesized micropine α-Fe_2O_3 particles show the single-crystal structure. A closer inspection of these particles reveals well-defined and highly ordered branches shown in Fig. 1.5a–e distributed on both the sides. The TEM observations also revealed that the micropine dendrites self-assembled to form a sixfold snowflake-like structure.

There is a crucial role of concentration and time in the formation of different morphology of iron oxide. They observed that decrease in the sharpness of the dendrites, thicker the nanorod branches of dendrite with increasing the concentration of $K_4[Fe(CN)_6]$. However, if we decrease the temperature below 150 °C, we need to extend the time to get similar NPs. Thus, from these results, they suggest that it is possible to control and tune the shape of dendritic nanostructures by controlling the kinetic parameters (temperature and concentration) of the reaction process (Polshettiwar et al. 2009b). Hu et al. (2007) applied a rapid microwave-assisted hydrothermal process to synthesize single-crystalline α-Fe_2O_3 nanorings in solution. Single α-Fe_2O_3 nanoring with a circular shape and an average outer diameter of about 100 nm and inner diameters ranging from 20 to 60 nm were obtained at 220 °C for 25 min. In addition, they also reported the microwave hydrothermal method to

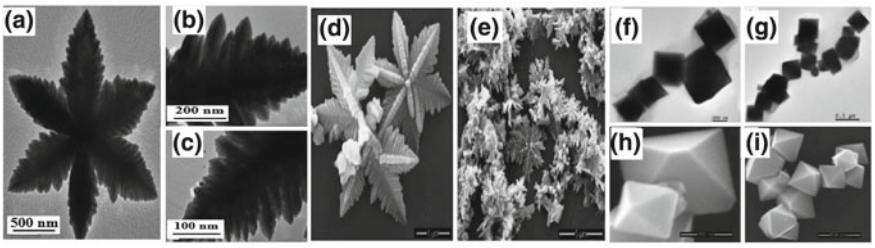

Fig. 1.5 TEM of **a** snowflake and **b**, **c** pine α-Fe_2O_3, SEM image of α-Fe_2O_3 (**d**, **e**) and TEM (**f**, **g**) and FE-SEM (**h**, **i**) of cobalt oxide. Reprinted with permission from Polshettiwar et al. (2009). Copyright 2009 American Chemical Society

synthesize monodisperse α-Fe_2O_3 nanocrystals with continuous aspect-ratio tuning and fine shape control. The initial molar ratio of Fe^{3+} to PO_4^{3-} was found to play a crucial role in the final morphology of the α-Fe_2O_3 products. A variety of morphologies including ellipsoids/spindles with aspect ratios ranging from 1.1 to 6.3, all nanosheets, nanorings, and spheres were obtained with pH of 1.8–2.3 at 220 °C for 10–25 min. MW-assisted hydrothermal heating of $K_3[Co(CN)_6]$ in water fabricated cobalt oxide in good yield. TEM and SEM studies, shown in Fig. 1.5f–i, revealed the formation of octahedral NPs with sizes ranging from 200 to 500 nm. For an octahedral crystal, every facet is close to an equilateral triangle. All the surfaces are smooth, and there are no defects, with crystallite size 46.21 nm. The effects of substrate concentration and reaction temperature on the morphology of the cobalt oxide NPs were also studied; however, no significant changes were observed in NPs (Polshettiwar et al. 2009b).

Kooti et al. (2011) synthesized maghemite NPs using $Fe(acac)_3$ as an iron precursor, PEG-200 as a size controller, and NaCl as an MW absorber. This mixture was irradiated for 5 min at 1000 W. NPs were imaged by TEM and SEM, revealing an average core size of 13 nm and NP agglomeration. Bano et al. (2016) carried out a MW-assisted green synthesis of superparamagnetic NPs using fruit peel extracts as a biogenic reductant. Mixtures were subjected to MW irradiation at 800-W power in 30-s pulses. Obtained NPs were then surface engineered via carbodiimide (functional group, RN=C=NR) chemistry to functionalize them with PEG-6000 or succinic acid. Size ranged between 17 and 25 nm with an almost spherical morphology. NPs presented a good colloidal stability and water dispersibility and a large r_2 value of 225 mM^{-1} s^{-1}. Synthesized samples were shown to be hemocompatible at concentrations as high as 400 μg/mL. Their utility in photodynamic therapy was assessed in HeLa cells, which showed 23% decreased survival. Sathya et al. (2017) synthesized water-dispersible magnetite NPs by reducing $Fe_2(SO_4)_3$ using sodium acetate as an alkali, PEG (5–6 kDa) as a capping ligand, and ethylene glycol as a solvent and reductant. Reactants were heated to 200 °C in 10 s in the MW and held at that temperature for different reaction times (from 10 to 600 s). X-ray diffraction (XRD) data showed magnetite crystalline samples with NP core sizes between 9 and 24 nm. The hydrodynamic size of synthesized NPs, measured by dynamic light scattering (DLS), ranged from 35 to 141 nm, increasing with reaction time. Size distribution was narrow for all samples. Nanocluster size increased with reaction time from ~27 nm (10 s reaction time) to ~52 nm (600 s reaction time). Aivazoglou et al. (2018) reported the synthesis of magnetite and maghemite NPs, analyzing the effect of reaction time, MW power, and capping agent on the properties of synthesized NPs. They have carried out separate sets of syntheses. With several syntheses having different MW powers, reaction time with capping and non-capping agents, their average size of NPs ranged from 10.3 to 19.2 nm, with a faceted and crystalline morphology. Their results showed that MW power and reaction time play a pivotal role in controlling NP size and maghemite presence, whereas ammonia concentration is not as relevant. PEG-assisted synthetic route rendered better results in terms of NP size and oxidation resistance. Mohamed and Hessien (2018) have synthesized nickel ferrite $NiFe_2O_4$ particles in nanosize scale using microwave-assisted hydrothermal method at 180 °C

for different periods of time (from 2 to 24 h). The prepared samples had an average particle size in the range of from 20 to 40 nm, as observed by using TEM and X-ray diffraction. The nickel ferrite powders were all considered as superparamagnetic materials. The values of coercivity and saturation magnetization were increased by increasing the period of synthesis time.

Polyol Synthesis

The polyol synthesis is reduction reaction method to prepare magnetic NPs with different morphology, also recognized as an inversed sol–gel method (i.e., an oxidation reaction) (Laurent et al. 2008). It designates the liquid-phase synthesis in high-boiling, multivalent alcohols and is mainly directed to NPs. As chemically, ethylene glycol (EG) is very common and simplest reagent in the polyol family. Based on EG, the polyols comprise two main series of molecules: (i) diethylene glycol (DEG), triethylene glycol (TrEG), tetraethylene glycol (TEG), and so on up to polyethylene glycol (PEG) and (ii) propanediol (PDO), butanediol (BD), pentanediol (PD), and so on (Table 2).

In such synthesis process, the polyols not only serve as solvents but also consider as reducing agents, which apply as stabilizers to control particle growth and prevent interparticle aggregation. The high quality of the as-prepared metal particles with uniform size and shape as well as low degree of agglomeration leads toward a great impact of the polyol synthesis. In the typical reaction process, an iron precursor compound is suspended in a liquid polyol. The suspension is stirred and heated to a given temperature that can reach the boiling point of the polyol. Usually, polyols allow for enormous adaptability and flexibility of the polyol synthesis. In principle, the boiling point of the polyols increases with the number of OH functionalities (see on Table 2) and with increasing molecular weight and thus polarity and viscosity

Table 2 Summary of mostly use polyols for the synthesis of materials (Dong et al. 2015)

Polyol	Acronym	Boiling point (°C)
HO–CH_2–CH_2–OH	EG	197
HO–CH_2–CH_2–O–CH_2–CH_2–OH	DEG	244
HO–(CH_2–CH_2–O)$_2$–CH_2–CH_2–OH	TREG	291
HO–(CH_2–CH_2–O)$_3$–CH_2–CH_2–OH	TEG	314
HO–(CH_2–CH_2–O)$_n$–CH_2–CH_2–OH	PEG	>350
HO–CH_2–CH_2–CH_2–OH	PDO	213
HO–CH_2–CH_2–CH_2–CH_2–OH	BD	235
HO–CH_2–CH_2–CH_2–CH_2–CH_2–OH	PD	242
HO–CH_2–CH_2(OH)–CH_2–OH	GLY	290
C(CH_2OH)$_4$	PE	276

of the polyols proportional with increasing molecular weight (Jokerst et al. 2011; Cheng et al. 2011).

Cai and Wan (2007) fabricated monodisperse Fe_3O_4 NPs by using different types of polyols, i.e., ethylene glycol (EG), diethylene glycol (DEG), triethylene glycol (TREG), and tetraethylene glycol (TEG), to reduce $Fe(acac)_3$. Among them, only the TREG results non-agglomerated Fe_3O_4 NPs with uniform shape and narrow size distribution. Their results illustrate that the polyol solvent plays a crucial role to determine the morphology and colloidal stability of the resulting particles. Hachani et al. (2016) have synthesized water-dispersible IONPs successfully via a simple and reproducible polyol synthesis tuning the size and magnetic properties by modifying the solvent, reaction time, and concentration of iron precursor $Fe(acac)_3$. The as-synthesized NPs had a high saturation magnetization (ca. 80 emu g^{-1}) but were not stable as indicated by the hydrodynamic diameter measurements and their precipitation in solution. These unstable IONPs were coated by 3,4-dihydroxyhydrocinnamic acid (IONP-DHCA) which demonstrated long-term stability, even when subjected to various salt concentrations (up to 1 M NaCl). The potential of these novel particles as MRI contrast agents is demonstrated with better relaxivity values when compared to commercial contrast agents. Miguel-Sancho et al. (2011) have synthesized TREG-coated and dimercaptosuccinic acid (DMSA)-coated SPIONs via polyol-mediated synthesis presenting particle size homogeneity (4.8 ± 2 nm) and a good initial particle size distribution, with a mean hydrodynamic size of 15.7 ± 2 nm. The modification of the TREG coating by a multistep process yielded only a moderate increase in stability of the SPION against prolonged exposure to 37 °C (exposure against increased saline concentrations was not tested) but produced a coating with terminal carboxylic groups capable of anchoring a bio-functional antibody, whereas comparatively best results were obtained with DMSA-SPIONs, which yielded a well-dispersed suspension of particles and showed excellent long-term stability, even when subjected to variations in the temperature and saline concentration. Miguel-Sancho and co-workewrs claimed that their methods to modify the surface of the NPs by TREG-coating are relatively easy to implement and use well-established chemistry and procedures and hence have the potential to be applied in a wide variety biomedical application (Miguel-Sancho et al. 2011).

Liquid-Phase Synthesis: Hybrid Nanomaterials

There is rapid progress in the development of novel materials for multimodal imaging applications, drug targeting, biosensing, and several therapies in nanomedicine and have been a area of great interest. Multimodal magnetic nanomaterials could be utilized as diagnostic, surgical, and drug delivery tools, which could help in the diagnosis and treatment of cancer and many other diseases. Owing to their small size, optional functionalization with specific biomarkers (e.g., antibodies, receptors, etc.), and combination of magnetic and fluorescent or plasmonic properties, such

nanocomposites open the unique possibility of controlled target-directed applications (Xie et al. 2017; Yu et al. 2017; Edel et al. 2016; Lim and Gao 2016; Giner-Casares and Liz-Marzán 2014). The novel material development at the microscale to nanoscale has progressed from single-particle synthesis to multi-component assemblies or hierarchical structures, where two or more pre-synthesized nanomaterials are conjugated to extract multifunctionality. These ensembles are termed as nanohybrids. The underlying focus of nanohybrids synthesis is property modulation, which results in an alteration to inherent physicochemical properties, i.e., size, shape, composition, and surface chemistry. Such changes also give rise to novel emerging properties. Size and shape modulation alongside physical or chemical functionalization are used to achieve hierarchical and heterostructures (Paek et al. 2011; Banin et al. 2014; Al-Arbash 2006; Schumacher et al. 2009; Saleh et al. 2014). Such functionalization has altered inherent surface attributes and extracted novel electronic configuration, intrinsic hydrophobicity, dissolution properties, etc., from nanoscale materials. The successes of such manipulations have further encouraged achieving a higher degree of functionality by combining multiple NPs, each possessing unique and novel advantages. For example, nanoscale iron oxide AuNPs, AgNPs, and PtNPs individually possess plasmon resonance and superior charge carrying capability, respectively. However, careful combination of two or more of these materials enhanced their functional performance as observed in the development of the first sets of bimetallic NHs. Silica, gold, and silver NPs (SiNPS, AuNPs, and AgNPs) as well as photoluminescence in the form of fluorescence (semiconductor quantum dots, e.g., CdSe or CdTe (Deng et al. 2012)) or phosphorescence (doped oxide materials, e.g., Y_2O_3), or magnetic moment (e.g., manganese or cobalt oxide NPs) (Vestal and Zhang 2003) have emerged as a broad new research field in the domain of colloids not only for their optical properties, but also for high chemical stability, catalytic use, and size-dependent properties (Hostetler et al. 1998; Sardar et al. 2009; Moon et al. 2010) and thus have gained interest over the decades because of appealing properties, such as catalytic and antibacterial activity which open perspectives in biomedical applications (Xuan et al. 2012; Ding et al. 2012; Pan et al. 2018; Xu et al. 2010). The merits of such NPs are aggregation phenomena can be avoided by protecting agents such as thiols or aminic compounds (Moon et al. 2010). There are many methods for the synthesis of small, monodisperse NPs as well as the control of the shape of such SiNPs, AuNPs, and AgNPs, can be discussed below briefly. Such multifunctional bimetallics were used as magnetic resonance imaging (MRI) agents with added nanoheating capabilities, useful for laser-irradiated drug delivery systems.

Magnetic Silica/Carbon Interface

Silica-Coated IONPs (IONP@Silica)

Silica-coated IONPs (IONP@silica) are a classical and important composite material for both fundamental study and bio-applications. Silica coating helps to enhance the

Table 3 Summary of synthesis method with their merits and demerits

Synthesis method	Merits	Demerits
Stober process	Controllable silica shell and uniform size, high crystallinity	Lack of understanding of its kinetics and mechanism
Microemulsion	Control of particle size, highly homogeneous	Poor yield, time consuming, and more amount of solvents required
Aerosol pyrolysis	Hermitically coated	Complex experimental condition

dispersion in solution because the silica layer could screen the magnetic dipolar attraction between magnetic IONPs and such coating would increase the stability of IONPs and thus protect them in an acidic environment. Since silica contains an abundant silanol groups on its layer, IONP@silica could be easily activated to provide the surface of NPs with various functional groups. Silane has unique properties that easily bind on the surface of IONPs through OH groups. For pragmatic applications, IONP should be coated with a homogeneous silica layer without core-free silica particles, regardless of the size of the NPs. For instance, as a heating source and magnetic guidance, IONPs play an important role in hyperthermia and targeted drug delivery, and the existence of core-free silica particles will lead to a loss in the effective dose of IONPs. The major reason causing uneven heating in hyperthermia and tissue distribution of the targeted drugs can be attributed to the unequal core number and silica shell thickness. Until now, mainly, three different approaches have been explored to designed IONP@silica nanomaterials; they are (a) the Stober process, (b) microemulsion method, and (c) aerosol pyrolysis method as tabulated in Table 3 with their merits and demerits (Zhu et al. 2018).

Generally, the IONPs were homogeneously dispersed in the alcohol, then after added the silane, and finally the water or ammonia aqueous solution was dropped into the mixed solution and IONP@SiO_2 formed. Tetraethoxysilane(TEOS), vinyltriethoxysilane (VTEOS), and octadecyltrimethoxysilane are the most common used silanes (Zhu et al. 2010; Cao et al. 2013). Lu et al. (2002) have shown that how ferrofluids can be directly coated with silica shells by the hydrolysis of TEOS. First, they have taken water-based ferrofluid (EMG 340) and diluted with deionized water and 2-propanol. Ammonia solution and various amounts of TEOS were added stepwise to the reaction mixture under stirring. The coating step was allowed to proceed at room temperature for about 3 h under continuous stirring. The coating thickness could be varied by changing the amount of TEOS. Since the iron oxide surface has a strong affinity toward silica, no primer was required to promote the deposition and adhesion of silica. Owing to the negative charges on the silica shells, these coated magnetic NPs are re-dispersible in water without the need of adding other surfactants. Xuan et al. (2012) have synthesized monodispersed γ-Fe_2O_3@meso-SiO_2 via Stober process. The size of the magnetic core and the thickness of the shell were controlled by tuning the experimental parameters. The magnetic property of the γ-Fe_2O_3 porous core enabled the microspheres to be used as a contrast agent in magnetic resonance imaging with a high r_2 (76.5 s^{-1} mM^{-1} Fe) relaxivity. The biocompatible

composites possess a large Brunauer-Emmett-Teller (BET) surface area (222.3 m^2 g^{-1}); the composite NPs have been used as a bifunctional agent for both MRI and drug carriers. Pinho et al. (2012) noted that the increase of the silica coating thickness will cause a significant decrease in the r_1 and r_2 relaxivities of their aqueous suspensions. Likewise, Pinho et al. (2010) concluded that the amount of silane used is a key factor for tuning the silica shell thickness, and the adequate silica shell thickness can therefore be tuned to allow for both a sufficiently high response as a contrast agent and adequate grafting of targeted biomolecules. Zhao et al. (2005) have prepared uniform magnetic nanospheres having diameter 270 nm with a magnetic core and a mesoporous silica shell through Stober process. These NPs were double coated with mesoporous silica shell by a simultaneous sol–gel polymerization of TEOS and n-octadecyltrimethoxysilane (n-OTMS).

The microemulsion syntheses, in which micelles or inverse micelles, were used to confine and control the coatings of silica over, core NPs. It is noteworthy that this method requires much effort to separate the core–shell NPs from the large amount of surfactants associated with the microemulsion system. Tartaj and Serna (2003) reported a synthesis of monodisperse air-stable superparamagnetic α-Fe nanocrystals encapsulated in nanospherical silica particles of 50 nm in diameter. The iron oxide NPs are embedded in silica by the reverse microemulsion technique, and the α-Fe is obtained by reduction with hydrogen at 450 °C. Vestal and Zhang (2003) discussed a reverse micelle microemulsion approach which was also reported to coat a layer of silica around spinel ferrite NPs of $CoFe_2O_4$ and $MnFe_2O_4$. Cheng et al. (2012) presented a straightforward synthesis method for magnetically functionalized silica nanotubes, i.e. (Fe_3O_4-CNTs)@SiO_2. First, they prepared Fe_2O_3-CNT@SiO_2 and reduced to Fe_3O_4-CNT@SiO_2 in the presence of Ar at 800 °C for 8 h and finally the obtained Fe_3O_4-CNT@SiO_2 oxidized to γ-Fe_2O_3@SiO_2. The method employs carbon nanotube templates and can be easily scale up to achieve economic and fast production of the material. The material exhibits a considerable magnetization and has a hollow structure which suggests applications with multifunctional character. Their experiments indeed show that local heating is induced by applied alternating magnetic fields which showed the materials' potential for magnetic hyperthermia therapies, as increasing temperature with the application of magnetic field, as shown in Fig. 1.6. However, this heating of nanoparticles in higher field (>50 kA/m) is just to have an idea of change in temperature, not recommended for clinical test. In addition, it can serve as a drug carrier system since a significant amount of rhodamine B was loaded to the material and its release was studied. Interestingly, encapsulated magnetic NPs divide into two differently sized portions, i.e., into particles in the 10 nm and in the 100–200 nm range, respectively. This behavior may be exploited for different magnetic functions since small particles are beneficial when aiming at magnetic hyperthermia while larger particles are needed if an external magnetic field gradient shall exert force for moving particle.

Ding et al. (2012) reported the coating regulations of Fe_3O_4 NPs by the reverse microemulsion method to obtain Fe_3O_4@SiO_2 core–shell NPs. Such regulation produces core–shell NPs with a single core and with different shell thickness and especially can be applied to different sizes of Fe_3O_4 NPs and avoid the formation of

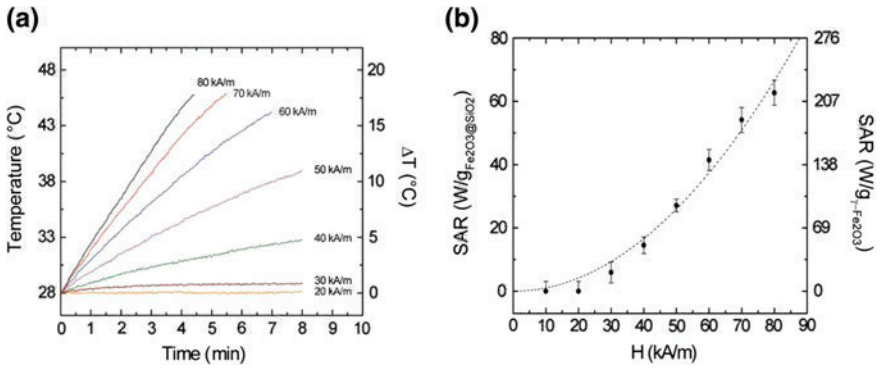

Fig. 1.6 **a** Temperature versus time upon application of AC magnetic fields at various field strengths and a frequency of $f = 120$ kHz and **b** corresponding SAR value for the γ-Fe_2O_3@SiO_2. Reprinted with permission from Chen et al. (2012). Copyright 2012 American Chemical Society

core-free silica particles. They found that the small aqueous domain was suitable to coat ultrathin silica shell, while the large aqueous domain was indispensable for coating thicker shells. To avoid the formation of core-free silica particles, the thicker silica shells were achieved by increasing the content of either TEOS through the equivalently fractionated drops or ammonia with a decreased one-off TEOS. Ye et al. (2012) have synthesized Fe_3O_4@mSiO_2 NPs and performed an in-depth study of the effects of surface coating on relaxivities of iron oxide particles for MRI. Tunable relaxivities were obtained by varying the thickness of the mSiO_2 coating layer of Fe_3O_4@mSiO_2 NPs. It was found that r_1 shows a dramatic decrease accompanied by a smaller decrease in r_2, with an increase in mSiO_2 coating thickness. Consequently, Fe_3O_4@mSiO_2 NPs exhibit enhanced MRI efficiency, which is ca. 21 times higher than that of the commercial T_2 contrast agents. They studied biocompatibility of obtained NPs and found that Fe_3O_4@mSiO_2 NPs have no negative impact on cell viability, which supports the potential application of these particles as a highly efficient and biocompatible MRI T_2 contrast agent.

Carbon-Coated IONPs (IONPs@C)

Carbon has unique chemical, thermal stability, and high electrical conductivity properties. Due to this reason, carbon and its isomer have been used widely in material science as protecting agents.

The carbon coating provides an effective oxidation barrier and prevents corrosion in magnetic core materials. Hydrophilic carbon coating on iron oxide nanoparticle cores endows better dispersibility and stability than those shown by bare IONPs (Bae et al. 2012). Park and Myung (2014) have shown schematic synthesis process regarding the carbon-coated magnetite nanoparticles, as shown in Fig. 1.7. They proposed that, as soon as the crystal seeds of Fe_3O_4 are formed under the synthesis