Review

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Synthesis and applications of surface-modified magnetic nanoparticles: progress and future prospects

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Abstract: The growing use of magnetic nanoparticles (MNPs) demands cost-effective methods for their synthesis that allow proper control of particle size and size distribution. The unique properties of MNPs include high specific surface area, ease of functionalization, chemical stability and superparamagnetic behavior, with applications in catalysis, data and energy storage, environmental remediation and biomedicine. This review highlights breakthroughs in the use of MNPs since their initial introduction in biomedicine to the latest challenging applications; special attention is paid to the importance of proper coating and functionalization of the particle surface, which dictates the specific properties for each application. Starting from the first report following LaMer's theory in 1950, this review discusses and analyzes methods of synthesizing MNPs, with an emphasis on functionality and applications. However, several hurdles, such as the design of reactors with suitable geometries, appropriate control of operating conditions and, in particular, reproducibility and scalability, continue to prevent many applications from reaching the market. The most recent strategy, the use of microfluidics to achieve continuous and controlled synthesis of MNPs, is therefore thoroughly analyzed. This review is the first to survey continuous microfluidic coating or functionalization of particles, including challenging properties and applications.

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1 Introduction

Nanotechnology is a discipline focused on understanding, manipulating and designing materials with at least one dimension in the range of 0.1–100 nm. These materials can be integrated into microscopic and macroscopic systems, providing a basis for other efficient and multifunctional processes in fields such as electronics, optics, manufacturing, energy, water and wastewater treatment, air filtration, cosmetics, medicine, biotechnology and the food sector. As the grain size of a nanomaterial decreases, its surface area increases for a given volume, resulting in a higher fraction of atoms at the surface and a lower binding energy per atom than in the bulk materials. The discontinuous behavior of nanomaterials is explained by quantum mechanics rather than classical approaches. These surface and quantum size effects yield properties different from those of the bulk materials, including magnetism in materials that are nonmagnetic, changes in melting and other phase transition temperatures, and variations in the ability to accept or donate electrical charge.

Nanomaterials are obtained by two main approaches: "bottom-up" or "top-down". Bottom-up methods synthesize nanomaterials via the assembly of atoms or molecules, while top-down strategies reduce the dimensions of the bulk material (Buzea et al. 2017; Franks 1987; Roduner 2006; Sanchez and Sobolev 2010; Sullivan et al. 2014). Among nanomaterials, nanoparticles (NPs) composed of pure iron, nickel, cobalt and their oxides, ferrites and metallic alloys, known as magnetic nanoparticles (MNPs), deserve special attention (Duan et al. 2018; Faraji et al. 2010; Majidi et al. 2014). Interest in these materials first arose in 1930, when Frenkel and Dorfman predicted that particles made of ferromagnetic material with a diameter under a critical value would generate large net

magnetization (Frenkel and Doefman 1930). Other properties of these particles are their high loading capacity, chemical stability and low intraparticular diffusion rate. Applications of MNPs as magnetic catalysts, photocatalysts, sensors, adsorbents and energy and data storage devices have been reported (Frey et al. 2009; Gómez-Pastora et al. 2014; Kaur et al. 2014; Rossi et al. 2013; Zhang et al. 2010); particularly notable is their use in biomedical applications such as the transport and controlled release of drugs, cancer therapy, magnetic separation or magnetic resonance imaging (Gómez-Pastora et al. 2017b; Hao et al. 2019; Pankhurst et al. 2003; Sandhu et al. 2010).

In this paper, the different methods of synthesis of surface-modified MNPs and their major applications will be critically reviewed, with the aim to extract valuable conclusions that will help future research. First, breakthrough applications of MNPs over the years will be broadly analyzed, discussing novel challenging applications which are receiving special attention lately; in addition, the role of proper coating and functionalization to modify the NP surface for their use in different fields will be elaborated. Then, conventional synthetic routes to obtain MNPs will be discussed, with in-depth descriptions of wet chemistry, physical and biogenic approaches; including their advantages, drawbacks, potential applications of the synthesized particles and the most relevant and recent works in the field. A separate section focuses on progress made in the synthesis of MNPs with controlled characteristics, with special attention to the use of microfluidic devices for continuous synthesis, reported applications, and, comparative analyses with previously described conventional methods. Finally, one of the strengths of this review is that the implementation of coating and functionalization steps in continuous microdevices is reviewed for the first time in the literature, and the most relevant characteristics are highlighted. The authors strongly believe that the information collected in the review advances the state of the art on the synthesis and applications of surface-modified MNPs.

2 Breakthrough applications of surface-modified MNPs

To take advantage of their unique optical, electronic and magnetic properties, ferromagnetic particles must be coated and functionalized with specific materials to convert the magnetic cores into robust MNP systems that are viable for a wide range of applications (Bychkova et al. 2012; Sheng-Nan et al. 2014; Xie et al. 2014). A proper coating not only reduces agglomeration and water insolubility but also prevents oxidation and corrosion in ambient conditions. Additionally, the coating allows the further anchorage of functional groups, other particles, molecules or specific binding sites that can be conjugated with therapeutic, diagnostic and targeting ligands.

The most commonly used materials for coating MNPs are small organic molecules, which can be classified into the following groups: i) carboxylates, phosphates or phosphonates, which are used to stabilize NPs and to prevent oxidation and aggregation by forming liposomal or micellular structures (Mosayebi et al. 2017); ii) amino acids like phenylalanine, tyrosine, arginine, lysine or cysteine, which provide biocompatibility and an active group for interactions with a variety of biomolecules and ligands (Ebrahiminezhad et al. 2012); iii) polymers, either natural like dextran or synthetic like PEG, which are used to prevent oxidation, overcome biological barriers and facilitate the conjugation of targeting ligands; iv) copolymers, which combine the properties of single polymers (Dadfar et al. 2019); v) organic surfactants like oleic acid, stearic acid or lauric acid, which provide hydrophilicity and increase colloidal stability (Bloemen et al. 2012); vi) oxides such as silica, which enable further functionalization and provide hydrophilicity, heat resistance, low specific gravity, high surface area, stability under aqueous conditions, mechanical strength and negative charge at blood pH, thereby preventing aggregate formation in biofluids; and finally, vii) metals like gold, which is favored for its lack of toxicity and ease of functionalization with, for example, molecules, proteins or DNA (Arias et al. 2018).

MNPs were first successfully applied in biomedicine for magnetically guided drug delivery using an *in vitro* analog of the human circulatory system by Senyei et al. (1978), who described the synthesis of 1 μm microspheres consisting of an albumin matrix in which a prototype drug (adriamycin HCl) and magnetite particles were entrapped. The drug delivery application was later improved by Malaiya and Vyas (1988) via the addition of a silicone oil (polydimethylsiloxane) shell to the magnetic particles. The coating material was added to reduce the density of the particles, enhance their dispersibility and wettability in nonaqueous media, and allow further embedding of indomethacin, which was selected as a model drug.

Over the next decade, the scientific community focused attention on applications of MNPs as imaging contrast agents. For example, the application of MNPs as contrast agents for the detection of liver cancer was reported by Reimer et al. (1990). They synthesized ultrasmall superparamagnetic iron oxide (USPIO) coated with arabinogalactan, a galactose-containing polysaccharide that was selected for its affinity toward asialoglycoprotein receptors

on hepatocytes, with the aim of minimizing biologically nonspecific adsorption events. The use of MNPs as antibody magnetic resonance imaging agents targeting sites of acute inflammation for *in vivo* detection of specific diseases was subsequently studied by Weissleder et al. (1991). They reported the synthesis of <5 nm monocrystalline iron oxide nanocompounds (MIONs) whose surfaces were linked with amino acid groups to stabilize the colloid against aggregation and enable subsequent covalent binding of the antibody human polyclonal immunoglobulin G. MNPs were later used as contrast agents by Elste et al. (1996) to study the effects of muscular activity and hyperthermia on lymph node uptake. Superparamagnetic iron oxide particles were coated with carboxydextran to help the particles cross the endothelium. Carboxydextran-coated superparamagnetic particles were also used by Bremer et al. (1999) as contrast agents for specific imaging of the liver and spleen.

In fact, biomedical applications have been the most studied and reported applications of MNPs. Ito et al. (2005) were the first to review the state of the art of the different medical applications of functionalized MNPs; they described advances in the use of MNPs in magnetic separation, magnetic resonance imaging, hyperthermia and tissue engineering. Other applications of MNPs, like drug delivery and gene delivery, were reviewed by Hao et al. (2010), with special emphasis on the need for particle functionalization to obtain multifunctional magnetic systems. Novel bioapplications of functionalized MNPs were first reviewed by Cardoso et al. (2017), including theragnosis and applications with lab-on-a-chip devices. The uses of multifunctional MNPs were reviewed by Clemons et al. (2018), who were the first to analyze advances in biosensing applications. One of the most recent reviews of bioapplications of functionalized MNPs was published by Anderson et al. (2019) and included novel uses of MNPs, such as antimicrobial and antiviral applications or anticancer drug delivery.

The use of functionalized MNPs as magnetic carriers for the capture and separation of biomolecules from biological fluids is a biomedical application that has received special attention recently. These MNPs show high mobility, resulting in short diffusion distances and increased efficiency and permitting lower doses and faster kinetics compared to conventional adsorbent materials. These benefits reduce operating costs and contamination and improve selectivity (Gómez-Pastora et al. 2017b; Pankhurst et al. 2003). Recent studies have shown that extracorporeal devices can be used to separate toxins from the bloodstream by introducing MNPs functionalized with the proper antitoxin group into the patient's blood. Microphoretic microfluidic separation devices (MSDs) are considered suitable for this type of separation and are an excellent example of process intensification. Numerous designs have been proposed to perform continuous capture and separation using a single device; an example is shown in Figure 1.

The first stage is the capture process, in which the functionalized MNPs are injected into the microdevice and key compounds with acceptable affinity for the functionalized surface are captured through specific ligand-receptor binding without affecting the rest of the biological fluid factors. The biological fluid containing the loaded MNPs then flows to the second stage for magnetic recovery. In the same way, a buffer solution is introduced to collect the loaded MNPs, and both phases circulate with cocurrent flow throughout the device. Permanent magnets located next to the device generate a magnetic field perpendicular to the direction of flow, which diverts the MNPs from the biological fluid stream and into the buffer solution stream. As a result of this process, the treated biological fluid leaves the system through one outlet, while the loaded MNPs are deflected into the buffer solution and leave the device through the second outlet (Basauri et al. 2019; Gómez-Pastora et al. 2017c, 2018, 2019; González-Fernández et al. 2020; Kang et al. 2014; Zhou et al. 2010).

In the last two decades, potential applications of MNPs have expanded to fields such as catalysis, magnetic data storage, magnetic energy storage and environmental

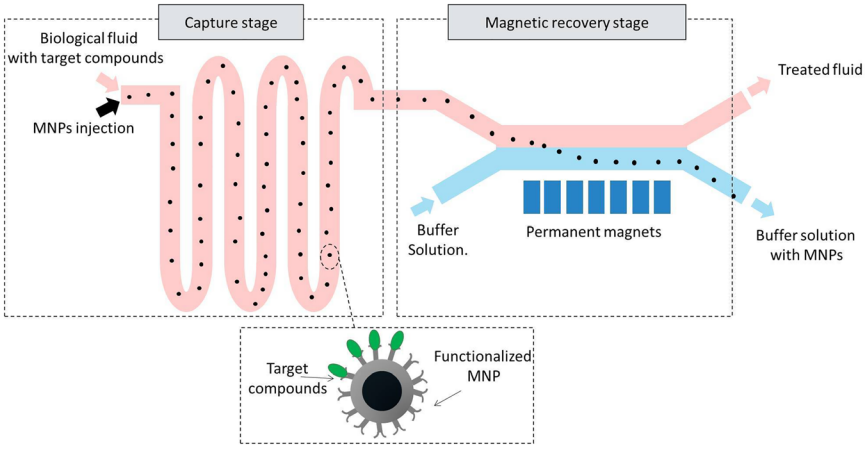

Figure 1: Use of MNPs for the capture and micro-magnetoforetic separation of toxins from biofluids.

remediation. The coating of MNPs for their use as catalysts is of special interest to prevent the formation of large aggregates and to achieve good dispersibility and stability in solution. Functional groups can improve the catalyst activity of MNPs by manipulating their hydrophobicity or hydrophilicity for selective solubilization in either nonpolar organic solvents or polar aqueous medium. The resulting MNPs can act as reagents, intermediates, scavengers or chelators for the preparation of various compounds. MNPs can also serve as supports for the anchorage of both heterogeneous and homogeneous catalysts to stabilize and recycle them (Duanmu et al. 2006; Gružauskaitė et al. 2020; Liu et al. 2012; Ostovar et al. 2019; Zhang et al. 2012). In 2014, catalytic applications of carbon-coated MNPs were reviewed by Kainz and Reiser (2014). These coated particles are modified with dendrimers or functionalized with polymers for the attachment of catalysts, scavengers or reagents and have been widely used as hybrid materials in the extraction of analytes or contaminants from aqueous solutions, for metal-, organo- and bio-catalysis, and in organic synthesis.

The uses of magnetic core–shell nanostructures as substrates for catalyst immobilization, MNPs bound to inorganic catalytic mesoporous structures, catalytically active small organic molecules and polymers, and magnetic nanocomposites bound to enzymes for enzymatic catalysis were reviewed in the same year by Govan and Gun'ko (2014). Later, the use of magnetic nanophotocatalysts to obtain more efficient, economic and environmentally friendly water purification processes was reviewed by Gómez-Pastora et al. (2017a). Motivated by increasing interest in the use of gold nanocatalysts and the possibility of their incorporation in MNPs to allow magnetically driven recovery, Kazemi recently reviewed progress in applications of gold reusable nanomagnetic catalysts in organic synthesis (Kazemi 2020). Functionalization is also useful for the application of MNPs in energy or data storage by combining the properties of different materials to obtain a diversified composition. The production of MNPs functionalized with a NH_2-dendrimer was reviewed by Chandra et al. (2015), who assessed the viability of using theses NPs as electrode materials in electrochemical supercapacitors for the fabrication of energy storage devices. They demonstrated that the material showed high specific energy capacitance, charge storage, delivery capabilities and enhanced charge/discharge rates.

Finally, the functionalization of MNPs is of great importance for environmental applications. Functional groups can enhance the selectivity of MNPs for use as magnetic sensors to detect and adsorb harmful substances. The first review regarding the applications of functionalized MNPs as sensors and adsorbents was published by Jung et al. (2011). The particles were applied to the selective detection and separation of toxic metals such as lead, copper, mercury, methylmercury, uranyl and other heavy metal ions present in environmental and biological samples. Subsequent developments in the use of MNPs as sensors for the detection of toxic metal ions included a turn-on fluorescent sensor based on Fe_3O_4@SiO_2 core-shell MNPs functionalized with pyrene (Chen et al. 2013) as a novel method for the detection of Hg^{2+} in environmental water and serum samples; iron NPs with silica shells functionalized with amine groups as colorimetric sensors for the detection of ions including Co^{2+}, Cu^{2+}, Fe^{2+} and Hg^{2+} (Jeong et al. 2015); Fe/Fe_3O_4 NPs functionalized with 3-(3,4-dihydroxyphenyl) propionic acid for the detection of Pb^{2+}(Yang et al. 2016); and fluorescent magnetic core-shell NPs functionalized with amino groups and modified 3,5,7,2′,4′-pentahydroxyflavone for the detection of Cu^{2+} (Rosa-Romo et al. 2016). The successful use of MNPs as adsorbents of environmental pollutants has been widely studied in the last decade (Bringas et al. 2015; Gómez-Pastora et al. 2014; Saiz et al. 2014; Thammawong et al. 2013). Advances in the application of surface-functionalized MNPs for the capture of toxic substances in wastewater treatment were recently reviewed by Gao (2019), who reported good characteristics of MNPs with surfaces modified by inorganic materials, organic small molecules, natural biopolymers, synthetic polymers and synthetic-natural composite polymers for the removal of contaminants due to improved adsorption performance, stability and dispersibility in water.

In summary, surface modification of MNPs has played an important role in progress in a wide range of applications. In the last decade, advances in the effective coating and surface functionalization of MNPs have resulted in the evolution of particle applications from drug delivery and resonance imaging to theragnosis and therapy, biosensing, high-performance magnetic bioseparation, catalytic reactions, data storage devices and detection and separation of environmental pollutants.

3 Synthesis of surface-modified MNPs by conventional methods

The growing interest in the use of MNPs has underscored the need to find alternatives for their synthesis, coating and functionalization. Lamer and Dinegar (1950) were the first to attempt to obtain monodisperse colloidal particles. According to LaMer's theory, in order to obtain monodisperse NPs, the synthesis should be split into two separate steps.

First, in the nucleation step, the concentration of monomers increases, and individual molecules start to nucleate. Second, in the growth step, the monomer concentration starts to decrease, no new nuclei form, and monomers start to attach to the preformed nuclei to form NPs. Several synthesis strategies were subsequently developed to obtain particles with the desired sizes, shapes, and magnetic and chemical surface properties for use in in the above applications.

3.1 Challenges in the synthesis of MNPs

An appropriate synthesis method should allow the control of critical variables, including size, size distribution, shape and crystal structure, which influence the physical properties of the particles. Size depends on numerous process variables, such as residence time, flow rates of reactants, concentration of precursors, pH and temperature. Controlled contact between phases, appropriate mixing, and separation of the nucleation and growth steps are essential to achieve monodisperse size and shape distributions. A smaller particle size decreases the density of energy levels, which change from continuous to discrete in form, widening the particle energy gap. As the energy gap spacing increases, new electrical properties appear that are of considerable interest in electronic applications to obtain smaller and faster products (Chen et al. 2018a; Erdem 2013; Pan et al. 2016; Shyamaldas et al. 2020). Moreover, particle size strongly influences the magnetic properties of particles. MNPs act as single-domain magnets when their size is below a critical diameter (Dc), which is material-dependent. MNPs below this size are uniformly magnetized, with all spins aligned in the same direction, as shown in Figure 2 (Wu et al. 2016).

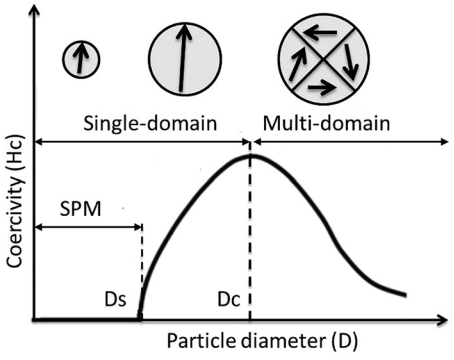

Figure 2: Dependence of the coercivity with the particle diameter, for a ferromagnetic material. Adapted from Wu et al. (2016).

Further decreases in MNP size beyond a certain value (Ds) result in superparamagnetic (SPM) behavior, a phenomenon that causes a strong response to an external field and enables the recovery or separation of the particles from complex multiphase systems under the action of a magnetic field. SPM materials show high values of magnetic saturation several orders of magnitude greater than the usual values for paramagnetic materials. In addition, the magnetic properties of SPM particles are lost when the external field is removed, as the coercivity value is zero; therefore, they do not attract each other, reducing the risk of agglomeration when used in different applications (Chen et al. 2018b; Gómez-Pastora 2018; Kamble et al. 2015; Lan et al. 2011; Li et al. 2017; Lu et al. 2007; Pan et al. 2016; Wu et al. 2016). Size not only influences the physical properties of MNPs but is also a crucial variable when MNPs are introduced into the human body. If the particles are too large, they may be taken up by the reticuloendothelial system, increasing the chances of vessel embolism; if they are too small, they can be excreted from the body through small pores of the basal lamina of the kidney. The optimal size range for biological applications is 10–100 nm (Ansari et al. 2019; Mosayebi et al. 2017).

The crystal structure of particles also influences their magnetic properties and thus is an additional variable of interest. The crystal structure affects the intrinsic spin-orbital interaction, which is measured by the magneto-crystalline anisotropy constant. When this constant decreases, the coercivity value of the particles decreases as well. During synthesis, variables such as temperature, sonication time or reactant flow rate determine the crystal structure (Li et al. 2017; Wu et al. 2016; Zhao et al. 2011). Shape is yet another determinant of the magnetic properties of particles. For example, spherical MNPs present isotropic structure, while ellipsoidal NPs present shape anisotropy and dynamic reorientation of rods, producing a release of heat with applications such as magnetic hyperthermia therapy. Cubic MNPs show higher values of coercivity and remanent magnetization compared with spherical ones due to differences in orientation of the polycrystalline structure and consequently spin alignment; unidimensional MNPs present shape anisotropy, which enhances magnetic coercivity; and elongated and disk-like MNPs exhibit large lateral drift velocities and low hydrodynamic forces, which favor cellular uptake for biomedical applications (Ansari et al. 2019; Kudr et al. 2017; Mosayebi et al. 2017; Wu et al. 2016; Yüksel 2019).

Once the particles are synthesized, their main properties should be characterized in order to demonstrate the quality of the obtained material; for such purpose, different analytical techniques are commonly employed. First,

Fourier-transform infrared spectroscopy is a technique applied to characterize the emission, absorption or photoconductivity spectrum, and thus, to identify the different functional groups of a solid (Griffiths and De Haseth 2007). Another frequently used technique is dynamic light scattering, both for the measurement of the zeta potential, that is, the electrokinetic potential of a colloidal dispersion; and for the quantification of the hydraulic diameter, which is affected by the interactions of the functional groups in the surface of the particles (Jacobs et al. 2000; Saiz 2015; Wilkinson and McNaught 1997; Yokoi et al. 2004).

One additional technology is electron microscopy, which is often used to analyze the size, morphology, structure and chemical composition of the synthesized particles (Zhou et al. 2006). In addition, thermogravimetry is a method of thermal analysis normally used to obtain information about the physical and chemical changes of the synthesized material as a function of the increase in temperature (Coats and Redfern 1963). Finally, the magnetization curves of the material are characterized, and the values of magnetic saturation or maximum magnetization as well as the coercivity or resistance of the material to be damaged once magnetic saturation is reached are determined. If the magnetization curves shows a negligible value of coercivity in the scanning fields, then the material can be considered superparamagnetic (Buschow 2006; Castrillón 2012)

3.2 Methods for the synthesis of MNPs

The large-scale synthesis and functionalization of MNPs is a key issue for their successful application and remains a scientific and technical challenge. Conventional approaches consist of batch processes, which can be classified into three main categories: I) 90% are chemical routes, also called bottom-up strategies; II) 8% are physical routes, or top-down strategies; and III) the remaining 2% are biological routes (Ansari et al. 2019). Among chemical routes, coprecipitation and thermal decomposition are particularly notable, as they are two of the first methods used to synthesize MNPs as well as the most widely studied (Koo et al. 2019; Lin and Samia 2006; Liu et al. 2020; Stanicki et al. 2015). Figure 3 details the main techniques in each category and summarizes their advantages, limitations and potential applications.

Coprecipitation was the first reported chemical route to synthesize MNPs. Massart (1981) reported the synthesis of particles with a size of 12 nm by a coprecipitation method in alkaline media without any stabilizing molecule. After the reaction, the precipitate was isolated and further treated with tetramethylammonium hydroxide to obtain an alkaline ferrofluid or with perchloric acid to obtain an acidic solution (Figure 4). Bee et al. (1995) proposed small modifications to Massart's method with the aim of obtaining smaller particles, including an additional wash step with distilled water after the reaction and the use of HNO_3 for the acidic treatment instead of perchloric acid. These changes allowed the production of particles of approximately 8 nm in size and their further stabilization by peptization to obtain a ferrofluid that was stable in physiological medium (pH 7) and thus viable for biomedical applications. In the next two decades, several authors introduced major changes to the process described by Massart in order to achieve better control of particle size. For example, stirring appears to be a key variable to reduce particle agglomeration, and working under an inert atmosphere like N_2 or Ar prevents oxidation of the material. Different alkaline solutions, temperatures and times of reaction have also been tested (Kim et al. 2001; Mykhaylyk et al. 2012; Rashid et al. 2020; Shen et al. 2007; Yusoff et al. 2018).

In addition to being well-characterized, MNP synthesis via coprecipitation offers the possibility of process scale-up. Coprecipitation is a simple, cheap and efficient method that permits the production of superparamagnetic iron oxide nanoparticles (SPIONs). However, its bottleneck is control of size and size distribution. Parameters like temperature, precursor concentrations, reaction time and nature of the solvent influence the characteristics of the particles produced and need to be precisely controlled. This, together with the tendency of the particles to agglomerate, makes it difficult to control particle size and size distribution as well as their magnetism and dispersibility (Frimpong and Hilt 2010; Kaur et al. 2014; Sandhu et al. 2010; Stanicki et al. 2015; Yadollahpour 2015).

Another frequently used technique for MNP synthesis is thermal decomposition. Rockenberger et al. were the first authors to report the use of the technique and they adopted a two-step process. Rockenberger et al. started with an iron precursor and an alkaline solution using two different temperatures and reaction times. The solution was subsequently cooled to room temperature, and the particles were precipitated by alcohol or re-dispersed in solvent (Figure 5). Using this method, particles with a size of 6–7 nm were obtained. In the following two decades, several authors further optimized the operation; to this end they centrifuged the dispersion to facilitate separation of the precipitate and applied different temperatures, reaction times and precursors including surfactants and solvents, which act like stabilizers to obtain monodispersed particles (Farrell et al. 2003; Hyeon et al. 2001; Orsini et al. 2018; Park et al. 2004;

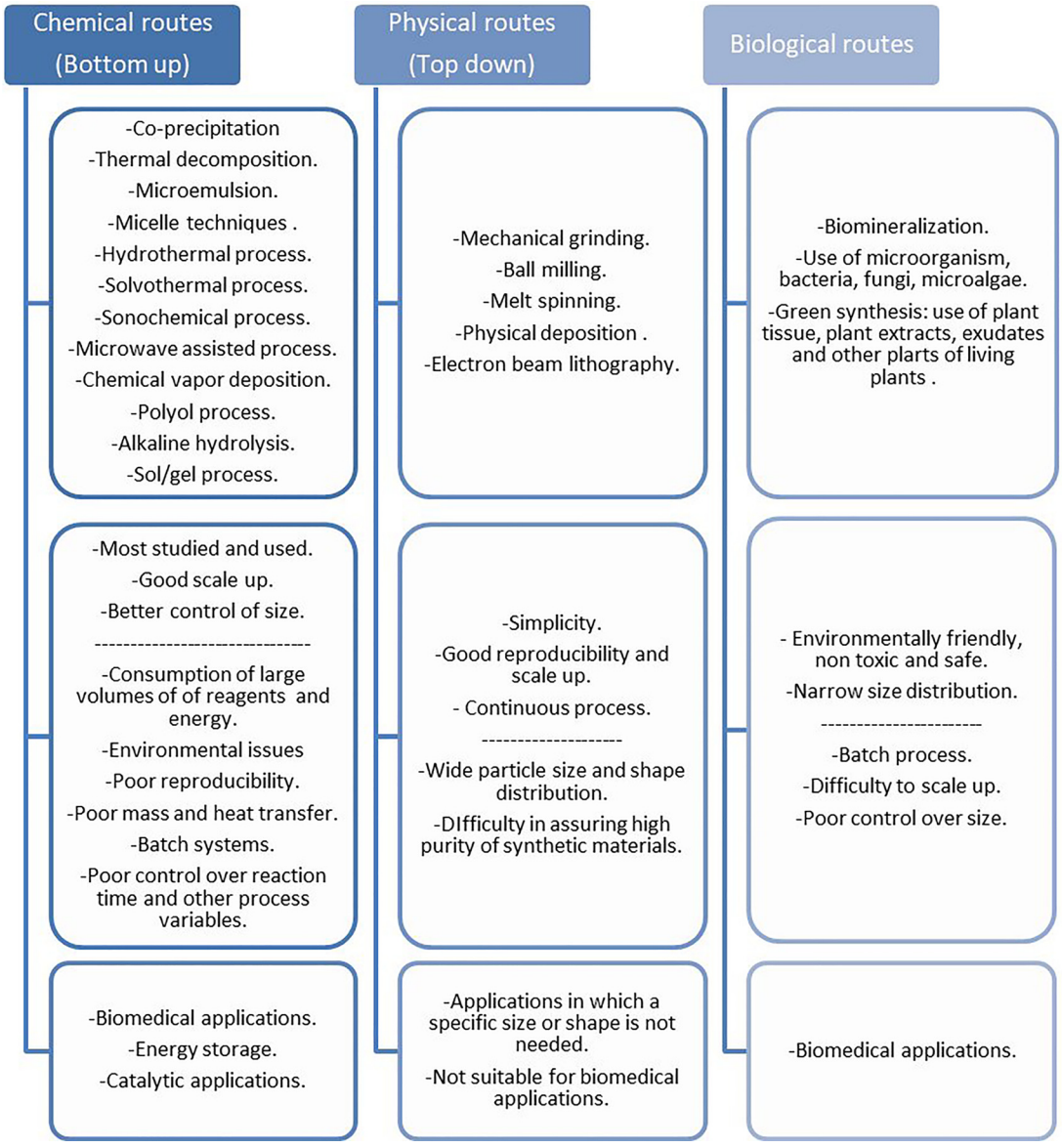

Figure 3: Scheme of technologies to synthesize MNPs, with their advantages, limitations, and potential applications.

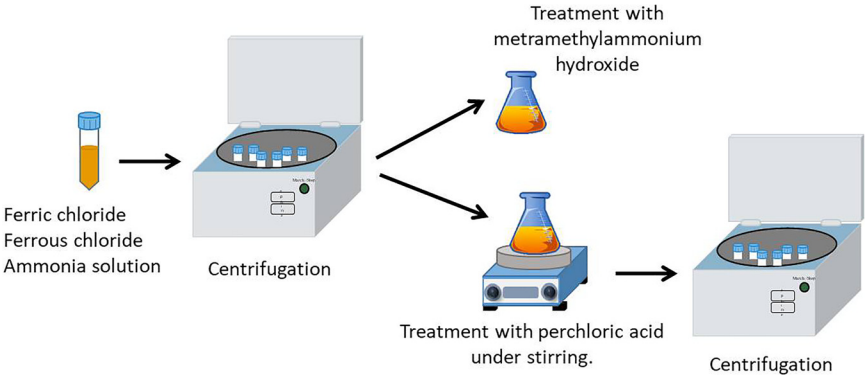

Figure 4: MNPs synthesis based on coprecipitation. Adapted from the study by Massart (1981).

Rippe et al. 2020; Xu et al. 2009). Thermal decomposition has also been used to synthesize magnetic particles containing metals other than iron, such as $CoPt_3$ nanocrystals, which have potential applications in ultrahigh-density magnetic recording systems, and NiO and Ni NPs, which have applications as conducting materials or catalysts (Chen et al. 2007; Davar et al. 2009; Ghosh et al. 2006; Shevchenko et al. 2002).

The main advantages of thermal decomposition are i) the particle size is easily controlled, so a narrow particle size distribution can be achieved; ii) high productivities are possible; and iii) the technique can be scaled up. Thermal decomposition produces particles with more controlled sizes and narrower particle size distributions compared to those produced by coprecipitation, and thus particles produced by thermal decomposition are preferred for biomedical applications, where a specific particle size is essential. Although narrow particle size distributions can be achieved by thermal decomposition, finding the optimal conditions is a challenging task. For instance, increasing reaction times and temperature improves the magnetic properties of particles but also increase the particles' growth and produce a wider size distribution. Thermal decomposition is an expensive, energy-consuming and complicated method due to the large number of precursors, large volumes of reagents and high temperatures required. There is still a need for a more reliable and simplified technique with better stoichiometric control (Chen et al. 2018b; Kaliamurthi et al. 2019; Koo et al. 2019; Schladt et al. 2011).

Chemical routes other than coprecipitation and thermal decomposition have been explored for the synthesis of MNPs, like microemulsion, micelle techniques, hydrothermal processes, solvothermal processes, sonochemical processes, microwave-assisted processes, chemical vapor deposition, polyol processes, alkaline hydrolysis or sol/gel processes. Although the wet chemistry routes are the most studied and have been successfully used in applications such as biomedicine, catalysis and energy storage, they share some disadvantages. The wet chemistry routes are batch processes with poor reproducibility and large consumption of reagents and energy, causing negative environmental impacts. In addition, it is difficult to rapidly change the conditions of the process, i.e., temperature, mixing and residence times, and to separate the nucleation and growth steps as described in LaMer's theory in order to obtain a narrow distribution of particle sizes (Anderson et al. 2019; Kaliamurthi et al. 2019; Kaur et al. 2014; Osaka et al. 2006; Schladt et al. 2011; Shan et al. 2015; Yadollahpour 2015). While physical strategies are continuous and simple processes with good reproducibility and potential for scale up, they are rarely used because they produce particles with a wide particle size and shape distribution, making them unviable for applications in which a specific size or shape is needed (Duan et al. 2018; Mehta 2017). Lastly, biological routes are an environmentally friendly, nontoxic and safe option that provides narrow size distributions; however, these synthetic routes cannot be operated in continuous mode, are difficult to scale up and still need to be further investigated (Majidi et al. 2014; Vaseghi et al. 2017).

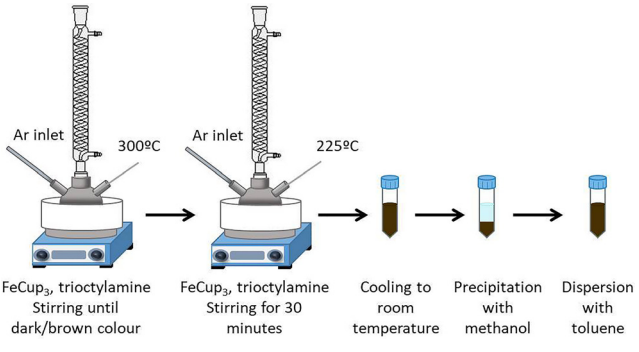

Figure 5: MNPS synthesis by the thermal decomposition process. Adapted from Rockenberger et al. (1999).

3.3 Coating and functionalization of MNPs

Coating MNPs yields a core-shell structure in which the magnetic particle forms the core and the coating material forms the protecting shell. The most common approach for coating MNPs is *in situ* coating during synthesis. In this case, the coating material is added during the synthesis process, and thus the reaction solution contains the precursors for the synthesis of the magnetic cores, which nucleate inside the coating materials (Kamali et al. 2018; Lu et al. 2007). An example of this technique is the synthesis of dextran-coated Fe_3O_4 MNPs reported by Hong et al. (2008), who followed a one-step method using dextran and iron (III) chloride hexahydrate as precursors. These particles were intravenously injected into rabbits to study the biodistribution of ferrofluid in organs and blood. However, *in situ* coating is limited by the need for compatibility between the coating materials and the reaction conditions; for example, the coating materials should have good solubility at the pH values required to precipitate the MNPs.

To overcome these limitations, the coating can be deposited in an independent step, after synthesis has taken place; this is called postsynthesis coating (Gruttner et al. 2013; Mosayebi et al. 2017). This method has been successfully applied in several works, for example, the coating

of Fe_3O_4 microspheres with a carbon layer prepared by the hydrothermal treatment of glucose (Kong et al. 2011) for use as a catalyst support, the coating of Fe_3O_4 NPs with aminodextran for use in magnetic resonance imaging (Chen et al. 2011), the polymeric encapsulation of Fe_3O_4 NPs with PEG (Neamtu et al. 2018) for their use as catalysts in the degradation of persistent organic pollutants in aqueous medium, the coating of MNPs with fluoropatite (Karthi et al. 2017) for their potential use in biomedical applications or the coating of cobalt ferrite cores with an hydroxyapatite shell (Karthickraja et al. 2019) for their application in biomedicine. In all those cases, the magnetic particles were first synthesized and then coated with the selected material in a separate stage.

A proper coating not only protects the MNPs but also permits further surface functionalization. It is possible to design a synthesis process to obtain surface-modified MNPs for a specific application by combining *in situ* coating with further postsynthesis functionalization. There are two general approaches for MNP functionalization: ligand addition and ligand exchange (Bohara et al. 2016; Faraji et al. 2010; Frimpong and Hilt 2010; Wu et al. 2016). In ligand addition, amphiphilic molecules interact with the hydrophobic part of the surfactant attached to the MNP surface, forming a double layer that covers the surface of the MNP. The amphiphilic molecules possess a hydrophilic region responsible for MNP dispersion in aqueous solution and further functionalization. An example of the ligand addition technique was reported by Seo et al. (2006), who synthesized magnetic core-shell nanocrystals with a FeCo core and a single-graphitic shell and subsequently functionalized them with the amphiphilic ligand PEG-phospholipid to modify the hydrophobic surface of the particles.

By contrast, in ligand exchange, the hydrophobic ligands attached to the surface of the MNPs are replaced with new functional ligands by exchange reactions. The new ligands have one functional group for binding to the particle's surface via strong chemical bonds and another group, normally hydrophilic, enabling dispersal of the MNPs in aqueous solution and further functionalization. In addition, to achieve proper functionalization, it is important to employ functional groups that show affinity towards the particle's surface and do not exist in the form of isolated clusters. Ligand exchange has been reported in several publications; for instance, Zhu et al. (2011) described the surface functionalization of oleic acid-coated hydrophobic MNPs with peptide dendritic ligands via ligand exchange.

In summary, the drawbacks and limitations of conventional synthesis systems, especially the difficulty of controlling the process variables and separating the nucleation and growth steps to control particle size, highlight the need for new and advanced methods of MNP synthesis. Furthermore, despite the extensive study of batch processes for conventional coating and functionalization, a number of issues remain to be improved for large-scale, high-efficiency MNP applications. The main challenges are better control of the reactant flow rates and reducing reaction times to achieve a uniform layer of coating and functionalizing material on the surface of the MNPs with a very narrow size distribution. In addition, reducing the reactant volume and energy consumption is important for achieving safe and efficient systems. Consequently, in recent years there has been increasing interest in microfluidics, which allows both the synthesis and functionalization or coating of MNPs in continuous operating mode, thus facilitating the control of process variables and generating MNPs with a more uniform shape and size distribution.

4 Progress in the synthesis of MNPs

4.1 Continuous microfluidic synthesis

There is growing interest in the use of microfluidics for the continuous synthesis of MNPs. Microdevices offer numerous advantages, most notably reduced energy costs, small size, and low reactant volume consumption, enabling better control of variables. Fluid flow in microdevices is under the laminar regime with small residence times; in addition, microdevices offer a high area/volume ratio, improved mass and heat transfer, and the possibility to work within a continuous process. Moreover, with the use of microfluidics, the nucleation and growth steps can be separated into two different devices to achieve a narrow particle size distribution. Variables such as residence time, microchannel diameter, reactant flow rates and temperature can be adjusted to obtain the required particle size. Microreactors for the synthesis of MNPs can be classified according to different criteria, such as the manufacturing material, number of flowing phases, flow patterns or geometry (Krishna et al. 2013; Luo et al. 2011; Sebastián 2016; Tian et al. 2019; Zhao et al. 2011).

Single-phase flow devices are the most investigated and controllable type of microreactors, with a parabolic velocity profile and continuous laminar flow. These devices can be classified into two groups: capillary microreactors and coaxial flow microreactors. Capillary microreactors have the simplest design and are compatible with high

temperatures. However, particles tend to adhere to the walls of capillary microreactors, causing channel blockages and giving rise to wide distributions of residence time and size. A typical capillary microreactor consists of several streams of reagents flowing within separate capillaries that pass through a micromixer before entering a single capillary that acts as the reaction zone and that can be submerged in a hot water or oil bath. The use of a micromixer is of vital importance to enhance mixing and prevent a wide particle size distribution due to laminar flow. Capillary microreactors have been widely used for the synthesis of MNPs in the last two decades (Eluri and Paul 2012; Glasgow et al. 2016; Jiao et al. 2015; Kawasaki et al. 2010; Lin et al. 2017; Miyake et al. 2005; Salazar-Alvarez et al. 2006; Simmons et al. 2013; Song and Henry 2009; Song et al. 2006, 2009; Thu et al. 2016; Uson et al. 2018; Xu et al. 2015).

Recently, Smith et al. (2017) used a precipitation method with a capillary microreactor to produce Co and Ni NPs with particles sizes in the range of 300–500 nm. Suryawanshi et al. (2018) synthesized iron oxide NPs following a precipitation method in a microdevice consisting of a copper tube arranged spirally with a Y-shaped micromixer for reagent injection. The resulting particles ranged in size from 6.3 to 9.8 nm, depending on the residence time. Iron oxide NPs were also synthesized by Bemetz et al. (2018), who employed a continuous precipitation method within a microdevice constructed from tape and polymer foil. The precursor was pumped through a central microchannel and sheathed between several outer streams by means of a 3-D flow-focusing micromixer in order to avoid channel clogging and to enhance diffusive mixing. MNPs with sizes of 24.6 ± 7.1 nm were obtained and coated with alendronate for use in medical treatments.

Coaxial flow microreactors are developed by the assembly of coaxial dual tubes as shown in Figure 6, which depicts a polydimethylsiloxane (PDMS) microdevice designed Abou-Hassan et al. (2008). In this system, the precursor is pumped through the inner tube (Qin) to reduce particle adhesion to the wall. Other authors have synthesized MNPs using coaxial flow microdevices (Abou-Hassan et al. 2012; Nguyen et al. 2014).

In contrast to single-phase flow devices, multiphase flow microreactors show a recirculatory velocity profile and segmented flow. In these devices, the intervention of a second phase allows particle separation from the channel walls, enhances mixing and produces a homogeneous time distribution, reducing the tendency to produce wide particle size distributions and channel blockage. However, compared with single-phase flow, the addition of a second phase increases the complexity of the process and could interfere with particle formation. These systems can be classified into two groups: gas/liquid (G/L) microreactors and droplet microreactors. In G/L microreactors, the liquid phase contains the reactants, while the gas phase is used to form gas slugs and thus achieve segmented flow. The selected gas can act as an inert phase, oxidant, reductant or mobile reservoir to efficiently supply reactants to the liquid phase. Nevertheless, these devices are not suitable for high temperatures due to the potential change in gas volume. A polytetrafluoroethylene (PTFE) microreactor was used by Larrea et al. (2015) to produce iron oxide nanostructures following a precipitation method (Figure 7). The two inlet aqueous phase solutions were injected in a Y-shaped micromixer inside an ultrasound bath in order to prevent the formation of micrometric aggregates and to narrow the residence time distribution. In the subsequent reaction stage, the gas-liquid slugs directed the crystallization of MNPs, and a stream of pure inert gas (N_2, H_2, O_2 or CO) prevented the oxidation of magnetite into maghemite. Particles with sizes ranging from 23 to 70 nm were obtained.

Droplet microreactors employ emulsion, double emulsion or coalescence to form nanodroplets in a second

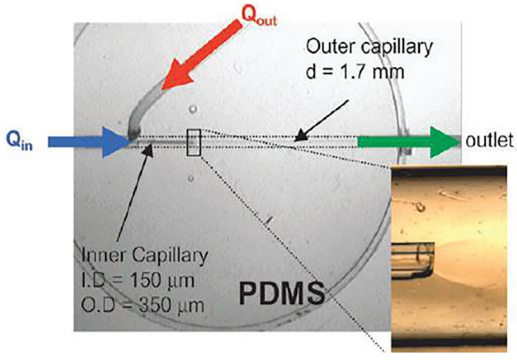

Figure 6: Scheme of coaxial flow microreactor systems employed to synthesize MNPs. Reproduced with permission from Abou-Hassan et al. (2008).

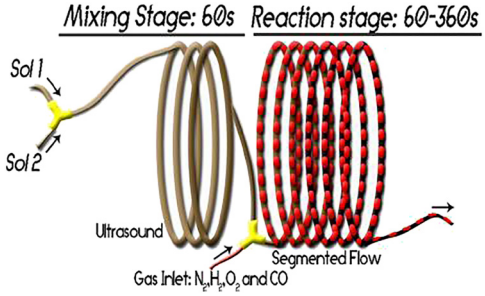

Figure 7: Scheme of G/L segmented flow microreactor system employed to synthesize MNPs. Reproduced with permission from Larrea et al. (2015) under the creative common license (http://creativecommons.org/licenses/by/4.0/).

continuous phase, also called the carrier. In these systems, the solutions must remain in the liquid phase, and mixing should be avoided; the high flow rates of the droplets and effective separation of the NPs from the second aqueous phase are the most challenging issues associated with this technology. Moreover, droplet microreactors are difficult to implement at large scale due to the high cost of the carrier. Several authors have investigated the synthesis of MNPs by means of droplet microreactors (Erdem 2013; Frenz et al. 2008; Maich et al. 2012), The most recent advance in this technique was reported by Ma et al. (2019), who used a polymethacrylate (PMA) droplet microreactor to produce iron oxide NPs (Figure 8) following a precipitation approach. N-Hexadecane served as the second phase, and particles with an average size of 7 nm were obtained.

The most widely used mechanism for the synthesis of MNPs in microdevices is coprecipitation, which has been applied within every kind of microrreactor system, as it is a simple, cheap and efficient method. The bottleneck of this approach is the control of particle size and particle size distribution, something that can be overcome thanks to the use of microfluidics (Hao et al. 2018b). The other route that has also been applied using capillary single-phase microrreactors is thermal decomposition (Uson et al. 2018). Thermal decomposition and coprecipitation are the first synthesis routes of MNPs to appear and the most widely studied, and they had been extensively described and analyzed in Section 3.2 "Methods for the synthesis of MNPs".

4.2 Comparison of conventional synthesis with microfluidics-assisted synthesis

Microreactors can operate in continuous mode under laminar flow conditions, thus providing shorter residence times and improved mixing thanks to their different geometries and the possibility of incorporating micromixers. Table 1 compares batch and continuous synthesis of MNPs by the coprecipitation method. Rashid et al. (2020) employed a conventional method using a batch reactor with a residence time of 90 min and a regime in the transition between laminar and turbulent. This system produced particles with sizes of 10–18 mm, which were used as additives in different polymeric materials, where size is less important. By contrast, Suryawanshi et al. (2018) used a capillary microdevice to perform continuous synthesis with residence times of a few minutes, a laminar regime and enhanced mixing, based on the use of a Y micromixer and a microreactor with spiral geometry. Particles with sizes ranging from 6.3 to 9.8 nm were obtained and considered viable for a wide range of applications.

Table 1: Comparison of MNPs synthesized following a coprecipitation method by a conventional system and a continuous microreactor.

	Batch synthesis	Continuous synthesis
Type of reactor	Coprecipitation applied in a batch reactor	Continuous coprecipitation applied with a capillary microreactor
Residence time	90 min	6.3–9.01 min
Regime	Transition between laminar and turbulent	Laminar
Mixing quality	Good	Superior mixing using Y-shaped micromixer and a spiral MR
Scalability	Good	Very good
Size distribution	10–18 nm	6.3–9.8 nm
Applications	Additives in different polymeric materials	Catalysis, pigments, electronic energy devices, biomedical applications, wastewater treatment
References	(Rashid et al. 2020)	(Suryawanshi et al. 2018)

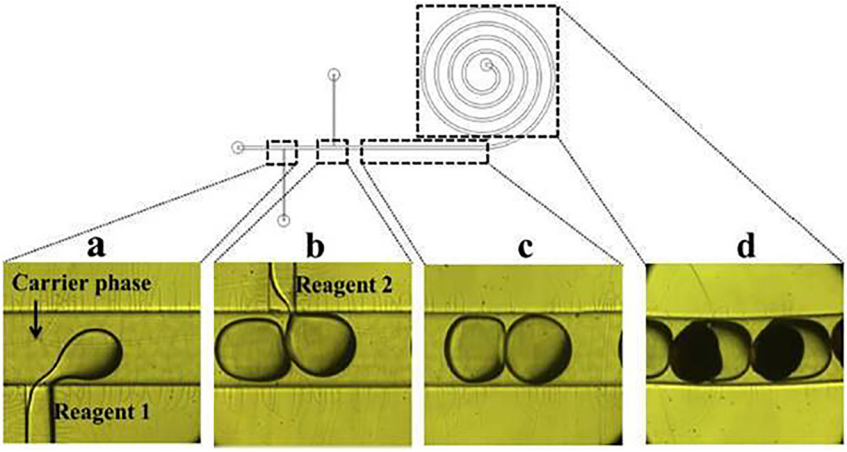

Figure 8: Droplet flow microreactor system employed to synthesize MNPs consisting on droplets: (a) dispersion, (b) collision, (c) pairing and (d) fusion. Reproduced with permission from Ma et al. (2019).

Compared with coprecipitation, thermal decomposition provides particles with smaller sizes and narrower size distributions for use in applications in which size is more important. Table 2 compares two of the latest reports of particle synthesis following a thermal decomposition method. In the first (Rippe et al. 2020), a batch reactor was used under a turbulent regime for 3 h. The synthesized particles had an average size of 7.8 ± 0.8 nm and were applied as drug-loaded nanobeads targeting specific organs of the body. In the second case (Uson et al. 2018), a stainless steel microreactor was designed with a meandering geometry to enhance mixing. Particles were synthesized within residence times of a few seconds and with sizes smaller than 4 nm, making them viable for nanomedicine applications.

Scalability is a considered a key factor in both batch and continuous processes in order to obtain higher productivities and convert laboratory-scale synthesis into large-scale processes. In the case of batch reactors it consists on increasing the size of the reactor so that it can work with larger volumes; working with such volumes is a challenging task, as it results in a lower control of reaction variables such as reaction time, reactant flow rates, mixing of reactants or temperature gradients, thus affecting negatively in the properties of the produced particles, for example, their size, size distribution or shape. In the case of microfluidics, the preferred alternative to increase the production rate of nanoparticles is parallelization, which consists on numbering up the devices instead of increasing the dimension of the channels. Parallelization implies a high initial capital investment; however, regarding the long-term costs, production at this scale gives place to lower costs than batch processes due to the reduced need of reactant volumes and energy consumption. Furthermore, the main advantage of having parallel processing reactors is that it allows working with conditions identical to the optimized lab-scale (Makgwane et al. 2014; Mosayebi et al. 2017; Sebastian 2016; Uson et al. 2018).

Table 2: Comparison of MNPs synthesized following a thermal decomposition method by a conventional system and a continuous microrreactor.

	Batch synthesis	Continuous synthesis
Type of reactor	Thermal decomposition applied in a batch reactor	Continuous thermal decomposition applied with a stainless steel microreactor
Residence time	3 h	9.6–27.4 s
Regime	Turbulent	Laminar
Mixing quality	Good	Enhanced with a meandering microchannel that promotes fast passive mixing
Scalability	Good	Very good
Size distribution	7.8 ± 0.8 nm	<4 nm
Application	Drug-loaded nanobeads towards specific organs of the body	Nanomedicine applications
Reference	(Rippe et al. 2020)	(Uson et al. 2018)

4.3 Continuous coating and functionalization

The implementation of coating and functionalization techniques in microdevices promotes faster and more effective processes. In the last decade, two different approaches have been studied. In the first approach, coating or functionalization is carried out together with the synthesis step in a single microdevice. In the second approach, coating or functionalization of MNPs is performed in an independent postsynthesis microdevice, potentially connected to the synthesis device to work in continuous mode. This review is the first to include advances in coating and functionalization of MNPs by means of microfluidics and addresses the most recent advances in the literature studies.

The advantage of simultaneous synthesis and coating or functionalization is that the whole process can be performed in a single step. However, the coating materials must have good solubility at the pH necessary for the particles to precipitate. The main drawback of this strategy is the reduced magnetic susceptibility of the MNPs due to the impermeabilization of the magnetic core (Mosayebi et al. 2017). In the last decade, numerous authors have reported the use of microfluidics for simultaneous synthesis and functionalization or coating of MNPs with polymers (dextran), metals (zinc, gold) and oxides (silica); these particles aimed to be used in biomedical applications such as MRI, hyperthermia, targeting of tumor cells, photothermal therapy and biosensing. The first such report was the use of a PTFE droplet microreactor for the synthesis of iron oxide NPs and coating with dextran in 2012 by Kumar et al. (2012). An average particle size of 3.6 ± 0.8 nm was achieved via a continuous precipitation process. The dextran coating ensured biocompatibility, allowing the direct use of the particles for biological applications without further functionalization.

Wang et al. (2015) subsequently proposed the use of a capillary microreactor for the synthesis of core-shell particles. As shown in Figure 9, the device comprised three zones; the first zone consisted of a thermostatic tank

where the two inlet solutions were heated independently and then introduced into a Y-shaped mixer; the second zone, in which the reaction took place, consisted of a thermostatic tank with tubular stainless steel tubing; finally, the third part included a beaker submerged in a thermostatic bath, in which the solution was stirred under an inert atmosphere. This device was employed to synthesize $Fe_{(1-x)}Zn_x@Zn_{(1-y)}Fe_yO–(OH)_z$ nanohybrids and $(CoFe)_{(1-x)}Al_x@Al_{(1-y)}(CoFe)_yO–(OH)_z$ NPs following a coprecipitation method. Both materials had a 2.42 ± 0.30 nm metal alloy core, with a 3.22 ± 0.26 nm doped metal oxide shell for the nanohybrids and a 1.20 ± 0.12 nm shell for the NPs. When used as contrast agents in dual-mode MRI, they showed better performance than conventional Gd-based contrast agents.

Simmons et al. (2015) later described a microdevice (Figure 10A) for the synthesis of <5 nm iron oxide NPs doped with Zn following a precipitation method. Due to their increased magnetization, the Zn-doped MNPs were intended to be applied as MRI contrast agents and for hyperthermia treatment of cancer cells. Liang et al. (2017) used a microdevice to form $Fe_{(1-x)}Zn_x@Zn_{(1-y)}Fe_yO$ nanocrystals with a core-shell structure following a coprecipitation method. Sizes ranging between 4.8 ± 0.6 nm and 6.0 ± 1.3 nm were obtained, depending on the initial Fe/Zn ratio. The synthesis of $Fe@Fe_3O_4$ core-shell NPs using a capillary microreactor was reported Xiaoxiong et al. (2018Xiaoxiong et al. 2018), who followed a coprecipitation method and obtained an average particle size of 8.2 ± 1.2 nm. The core-shell NPs were then activated and coupled with ginsenoside for use in MRI and applied to an *in vivo* mouse model. Magnetite NPs were subsequently synthesized and coated with dextran by means of a coprecipitation method in a microdevice designed by Ohannesian et al. (2019), obtaining an average size of 10 nm. Iron precursors, reducing solution and dextran were introduced via independent polyethylene microchannels, arriving at a Y-shaped connector and, finally, the outlet. The resulting particles were considered good candidates for hyperthermia therapy.

More recently, the synthesis of iron oxide/gold core-shell NPs in the droplet-type microreactor shown in Figure 10B was investigated by Ahrberg et al. (2020). They used a precipitation method with mineral oil as the carrier phase. The microsystem consisted of a first capillary junction for magnetite droplet generation and three consecutive junctions for injection of the gold precursor solution to form the gold shell. An average particle size of 13.1 ± 2.5 nm was obtained, and good performance of these particles was observed in three different applications: photothermal therapy, surface-enhanced Raman scattering (SERS) biosensing and MRI. The same year, Ma et al. (2020) designed a polymethyl methacrylate (PMMA) microfluidic device consisting of two chips connected with PTFE tubes. As shown in Figure 10C, the first chip was used to synthesize $KGdF_4$ NPs doped with Ln^{3+} (Ln = Ce, Gd, Tb, Eu); a T-shaped mixer was used to combine Tb^{3+}, Eu^{3+}, Ce^{3+} and Gd^{3+} precursors, and then KF solution was added to start the reaction. The second chip had a T-shape and was used to functionalize the Ln^{3+}-coated particles with hyaluronic acid. The final functionalized particles had an average size of 170 ± 18 nm as measured by TEM and showed utility in specific targeting of tumor cells.

Independent continuous coating or functionalization requires an additional step after synthesis. In these methods, coating is accomplished mainly by physisorption or chemisorption (Mosayebi et al. 2017). Several authors have reported the use of microfluidics for coating or functionalization and obtained NPs that have been successfully applied in catalysis reactions or biomedicine, including MRI, drug delivery, drug release, biomolecule detection and tumor cell capture. First, the use of a PTFE coaxial-flow microreactor consisting of three microdevices, shown in Figure 11A, was proposed by Abou-Hassan et al. (2009). Each microdevice had two streaming reagents, and mixing occurred by diffusion at the point of confluence. In the initial microdevice, 3-aminopropyl-triethoxysilane (APTES) was anchored on the surface of superparamagnetic Fe_2O_3 structures; in the second one, two sol-gel precursors were added, tetraethyl orthosilicate (TEOS) and APTES labeled

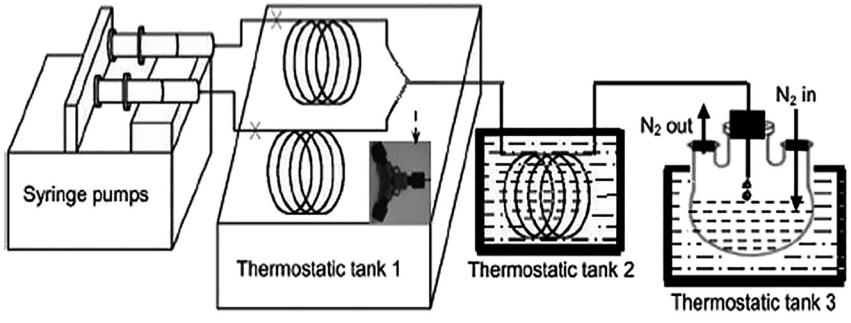

Figure 9: Scheme of microreactor system used to perform the simultaneous synthesis and coating of MNPs. Reproduced with changes with permission from Wang et al. (2015).

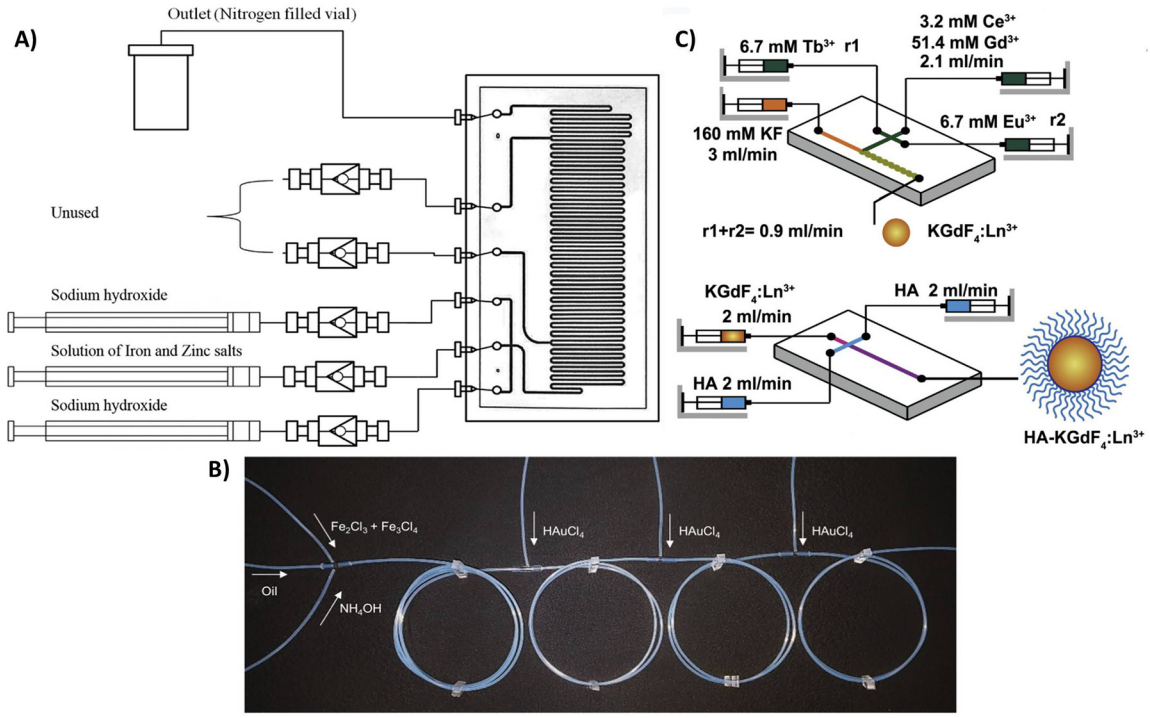

Figure 10: Scheme of microreactor systems used to perform the simultaneous synthesis and coating of MNPs.
(A) Reproduced with permission from Simmons et al. (2015), (B) reproduced from Ahrberg et al. (2020) under the creative common license (http://creativecommons.org/licenses/by/4.0/) and (C) reproduced with permission from Ma et al. (2020).

with the fluorescent dye rhodamine B isothiocyanate (RITC); finally, in the third microdevice, the reaction occurred in the presence of an alkaline solution of ammonia. The final output was MNPs encapsulated by a fluorescent polysiloxane layer; the MNPs had nearly spherical core-shell structures with an average size of 50 nm and were applied as contrast agents for molecular imaging. Lee et al. (2012) employed a silicon-Pyrex microfluidic reactor for the continuous functionalization of core-shell MNPs with platinum (Pt). The microdevice comprised three separate inlets for the MNPs, the Pt precursor and the reducing agents, followed by a mixing zone and reaction zone. Different reducing agents were evaluated, and the best results were obtained with ethylene glycol, achieving Pt particles of 2.4 ± 0.2 nm attached to the surface of the magnetic silica nanospheres. These particles were applied for continuous catalytic reactions in a packed bed microreactor.

Alorabi et al. (2017) reported the use of a chip with colaminar polyelectrolyte solutions and washing streams, shown in Figure 11B, to coat oil-based ferrofluid droplets previously stabilized with surface-active polyvinylpyrrolidone (PVP). These multi-layered polyelectrolyte microcapsules were fabricated for potential drug delivery applications. The use of a five-run spiral-shaped microreactor with two inlets and one outlet, shown in Figure 11C, was subsequently investigated Hao et al. (2018a). It was used to obtain silica magnetic microflowers (SMMFs) with a multi-layered structure and an average size of 15 nm. PVP and FeCo MNPs were introduced in the first inlet, while TEOS and hexadecylamine (HAD) were introduced in the second. An antiepithelial cell adhesion molecule (EpCAM) antibody was then conjugated on the particle surface to capture circulating tumor cells through a microfluidic screening chip. The same year, fluorescent MNPs, PEG@Fe_3O_4@Rhb, with sizes of 2.8–19.2 nm were produced by Yang et al. (2018) using a PDMS droplet-type microreactor. The inlet aqueous solution consisted of polyethylene glycol diacrylate (PEGDA), polyethylene imine-Fe_3O_4 (PEI-Fe_3O_4) MNPs and acryloyl-rhodamine B dye (RhB), which were introduced in the flow-focusing zone of the microdevice, to form the mother droplets, as shown in Figure 11D; then, mineral oil was added in a T-junction zone to split the mother droplets into daughter droplets; finally, RhB was covalently linked to the PEG in the UV exposure zone, and the Fe_3O_4 MNPs were encapsulated. These particles were synthesized for applications in biomolecule detection, drug delivery and drug release systems.

Microdevices have also been used to functionalize non-magnetic particles using MNPs. Non-magnetic

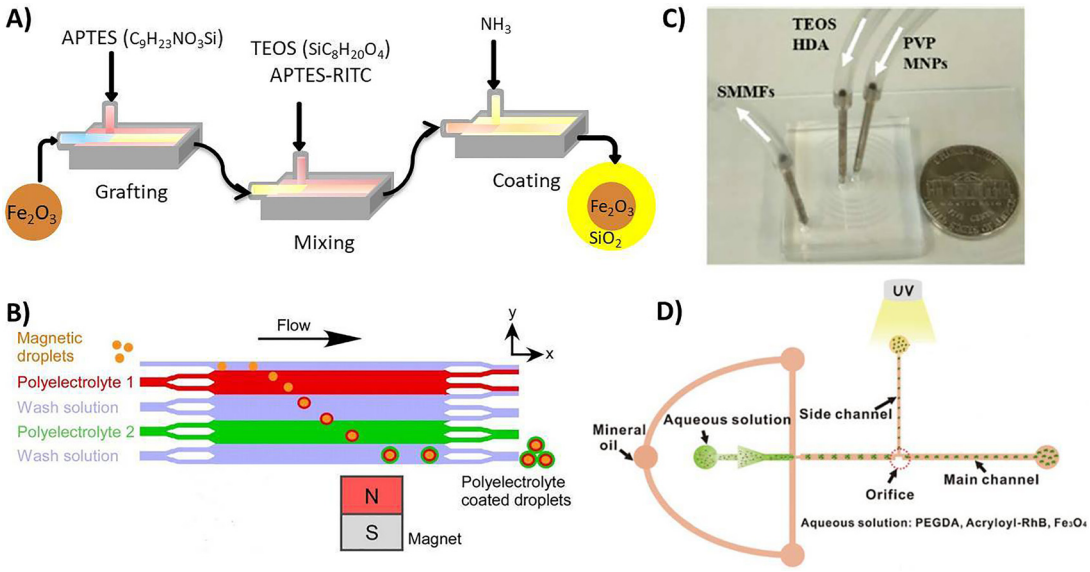

Figure 11: Scheme of microreactor systems used to perform the continuous functionalization or coating of MNPs.
(A) Adapted from Abou-Hassan et al. (2009), (B) reproduced with permission from Alorabi et al. (2017), (C) reproduced with permission from Hao et al. (2018a) and (D) reproduced with permission from Yang et al. (2018).

particles have been coated or functionalized with SPIONs to take advantage of their magnetic properties in applications such as MRI, separation, purification, bioimaging, theranostics or catalysis. Similarly, MNPs such as Co or Gd NPs have been used to coat core-shell particles and provide magnetic properties for enhanced MRI and catalysis.

Hassan et al. (2013) analyzed a continuous process for the coating of silica NPs with Au and MNPs using two consecutive glass microreactors, as shown in Figure 12A. In the first microreactor, Au NPs were assembled with silica labeled with the fluorescent dye rhodamine B isothiocyanate (SiO_2-RITC), while in the second, magnetic NPs were attached to the surface of the previously formed structures. The resulting multifunctional structures have many imaging applications. A coaxial flow microfluidic device (Figure 12B) was subsequently used by Qiu et al. (2015) to produce core-shell NPs with Fe_3O_4 MNPs embedded in their cores. First, the previously prepared MNPs were dispersed in the inner phase (IP), which consisted of an aqueous solution of the surfactant Pluronic F/127, carbon black, glycerol and dyes. This inner solution was pumped into the injection tube and sheared into inner cores functionalized with the MNPs by coflow with the middle phase (MP), which was composed of ethylene glycol dimethacrylate, polyglycerol polyricinoleate and 2-hydroxy-2-methylpropiophenone. The core-shell structure was then formed through coaxial flow of the outer phase (OP), composed of Pluronic F/127, carbon black and glycerol. Finally, the particles were collected in a Petri dish with a receiving phase (RP) composed of calcium

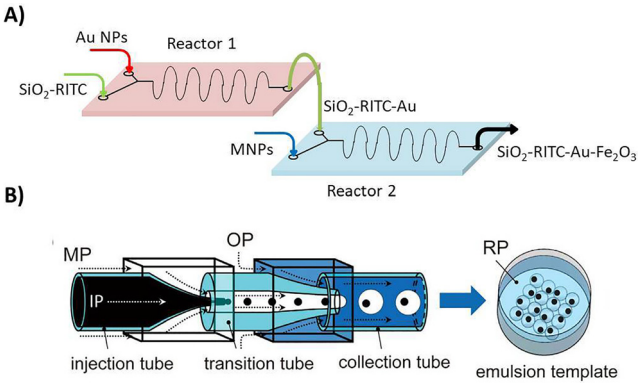

Figure 12: Scheme of microreactor systems used to obtain NPs with magnetic coatings.
(A) Adapted from Hassan et al. (2013) and (B) reproduced with permission from Qiu et al. (2015) under the creative common license (http://creativecommons.org/licenses/by/4.0/).

chloride, glycerol and Pluronic F/127. The dish was placed under a UV lamp to perform an off-chip photopolymerization process. The final particles have potential applications in micro-rheological characterization and image enhancement.

Core-shell particles with a core of SiO_2 and a magnetic shell of Co_3O_4 were synthesized by Straß et al. (2017), who obtained an average particle size of 165 ± 22 nm. In this approach, the inputs were injected into an ethylene tetrafluoroethylene (ETFE) T-shaped mixer and finally arrived at

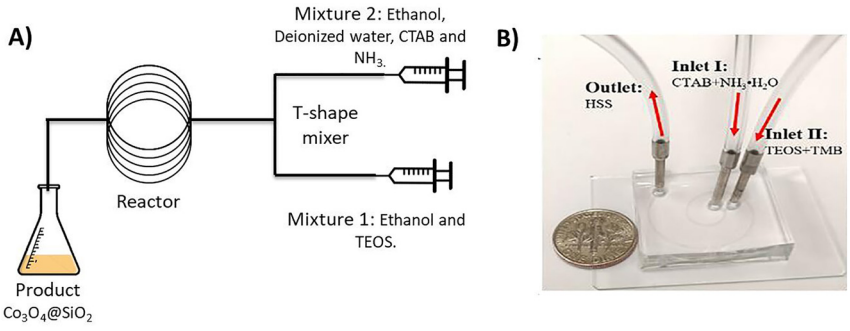

Figure 13: Scheme of microreactor systems used to obtain NPs with magnetic coatings. (A) Adapted from Straß et al. (2017) and (B) reproduced with permission from Hao et al. (2019).

spiral-shaped PTFE tubing, as shown in Figure 13A. These NPs were synthesized for applications in Fischer-Tropsch synthesis, as the shell stabilizes the core during the reaction and prevents catalyst aging and deactivation. A two-run spiral-shaped microreactor fabricated from PDMS was proposed by Hao et al. (2019) for the synthesis of magnetic particle-doped hollow spherical silica with a porous shell. In this device, cetrimonium bromide (CTAB), ammonia and iron oxide NPs were introduced in the first inlet, while TEOS and 3,3′,5,5′-tetramethylbenzidine (TMB) were introduced in the second, as shown in Figure 13B. These kinds of multifunctional materials can be used in separation, purification, bioimaging, catalysis and theranostics.

These advances highlight that continuous coating and functionalization of magnetic particles is a booming field. This approach holds promise as an alternative for developing continuous processes for the synthesis, coating and anchoring of functional groups, specific binding sites, molecules, or other particles in order to generate MNPs adapted to the requirements of different fields of application.

5 Outlook and future perspectives

This review discusses advances in the synthesis, coating, functionalization and applications of MNPs. In recent decades, interest in these materials has grown, and the scope of their applications has expanded greatly. MNPs have been successfully used as photocatalysts, catalytic supports, electrode materials and adsorbents. In addition, biomedical applications have evolved rapidly from drug delivery to the development of high-performance separation processes incorporated in microfluidic systems for diagnosis and disease control.

This progress in magnetic particle applications has been made possible by advances in methods for synthesis and surface modification. There is growing interest in the implementation of these processes in microdevices, as microfluidics permit greater control and safety, allowing the synthesis of MNPs with smaller sizes and narrower size distributions. The most recent developments have been the implementation of coating or functionalization steps in microdevices, either simultaneously with synthesis or as a single postsynthesis procedure, in order to achieve continuous processes. Thus, in the last decade, microreactors have been designed to obtain core-shell MNPs with polymers, gold or iron alloys or to functionalize NPs with metals such as zinc, platinum or rare earths.

Despite this progress, several hurdles in the synthesis and surface modification of particles remain, such as the design of reactors with suitable geometries, the appropriate control of operating conditions and, in particular, reproducibility and scalability. Therefore, further research is needed to achieve continuous procedures for the synthesis of particles with the necessary sizes, properties and surface functional groups for novel applications.

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