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Review

Pharmaceutical Applications of Iron-Oxide Magnetic Nanoparticles

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Abstract: Advances of nanotechnology led to the development of nanoparticulate systems with many advantages due to their unique physicochemical properties. The use of iron-oxide magnetic nanoparticles (IOMNPs) in pharmaceutical areas increased in the last few decades. This article reviews the conceptual information about iron oxides, magnetic nanoparticles, methods of IOMNP synthesis, properties useful for pharmaceutical applications, advantages and disadvantages, strategies for nanoparticle assemblies, and uses in the production of drug delivery, hyperthermia, theranostics, photodynamic therapy, and as an antimicrobial. The encapsulation, coating, or dispersion of IOMNPs with biocompatible material(s) can avoid the aggregation, biodegradation, and alterations from the original state and also enable entrapping the bioactive agent on the particle via adsorption or covalent attachment. IOMNPs show great potential for target drug delivery, improving the therapy as a consequence of a higher drug effect using lower concentrations, thus reducing side effects and toxicity. Different methodologies allow IOMNP synthesis, resulting in different structures, sizes, dispersions, and surface modifications. These advantages support their utilization in pharmaceutical applications, and getting suitable drug release control on the target tissues could be beneficial in several clinical situations, such as infections, inflammations, and cancer. However, more toxicological clinical investigations about IOMNPs are necessary.

Keywords: magnetic nanoparticles; iron oxide; pharmaceutics; magnetism; therapy; development; nanotechnology

1. Introduction

In the last few decades, the use of iron-oxide nanoparticles displaying magnetic properties attracted great interest in many application areas, from magnetic recording media to pharmaceutical applications such as therapy and drug delivery [1–14]. Each application of these nanoparticles needs specific and, sometimes, different properties [1,12,15]. For example, temperature control is very important in some applications. Particles should be stable and have a switchable magnetic state to represent bits of information, independent of temperature fluctuations [1].

Furthermore, the biological environment is very important when magnetic nanoparticles are applied in biology, medical diagnosis, and therapy [1,3,4,12]. Dynamic nanoparticle assemblies can also be designed to respond to the environment, such as temperature, pH, magnetic field, light, ultrasound, electric pulses, redox gradients, or enzymatic activity. In this way, "smart" materials can be created by designed synthesis and assembly of nanoparticles. Their surface can receive ligands, and the final structure can display programmed responses to external stimuli for pharmaceutical applications [11]. This is an important strategy to be applied to biosensors, molecular imaging, novel theranostics, and drug delivery systems [11].

Since the early 1960s, metal oxides were used for magnetic separations [3,16]. Specifically, nanoparticles composed of iron oxide attracted great interest for pharmaceutical applications [1,3–6,11,12,17,18]. This mineral compound shows different polymorphic forms, such as hematite, magnetite, and maghemite [19]. Iron-oxide magnetic nanoparticles (IOMNPs) can be obtained via several methods (e.g., co-precipitation, sol–gel, microemulsion, and thermal decomposition), displaying unique electrical, optical, and magnetic properties [3]. Moreover, they are utilized to develop dynamic nanoparticle assemblies for pharmaceutical applications [11].

IOMNPs are chemically and physically stable, biocompatible, and environmentally safe [3,12,13]. The synthesis of these nanoparticles should be well known and controlled, because it is directly related to sizing, shape, coating, and stability [3,12]. Particles showing size higher than 200 nm are easily cleared by the reticuloendothelial system [20,21]. On the other hand, nanoparticles smaller than 8 nm in diameter can be easily excreted from the body through existent pores of the kidney's basal lamina (renal clearance), if surface charge and chemistry are optimized for this excretion pathway [22,23], thereby reducing the blood-circulating time of these nanostructures. A faster clearance may also occur for hydrophobic and negatively charged nanoparticles, which tend to suffer protein opsonization, being quickly recognized by phagocyte cells [24]. Suitable surface-coating of organic and/or inorganic coatings can surpass problems of cell toxicity and oxidation of IOMNPs [6,25]. Moreover, there are important investigations that need to be addressed, such as studies about clinical, biocompatibility, toxicological, and immunological parameters [6].

Recently, the interest for pharmaceutical applications, such as drug delivery, biosensors, theranostics, and antimicrobial agents effective against many bacteria species, increased [11,16,26]. Therefore, the present manuscript provides a review about the state of the art and advances of IOMNPs for pharmaceutical applications. The conceptual information about iron oxides, magnetic nanoparticles, methods of IOMNP synthesis, properties useful for pharmaceutical applications, advantages and disadvantages, dynamic assembly of IOMNPs, and the applications in the production of drug delivery, hyperthermia, theranostics, and as antimicrobials are addressed.

2. Iron Oxides and Nanoparticles

Iron oxides are mineral compounds found abundantly in nature, but they can also be synthesized in the laboratory [3]. They are composed of iron and oxygen, presenting more than one crystal structure and different structural and magnetic properties [27]. Magnetite (Fe_3O_4) is one of the most interesting crystallographic phases of iron oxide, due to its polymorphism and magnetic properties [3]. Moreover, iron (III) oxide (ferric oxide, Fe_2O_3) exhibits four different crystalline polymorphs (α, β, γ, and ε) with unique biochemical, magnetic, catalytic, and other properties. The highly crystalline α-Fe_2O_3 (hematite) and γ-Fe_2O_3 (maghemite) are found in nature, while the forms β-Fe_2O_3 and ε-Fe_2O_3 are generally synthesized. In addition, the amorphous Fe_2O_3 is characterized to have the Fe (III) ions surrounded by an oxygen octahedral, with the symmetry axes randomly orientated in a non-periodic lattice [3,27].

Magnetite, hematite, and maghemite are the main forms of iron oxide, and their structures can be defined according to the close-packed planes of oxygen anions together with iron cations in tetrahedral or octahedral interstitial sites [3,17,27]. Hematite is well known among the iron oxides and shows a weak ferromagnetic or antiferromagnetic behavior at room temperature, but it is paramagnetic above 956 K. Maghemite (γ-Fe_2O_3) is thermally unstable and can be transformed to hematite at higher temperatures. Moreover, maghemite and magnetite (Fe_2O_3) are easily magnetized, displaying high magnetic response when submitted to an external magnetic field [3,27]. They are metastable oxides in an oxidative atmosphere and, thus, they are oxidized to hematite (α-Fe_2O_3) when heated to a temperature above 673 K [28]. The form ε-Fe_2O_3 displays an orthorhombic crystal structure and it can be regarded as a polymorphous intermediate showing similarity to both α-Fe_2O_3 and γ-Fe_2O_3. In addition, its magnetic behavior is not fully understood [3].

In general, iron oxides were shown great interest due to their nanosized form, and these crystalline polymorphs can be suitable for specific pharmaceutical applications. They can generally be synthesized as particulate materials displaying sizes less than 100 nm that can suffer the influence of an external magnetic field and can, thus, be manipulated [11,12,16,27,29,30].

The development of magnetic resonance imaging contributed to the investigation and development of these nanoparticles [31]. Moreover, they were investigated as carriers for active agents for drug targeting [6]. In the last few decades, several studies showed the development of preparations containing IOMNP to be used for in vitro separation, tissue repair, cellular therapy, magnetic separation, magnetic resonance imaging, as spoilers for magnetic resonance spectroscopy, in drug delivery, hyperthermia, sensors for metabolites, and other biomolecules [6,11,12,16,18,30,32–35].

IOMNPs combine chemical accessibility in solution with physical properties of the bulk phase, due to characteristics between the solid and molecular states [36,37]. They show a complex process of synthesis and the obtaining of a monodisperse particle population of suitable size is dependent on the selection of experimental conditions [6,17,21,38]. Therefore, several studies investigated the fluid stability, through the control of particle size, materials, surfactants, and physical behavior [16]. Moreover, the synthesis process selection should consider the reproducibility and scaling up without any complex purification procedure (e.g., ultracentrifugation, size-exclusion chromatography, magnetic filtration, or flow field gradient) [16,38].

Over the last few decades, several IOMNP synthesis methods were investigated using either organic or aqueous phases: synthesis under constrained environment, hydrothermal and high-temperature reactions, sol–gel reactions, polyol method, flow injection, electrochemical, aerosol/vapor, and sonolysis [3,4,16,21]. In this context, the physical, chemical, and biological routes are the main approaches utilized for synthesis of IOMNP [6,17]. Table 1 summarizes the preparation methods of IOMNPs.

Table 1. Summary of preparation methods of iron-oxide magnetic nanoparticles (IOMNPs).

Routes	Methods	References
Physical	Pulsed laser ablation	[6,39–41]
	Pyrolysis	[6]
Chemical	Co-precipitation	[3,6,16,36–38,40–43]
	Microemulsion	[6,37,44]
	Hydrothermal and solvothermal syntheses	[1,3,6,38]
	Thermal decomposition	[6,38]
	Sol–gel synthesis	[3,16,17,21,32,37,38,43–46]
	Sonochemical	[43,47]
	Microwave-assisted synthesis	[6,48]
Biological	Biosynthesis	[6,49]

The synthesis of these nanoparticles into formulations should also be considered. These methodologies aim for the production of IOMNPs with improved characteristics of stability, biocompatibility, high dispersibility, suitable shape, and controlled size [1,3,6,17].

The preparation of IOMNPs in hydrogels, gels, emulsions, or other types of formulations can be accomplished considering several methods: blending, in situ, and grafting onto. These methods are usually employed because they save time and reduce the number of steps. The grafting-onto method is widely used and is the only one that forms covalent bonds between the IOMNPs and the system [50]. Liu and collaborators prepared fiber-like composites of hematite via the in situ addition of an amount of Fe^{+3} into swollen regenerated cellulose [51]. Moreover, via the blending method, the IOMNPs are synthesized separate from the formulation, and then the precipitated and dry particles in the system are dispersed. For example, iron fluid was prepared and added to an *n*-isopropylacrylamide dispersion to produce a magnetic hydrogel [50,52].

Another important point to be considered during IOMNP preparation for pharmaceutical formulations is that they must exhibit the combined characteristics of high magnetic saturation and a peculiar surface coating of particles [17]. IOMNPs should be nontoxic, biocompatible and, sometimes, must also allow a targetable delivery with particle localization in a specific area [3,13,16,36]. Therefore, it is necessary that the surface of particles displays suitable characteristics to enable their utilization in several in vitro and in vivo applications. However, these characteristics should not affect the stability and magnetization of particles. IOMNPs can be directed to a target site using an external magnetic field. Moreover, they can bind to antibodies, nucleotides, proteins, enzymes, or drugs [38]. Therefore, the surface of these particles could be modified creating new atomic layers of inorganic metallic (e.g., gold), organic polymer, or oxide surfaces (e.g., silica or alumina) [6,17,25,36,53]. Assemblies of IOMNPs are also possible, resulting in nanostructures with physical and chemical properties different from those of both individual IOMNPs and their bulk aggregates. For example, these assembled nanoparticles can be developed to respond to either endogenous or exogeneous stimuli [11].

3. Characteristics of IOMNPs for Pharmaceutical Applications

The use of IOMNPs received important attention in bioscience [21]. Their behavior is dependent on temperature, and their uses for pharmaceutical applications should be considered at different temperatures (e.g., body and room temperatures). Pharmaceutical applications require the particles be stable in a physiological environment (aqueous environment and pH ~7) [1,3].

Furthermore, the charge, size, surface chemistry, and both coulombic and steric repulsions of particles are very important variables which are involved in the colloidal stability of IOMNP dispersion [3,13,19,25]. Sometimes, IOMNPs should be protected (encapsulated, coat, or dispersed) with biocompatible polymer(s) in order to avoid aggregation, biodegradation, and alterations from the original structure [3]. This strategy can also enable entrapping the bioactive agent on the particle via adsorption or covalent attachment [3]. Moreover, dynamic assemblies are also possible due to the assistance of surface ligands [11,54].

IOMNP biocompatibility and toxicity are dependent on the nature of the magnetically responsive components of particles. Moreover, iron-oxide nanoparticles such as magnetite (Fe_3O_4) or its oxidized form maghemite (γ-Fe_2O_3) are the most utilized [1]. They must be made of a non-immunogenic and non-toxic material, with size of particle small enough to stay in the circulation after administration and to pass through the thin capillaries of tissues and organs, in order to avoid vessel embolism [1]. Moreover, IOMNPs must show a high magnetization in order to be controlled in the blood and be immobilized just close to the targeted tissue by a magnetic field [1,13].

Size and surface functionality are the two major factors that play an important role for the pharmaceutical applications of IOMNPs [11]. Even without targeting surface ligands, their diameters greatly affect in vivo biodistribution [25]. Nanoparticles displaying diameter greater than 200 nm can easily be cleared by the reticuloendothelial system. However, particles sizing less than 8 nm can easily be excreted from the body through existent pores of the kidney's basal lamina [6], reducing their blood-circulating time. The diameter range of 10–40 nm (including ultra-small IOMNPs) is fundamental for prolonged blood circulation, allowing the nanoparticles to cross capillary walls and often be phagocytized by macrophages trafficking to the lymph nodes and bone marrow [1]. Therefore, the size of IOMNPs enables their lower sedimentation, higher effective surface area (mainly for particles sizing less than 100 nm), and improved tissular diffusion [1,3,13,55].

Furthermore, hydrophobic and negatively charged nanoparticles tend to suffer proteic opsonization and are quickly recognized by phagocytic cells [55], resulting in faster clearance. The success of an IOMNP-based nanosystem is also directly related to the properties of the coating material and the IOMNP limitations can normally be overcome using a suitable surface coating [6,55]. Natural and synthetic polymers, surfactants, gold, silica, and peptides were proposed as coating materials for

IOMNPs [6,25]. Nature, spatial configuration, and shape of the coating play an important role in system performance [6,55].

4. IOMNP Assemblies and Clusters

Over the past two decades, scientists investigated the assembly of nanoparticles to create smart materials for applications in pharmacy [11]. Using nanoarchitectonics, designed nanoparticles can show the ability to change their properties according to the environmental conditions. They can respond to different stimuli from either endogenous (e.g., pH, redox, enzyme) or external (e.g., temperature, light ultrasound and/or magnetic field) sources [56].

The use of IOMNPs in pharmaceutical applications requires their contact with biological fluids (e.g., blood, serum, lymphatic fluid, etc.). Therefore, this contact and their interactions with components of the biological system can adsorb proteins in some degree, resulting in aggregates. As a consequence, a new structure is formed displaying different characteristics (size, aggregation state, interfacial properties, etc.) from individual IOMNPs, affecting IOMNP interaction with cells [57]. Therefore, the formation of clusters and assemblies of IOMNPs can result in structures with physical and chemical properties different from individual nanoparticles and their bulk aggregates, and they can be useful for pharmaceutical applications [11].

In particular, dynamic IOMNP assembly is a type of nanoarchitectonics based on ligand-assisted functional achievement, constituting a strategy to build high-precision materials. IOMNPs can be employed as a substrate to construct responsive assemblies or clusters under the assistance of suitable ligands. In this context, IOMNPs can be utilized as magnetic-force-guided targeting for drug delivery systems due to their magnetic properties [4,58].

Considering their pharmaceutical applications, IOMNPs and their clusters and assemblies must show colloidal stability and biocompatibility in various biological environments [3,12,13,16]. Small molecules, biomacromolecules, and polymers can be utilized as ligands to mediate IOMNP assemblies [7,9,57]. However, small-molecular ligands generally show low stability and biocompatibility, and it is hard to find a small-molecular ligand [11,59].

Polymers are very useful to obtain IOMNP assemblies, and they often can contribute to obtaining smart systems with improved pharmacokinetics with long circulation times, targeting, and controlled release [60].

In this context, the use of stimuli-responsive polymers as ligands to obtain IOMNP assemblies is a good strategy. Temperature-, light-, and pH-sensitive polymers are often used. Considering the biological environment, the pharmaceutical applications generally occur in aqueous medium. IOMNPs show affinity to water; however, the structural alteration of water around interfaces and solutes can increase the intermolecular interactions (hydrophobic interactions) conducing to the assembly [11].

Many types of biomacromolecules can also be utilized to for assembling nanoparticles, such as peptides, polysaccharides (chitosan and dextran), nucleic acids, and proteins. The nanoparticle assemblies using proteins can be based on the modification of substrates on the nanoparticle surface. A protein has multiple binding domains, which can be used for nanoparticle aggregation via crosslinking the corresponding substrates or via binding between antibodies and antigens [11,59].

Table 2 shows a list of ligands utilized for IOMNP assemblies and cluster formation. In addition, clusters of IOMNPs were obtained using silica [61]. Nanochains and nanobundles were fabricated via the simultaneous magnetic assembly of superparamagnetic nanoparticle clusters using an additional layer of ligand (deposited silica) using a sol–gel process. The investigators observed that this magnetically responsive superparamagnetic could lead to applications in the treatment of cancer.

Bioengineered spider silk was used as a ligand for the assembly of IOMNPs. Due to its mechanical properties, biocompatibility, and biodegradability, spider silk enables the fabrication of composite spheres, which can be potentially applied for the therapy of cancer by combined treatment via drug delivery and hyperthermia [62].

Investigations about IOMNP assemblies are based on fundamentals, design, and fabrication. However, the development of several applications of these smart systems is only at the basic stage and their real application to clinical trials is dependent on more studies [11].

Table 2. Examples of biomacromolecules and polymers used as ligands for assembly of iron-oxide magnetic nanoparticles (IOMNPs).

Classification	Ligands	References
Small molecules	Silica	[59,63]
	Dextran	[57]
Biomacromolecules	CXCR4-targeted peptide	[64]
	Biotin–streptavidin	[65]
	Tyrosine kinase and phosphatase	[66]
	Bovine serum albumin	[67]
	Spider silk	[62]
	Nucleic acids	[11]
Polymers	PEG-p(API-Asp)-p(DOPAAsp)-Ce6	[68]
	PVP	[69]
	p(MMA-co-DMA)	[70]
	p(NIPAM-co-AA)	[62]
	VCL-AAEM-VIm	[71]
	PMAA, PNIPAM	[72]
	PHOS-FOL-DOX	[73]
	Poly(allylamine)	[74]
	β-cyclodextrin	[75]
	DMSA, chitosan, PEG, PLGA, PEG-derived phosphine oxide (PO-PEG), PMAO (poly (maleic anhydride-alt-1-octadecene)),	[22,57,76]
	PEG–maleic anhydride	[67]
	PEG–poly(ε-caprolactone)	[77]

CXCR4 = C-X-C chemokine receptor type 4; PEG-p(API-Asp)-p(DOPAAsp)-Ce6 = Poly(ethylene glycol)-poly[1-(3-aminopropyl)imidazole –Aspartate]-poly(Dopamine-Aspartate)-Chlorine6; PVP = Polyvinylpyrrolidone; p(MMA-co-DMA) = Poly(methyl methacrylate-co-dimethylacrylate); p(NIPAM-co-AA) = Poly(N-isopropylacrylamide-co-acrylic acid); VCL-AAEM-VIm = poly(N-vinylcaprolactam-co-acetoacetoxyethyl methacrylate-co-N-vinylimidazole); PMAA = Poly(methacrylic acid); PNIPAM = Poly(N-isopropylacrylamide); PHOS-FOL-DOX = Triblock copolymer [cis-5-norbornene-6-(diethoxyphosphoryl)hexanote]-[norbornene grafted poly(ethyleneglycol)-folate]-[norbornene derived doxorubicin]; DMSA = Dimercaptosuccinic acid; PLGA = poly(lactic-co-glycolic acid).

5. Pharmaceutical Applications

IOMNPs can be used for pharmaceutical applications [1], and the advances in magnetic resonance imaging (MRI), cell separation and detection, tissue repair, magnetic hyperthermia, and drug delivery strongly benefited from employing IOMNPs [11]. These nanoparticles possess very important characteristics, such as superparamagnetism, size, and the possibility of receiving a biocompatible coating. Therefore, ongoing researches are focused on reducing drug concentration, toxicity, and other side effects, and improving the therapy [6,18,21,32].

The pharmaceutical applications of IOMNPs can be classified according to their application inside or outside the body. For external applications, the main use of these nanoparticles is in diagnostic separation, selection, and magnetorelaxometry [1,32]. In this context, they can be administered

in a patient for diagnostic applications (nuclear magnetic resonance or magnetic particle imaging), drug delivery, hyperthermia, or as an antimicrobial [1,3,21,78].

5.1. Diagnostic Applications

Magneto-pharmaceuticals are a new class of preparations utilized for clinical diagnosis using the NMR imaging technique. In magnetic resonance imaging (MRI), these formulations must be administered to the patient in order to enhance the image contrast between the normal and diseased tissue and/or indicate the status of organ functions or blood flow [1,32].

Magnetic particle imaging (MPI) is a new, non-invasive, whole-body imaging technique that can detect superparamagnetic iron-oxide nanoparticles similar to those used in MRI. Based on tracer "hot spot" detection instead of providing contrast on MRI scans, MPI is truly quantitative. Without the presence of an endogenous background signal, MPI can also be used in certain tissues where the endogenous MRI signal is too low to provide contrast. Its applications include MPI cell tracking, multiplexed MPI, perfusion and tumor MPI, lung MPI, and functional MPI [8,18].

5.2. Drug Delivery

The research and development of therapeutic drug delivery systems increased with the development of new materials and technologies. The development of biotechnology and the understanding of physiological mechanisms also allowed obtaining more specialized pharmaceutical systems. Therefore, the number of strategies for the development of drug delivery systems showing enhanced properties in relation to modifying and controlling the delivery of active agents increased [32,79].

In this context, nanotechnology is utilized as one of the most common strategies for controlling the drug delivery, and increasing the efficiency, safety, and quality of the systems. Moreover, patient therapy is improved as well.

IOMNPs can be used for controlling the drug delivery [1,6,32,78] and they can enable drug targeting, one of the most important strategies [79]. The application of an external magnetic field together with these nanoparticles and/or magnetizable implants allows the delivery of particles to the desired site, fixing them at the target tissue while the active agent is released, and acting locally (magnetic drug targeting) [32]. This strategy can eliminate side effects and reduce the dosage required.

In this context, IOMNPs are undergoing trials to investigate the possibility that they can be implemented as drug carriers. As the properties of these nanoparticles and the success in delivering active agents are strongly dependent on the composition of the external coating, polymeric layers, capsules, particles, or vesicles were proposed [32]. The modifications of the surface of these particles are generally accomplished using organic polymers and inorganic metals or oxides to make them biocompatible and suitable for further functionalization via the attachment of various bioactive molecules [78].

However, several important criteria should be considered in order for the drug delivery system containing IOMNPs to be effective. The delivery system should be easily dispersed in aqueous media and also provide functional groups, which can be further modified in order to control the drug release or bind targeting units [6,32].

Nanostructured systems composed of a core–shell design are much utilized to attach different drugs to IOMNPs. The core is formed by nanoparticles and the shell represents the surface coating for nanoparticle functionalization. This strategy can improve the system stability, pharmacokinetics, biodistribution, and biocompatibility [6,80].

Synthetic and natural polymers are the most common surface coating used in IOMNPs, due to their capacity to prevent oxidation and confer stability to the nanoparticles. Polyethylene glycol (PEG), poly(vinylpyrrolidone) (PVP), polyvinyl alcohol (PVA), poly(lactic-*co*-glycolic acid) (PLGA), and chitosan are utilized [17,30,32].

PEG is hydrophilic, uncharged, and biocompatible, and it was utilized for coating the IOMNPs due to non-fouling properties and reduced blood protein opsonization. As a result, the nanoparticles

can escape recognition by the immune system, increasing their time in blood circulation and their accumulation in the target cells/tissue [32,79].

PVP and PVA are also water-soluble synthetic polymers, widely used in pharmaceutical applications. Their emulsifying and adhesive properties enable the preparation of hydrogel structures. The hydrogen bonds between the polymer chains can involve the IOMNPs avoiding the agglomeration of nanoparticles [6,29].

A copolymer of polylactic acid and polyglycolic acid (PGA) displayed great potential for use in drug delivery systems [79]. This polymer presents solubility in most of the common solvents and can take different shapes and sizes, enabling the encapsulation of several types of molecules [6]. PLGA microparticles containing co-encapsulated dexamethasone acetate and IOMNPs were developed as one strategy to maintain the particles in the joint cavity via an external magnetic field, controlling the drug release for the treatment of arthritis and osteoarthritis [81].

Chitosan is a natural, biocompatible, biodegradable, and low-toxicity material obtained by chitin deacetylation. Its long chain, generated via the combination of 2-amino-2-deoxy-β-D-glucan with glycosidic linkages, results in a positive charge, driving the systems to the cell membrane which is negatively charged [22]. Therefore, chitosan-coated IOMNPs can display mucoadhesive properties and increase the nanoparticle retention in the target sites [6,82]. The thermal and magnetic properties of IOMNPs are not changed by chitosan coating and, therefore, several systems were developed [6,17]. Chitosan of low molecular weight can protect these nanoparticles from aggregation due to the electrostatic repulsion between the positively charged nanoparticles [83]. However, this polymer shows some limitations as a coating material, due to the partial protonation of its amino groups in water at physiological pH, which reduces chitosan solubility. Chemical changes in chitosan can overcome these problems, making chitosan derivatives more water-soluble [84,85].

IOMNPs can also receive organic surfactants, inorganic compounds, and bioactive molecules on its surface. Organic surfactants are utilized for the functionalization of IOMNPs, mainly when synthesized in organic solutions. Dimercaptosuccinic acid can result in nanoparticles with an anionic surface, avoiding opsonization and clearance by the reticuloendothelial system, reducing the cell toxicity [6]. Oleic acid and trisodium citrate are also capable of stabilizing nanoparticles by creating repulsive forces (mainly steric repulsion) to balance the magnetic and van der Waals attractive forces [86]. Considering that the long hydrocarbon chains of the surfactants can result in hydrophobic nanoparticles, surfactants showing lower values of critical micelle concentrations were used in order to obtain more efficient coatings of the IOMNPs, with improved dispersion capacity in solutions and lower nanoparticle clustering [87].

Inorganic compounds such as carbon, metals, silica, oxides (metal and non-metal), and sulfides were used in IOMNP systems, displaying the advantage of increasing the antioxidant properties of these nanoparticles [1,3,6,37]. SiO_2 can enhance the IOMNP dispersion in solutions, making them more stable and protected in acidic medium [37]. Carbon-based coatings show chemical and thermal stability, good electrical conductivity, and solubility, and they serve as a barrier against IOMNP oxidation [6]. Moreover, the electron transfer between silver and IOMNPs in a nanosystem creates a positively charged silver coating, allowing the conjugation of different antibiotics to the silver-decorated nanoparticles [88]. The use of metal coatings with modifications involving compounds such as thiol can enable their linkage with diverse biomolecules; oxides and sulfides are common in IOMNPs to stabilize the nanosystem and enable good magnetic properties [6].

Considering that the choice of a coating for the IOMNPs must take into account their intrinsic properties and the purpose of the system, ZnO was considered as the most appropriate compound for an anticancer nanosystem due to both its intrinsic anticancer properties and biocompatibility [89].

Peptides, lipids, and proteins are examples of bioactive molecules that can be used in IOMNP-based systems. They should be able to maintain the stability of the nanoparticles and the magnetic properties as well [6]. Human and bovine serum albumin (HSA and BSA) can be attached to IOMNPs via desolvation [90]. IOMNPs coated with BSA show a negatively charged surface that avoids electrostatic

interactions with negative biological elements such as plasma and blood cells, thereby maintaining the stability of nanoparticles [91].

As IOMNPs show a greater reactive area than their micrometric counterparts and can cross biological barriers, their use in drug delivery systems is advantageous. Thus, different classes of drugs can be directly bound to these nanoparticles or to core–shell systems [6]. The binding occurs via adsorption, dispersion in the polymer matrix, encapsulation in the nucleus, electrostatic interactions, and/or covalent attachment to the surface, with the aim of improving their pharmacological properties [1,6,12,78]. In this context, IOMNPs were used as carriers of anticancer (e.g., doxorubicin, cetuximab, cytarabine, daunomycin, docetaxel, epirubicin, 5-fluorouracil, gemcitabine, methotrexate, mitoxantrone, paclitaxel, and carmustine), alternative (curcumin, hypericin, propolis, berberine, sanazole, and essential oils), immunosuppressive (e.g., mycophenolate mofetil), anticonvulsant (e.g., phenytoin and 3-mercaptopropionic acid), anti-inflammatory (e.g., ketoprofen, furan-functionalized dexamethasone peptide, and prednisolone), antibiotic (e.g., streptomycin, rifamycin, anthracycline, fluoroquinolone, tetracycline, cephalosporin rifampicin, doxycycline, cefotaxime, ceftriaxone, amikacin, amoxicillin, bacitracin, cefotaxime, erythromycin, gentamicin, kanamycin, neomycin, penicillin, polymyxin, streptomycin, and vancomycin), and antifungal (e.g., nystatin, ketoconazole, amphotericin B) agents [6,92].

5.3. Hyperthermia

When IOMNPs are subjected to an altering current (AC), the magnetic field randomly flips the magnetization direction between the parallel and antiparallel orientations [1,6,29,32]. Magnetic energy can be transmitted to the nanoparticles in the form of heat, and this property can be used in vivo to raise the temperature of tumor tissues. Pathological cells are more sensitive to hyperthermia than healthy ones, leading to their destruction [1,6]. Magnetite cationic liposomal particles and dextran-coated magnetite were shown to be effective for the treatment of tumor cells by hyperthermia [1,16,28].

This strategy is very advantageous due to the magnetic hyperthermia heating the restricted tumor area. In addition, the use of nanometer-size particles (subdomain magnetic particles) is better than using micron-sized particles (multidomain) due to nanoparticles absorbing much more power at tolerable AC magnetic fields [6,32]. Therefore, well-defined synthetic routes are necessary to obtain particles displaying suitable size and shape and, as a consequence, to obtain a rigorous control in temperature [1].

5.4. Antimicrobial Activity

The World Health Organization (WHO) suggested in 1993 some drug use indicators to ease the investigation on drug-prescribing patterns [93]. It would help promote rational drug use, mainly looking to avoid bacterial resistance [94].

However, we saw an over-prescription of antimicrobial medicines during the last three decades; this, together with the global public health concerns regarding bacterial resistance to conventional drugs, shows how fundamental it is to try different types of treatments.

Antimicrobial resistance is an old and huge concern for public health systems, having grown rapidly in recent times, spreading the preoccupation to economics [92,95–97]. The use of gold, silver, aluminum, and iron oxide as antimicrobials was previously proven [29,98–102].

Nanomaterials can show antimicrobial activity via cell membrane damage, releasing toxic metals (which can react with proteins, leading to a loss in protein), and damaging DNA, RNA, and proteins via reactive oxygen species generation. These mechanisms conduce to inhibition or killing of the microorganisms [103].

Therefore, IOMNPs stand out as a possible choice to treat infectious diseases. The use of IOMNPs to oppose microorganism infection is quite relevant when thinking about this resistance. However, it may not overcome all kinds of bacterial resistance [97,104–108].

IOMNPs may act as actual antimicrobial agents, or even in a synergistic way with antimicrobial agents [29,98]. A dosage form containing IOMNPs synergically mixed with streptomycin was already developed; it was prepared in a chitosan-based structure. They performed a modified release from this system, enhancing the base activity of the streptomycin against methicillin-resistant *Staphylococcus aureus* (MRSA) [109]. Moreover, it was observed that a smaller size of the IOMNPs led to higher antimicrobial activity. Thus, it was observed that nanoparticles ranging from 10 to 80 nm in size could penetrate the *Escherichia coli* membrane and cause bacteria inactivation [16,98,110].

IOMNPs exhibit a number of advantages compared to conventional antimicrobial agents: they are less susceptible to bacterial resistance; they may be functionalized to several preferred targets or activities; they may be associated with natural or synthetic drugs; and it is possible to stimulate them with different sources such as heat, pH, magnetic field, light, etc. Nanoparticulate systems can also cross some barriers that the normally employed drugs cannot, such as the blood–brain barrier [16,108,111].

The use of IOMNPs as antimicrobial delivery systems against microorganisms located in different sites with difficult access is important. However, it is important to emphasize that most of the prepared IOMNPs show intrinsic antimicrobial activity without the addition of antibiotics [112].

Moreover, subcellular nanoparticle delivery is an important approach to justify the use of IOMNPs as antimicrobials. These nanoparticles show a high surface-area-to-volume ratio, which results into surfaces with very high free-energy content. In order to decrease this energy and become relatively stable, the surface interacts with possible interactomes present in the cell. The subcellular delivery involving the transfer of various drugs and bio-active molecules (e.g., proteins, peptides, DNAs) through the cell membrane into cells constitutes a very important strategy for antimicrobial applications as well [113].

Once IOMNPs enter the biological environment, they can adsorb surrounding biomolecules, conducing to the formation of a protein corona on the nanoparticle surface. The substances present in the environment where IOMNPs are located (e.g., proteins, metabolites, inorganic salts) and also the nanoparticle shape, size, chargeability, and surface modification can influence the formation of the protein corona [67]. Microorganisms can recognize the protein corona attached to the IOMNPs instead of the nanoparticles themselves. Thus, the destination of nanoparticles in the body and infected sites is dependent on the protein corona, which can also be fabricated by dynamic assemblies [11,77,80]. Protein crowns can determine the endocytosis or adsorption on cell/microorganism membranes, their circulation in the blood, or their maintenance in extracellular tissue for a long time [80,114].

The ability of IOMNPs to adsorb and penetrate into biofilms can be due to their physicochemical characteristics (hydrophobicity, surface charge, and high area ratio by volume) [6]. The antimicrobial activity of the agent erythromycin coupled to IOMNPs against bacterial cultures of *Streptococcus pneumoniae* was improved, and the bacterial viability was diminished in the presence of nanoparticles. Moreover, it was observed that IOMNPs helped erythromycin cross the capsule of the bacterium [115].

The bacteriocin nisin displays a wide spectrum of antimicrobial activity. However, it is commonly inefficient against Gram-negative bacteria. Targeted magnetic nisin-loaded nano-carriers (IOMNPs capped with citric, ascorbic, and gallic acids) were fabricated and tested to overcome the nisin resistance of bacteria. High pulsed electric and electromagnetic fields were applied, and Gram-positive *Bacillus subtilis* and Gram-negative *Escherichia coli* were utilized as cell models. This strategy increased the antimicrobial efficiency of nisin similar to electroporation or magnetic hyperthermia methods, and a synergistic treatment was also shown to be possible [116].

Some explanations for the IOMNP mechanism of action exist. One of them is clarified by the composition. IOMNPs are composed mainly by magnetite and maghemite, which have iron ions (Fe^{2+} and Fe^{3+}). These ions may cause the generation of reactive oxygen species (ROS), specifically superoxide (O^{2-}) and hydroxyl (−OH) or hydrogen peroxide (H_2O_2), or even singlet oxygen ($^1O_2$). These radicals may increase the ROS stress inside the microorganism's cells, leading to an inhibition of their growth and multiplication. ROS may damage the DNA in bacteria and also protein production [101,117,118].

A second possible mechanism is that the electrostatic energy of the nanoparticles could be used to bind them to proteins or to the cell membrane, leading to disruption of the essential functions, causing cell death [108,119–123].

Also, IOMNPs may act on the efflux pump of some microorganisms, acting as inhibitors to this pump that aids the cell to eliminate substances that may harm the organism; hence, it could even transport antimicrobial drugs to the outside, leading to a reduction in the drug efficacy [108]. Christena and collaborators prepared magnetic nanoparticles (MNPs) with casein, and they evaluated the inhibition property of the MNPs against the efflux pump of *Pseudomonas aeruginosa* and *Staphylococcus aureus* [124]. They showed that those MNPs were able really inhibit the activity of the efflux pump of those bacteria and, in this sense, would increase the activity of other antimicrobial drugs.

Interestingly, IOMNPs associated with propolis extract (PE) for an intraperiodontal pocket release were shown to be useful for the treatment of periodontal disease [29]. They showed that the incorporation of PE in the formulation containing IOMNPs increased the efficacy of the natural product against *Candida* spp., showing a great synergy between the PE and the IOMNPs.

An extract of *Argemone mexicana*, together with IOMNPs, was evaluated against *Escherichia coli*, *Proteus mirabilis*, and *Bacillus subtilis* [98]. They also stated a good interaction between the IOMNPs and the natural extract for antimicrobial activity.

Not only natural extracts were evaluated with IOMNPs against microorganisms. Maleki and collaborators functionalized IOMNPs with the antimicrobial peptide cecropin mellitin (CM) and evaluated them against *Staphylococcus aureus* and *E. coli* [125]. They also showed that this incorporation presented a synergic interaction.

In this context, IOMNPs can contribute to improving antimicrobial treatments by targeting specific and hard-to-reach sites where pathogens are harbored. Moreover, they can optimize physicochemical characteristics, enabling the clinical use of new antimicrobial agents, or their administration using more convenient routes [103].

5.5. Other Pharmaceutical Applications

Considering the characteristics of IOMNPs, they can also be utilized in the therapy of Alzheimer's disease. Magnetic Fe_3O_4 nanoparticles can interact with lysozyme amyloids in vitro, reducing the amyloid aggregates and promoting depolymerization. The proposed mechanism of the anti-aggregating action of these particles is based on the adsorption and adhesion of lysozyme molecules to the nanoparticles, decreasing the free lysozyme molecular concentration and hampering the nucleation process and fibrillogenesis [126]. However, further investigations are necessary to explore the detailed molecular mechanisms of the anti-amyloidogenic ability of the particles [32].

IOMNPs can deliver photosensitizers in photodynamic therapy (PDT) [32]. The combination of magnetic drug targeting and PDT can be accomplished using dextran coatings to prevent the nanoparticle aggregation and to allow for the linkage of hypericin. This strategy can increase the selectivity and reduce the side effects of PDT, as the therapy occurs only in the site where the IOMNPs are accumulated due to an external magnet, under the influence of a laser [127].

The integration of multiple moieties into a single nano-platform based on IOMNPs for diagnostic and treatment was also proposed. Additionally, IOMNPs can be used to integrate the diagnosis and therapy in one step. Currently, theranostic constitutes an important tendency in research [128]. Considering the unique magnetic properties of IOMNPs, they attracted great interest due to their use as MRI contrasting agents and for the therapy of tumors and other disorders. Cancer magnetic theranostics is attracting increasing interest and can provide a powerful strategy for cancer therapy. Theranostics based on IOMNPs enables tracking the theranostic agent's location, constantly controlling the therapeutic process, and evaluating the efficacy of the treatment [14]. Therefore, it is possible to improve the efficiency and functionality of the therapy [129].

6. Toxicity

Nanotoxicology refers to the study of the potentially harmful effects of nanomaterials on living organisms [21]. Nanoparticles can enter the human body through respiratory inhalation, dermal absorption, or via an oral route. They have nano size and can move across the olfactory mucosa, alveolar membrane, capillary endothelium, and the blood–brain barrier. Therefore, it is very important to understand the potential toxicity associated with IOMNPs, considering the range of surface modifications enabling functionalities of these nanoparticles [21,32,87]. In vitro and in vivo studies on IOMNP toxicity showed some conflicting results [6]. Changes in nanoparticle size and shape were reported as factors inherent to nanosystems able to influence their toxicity. Rod-shaped and nano-sized IOMNPs were shown to be more toxic than sphere-shaped and micrometric particles, respectively [130]. The configuration of the nanosystem can also influence IOMNP toxicity [6].

Furthermore, cell cytotoxicity and genotoxicity may be affected by the surface charge of IOMNPs. Positively charged nanoparticles were shown to be more toxic, because they may undergo nonspecific interactions and adsorptive endocytosis with the negatively charged cell membrane, thus increasing their intracellular accumulation and affecting cell membrane integrity [130]. The influence of other factors (e.g., concentration, form of administration, type of coating, and cell line) may explain the different results for toxicity of these nanoparticles, and they were properly revised in Reference [6].

The mechanisms of IOMNP toxicity for different cell lines are partially explained by the production of reactive oxygen species (ROS), which causes cellular oxidative stress [38,131]. When IOMNPs are taken up by cells via endocytosis, they tend to accumulate in the lysosomes and are degraded to iron ions. These ions would be able to pass through the membranes and reach regions such as the mitochondria and cell nucleus. There, they could react with hydrogen peroxide and oxygen, generating ROS [6].

Iron overload caused by exposure to IOMNPs can also conduce to serious deleterious effects and lead to cell death. Therefore, a high dose of IOMNPs could promote elevated lipid metabolism, breakage of iron homeostasis, and exacerbated loss of liver functions [6]. In contrast, magnetite (Fe_3O_4) was shown to increase the level of lipid peroxidation and decrease the antioxidant enzymes in human lung alveolar epithelial cells (A-549), displaying a concentration-dependent toxicity in vitro [132].

The strategy to coat the surface of IOMNPs is utilized to make these nanoparticles biocompatible and non-toxic, due to the lower number of oxidative sites, with consequently lower DNA damage [20]. To avoid the higher iron intracellular ROS production, coated IOMNPs using lauric acid, a protein corona of BSA, or dextran were developed and were shown to not promote genotoxic effects on human granulosa cells [133]. Polymers (e.g., PLGA) and essential oils (e.g., patchouli essential oil) were shown to reduce the toxic effects of IOMNPs [6].

Therefore, there is an increasing necessity to perform additional tests other than cell viability assays to increase the knowledge about the toxic effects of these IOMNPs.

7. Concluding Remarks

The use of IOMNPs in pharmaceutical areas increased in the last two decades. The uses of these nanoparticles are due to their excellent properties in terms of size, mechanical, optical, and magnetic properties, displaying great potential for pharmaceutical applications. Their surface can be functionalized with targeting ligands, as well as imaging and therapeutic moieties, enabling the development of multifunctional, multimodal nanoagents.

However, these nanoparticles should be stable and have a switchable magnetic state, independent of temperature fluctuations and considering the biological environment. The synthesis process selection should consider the reproducibility and scaling up without any complex purification procedure. Therefore, several synthesis methods were investigated using either organic or aqueous phases, and they are classified into physical, chemical, and biological approaches. Moreover, the synthesis of these nanoparticles into formulations is possible, aiming at the production of more stable, biocompatible, highly dispersible, shape- and size-controlled nanoparticles.

The protection (encapsulation, coating, or dispersion) of IOMNPs with biocompatible materials can avoid their aggregation, biodegradation, and alterations from the original state and also enable entrapping the bioactive agent on the particle via adsorption or covalent attachment. In this context, IOMNPs show great potential for use in nanostructured pharmaceutical systems for target drug delivery, improving the therapy as a consequence of a higher drug effect using lower concentrations, thus reducing side effects and toxicity. Different methodologies of synthesis allowed the preparation of IOMNPs displaying different structures, sizes, dispersions, and surface modifications. These advantages support the utilization of IOMNPs in pharmaceutical applications, and getting suitable drug release control on the target tissues could be beneficial in several clinical situations, such as infections, inflammations, and tumors. However, more toxicological clinical investigations about IOMNPs are necessary, considering their pharmaceutical applications.

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