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Review

Magnetic Nanoparticles: Synthesis, Characterization, and Their Use in Biomedical Field

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Abstract: In recent years, the use of magnetic nanoparticles (MNPs) in biomedical applications has gained more and more attention. Their unusual properties make them ideal candidates for the advancement of diagnosis, therapy, and imaging applications. This review addresses the use of MNPs in the field of biomedicine encompassing their synthesis, biofunctionalization, and unique physicochemical properties that make them ideal candidates for such applications. The synthesis of magnetic nanoparticles involves a range of techniques that allow for control over particle size, shape, and surface modifications. The most commonly used synthesis techniques that play a crucial role in tailoring the magnetic properties of nanoparticles are summarized in this review. Nevertheless, the main characterization techniques that can be employed after a successful synthesis procedure are also included together with a short description of their biomedical applications. As the field of magnetic nanoparticles in biomedical applications is rapidly evolving, this review aims to serve as a valuable resource, especially for young researchers and medical professionals, offering basic but very useful insights into recent advancements and future prospects in this highly interdisciplinary research topic.

Keywords: magnetic nanoparticles; biomedical applications; nanomaterials

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1. Introduction

From a dimensional point of view, nanomaterials can be divided in three main classes: two-dimensional nanomaterials (2D), such as thin films; one dimensional materials (1D), exemplified by nanowires and nanotubes; and zero-dimensional systems (0D), represented by nanoparticles (NPs) and quantum dots (QDs). In this review we will focus on a special class of nanoparticles (NPs): magnetic nanoparticles (MNPs).

MNPs are materials with dimensions in the nanometer range, typically between 1 and 100 nanometers. At this scale, unique magnetic properties emerge, distinguishing them from their bulk counterparts. MNPs represent a special class of NPs that can interact with an external magnetic field as a direct consequence of their superparamagnetic, ferrimagnetic, and/or ferromagnetic properties.

Their synthesis involves various methods designed to control the size, shape, and properties of these nanoscale materials. Commonly used methods are chemical methods, especially co-precipitation, sol–gel synthesis, and thermal decomposition [1]. Additionally, biological methods, such as biomimetic synthesis using microorganisms or plant extracts, offer eco-friendly alternatives [2], while physical methods offer precise control over nanoparticle size, but may require specialized equipment and controlled environments [3].

A "typical" architecture of the MNPs consists of a core and a coating shell, respectively. The core commonly consists of magnetic elements (Fe, Ni, Co, etc.) as well as their

corresponding oxides, while the coating shell is responsible for limiting the interaction of the NPs with the medium, thus preserving their structure and properties. The high surface area of MNPs allows for easy surface modifications, making them versatile for various applications. In view of their use in biomedical applications, the coating plays a crucial role in providing the enhanced biocompatibility of MNPs, without affecting their unique magnetic properties. However, the characterization of such nanostructures is of major importance when it comes to biomedical applications. In this regard, many different techniques were developed that can be used to evaluate the physical and chemical properties of MNPs.

Since MNPs simultaneously possess magnetic properties and experience confinement effects in all three dimensions, a wider range of novel properties that can be harnessed for practical biomedical applications and the exploration of fundamental scientific phenomena can be envisaged.

This paper explores the remarkable properties of MNPs, offering insights into their synthesis and characterization methodologies alongside their applications in the biomedical field. In biomedicine, MNPs show promise for targeted drug delivery, magnetic hyperthermia for cancer treatment, and improved contrast in magnetic resonance imaging. Furthermore, MNPs provide a platform for interdisciplinary research with broad implications for practical applications and scientific exploration. The comprehensive and complete review of relevant aspects related to the synthesis, characterization, and potential applications of MNPs is reflected in the abundance of high-quality bibliographic resources within this scientific work. The novelty lies in its friendly approach to the subject matter and the clear delivery of concepts. This article has the potential to introduce even the most inexperienced readers to the captivating world of magnetic nanoparticles.

2. Synthesis Methods

Significant progress has been made in the synthesis of magnetic nanoparticles (MNPs) in the past decade. The emphasis has been on creating different techniques capable of generating MNPs with certain attributes such as size, shape, magnetic properties, and stability. Compatibility with living organisms is a very important issue that needs to be addressed especially in the case of their use in biological applications. A wide range of synthesis methods were developed over time. These synthesis methods can be divided into physical, chemical, and biological processes (Figure 1). The methods encompassed in this study are ball milling [4], laser ablation, and other physical techniques, coprecipitation, thermal decomposition, hydrothermal synthesis, microemulsion, and the sol–gel technique. Other non-thermal and biological synthesis methods are also mentioned. Each of these methods possesses distinct mechanisms and circumstances for generating MNPs, customized to meet certain requirements and applications [5].

2.1. Physical Methods

Both top–down and bottom–up strategies are utilized in the process of producing magnetic nanoparticles (MNPs) by means of physical methods of synthesis. They represent the two basic physical procedures that are carried out. Top–down techniques involve the process of breaking down bulk materials into nanosized particles. Bottom–up approaches, on the other hand, are used to construct nanoparticles by assembling them from atomic or molecular components. Both methods are essential in the field of nanoparticle synthesis; each has its own set of advantages and disadvantages, and the decision between the two is frequently determined by the particular requirements of the application that the MNPs are meant to be used for.

The physical synthesis methods of magnetic nanoparticles (MNPs) involve a range of procedures that mostly rely on mechanical or physical processes to generate nanoparticles.

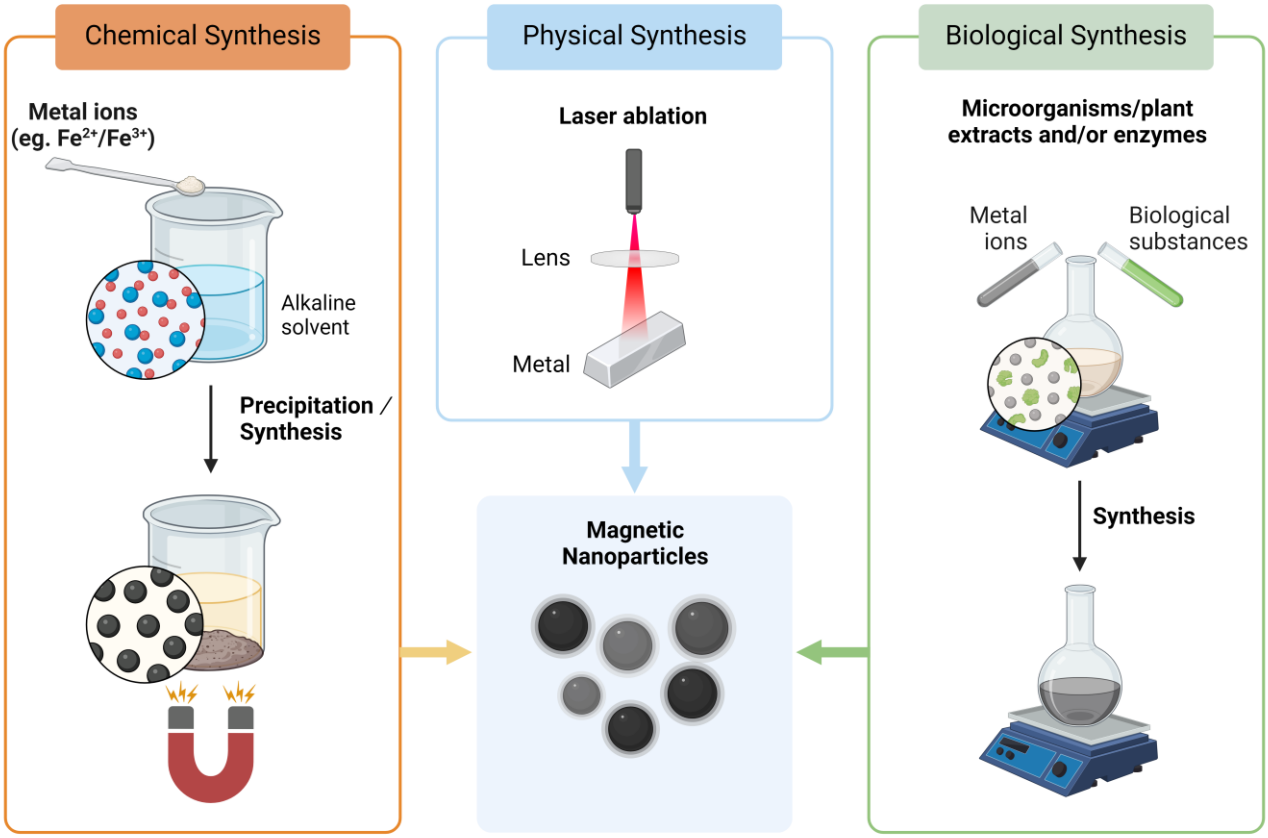

Figure 1. A brief representation of MNP synthesis methods. Created with BioRender.com, accessed on 7 February 2024.

2.1.1. Lithography

This versatile technique has been employed for the synthesis of a wide range of nanoparticles including MNPs. Lithography is part of the micropatterning technique being based on a controlled transfer of patterns from a mask or template to a substrate, allowing for the precise positioning and arrangement of nano-sized features. Over time, the technique has been optimized and new methods have been implemented: electron beam, scanning, nanosphere, and colloidal lithography, together with soft nanoimprinting [6].

2.1.2. Mechanical Milling

The ball milling technique is a popular physical process that involves the mechanical grinding of coarse-textured particles into fine nanoparticles, using a top–down approach. This technique, initially pioneered in the 1970s, is straightforward and practical. It entails utilizing a cylindrical jar with a hollow center (containing steel balls) that crushes the solid substance into a powder of nano/micrometric dimensions. Although ball milling is successful, it is limited by the possibility of product contamination and the generation of particles with a broad range of sizes [4].

2.1.3. Laser Evaporation

Laser evaporation, also referred to as laser ablation or vapor deposition, is an additional physical technique that follows a bottom–up strategy. This method involves the formation of nanoparticles by the condensation process from either a liquid or gaseous phase. High-energy lasers are utilized to vaporize raw materials when concentrated by a laser beam. The vaporous substance is subsequently cooled in a gaseous state, causing fast condensation and nucleation, ultimately leading to the creation of nanoparticles. This pro-

cess is cost-effective, efficient, and does not generate any hazardous waste, unlike certain wet chemistry procedures [7–11].

2.1.4. Wire Explosion

The wire explosion method is a novel physical methodology used to synthesize MNPs. The procedure is both safe and clean, and it is highly efficient without the need for additional stages like separating nanoparticles from the solution or treating leftovers. This technique has been employed to synthesize iron oxide magnetic nanoparticles (MNPs) specifically for applications involving arsenic removal from water. Although the nanoparticles created using this process are ecologically friendly and energy-efficient, they are not uniformly dispersed, which may restrict their use in some applications [12–14].

2.1.5. Gas-Phase Synthesis

The gas-phase synthesis method is part of the bottom–up methods and was implemented for developing multifunctional nanoparticles [15]. The procedure involves the formation of nanoparticles directly from gaseous precursors providing control over size, composition, and crystallinity. There are two common gas-phase synthesis methods: chemical vapor condensation (CVC) and inert gas condensation (IGV).

CVC is based on the reduction of the metal precursors in the gas phase. In this regard, volatile metal precursors such as metal halides or carbonyls are used as chemical precursors. They are reduced at high temperatures, leading to the formation of MNPs that are cooled down and collected.

During the IGV process, the nanoparticles are produced as a condensation result after the inert gas-based cooling of the vapor produced by the vacuum evaporation of metal atoms or clusters.

The main advantage of the gas-phase synthesis procedures refers to their good control over particle size [16].

2.2. Chemical Methods

Chemical methods represent one of the major directions in this vast, dynamic, and rapidly evolving field of nanoparticles' synthesis. The chemical synthesis of magnetic nanoparticles involves several methods, each with its own set of advantages and limitations. In the following paragraphs we will describe the main procedures belonging to this class that are reported in the scientific literature for the synthesis of MNPs.

2.2.1. Precipitation and Coprecipitation

Precipitation and coprecipitation stand out as the prevailing techniques for the fabrication of MNPs consisting of magnetic metal oxide nuclei from corresponding salts [17,18]. These MNPs possess a regulated size and magnetic properties, owing to the straightforward, adaptable, and less detrimental procedures employed for their synthesis [17–20]. Moreover, these approaches are secure, economical, and necessitate a lower synthesis temperature compared to alternative conventional methods [21,22]. Precipitation and coprecipitation are particularly suitable when there is a demand for the production of large quantities of nanocrystals [19].

In a typical scenario, metal ions are employed to dissolve in a solvent and to form a solution containing these metal ions, that will be further used for MNP production [19]. A common illustration of MNPs synthesized through these methods is Fe_3O_4 or γ-Fe_2O_3 NPs, obtained from ferrous (Fe^{2+}) and ferric (Fe^{3+}) salts dissolved in an alkaline solution [17,20]. The typical composition involves a 2:1 ratio of Fe^{2+} and Fe^{3+} salts, either at room temperature or an elevated one (80–85 °C) [20]. Once the reaction concludes, a precipitate of Fe_3O_4 forms at reactor's base. It can be recovered through either centrifugation or magnetic isolation [20]. The expected pH range for the resulting precipitate is between 7.5 and 14 [20]. It's noteworthy that the synthesis of this MNPs type heavily relies on the sources of metal ions and factors such as the temperature, pH, and ionic strength of the reaction

medium [17]. In fact, a majority of commercially available iron oxide nanoparticles (IONPs) are synthesized using the aforementioned methods [23,24].

Other researchers obtained manganese ferrite ($MnFe_2O_4$) NPs using ferric chloride ($FeCl_3$) and manganese (II) chloride ($MnCl_2$) as metal ions sources, and sodium hydroxide (NaOH) as a precipitant [25]. $MgFe_2SO_4$ nanocrystals can be generated through the coprecipitation of Fe^{3+} and Mg^{2+} ions, facilitated by the addition of NaOH [26].

2.2.2. Thermal Decomposition Method

The thermal decomposition method, also referred to as pyrolysis, was developed to overcome the limitations of the co-precipitation technique by utilizing non-aqueous solvents with elevated boiling points [27]. This method is employed to produce highly crystalline and uniformly sized MNPs [20]. Primarily, it involves the elevated temperature-induced decomposition of organometallic compounds in organic solvents, conducted in the presence of stabilizing agents, such as surfactants [19,28,29].

Various organometallic precursors of NPs include those synthesized with acetylketonates, N-nitrosophenylhydroxylamine, and carbonyls possessing various metallic centers such as $Fe^{2+,3+}$, $Mn^{2+,3+}$, $Co^{2+,3+}$, $Ni^{2+,3+}$. Stabilizing agents like fatty acids, oleic acids, and hexadecylamine are frequently utilized [30]. The type of the NPs depends on the chosen organometallic compound used as a source [17].

The temperature requirement varies based on the precursor type [19]. To achieve a high degree of uniformity and a size ranging from 4 to 30 nm, the optimal temperature falls within the 100–350 °C range [31,32]. Some authors consider that the temperature, reaction time, type of surfactants and solvents, and aging period should be adjusted according to the desired shape and size [33,34]. For instance, NP size was controlled by adapting the reaction time, resulting in sizes of 4, 12, and 60 nm for times of 1, 10, and 24 h, respectively [17]. The reaction time also influenced the morphology of the NPs, a transition from spherical NPs (at an early stage) to cubic ones (over longer times) being observed [17].

Significant findings include the synthesis of monodispersed iron oxide MNPs ranging from 6 to 20 nm through the polymer-catalyzed decomposition of $Fe(CO)_5$ [35,36]. Iron oxide MNPs (IOMNPS) were synthesized from metal fatty acid salts, yielding nearly monodispersed NPs with adjustable sizes between 6 and 50 nm and shapes evolving from points to cubes with increasing reaction time [37].

It is noted that any remaining surfactants may impact surface modification efficiency [20]. Oleic acid, hexadecylamine, and fatty acids are the most commonly used surfactants in this method [20].

MNPs synthesized using this method exhibit promising potential as magnetic resonance imaging (MRI) contrast agents for diagnosing cancerous tissue [17]. Other advantages of this method include high crystallinity, dispersibility, uniformity, homogeneous shape, and a fine particle size distribution [38,39].

Despite these substantial advantages, this method requires extensive purification steps of the synthesized MNPs (especially for biomedical applications) [40] due to the production of toxic organic-soluble solvents [41]. Additionally, this method is time-consuming and has low product yields [20].

2.2.3. Hydrothermal Method

The hydrothermal method, also known as solvothermal, is a "bottom–up" synthesis technique for IOMNPs, conducted in an aqueous solution under elevated pressure and temperature, typically using autoclaves or reactors [42,43]. Primarily, it involves the rapid nucleation and growth of newly synthesized MNPs, resulting in pure particles with controlled morphologies [44].

During the hydrothermal process, hydrolysis and oxidation reactions occur in order to generate MNPs [45]. Some authors emphasize that the morphology and crystallinity of the as-synthesized MNPs depend on the proper mixing of solvent, duration, pressure,

and temperature [19]. It's crucial to note that crystal formation relies on the solubility of minerals in water [19].

Impressive results achieved using this method include synthesis of Fe_3O_4 NPs with a size of 15 nm and a spherical shape, successfully employed in tumor MRI applications [46]. Additionally, chitosan coated Fe_3O_4 NPs, sized at 25 nm, were prepared and utilized for magnetic based enzyme immobilization [47].

However, this method has drawbacks such as: the inability to synthesize particles smaller than 10 nm and slow reaction kinetics at high temperatures [48]. It requires careful execution and specialized equipment, making the protocol laborious [49]. Despite these challenges, there are noteworthy advantages, including the production of NPs with a desirable shape, size, high crystallinity, and consistent composition, offering magnetic tuning and greater control over dispersion [48,49].

2.2.4. Polyol Method

The polyol method stands out as one of the simplest approaches for nanoparticle synthesis. This technique facilitates the synthesis of nanoparticles from inorganic compounds, including alloys, sulfides, oxides, fluorides, etc., [50]. It presents significant advantages by enabling the cost-effective single-step production of high-crystalline hydrophilic MNPs that can be easily scaled up [51].

In this method, polyols serve multiple roles, acting as a polar organic solvent for metal precursors, reducing agent, and, in certain instances, complexation agent for metal cations [20]. The polyol process has demonstrated its ability to control MNPs' morphologies, ranging from single-core spherical MNPs to more intricate multicore nanostructures, including hollow spheres and nanoflowers [51]. Additionally, adjusting the reaction temperature can increase NP size [52].

This technique possesses several advantages, including the elimination of separate calcination steps and the use of polyol as the sole solvent [53]. Furthermore, polyols are recognized as cost-effective and environmentally friendly solvents, widely employed in various industries [53].

2.2.5. Sol–Gel Method

The sol–gel method is a wet chemistry procedure involving the formation of a gel at room temperature through hydrolysis and polycondensation reactions of metal alkoxides [19,42]. Metallic salts are dissolved in water or other solvents, forming a homogeneously dispersed sol or colloidal solution [48]. Van der Waals forces between the particles are induced. The interaction between the particles intensifies through stirring and temperature increase [19]. The mixture undergoes heating until the solvent is evaporated, resulting in the solution drying and the ultimate formation of a gel [19,54].

This method is particularly effective for the synthesis of iron oxide MNPs and silica coated MNPs. It enables the production of MNPs in significant quantities with controlled sizes and well-defined shapes [19].

2.2.6. Microemulsion Method

Microemulsion is a system of water, oil, and an amphiphilic surfactant that forms a stable, thermodynamically stable dispersion. The process involves the incorporation of precursor materials into different phases of the microemulsion, leading to NP formation. Chemical reactions occur within the confined spaces of the microemulsion droplets, leading to the formation of nanoparticles [55].

Different variations of microemulsion methods exist:

- **reverse microemulsions**, where water is dispersed in an oil phase with a surfactant;
- **direct microemulsions**, where oil is dispersed in a water phase with a surfactant;
- where both oil and water are present in a comparable amount [56].

The advantage of using the microemulsion method is precise control over NP size, shape, and composition [55]. Several parameters (water-to-surfactant ratio, concentration

of the reactants, and surfactant film flexibility) influence the size of MNP microdroplets [57]. This method's drawbacks are polydispersity, a low yield of NPs, large solvent volumes, and poor versatility in metal precursors compared to coprecipitation and thermal decomposition [17].

2.2.7. Pyrolysis Methods

Spray pyrolysis is a technique commonly used for the synthesis of various materials, including MNPs. This method involves the formation of fine droplets of precursor solutions that are sprayed into a high-temperature environment. The solvent evaporates, and the remaining solute undergoes chemical reactions to form the desired material, collected on a substrate [58].

In precise context of MNP synthesis, spray pyrolysis offers several advantages: controlled particle size, homogeneous coating, scalability, versatility, and tunable magnetic properties [59].

Laser pyrolysis is a method which involves the use of CO_2 laser irradiation to induce chemical reactions in a precursor material, leading to the formation of NPs. The principle consists of focusing a high-intensity laser beam on a precursor material in the gas or aerosol phase. The laser energy is absorbed by the precursor, leading to its rapid heating and decomposition. The resulting chemical reactions lead to the formation of NPs, which are then collected on a substrate [3]. This technique offers both advantages (rapid heating, high purity, fine tuning) and characteristics that need to be improved (scalability and cost) [60].

2.2.8. Non-Thermal Methods

Non-thermal methods for the synthesis of MNPs refer to techniques that do not involve high temperatures during the production process. These methods are often preferred for their ability to produce NPs with unique properties and for avoiding issues related to thermal decomposition or aggregation [61].

Common non-thermal methods used for MNP synthesis are:

- **Chemical Reduction**

Magnetic nanoparticles are formed through the reduction of metal ions by chemical agents without the need for high temperatures. This method is simple, cost-effective, and can be used for a variety of metals. It is also commonly used for the synthesis of metal nanoparticles, such as gold, silver, and platinum nanoparticles [62].

- **Electrochemical Synthesis**

MNPs are produced through electrochemical reactions at the electrodes. Using this method, size and morphology control, simplicity and scale-up ability can be achieved. Also, it is worth mentioning that it is suitable for various materials, including metals, metal oxides, and conducting polymers [63]. Such methods have gained confidence in relation to conventional ones by allowing the synthesis of superparamagnetic nanoparticles in surfactant or stabilizing agent-free conditions [64]. Moreover, new methods showed increased efficiency in obtaining multimetallic nanoparticles [65].

- **Microwave-Assisted Synthesis**

Microwave radiation is used to heat reaction mixtures, facilitating rapid and uniform heating. This method possesses faster reaction rates, higher yields, and reduced energy consumption compared to conventional heating methods. It is applied to a wide range of materials, including metals, metal oxides, and carbon-based nanoparticles [66].

- **Ultrasound-Assisted Synthesis**

Ultrasonic waves are applied to a reaction mixture, leading to acoustic cavitation and promoting particle formation. This technique has rapid reaction rates, control over particle size, and improved homogeneity. It is used for metals, metal oxides, and organic nanoparticles [67].

2.3. Biological Methods

The field of nanotechnology has witnessed the rise of a significant field known as biological synthesis of magnetic nanoparticles (MNPs). This approach offers an environmentally friendly and sustainable alternative to conventional physical and chemical manufacturing techniques. This method employs biological entities, such as microorganisms, plant extracts, and enzymes, to synthesize MNPs. Each of these biological entities holds distinct advantages and is suited for a range of applications, as follows:

- **Microorganism-based synthesis** involves the utilization of microorganisms, including bacteria, fungi, viruses, and actinomycetes, to generate MNPs. The presence of microorganisms greatly enhances the efficiency of metal ion reduction, hence facilitating NP synthesis. Magnetotactic bacteria are renowned for their ability to synthesize MNPs intracellularly. The nanoparticles are employed for orienting themselves in geomagnetic fields [68,69]. Furthermore, the use of fungi in the production of MNPs has been extensively recorded. Various fungal species have been recognized for their ability to generate iron oxide nanoparticles, which have significant promise in the domains of remediation and biomedicine [70,71].
- **Plant extracts**, including phytochemicals, are utilized in the manufacture of nanoparticles. They serve as both reducing and stabilizing agents. This is achieved through the utilization of botanical extracts. The method's simplicity, cost-effectiveness, and scalability are driving its increasing worldwide popularity. Numerous plants have been employed for this objective. Diverse parts of plants such as leaves, stems, and roots were employed to provide the necessary bioactive constituents. For instance, the utilization of plant extracts, such as aloe vera and green tea, has proven to be successful in the production of IONPs. The nanoparticles showed promise in the areas of drug delivery and magnetic resonance imaging (MRI) applications [34,72].
- **Enzymatic synthesis** process employs specific enzymes to catalyze the reduction of metal ions in order to produce metal nanoparticles. Enzymes have significant control over the nucleation and growth processes, leading to the formation of NPs that exhibit a uniform size and shape. The enzymatic approach is extremely intriguing for use in medical and pharmaceutical areas due to its exceptional biocompatibility and precision. Several enzymes are currently under investigation [72,73] as a direct consequence of growing research efforts in this area. Moreover, some protein assisted synthesis models were implemented for biosensing applications [74].

Since these methods apply biological principles for nanoparticle formation, they are also called biomimetic synthesis procedures [75]. These techniques are not only environmentally benign, but they yield products that are highly suitable for delicate applications such as drug administration, bioimaging, and environmental remediation. Due to their high biocompatibility and minimal environmental impact, they represent a very promising research topic in the field of nanotechnology.

2.4. Coating of Magnetic NPs

In order to improve the functionality, stability, and biocompatibility of MNPs, the coating process is an essential step. This is especially true for applications in biomedicine and environmental research. MNPs can be coated with a variety of different molecules, including:

Polymeric Coatings: polymers, both natural and synthetic, are frequently utilized for MNP coating. Due to their biocompatibility and capacity to inhibit particle aggregation, synthetic polymers such as poly(ethylene glycol) (PEG) [76], poly(vinyl alcohol) (PVA) [77], and poly(lactic acid) (PLA) [78] are among the most preferred options.

Coatings made of Silica: silica coatings are applied to MNPs in order to increase their reactivity and their potential for functionalization. The surface of an MNP consisting of maghemite or magnetite, for example, can be coated with silica. The silica shell can be further modified with a variety of functional groups by the formation of covalent bonds between organo-silane molecules and the silica shell. This approach is especially useful for

attaching fluorescent dyes and/or other functional molecules to the outer surface of MNPs, which represent a particularly advantageous use [79–81].

MNPs can be coated either during the synthesis process (in situ) with stabilizers such as surfactants or polymers, or after the synthesis process (post-synthesis) with materials such as monolayer ligands, mixtures of polymers, biomolecules, and inorganic compounds. In situ coatings are more common than post-synthesis procedures [82]. When it comes to functionalizing MNPs for specific purposes, such as medical applications, where it is important to bind biological ligands to NP' surfaces, post-synthesis procedures offer a wider range of options [83–86].

When it comes to medical diagnostics, drug delivery, or environmental cleanup, each form of coating confers particular features which align with the application that is they are specifically meant for. The functioning, biocompatibility, and stability requirements of MNPs need to be taken into consideration before deciding the coating selection.

3. NP Properties and Characterization Methods

The physico-chemical characterization of MNPs is an essential process that requires the use of a wide range of advanced techniques in order to determine the magnetic, chemical, and physical characteristics of these particles. When it comes to understanding MNPs behavior and ensuring that they are suitable for a specific application, these methodologies are absolutely necessary. This is particularly relevant in the fields of biomedicine, environmental remediation, and nanotechnology. In the next subchapters some of the techniques that offer comprehensive insights into the size, composition, structure, and magnetic properties of this class of NPs will be presented. To improve the development of MNPs and to maximize their potential use in a variety of scientific and industrial applications, the precise selection of these characterization methods is crucial.

3.1. Physical Properties and Their Characterization

Precisely determining the properties of MNPs is extremely important. The physical properties of MNPs are highly dependent on their size, bearing in mind that as the size decreases to nanoscale, various physical properties can change significantly [87].

The size and shape of MNPs has a direct impact on their behavior and functionality, influencing features such as magnetic response, biocompatibility, and cellular uptake. As MNPs decrease in size, they may transition from multi-domain to superparamagnetic behavior, exhibiting negligible magnetic remanence and coercivity. Smaller MNPs often reach magnetic saturation more quickly under an external magnetic field as compared to larger particles. This property is crucial for applications such as magnetic storage and sensing [88].

For example, nanoparticles with a size less than 25 nm, such as magnetite, display a superparamagnetic behavior [89], which is an essential characteristic for applications like targeted medication administration and MRI.

Size can also influence the blocking temperature at which MNPs become magnetically blocked. Smaller particles typically have lower blocking temperatures [90].

Moreover, smaller MNPs have a higher surface area-to-volume ratio, making them more reactive and suitable for drug delivery or catalysis applications. This particularity allows for more effective functionalization by attaching targeting ligands or other molecules to achieve higher biocompatibility [88].

On the other hand, smaller nanoparticles are more prone to agglomeration due to increased surface energy [91].

The characterization of magnetic nanoparticles (MNPs), particularly for biomedical applications, encompasses a range of procedures that primarily examine MNPs' inorganic crystalline core and organic shell, which is required to inhibit the formation of MNPs aggregates and minimize the likelihood of an immune system reaction [92,93]. The main techniques capable of providing crucial insights into the physical characteristics of these NPs are transmission electron microscopy, dynamic light scattering and magnetometry methods.

3.1.1. Transmission Electron Microscopy (TEM)

TEM is essential for capturing high-resolution images of MNPs. It provides comprehensive information regarding their dimensions, form, and interior composition. This technique is crucial for observing the inorganic core and any organic shell present on the surface of the nanoparticles, offering crucial insights into their microstructure or ultrastructure. In contrast to other methods of size assessment, it accurately measures the true radius of samples. TEM, which requires desiccation before measurement, gives information about magnetic nanoparticles in their dry state . However, a significant limitation of TEM is its restriction to small sample sizes and the considerable time required for measurements. Furthermore, as operator bias can impact the selection of photos, researchers are recommended to refrain from introducing subjectivity. To obtain a statistically precise measurement of NPs' diameters, it is necessary to collect many images at an appropriate level of magnification. This will ensure that there is sufficient contrast between the particles and the background, while also allowing for the inclusion of multiple particles (a minimum of 300 in order to obtain adequate statistical data) in each image. The photos can thereafter be examined with a software application like ImageJ [94].

High-resolution transmission electron microscopy-electron energy loss spectroscopy (HRTEM-EELS) provides a comprehensive investigation of MNPs' composition. It is highly valuable for determining the elemental and electrical structures, including the characteristics of multifunctional NPs such as core–shell $Fe_3O_4/Zn_xCo_1-xFe_2O_4$ [95].

3.1.2. Scanning Electron Microscopy (SEM)

SEM is a powerful imaging method that uses electrons to examine the surface morphology of a sample at high resolution, enabling the detailed examination of individual nanoparticles [96].

In the case of MNPs, SEM provides quantitative information regarding their size, shape, and surface. SEM allows the visualization of surface modifications and functionalization, providing insights into their stability and potential applications [97]. SEM can reveal the agglomeration state of magnetic nanoparticles, which is important for understanding their behavior in different environments [98,99]. However, this technique does not directly provide information about the magnetic properties of MNPs which can be evaluated by means of magnetometry methods.

The SEM of MNPs is crucial for understanding their physical characteristics, which is vital for applications in drug delivery, magnetic hyperthermia, magnetic resonance imaging, and other biomedical and technological fields [97–99].

3.1.3. Atomic Force Microscopy (AFM)

AFM provides high-resolution topographical images of MNPs by allowing the visualization of surface morphology and size distribution. Moreover, this technique can be employed to map the magnetic properties of nanoparticles across a surface. This includes measurements of magnetic force, coercivity, and remanence, providing insights into the magnetic behavior of the nanoparticles.

When it comes to functionalizing MNPs, AFM can be engaged to assess the surface modifications involved in the interaction between nanoparticles and various molecules. The method can be used in conjunction with other imaging techniques for a rigorous characterization [100]. It must be mentioned that sample preparation is crucial to ensure accurate and reliable results.

3.1.4. Dynamic Light Scattering (DLS)

DLS is a technique employed to determine the hydrodynamic size of MNPs present in a liquid solution. It examines the patterns of light scattered by particles, which is crucial for understanding their behavior in colloidal suspensions.

3.1.5. Magnetometry

Comprehending and enhancing the magnetic properties of MNPs is essential for their effective application in diverse domains, particularly in biomedicine. The magnetic characteristics, including magnetic moment, coercivity, and responsiveness to external magnetic fields, determine the operational capabilities of MNPs in many applications such as MRI, targeted drug administration, hyperthermia, and magnetic data storage [66]. The optimization of these attributes guarantees the effectiveness, precision, and security of MNPs, rendering their evaluation through state-of-the-art methods such as Vibrating Sample Magnetometry (VSM) and/or Superconducting Quantum Interference Device (SQUID) Magnetometry essential [67,68].

VSM is a cost-effective and straightforward technique that offers accurate information about the value of the magnetic moment of the analyzed substance. The sample is positioned within a copper coil and subjected to an applied magnetic field. Subsequently, it is oscillated in a direction perpendicular to the field. The magnetic moment is quantified by detecting a variation in the electrical potential. This method is valuable for evaluating the magnetic moment in relation to temperature, magnetic field, and crystal orientation [101]. Nevertheless, VSM has a relatively lower sensitivity in comparison to more sophisticated techniques such as SQUID magnetometry [102].

SQUID magnetometry is renowned for its exceptional sensitivity and is employed to analyze superparamagnetic substances, which can be recognized by the absence of a hysteresis loop. Hysteresis loops, which depict the magnetization characteristics of a material, play a vital role in comprehending magnetic features such as remnant magnetization and coercive field. Superparamagnetic nanoparticles, which have a single magnetic domain, do not display a hysteresis loop like ferromagnetic ones [101,103]. This method also aids in determining intrinsic characteristics, such as the Curie temperature for ferromagnetic substances and the Neel temperature for antiferromagnetic materials [102,103].

3.2. Chemical Properties and Their Characterization of MNPs

From a chemical point of view, MNP characterization involves determining their composition, structure and surface properties. To achieve such information, different analytical techniques can be employed. In the next paragraph many of them are briefly presented.

Usually, MNPs contain magnetic materials such as iron oxide, magnetite, maghemite, but can contain other materials like cobalt, nickel, or alloys. Such compositions are typically coated with silica, surfactants, or biocompatible materials (e.g., polymers). These coatings provide biocompatibility, functionality, and stability [104].

The surface properties, also called reactivity, are highly dependent on the surface area. This property controls the surface charge, interactions, oxidation state and heating efficiency of MNPs [104,105].

Chemical characterization ensures the quality and the consistency of the MNPs in achieving the desired specifications and properties required for particular applications. As for biomedical applications, safety and biocompatibility are parameters of crucial importance. Understanding reactivity and interactions between NPs and other entities is essential for such applications.

3.2.1. UV–Vis Spectrophotometry

UV–Vis spectrophotometry is a widely used technique for characterizing nanoparticles, particularly metal nanoparticles. It is used for quantitative analysis of nanoparticle concentration based on the Beer–Lambert Law, which relates absorbance to concentration.

This method relies on an NP–light interaction, leading to changes in the absorption spectra. When metal nanoparticles, especially noble ones like gold and silver, are exposed to light, they interact with the electromagnetic field, leading to phenomena such as surface plasmon resonance (SPR).

The absorption of light by nanoparticles leads to the occurrence of characteristic peaks in the UV–Vis spectrum. The position of the SPR peak is sensitive to factors such as the

NPs' size, shape, and surrounding medium. This is particularly useful for monitoring the progress of nanoparticle synthesis reactions [106].

3.2.2. Nuclear Magnetic Resonance (NMR)

Nuclear Magnetic Resonance (NMR) spectroscopy is a powerful analytical technique commonly used for the characterization of magnetic nanoparticles. While NMR has some limitations when it comes to studying nanoscale materials directly, it can provide valuable information about the structure, composition, and interactions involving nanoparticles.

NMR can be used for quantitative analysis, allowing the determination of NPs concentration in a sample. This is particularly useful for assessing the synthesis yield.

Surface functionalization can be analyzed by observing changes in chemical shifts and peak intensities. Ligands or surface coatings on nanoparticles can be characterized by NMR, providing insights into their composition and arrangement.

Nevertheless, MNPs' size and dispersion can be studied through NMR relaxometry.

Techniques such as diffusion-ordered spectroscopy (DOSY) can be employed to study the translational diffusion of nanoparticles [106].

3.2.3. Fourier Transform Infra-Red (FT-IR) Spectroscopy

It provides information about the molecular composition, functional groups, and chemical bonds present on the surface of MNPs.

FT-IR spectroscopy measures the absorption of infrared light by the sample. Different functional groups absorb specific wavelengths of infrared light, resulting in characteristic peaks in the spectrum. The Fourier Transform technique is used to convert the raw data into a Fourier Transform Infrared spectrum.

This technique is particularly useful for studying the surface functionalization of nanoparticles. Peaks in the spectrum can be assigned to specific functional groups, providing information about the ligands or surfactants attached to the NPs' surface. It can also identify chemical bonds present in the system, allowing researchers to characterize the composition of the material.

Other applications are materialized through quantitative analysis by enabling the determination of the concentration of functional groups on the nanoparticle surface, particle size evaluation by monitoring the chemical reactions and, last but not least, the NPs' agglomeration state quantification [106].

3.2.4. Raman Spectroscopy (RS)

RS represents a powerful set of methods that can be used to evaluate the structural and chemical properties of MNPs. The techniques are based on the inelastic scattering of the light that interacts with the sample due to molecular vibrations. Therefore, the resulting spectrum relies on the peaks corresponding to the vibrational modes of the MNPs. Modifications in peak positions or intensities, or the occurrence of new peaks, may provide valuable insights into the chemical composition, crystallinity, and structure [107–109].

3.2.5. Mass Spectrometry (MSp)

MSp methods can provide valuable information regarding nanoparticles structure, composition, and surface chemistry. MSp coupled with other techniques is useful for various analyses concerning the NPs' properties [110].

MSp coupled with liquid chromatography is suitable for studying ligands' nature and distribution. MSp combined with matrix-assisted laser desorption can be used to analyze the ligands or the capping agents attached at the surface of MNPs and to identify MNPs' size distribution [111].

Inductively coupled plasma MSp can support the elemental composition in order to understand their chemistry and to detect the presence of certain impurities [112].

MSp can ensure both quantitative and qualitative assays and can provide insights into structural characterization. However, it is important to use other complementary techniques for a better understanding of the NPs' properties [113].

3.2.6. Energy Dispersive X-ray Spectroscopy (EDS)

EDS is used in conjunction with Transmission Electron Microscopy (TEM) to perform elemental analysis. This approach is crucial for the identification of specific elements that have been absorbed onto the surface of MNPs, hence facilitating the study of surface coatings and alterations.

3.2.7. X-ray Diffraction (XRD)

XRD is employed to analyze the arrangement of atoms in the magnetic core, providing insights into their crystalline structure. It offers information regarding crystal arrangement, the distance between their lattices, and the dimensions of the crystallites. These factors are crucial in determining the magnetic behavior of these substances.

3.2.8. Small Angle X-ray Scattering (SAXS)

SAXS is a crucial technique for nanoscale analysis. It provides valuable information about the arrangement and self-organization of dispersed nanoscale colloids in their natural solutions. It possesses a distinct capability to investigate the averaged structural information of the materials, including information about the crystals' structure, lattice spacing, and crystallites size [114].

4. Biomedical Applications

Magnetic nanoparticles (MNPs) have become a crucial tool in the biomedical area, significantly transforming different diagnostic and therapeutic methods. Due to their distinctive magnetic properties, as well as their compatibility with biological systems and capacity to be modified on the surface, these materials are highly suitable for a wide range of applications, including magnetic resonance imaging (MRI) [115], targeted drug administration, and cancer therapy [116,117]. The adaptability of MNPs resides in their capacity to react to external magnetic fields, allowing for accurate regulation and manipulation inside biological systems. This characteristic is especially beneficial for targeted therapies, as it allows for the direct administration of medications or therapeutic agents to specific locations, hence reducing the occurrence of adverse effects throughout the entire body [118]. Moreover, their use in diagnostic imaging, namely in augmenting MRI contrast, facilitates enhanced and more intricate vision of internal body structures, resulting in enhanced diagnostic precision [20].

The potential of MNPs in biomedical applications is extensive, and current research is investigating novel and effective methods to employ these NPs. Future prospects involve the advancement of multifunctional MNPs with the ability to perform both diagnosis and treatment simultaneously, commonly known as 'theranostics' [119–121]. This integration holds the potential to improve personalized medicine, wherein treatment approaches can be customized to meet the specific needs of each patient. Furthermore, the investigation of MNPs in the field of regenerative medicine and tissue engineering offers a fresh and promising direction for scientific inquiry, with the potential to facilitate innovative approaches to tissue repair and regeneration [121].

MNPs have a significant benefit in their large surface area-to-volume ratio, enabling various functionalization and alterations that respond to specific biomedical requirements. The ability to adapt allows for the creation of magnetic nanoparticles (MNPs) with tailored characteristics, suitable for a range of uses including hyperthermia cancer treatment [122] and molecular detection. However, a notable disadvantage is the potential toxicity and biocompatibility. In this regard, the physical properties of NPs, such as the size, concentration, shape, and coatings, together with exposure time, the number of exposed cells, and chemical compositions are of major importance [93]. For example, iron oxide nanoparticles

enter the cell usually through endocytoses. The internalization process is highly dependent on their size [92,102] and coating [95]. At high doses, MNPs can lead to the generation of reactive oxygen species, affecting the cells' fate [96,97].

It is essential to ensure that MNPs do not cause negative immune reactions or gather in important organs in order to safely use them in medical treatments. Furthermore, the ongoing investigation of the enduring stability and deterioration of MNPs in biological systems is being conducted to address any possible health hazards.

Based on the unique magnetic properties of these nanoparticles, they are suitable for diverse applications as can be seen in Figure 2.

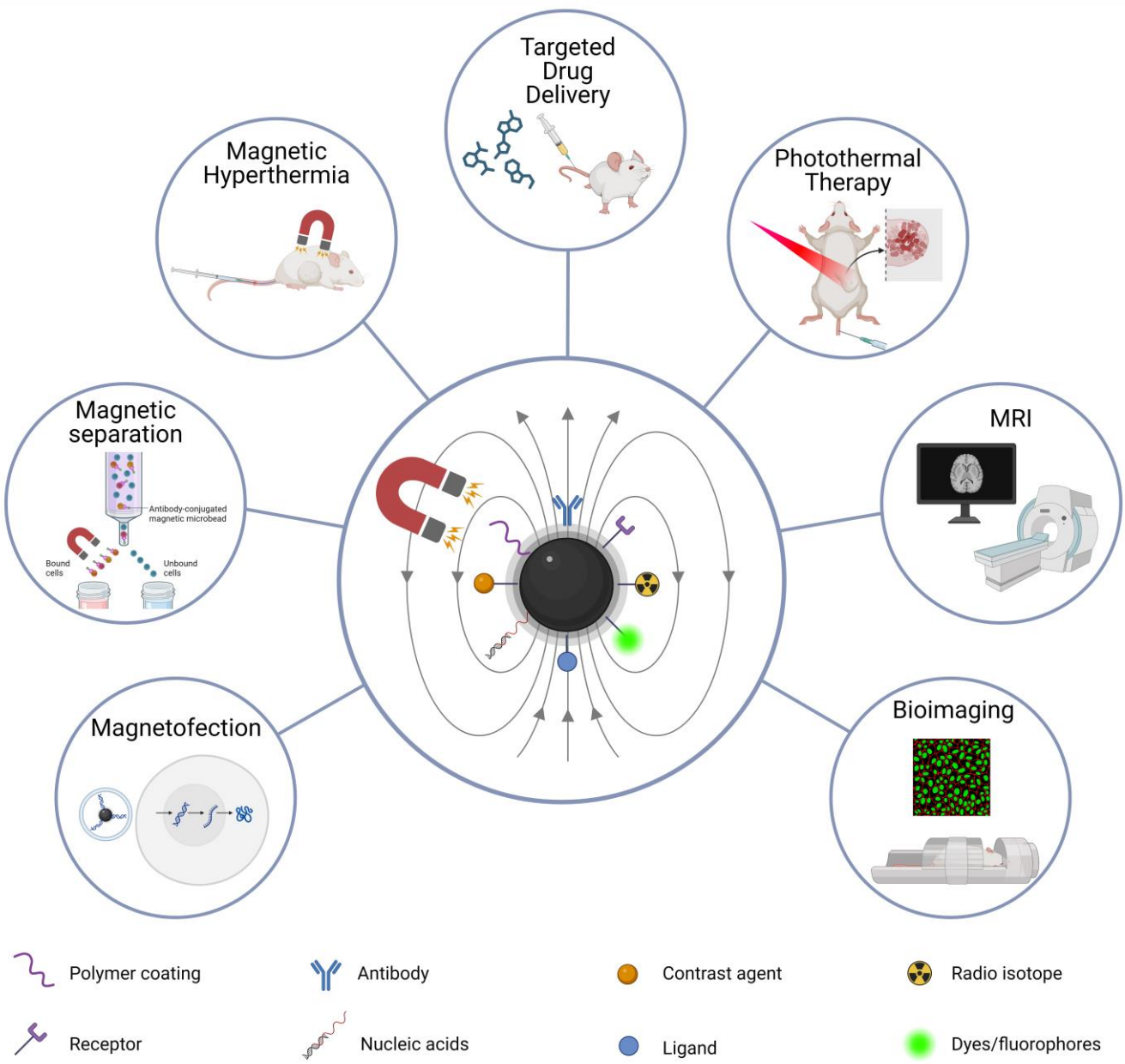

Figure 2. Biomedical applications of MNPs. Created with BioRender.com, accessed on 6 February 2024.

4.1. Magnetic Hyperthermia Therapy (MHT)

MHT takes advantage of MNPs' capacity to interact with an alternating external magnetic field in order to induce heat generation for cancer treatment applications by means of hyperthermia. This non-invasive technique elevates the temperature of tumors to

a range of 41–47 °C, causing cancer cell destruction through either apoptosis or necrosis. Magnetic nanoparticles (MNPs) are administered into the body, gather at the location of the tumor where they specifically aim, and raise the temperature of cancer cells without causing damage to nearby healthy tissues. This approach offers distinct advantages compared to chemotherapy, as it exhibits precise targeting and minimizes harm to healthy cells [123,124], being implemented in cancer treatment since the 1950s [125].

Many studies have been reported in the literature, but in the next rows we would like to highlight some of the recent and interesting findings in the field of MHT applications.

It has been shown that the effectiveness of various molecules (chemotherapeutics, nucleic acids, proteins) has been enhanced when they were used in conjunction with MHT [126–128]. In other cases, MNPs harmed the cells even in the absence of MHT [91].

Vilas-Boas et al. have proposed a combination between superparamagnetic and magnetic immuno-conjugated nanoparticles. The strategy was to treat the cancer cells with immuno-conjugated magnetic nanoparticles and then with superparamagnetic iron oxide nanoparticles (SPIONs) and, by applying an external alternating magnetic field, to enhance the efficacy of the treatment [129]. The study showed promising results offering new perspectives for the development of new nanostructures for cancer applications.

Developing inhalable composites is a very challenging aspect when it comes to lung cancer treatment. Magnetic nanocomposite microparticles via MHT can serve as an effective thermal therapy platform inducing targeted damage at the tumoral site [130].

Exosome-based research has been influenced by the advances of hybrid nanostructures in tumor targeting by means of MHT. For example, by attaching magnetic nanoparticles at the surface of the exosomes previously loaded with targeting and therapeutic molecules, and by applying an external magnetic field, it has been developed an anti-cancer hybrid drug delivery system [131].

Many drug delivery nanostructures take advantage of MHT in delivering their cargo at the tumor site. Such applications together with other valuable examples of MHT applications can be found in Table 1.

4.2. Targeted Drug Delivery (TDD)

As a direct consequence of their magnetic properties, MNPs can be employed as carriers for precise drug delivery, as they may be directed to certain tissues with the aid of an external magnetic field. This method enhances the bioavailability of medications and enables their targeted administration to affected tissue, while minimizing systemic effects. The focused administration of medication improves its therapeutic efficacy and minimizes the likelihood of adverse reactions [124,132–134].

TDD efficiency is highly influenced by the applied magnetic field, NP magnetism, size, shape, and surface coating, but also by extracellular and intracellular barriers [135]. Beside drugs, other molecules that can be loaded in MNPs involves nucleic acids, cells, proteins, or antibodies [135,136].

SPIONs coated with paclitaxel–chitosan and folate–polyethyleneglycol proved to be an efficient strategy for targeting fibrosarcoma. The nanosystem induced cancer cells' apoptosis and decreased tumor size [137].

An external magnetic field combined with ultrasound led to the development of a TDD system composed of magnetic nanoparticle coated liposomes and microbubbles as a therapy for atherosclerosis plaques. This strategy was based on MNPs' capacity to penetrate and migrate into inaccessible tissue during MHT. Nevertheless, the ultrasound field can increase the therapeutic compounds delivery and thus the targeting of the desired tissue [138].

Such approaches have been used in MNP research in theranostics, a new and interesting topic that recently gained a lot of attention [139–144].

MNPs loaded with nanoparticles containing growth factors were used both as delivery and labeling systems with a great potential in regenerative medicine [145].

Multifunctional magnetic nanoparticles, also known as smart drug delivery systems, can update already developed cancer therapies [143]. Such examples can be found in Table 1.

4.3. Photothermal Therapy (PTT)

PTT using magnetic nanoparticles involves the use of nanoparticles that possess both photothermal and magnetic properties. These nanoparticles can be designed to absorb light and convert it into heat, as well as respond to an external magnetic field. This combination allows for a targeted and controlled approach for treating diseases, particularly in the field of cancer therapy. PTT is a minimally invasive treatment that utilizes MNPs to effectively address cancer. This technique involves subjecting diseased tissues containing nanoparticles to near-infrared radiation (NIR), resulting in the production of heat and subsequent eradication of malignant cells. This method of localized heating is highly efficient in specifically targeting and treating cancers [146–148].

The success of PTT is highly influenced by the absorbance, radiative emission, stability, crystallinity, and size of the nanoparticle [149].

The synergic action of plasmonic gold nanoparticles in combination with MNPs has proved successful in targeting and treating cancer [150].

Iron oxide functionalized with alumina has shown therapeutic potential in treating nosocomial and antibiotic resistant bacterial infections [151]. The strategy was based on the magnetic properties of MNPs to form aggregates under an applied magnetic field and, with the help of alumina molecules attached at their surface, to be able to target bacterial species and then damage the formed bacterial population by means of NIR laser irradiation.

Radiolabeled molecule-coated MNP multifunctional hybrid nanostructures have been also reported as efficient PTT agents [152].

In light of the ideas presented above, PTT combined with MHT has offered promising results and a few more examples can be found in Table 1.

4.4. Magnetofection (MF)

Magnetofection is a technique that combines the use of magnetic nanoparticles with conventional transfection methods to improve the delivery of genetic material (e.g., DNA, RNA, or siRNA) into target cells. The goal is to enhance the efficiency and specificity of gene transfer by leveraging the magnetic properties of nanoparticles [153]. MF was employed to transport nucleic acids into cells for gene delivery purposes [153]. Magnetic nanoparticles (MNPs) that are attached to genetic material are inserted into the body and directed towards specific cells or tissues by using an external magnetic field capable of interacting with the MNPs. This technique improves the effectiveness of gene transfection, offering a potent tool for gene treatment and research purposes. Nucleic acid molecules can be indirectly attached to the MNPs surface using linkers [154] or directly through electrostatic interactions, especially in the case of polyethylenimine coatings [155,156], as presented in Table 1.

MF is very efficient due to its swift targeting and decreased cytotoxicity, providing notable benefits compared to conventional chemical transfection techniques [157–159].

Besides these applications, MNPs can be employed in efficient DNA isolation directly from biological samples. A higher separation capacity as compared to commercially available kits has been reported [160].

4.5. Magnetic Resonance Imaging (MRI)

Magnetic resonance imaging, or MRI, is a noninvasive medical imaging test that produces detailed images of almost every internal structure in the human body, including organs, bones, muscles, and blood vessels. In this regard MNPs were investigated as negative contrast agents suitable for tumor detection by means of MRI.

For example, iron oxide nanoparticles conjugated with various antibodies were used to image glioma [161,162], glioblastoma [163], breast [164], pancreatic [165], colorectal [166], prostate [167], and other cancers [168].

Multimodal cancer imaging involving MRI, computed tomography, positron emission tomography, single photon emission tomography, and near infrared fluorescence can be assessed by using MNPs [169].

Fluorescent-labelled MNPs offer versatile and powerful tools for visualizing biological structures and processes at molecular and cellular levels. Bioimaging using MNPs has shown promise in different preclinical studies for diagnosing diseases, monitoring disease progression, and evaluating treatment efficacy [170].

It is worth mentioning that SPIONs have already been used for human sentinel lymph node MRI to evaluate intermediate and high-risk prostate cancer [171,172]. An innovative method based on bimodal imaging using a new magnetic fluorescent hybrid tracer presented promising results in SLN detection as shown in the ongoing trial DRKS00032808 [173].

In addition, functionalizing MNPs with various radioisotopes has garnered interest for biomedical imaging, drug delivery, and targeted therapy. MNPs functionalized with radioisotopes serve as dual-modal imaging probes, combining the magnetic properties of MNPs with the radioactivity of the attached isotopes. This enables sensitive and quantitative imaging of biological processes, such as tumor targeting, inflammation detection, and organ-specific imaging [174]. Moreover, the addition of a targeting ligand (e.g., antibody or peptide) represents a promising strategy for targeted therapy and theranostic applications, especially in cancer [175].

Even if most of contrast agents approved by Food and Drug Administration are based on gadolinium, some MNPs are undergoing preclinical and clinical evaluation for safety and efficacy, with the goal of obtaining regulatory approval for clinical use. Plenty of commercial MNPs, used as agents involved in MRI applications, are available in the worldwide virtual market. However, a large portion of this category is still in the patenting stage. If this process will be successful, the range of MNPs employed in this field will increase considerably, since the use of MNPs has the potential to eliminate many of the current limitations (signal intensity, background signal, biocompatibility and toxicity, spatial resolution, biodistribution and clearance, magnetic field strength dependence, challenges in quantification) [176,177].

Table 1 contains other valuable examples of MNPs used as MRI agents and not only for cancer detection.

4.6. Magnetic Particle Imaging (MPI)

MPI technology was developed more than 10 years ago and is still evolving in the biomedical field [178]. The main relevant features of this dynamic domain are represented by harmless, cost-effective, and high-precision detection when combined with computed tomography [179]. MPI is based on the creation and superimposition of a static selection field and an oscillatory drive field by evaluating the non-linear magnetization properties of MNPs. For this specific type of application, the SPIONs represent the most suitable class of MNPs [180].

This technique acts as a true helper in diagnosing and treating various complex diseases, especially from the oncological and surgical field. One of the in vivo applications is represented by the quantitative analysis of MNPs by determining their concentration and distribution, which can improve imaging quality [181].

By combining MPI with MRI, one can investigate the molecular basis of some treatment mechanisms (Vivotrax from Magnetic Insight company, Alameda, CA, USA) [182]. Further examples can also be found in Table 1. The clinical translation of MNP-based imaging techniques is underway, with ongoing research focusing on safety, efficacy, and regulatory approval [183]. Continued research and development in this field holds great potential for advancing diagnostics, therapeutics, and personalized medicine.

4.7. Magnetic Separation (MS)

Among all these aforementioned methods, some authors reported the use of MNPs for cell separation. Their magnetic properties cause them to be recommended for use in various fields such as biotechnology, medicine, environmental sciences, and material sciences. MNPs can be used to remove contaminants from water or soil by selectively binding to pollutants, facilitating their easy removal under a magnetic field. In material science, MS using MNPs is used for material purification and separation, especially in nanotechnology. It can be applied in various industries for the separation of waste materials, making disposal and recycling processes more efficient.

MS is widely used in diagnostics, drug delivery, and bio separation processes. It can be employed to isolate specific cells, proteins, or nucleic acids.

For example, a tumor cell separation technique by means of dendrimer-assisted hydrophilic magnetic nanoparticles was implemented. These sensors were able to detect tumoral cells from blood samples, achieving a cell viability of 99% and a capture efficiency of nearly 80% [43].

MS by means of MNPs is very challenging because the properties of the nanoparticles should be carefully optimized, involving high synthesis and functionalization costs. However, the advantages offered by this method are of immeasurable value: high specificity and selectivity, a non-destructive and gentle separation process, and rapid and efficient separation [184].

Table 1 summarizes different remarkable examples of MNP use in biomedical applications found in the literature.

Table 1. A synthesis of biomedical applications of magnetic nanoparticles.

Application	Magnetic Nanoparticles Type	Diameter (nm)	Synthesis Method	Aim	Findings	References
Magnetic Hyperthermia Therapy	Manganese and zinc ferrite	80	Polyol based method	Investigation of NPs properties in vitro	Melanoma cellular toxicity of Zn ferrites NPs	[51]
	Iron oxide	19–50	Polyol based method	Investigation of NPs properties in vitro	Lung cancer cell lines toxicity	[185]
	SPIONs and magnetic-CXCR4 NPs	20 & 250		Targeting CSCR4 receptor of LN229 cancer cells	Magnetic-CXCR4 were disposed around the cell membrane, magnetic hyperthermia has induced cytotoxic effects	[91]
Targeted Drug Delivery	Doxorubicin and methotrexate dendritic chitosan PEG MNPs	20–50	Soft chemical methods and surface modifications	Co-delivery of doxorubicin and methotrexate to MCF-7 cells	High encapsulation efficiency of both drugs; biocompatibility with red blood cells; synergistic effects of the drug combination; reduced side effects; anti-cancer properties	[186]
	Polymeric nanoparticles loaded with curcumin, verapamil and oleylamine-coated superparamagnetic nanoparticles	280–287	Thermolysis method combined with emulsification/solvent evaporation	Multi-modal cancer thermotherapy and chemotherapy	High therapeutic efficacy in HepG2 cancer cells	[187]
	Doxorubicin and enzyme precursors covalently tethered on the silica-coated magnetite NPs	50	Chemical co-precipitation and surface modification	Tumor drug delivery and imaging	Stable and non-toxic nanosystem; anti-cancer effect; real-time monitoring of intracellular drug release; tumor cell imaging	[188]
Photothermal Therapy	MNPs decorated with gold NPs	5–20	Co-precipitation and surface decoration	Tumor site targeting	Apoptosis induction in cancer cells without damaging the healthy ones	[151]
	Maghemite nanoflowers	40–200	Microwave polyol process	Developing an efficient MHT and PTT agent	High crystallinity leads to increased magnetic properties	[149]
	Iron oxide NPs functionalized with ^{125}I-c(RGDyK) radiolabeled peptide	40	Thermal decomposition	Tumor targeting by means of MRI and SPECT	Low mononuclear phagocyte uptake; small amounts of MNPs accumulated in liver and spleen; therapeutic efficacy in glioblastoma	[152]

Table 1. *Cont.*

Application	Magnetic Nanoparticles Type	Diameter (nm)	Synthesis Method	Aim	Findings	References
Magnetofection	Polyethyleneimine MNPs loaded with siRNA	10–15	Chemical co-precipitation and electrostatic adsorption	Intracellular gene silencing and imaging	Therapeutic efficiency through apoptosis and autophagy induction in glioblastoma cells	[189]
	Polyethyleneimine iron oxide NPs loaded with gene vectors (pACTER-EGFP)	10	Co-precipitation and electrostatic adsorption	Gene expression mediation	Anti-tumor effect based on apoptosis on oral squamous cell carcinoma; high transfection efficiency	[190]
	Polyethyleneimine iron oxide NPs loaded with RNA sequences	100–156	Thermal decomposition	RNA delivery	Efficient protein knockdown in breast cancer	[191]
Magnetic resonance imaging	Iron oxide	6	Non-toxic metal salts-based protocol	Reproductive system evaluation in vivo	Sertoli cells damage in blood testicular barrier, organ accumulation and cytotoxicity	[192]
	Iron oxide	1–3	Modified thermal decomposition method	Testing tissue permeable contrast agents	Effective brain imaging	[193]
	Anti-mesothelin antibody conjugated with silica-coated iron oxide NPs	110–130	Solvothermal reaction and incubation with antibody	Pancreatic cancer in vitro and in vivo targeting and imaging	Efficient targeting of SW1990 cells; High stability and nontoxicity both in vitro and in vivo	[194]
Magnetic particle imaging	Iron oxide NPs	Unknown	Unknown	Preclinical evaluation of chimeric antigen receptor T cells in glioblastoma	Highly iron oxide NPs accumulation into tumor tissue	[182]
	SPIONs	200	Thermal decomposition	Preclinical investigation of MNPs after intra-articular joints injection	NPs were retained at least for 42 days into the tissue making possible the imaging measurements due to their biocompatibility	[195]
	SPIONs	5	Unknown	Ex vivo and preclinical evaluation of intraplaque hemorrhage in atherosclerosis	Imaging data quality was improved in atherosclerosis analysis	[196]
Magnetic separation	Microfluidic chip with MNPs	200	Soft lithography	To develop a MNPs assisted microfluidic system for cells selection	Low abundance cell capture and high recovery rate of the cells	[197]
	Dextran-, siloxane-, heparin- coated SPIONs	Unknown	Co-precipitation	Labeling of islet cells with MNPs for separation	High cellular viability after incubation with dextran—and heparin- coated MNPs; efficient method for islet cells purification	[198]
	Silica encapsulated iron oxide MNPs	100–200	Co-precipitation	Non-selective separation of bacterial cells	High separation efficiency in acidic environment (pH 2.2); surface charge of the MNPs is dictating the microbial selectivity; efficient method for environment monitoring	[199]

The progress in obtaining such nanostructures has led to the development of ones that nowadays are commercially available and serve various purposes, especially in biomedical field [200]. Many companies offer support in obtaining MNPs for drug delivery, diagnostics, and imaging applications. Merck KGaA (Darmastadt, Germany), Nano Research Elements Inc. (Dhanora Jattan, India), Fortis Life Sciences (Waltham, MA, USA), Nanografi Nano Technology (Istanbul, Turkey), Nanoshell LLC (North Salt Lake, UT, USA), Read International Corp. (Culver City, CA, USA), SkySpring Nanomaterials Inc. (Houston, TX, USA), Strem Chemicals Inc. (Newburyport, MA, USA), US Research Nanomaterials Inc. (Houston, TX, USA) are some of the companies that produce magnetic nanoparticles for the healthcare industry.

5. Conclusions and Future Perspectives

In recent years, there has been a substantial surge in research and development focused on magnetic nanoparticles intended for biomedical applications. The capacity to precisely control the size, shape, and surface characteristics of these nanoparticles has sparked widespread exploration of their potential uses. Magnetic nanoparticles offer distinct advantages, including their applicability in treatments like hyperthermia and the ability to be precisely directed to specific locations within the body using an alternating magnetic field. With a high surface-area-to-volume ratio, magnetic nanoparticles facilitate substantial substitution levels, making them well-suited for drug delivery. Furthermore, their incorporation into composites such as magnetic hydrogels or liposomes generating new classes of multifunctional hybrid nanostructures enhances their biocompatibility and broadens their potential in medical applications.

Several challenges persist with these systems. Firstly, the efficiency of magnetic nanoparticles (MNPs) is significantly influenced by their size and shape, necessitating the development of appropriate synthetic procedures and subsequent studies to ascertain optimal behavior of the resulting materials. Another concern is the aggregation of MNPs, which can impact their efficiency and pose potential toxicity issues. While toxicity studies must be conducted, it is worth noting that iron oxide nanoparticles, among those proposed for biomedical applications, are generally considered to be less toxic than many other nanoparticle types.

Continued research and innovation in these directions are likely to pave the way for more effective and personalized biomedical interventions using magnetic nanoparticles. Smart MNPs (SMNPs) possess additional functionalities beyond their basic magnetic properties. Such structures are designed to respond to specific stimuli or conditions, allowing for controlled and targeted TDD, MHT, MRI, MF applications. SMNPs can be designed to respond to specific local stimuli, such as changes in pH, temperature, or the presence of certain biomolecules. Moreover, external stimuli, such as magnetic fields, can allow the remote activation and manipulation of SMNPs within the body [201].

To establish the foundations for potentially clinically applicable results, it is imperative to conduct a literature review with a very strong interdisciplinary perspective. Therefore, the collaboration between nanomaterials and bioengineering can certainly provide synergistic effects in biomedical applications.

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