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Iron Oxide Nanoparticles (IONPs): Synthesis, Surface Functionalization, and Targeting Drug Delivery Strategies: Mini-Review

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Iron oxide-based magnetic nanoparticles (IONPs) have received remarkable attention in a wide range of applications because of their unique physicochemical properties' inheritance to the nanoscale. Among these nanoparticles (NPs), superparamagnetic iron oxide nanoparticles (SPIONs), as powerful noninvasive NPs, are widely used in nanomedicine applications such as targeted drug/gene delivery, magnetic separation, cancer therapy, and magnetic resonance imaging (MRI) hyperthermia because of their superparamagnetic activity and remarkable small size. The synthesis of SPIONs and surface modification of these NPs for biological applications is an interesting research topic. These NPs have high magnetic susceptibility, a single magnetic domain, and a controlled magnetic behavior due to the SPION superparamagnetic feature. This review aims to explore the recently developed synthetic routes of SPIONs and show the best parameters to prepare SPIONs using pulsed laser ablation in liquid "PLAL" for biomedical applications. Furthermore, we highlight the properties, coating, and functionalization of SPIONs and their importance for biomedical applications, including targeted drug delivery and cancer therapy.

Keywords: Iron oxide NPs; laser ablation; nanoencapsulation; drug delivery; cancer treatment.

1. Introduction

Nanotechnology is a new field of science that works with particles and materials in a range of size from 1 nm to 100 nm.[1,2] Due to the increased molecular interaction, a particle of this size can facilitate simple adsorption, absorption, and penetration.[3,4] Nanotechnology spans a wide range of scientific and technological sectors, including biological, pharmaceutical, agriculture, chemical, physics, electronics, and information technology.[5,6] The physical and chemical features of nanoparticles (NPs) can be exploited in a variety of applications, ranging from

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industry to medicine.[7,8] Medical applications and biotechnological advances include the separation and detection of cells, tissue repair, drug delivery, magnetic hyperthermia, cancer treatment, magnetic resonance tomography, biosensors, and antimicrobial activities.[9,10] Iron oxide-based magnetic nanoparticles (IONPs) have received considerable attention in a wide range of applications because of their unique physicochemical properties inherent to the nanoscale.[11,12] These NPs have gained significant benefits due to their unique characteristics, such as superparamagnetic and small size,[9,13] biocompatibility, biodegradability,[14,15] nontoxic, efficiently cleared from the human body through iron metabolism pathways,[16,17] physicochemical properties, drug conjugation/release, scaled up syntheses, and hence, optimizing the overall parameters for effective medical performance.[18,19] Various methods are used to synthesize SPION such as pulsed laser ablation in liquid "PLAL", gas phase deposition, chemical co-precipitation, hydrothermal synthesis.[3,20]

Nontoxic SPIONs can be used as drug delivery by coating their surface and conjugating with the active molecules or chemotherapeutic drugs. The effect of surface coating and the size of magnetic NPs have a significant role in therapeutic and diagnostic factors.[16,21] Iron oxides are conjugated with many components and lead to increased usage. The experiment tries to fabricate the metal oxide NPs into biodegradable after achieving the goal by coating them with variable materials including decanoic acid, polyethylene glycol (PEG), lactic acid, and oleic acid, as shown in Fig. 1. This coating process prevents accumulation and increases colloidal dispersion.[3,22] In addition, the techniques that have been suggested for the fabrication of NP coatings are often cumbersome, time-consuming, and pricey. They also have poor yields and are unable to accommodate enormous productions. In conclusion, NPcoatings bring about a reduction in the typical magnetic moment of the material by include nonmagnetic components in the final NPs.[23] Therefore, even if NPcoating turns out to be an essential prerequisite for the applicability of iron oxide nanomaterials in a wide variety of fields, the disadvantages associated with the coating methods that are currently in use severely restrict the potential applications for these NPs.[24] It is anticipated that future discoveries will center on hybrid materials such as iron oxide nanocomposites with graphene, carbon dots, or core-shell architectures with noble metals. One example of such a material is graphene.[25] These designed nanomaterials offer special potential for the construction of biomedical devices, nanocarriers for drug delivery systems, immunoassays, and of course, biosensors. Specifically, these nanomaterials hold great promise for the fabrication of biomedical devices. Iron NPs are not only providing fresh viewpoints on highly sensitive bioaffinity and biocatalytic assays, but also presenting novel strategies for the design of highly selective applications. One example of this is the discovery that iron NPs can be used to selectively target specific proteins.

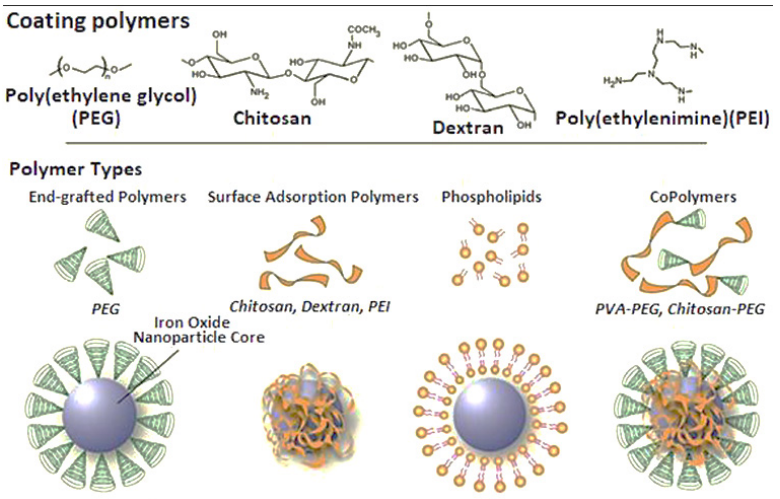

Fig. 1. Different kinds of coating polymers and copolymers are depicted in novel drug carrier systems.

Recent years of biomedical research have shown that magnetic NPs have the potential to be a useful tool for a variety of applications *in vitro* and *in vivo*. In the field of medicine, several strategies for diagnosis and treatment were researched, and these strategies provided a wide range of potential uses. Methods of special clinical importance include magnetic cell separation, magnetic resonance imaging (MRI), magnetically targeted administration of medicines, and magnetically induced hyperthermia.[26] It is the utmost importance that these particles do not have any toxic effects or are incompatible with biological organisms in order for them to be used in medical applications, particularly those that take place in living organisms. Investigations on particles that are relevant led to the development of a variety of microstructures and nanostructures with distinct variations in their surface chemistry, sizes, and materials. In the meanwhile, magnetic NPs are utilized in commercial applications as contrast agents for MRI scans and as separation tools for the monitoring of metastatic cancer cells in blood after the administration of systemic chemotherapy.[27] Investigation is still being done on the possibility of using magnetic NPs as a medicine delivery method and for inducing hyperthermia. When compared to traditional drug delivery systems, the use of magnetic NPs as drug carriers offers the significant benefit of a more targeted delivery of the system to the tissue of interest through the application of an external magnetic field. This is a significant improvement over traditional drug delivery methods. Endovascular delivery of nanomagnetic material is possible, making it possible to access even physiologically delicate and difficult to reach tissue. In addition to this, the drug carrier is able to penetrate tissue via the capillary system.[28]

This review presents the different important features of IONPs, such as size, magnetic properties, biocompatibility, and toxicity. In our work, we focus on the synthesis of SPIONs by PLAL because it is the best and most environmentally friendly method to produce an NP in a pure solvent without any additives that can contaminate their surface. In addition, it has low cost and a fast process. Finally, in our review, we talk about NPs surface coating and functionalization, which are considered excellent strategies for the biological applications in drug delivery, especially in cancer therapy.

2. IONPs Properties

IONPs such as hematite (α-Fe_2O_3) and magnetite (Fe_3O_4) are commonly used NPs for medical applications.[29,30] There are several reasons why cobalt and nickel are not suitable for use in biomedical applications, including the fact that they are easily oxidized and may be toxic.[30,31] Magnetite is also called black iron oxide, and is considered the most magnetic of any transitional metal oxide. While, hematite is known as ferric oxide and has a red color, as shown in Fig. 2.[32] In addition, it is weakly ferromagnetic at room temperature.[3]

2.1. *Size and magnetic properties*

Magnetite NPs (Fe_3O_4) display distinct magnetic characteristics that depend on their size. The bulk magnetite has a Curie temperature of 858 K and a multidomain magnetic structure, indicating ferrimagnetic. The coercivity of magnetite particles is maximum when the particle size is reduced to less than 100 nm, at which point the particles form a single domain. When the particle size of magnetite NPs is less than 20 nm, the magnetization of the NPs is randomized by thermal energy, resulting in the particles being highly magnetic. When a particle becomes superparamagnetic, it is said to have reached the blocking temperature (T_B), which may be calculated as $T_B = \mathrm{KV}/25\ k_b$, K is the magnetic anisotropy constant, k_b is the Boltzmann constant, V is the volume of NP.[33] It is important to the surface change of SPIONs to increase the colloidal stability. It is possible to modify SPIONS by coating them with a biocompatible hydrophilic polymer or polysaccharides.[34,35] In particular, superparamagnetism, which implies that the particles do not exhibit magnetic properties unless they are in the presence of an external magnetic field, is what makes SPIONs so intriguing. The fact that they

(a) (b)

Fig. 2. Hematite (α-Fe_2O_3) and magnetite (Fe_3O_4) powder.

behave in this way helps inhibit coagulation, which reduces the likelihood of agglomeration *in vitro* compared to other MNPs.[36] The structure of the magnetic domain is responsible for the relationship between magnetic behavior and size. After reaching a certain size threshold (usually 20 nm), the ferrimagnetic material is reduced to a single domain, which is characterized by uniform magnetism throughout the material. In the case of spinel ferrite NPs, ferrimagnetic behavior is observed, which means that the material is divided into magnetic domains, each of which is composed of antiparallel magnetic moments of many magnitudes, resulting in a net spontaneous magnetic moment. Spinel ferrite NPs exhibit ferrimagnetic behavior, in which the material is composed of magnetic domains, each of which is composed of antiparallel magnetic moments of different magnitudes. An applied magnetic field causes all of the magnetic moments of the domains to align with the magnetic field, leading to a very high net magnetic moment.[37] IONPs that have only one magnetic domain, such as these superparamagnetic oxides, display high magnetic susceptibility, which results in a stronger and faster magnetic reaction.[38] When it comes to NPs used in biomedicine, the impact of size of IONPs is also a key element to consider. The NP size should be less than (200 nm) to prevent rapid liver and spleen filtration and extend blood circulation time. On the other hand, particles of less than 10 nm size are more likely to be removed by renal clearance.[39,40] Urian *et al.* synthesized Fe_3O_4 NP coated with oleic acid of various sizes, and the results revealed Fe_3O_4 NPs with high crystallinity and spherical or polyhedral form, depending on the solvent used in the synthesis.[41]

2.2. *Biocompatibility*

In particular, magnetite (Fe_3O_4) NPs are widely applied due to their biocompatibility, high magnetic susceptibility, chemical stability, innocuousness, high saturation magnetization, and inexpensiveness. The evaluation of IONPs biocompatibility is necessary *in vivo* and *in vitro* before considering clinical applications. In another recent report, Temelie *et al.* investigated the biocompatibility of MNPs generated by using a turmeric-assisted process that was eco-friendly, simple, and unique. For the *in vitro* biocompatibility experiment, they employed normal fibroblasts (L929 cell line) and found no genotoxic effect or triggered cell death. The findings were confirmed by hemolysis analysis, which revealed no erythrocyte lysis. Their findings demonstrated that the generated MNPs are nontoxic and might be used in a variety of biological fields.[42] Chen *et al.* proved the biocompatibility and suitability of Fe_3O_4 NPs for biomedical application using some experiments such as *in vitro* cytotoxicity evaluation (MTT assays), hemolysis testing, micronucleus assay, determination of half-lethal dose using the MCF-7 cell line.[43]

2.3. *Toxicity*

In addition to physicochemical characteristics, contamination with poisonous elements, fibrous structure, high surface charge, and radical species formation,[44] there are numerous more important pathways for the cytotoxicity of NPs. SPIONs are very tiny particles that are comparable with biomolecules. Because of their tiny size, these molecules may be sequestered within numerous physiological systems, where they can interfere with the regular functioning of those systems. They have the potential to cross the blood–brain barrier, induce disruption of disruption of neuronal function, cross the nuclear membrane, and produce mutations.[45] The toxic effects of IONPs are often described as the formation of reactive oxygen species (ROS), which produce lipid peroxidation and disruption of the phospholipid bilayer membrane, ultimately leading to cell death. Due to their nanoscale size, IONPs are easily internalized by cells through the endocytosis process.[46] In both *in vitro* and *in vivo* studies, IONP-induced oxidative stress contributes significantly to the reported negative effects. Particle absorption and dissolution, as well as the release of free iron ions inside the catalytically active labile iron pool of the cell, have been hypothesized as possible mechanisms for this phenomenon. If IONPs are ingested by phagocytosis, they will be encapsulated inside a phagosome. These phagosomes can then merge with a lysosome, causing an acidic environment to destroy the contents of the lysosome. On the contrary, IONPs can dissolve and release free iron ions (Fe^{2+}).[47] Organelle membranes transport free iron ions by divalent metal transporter-1 (DMT1) into the cytosol,[46] where catalytically available iron can participate in the Fenton reaction and form ROS as shown in Fig. 3, an excess of which can ultimately cause DNA damage.[47] The

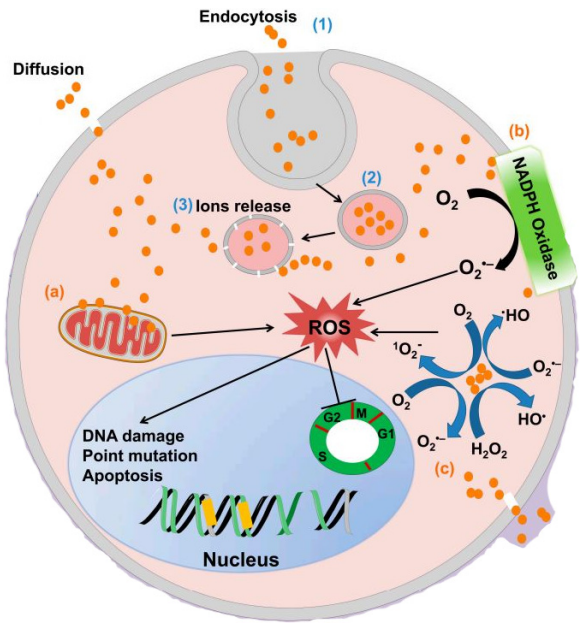

Fig. 3. The proposed mechanism behind the disruption of iron homeostasis disruption and subsequent adverse outcomes.

composition and properties of the SPION surface have a significant impact on the stability, dispersion, and biocompatibility of the SPION particles and their cellular cytotoxicity and uptake.[48]

3. Overall Prophase Research of Prepared IONPs by "PLAL"

In the last years, many studies appeared on IONPs by "PLAL" due to their benefit features, which will be explained later. The results of the research on the preparation of IONPs by "PLAL" summaries are given in Table 1.

4. Synthesis of IONPs by PLAL Technique

Over the last few decades, NP synthesis advanced at a breakneck pace. One of the most popular metals used to make NPs is iron. IONPs have been widely used for a variety of applications, particularly in the pharmaceutical and medical device industries.[57] There are many methods for preparing IONPs as a powder,[64] film,[65] and colloid for many applications such as multifunctional nanoscale devices in biological imaging, medical nanodiagnostics, and nanomedicine.[66] Common methods are PLAL, gas-phase deposition, chemical co-precipitation, hydrothermal synthesis, and sol–gel.[67,68] These methods have many positive and negative aspects, depending on size, shape, scalability, stability, production cost, and monodispersity. The co-precipitation method is fast and simple, but it produces NPs of different sizes and forms a waste stream that incorporates toxic substances.[69] PLAL, as shown in Fig. 4, is a promising top-down method to directly fabricate colloidal NP dispersions in an environmentally friendly manner.[70,71] The laser ablation method requires a short time. NPs can be obtained in a pure solvent, without additives that can contaminate their surface.[72,73] Furthermore, the "PLAL" has controlled temperature, pressure, and density. These conditions are not available in other methods.[57,74] Furthermore, IONPs produced by this method are distinguished by their high magnetic response, crystalline structures, rapidity, simplicity, and cost effectiveness, as well as the absence of the formation of by-products or chemical exposure that are harmful to the environment, as observed in conventional chemical processes.[1,57] The PLAL process, which is environmentally friendly, allows the production of metallic nanostructures without harmful chemicals or reagents. Cavitation bubbles are formed when a laser pulse interacts with a solid immersed in liquid, leading to the development of a plasma contained inside the bubble. NPs are formed within a bubble due to the rapid cooling of a high temperature laser-induced plasma, which occurs inside the bubble.[75] In addition to laser characteristics (such as flounce, spot size, and repetition rate), thermo-optical aspects of the target and the solvent environment are important considerations, with the ablation rate specified as a function of these factors.[76] The wavelength of the laser has a significant impact on the size and dispersity of the NPs. The increase in particle size is termed a decrease in wavelength.[77] When nanosecond laser pulses are utilized to synthesize vast amounts of NPs, the highest efficiency in the formation of NPs is found. When short (femto- and pico-second) pulses are employed, the productivity of the process may be greater at the beginning of the process than when nanosecond pulses are used; however, as the concentration of particles in the solution increases, the process efficiency reduces dramatically. This occurs as a result of the secondary interaction of laser radiation with particles in solution, which results in significant attenuation and scattering of the laser radiation.[78] Iwamoto *et al.* found that the use of poly (N-vinyl-2-pyrrolidone) (PVP) as a protective

Table 1. IONPs and their average size synthesis by "PLAL" methods with different parameters.

Author and year	NPs	Laser wavelength	Laser energy or fluence	Spot size	Liquid	Average size	(Refs.)
Liu *et al.* (2008)	FeO	1064 nm	80 mJ	2 mm	Poly (vinyl pyrrolidone) (PVP)	5–45 nm	49
Mollah *et al.* (2010)	IONPs, iron oxide nanowires	248 and 532 nm	120 mJ	—	water, ethanol, isopropanol, methanol, and glycol	Less than 100 nm	50
Amendola *et al.* (2011)	γ-Fe_2O_3, Fe_3O_4,Fe	1064 nm	5 J/cm^2	—	THF, DMF, DMSO, EtOH, AN, TOL	7–20 nm	51
Maneeratanasarn *et al.* (2012)	γ-Fe_2O_3	355 nm	1, 20, 40, 80 mJ	2 mm	Ethanol	8, 11–20, 11, 15 nm	52
Vahabzadeh *et al.* (2014)	Fe_3O_4, FeO	1064, 532 nm	3.5, 8 mJ	70, 800 μm	Water	7, 17 nm	53
Durdureanu *et al.* (2014)	γ-Fe_2O_3, FeO	1074 nm	1.1 J/cm^2	3 mm	citric acid	60 nm	54
Dadashia *et al.* (2015)	FeO, Fe	1064 nm	180 mJ	1 mm	water, acetone	27 and 30 nm	55
Svetlichnyi *et al.* (2017)	Fe_3O_4, Fe	1064 nm	150 mJ	—	Water	1–10 nm	56
Muniz *et al.* (2017)	Fe_3O_4/Ag	1064 nm	20 mJ	1 mm	Water	10–250 nm	57
Kurniawan *et al.* (2018)	ION	1064 nm	30 mJ	—	Water	5.3 nm	58
Svetlichnyi *et al.* (2019)	Fe_3O_4, α-Fe_2O_3, γ-Fe_2O_3, FeO, Fe	1064 nm	150 mJ	—	Water	2–80 nm	59
Rivera *et al.* (2020)	Fe_3O_4, α-Fe_2O_3, γ-Fe_2O_3	532 nm	90, 173, 279, 370 mJ	—	Water	25.868, 65.363, 42.176, 25.900 nm	60
Al-Kinani *et al.* (2021)	Fe@Au	532 nm	1.9, 2.2, 2.5 J/cm^2	1 mm	Water	66.14, 69.2, 77.88 nm	61
Adawiya *et al.* (2022)	Fe_3O_4@Au	532 nm	1.8, 2.3, 2.6 J/cm^2	1.5 mm	Water	52.37, 60.24, 72.45 nm	62
Bahjat *et al.* (2022)	Fe_2O_3/TiO_2	1064 nm	30, 60 mJ/cm^2	—	Water	170 nm	63

reagent dispersed large particles and that their dispersibility improved as the mole level of PVP increased and the crystalline sizes became smaller.[79] Liu *et al.* demonstrated that the higher the concentration of PVP solution used, the more stable the colloidal solutions that are produced. After being prepared, the colloidal solutions retain their stability without aggregation for many days.[49]

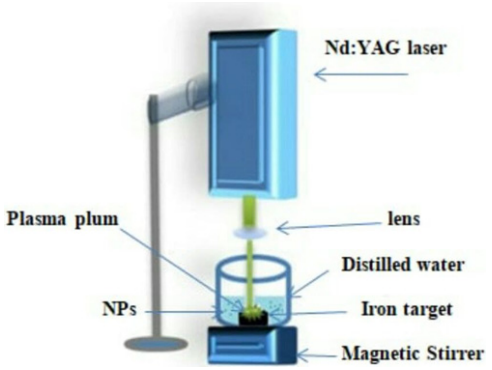

Fig. 4. Technique of PLAL.

5. SPION Coating and Functionalization

To conjugate organic or inorganic compounds on the surface of IONPs, the coating technique is the most widely used surface modification strategy.[80] Surface coatings are required to increase the colloidal stability of IONPs in a physiological environment, and these coatings are currently being developed. According to the literature, the primary goals of surface modification are enhanced NP dispersion, adjustment of surface activity, improvement of mechanical and physicochemical

characteristics, and increased biocompatibility of NPs.[80,81] These particles are very active at nanoscale sizes because the surface area-to-volume ratio is large and surface modification is required to keep the surface energy as low as possible while maintaining the requisite chemical stability.[82] As an added benefit, the coating prevents IONPs from aggregating, which might result in embolism. These NPs can be coated with different compounds, including amino acids, polymers, and fatty. The coating material may also impact the biodistribution of nanomaterials by influencing opsonization processes. For example, the ability of particular cells such as macrophages to trap IONPs, such as PEG, results in a longer period of period of period of period of blood circulation than citric acid.[83] The most commonly used polymers in the coating materials are as follows:

(1) Dextran

Dextran (DEX) is a polysaccharide possessing excellent water solubility and biocompatibility. The nonmagnetic shell effect that DEX has on the IONPs causes a reduction in their saturation magnetization. DEX also has a number of benefits, including lessens of IONPs cytotoxicity, therefore increasing their biocompatibility while also enhanced the nanocarrier efficiency, and affecting on the IONs properties, such as stability, crystallinity, magnetism and size. Due to its biodegradability, DEX is employed as a coating for nanocarriers used in the delivery of drugs, and it decreases the drug's toxicity and negative effects in the living body. It is distinguished by highly effective drug loading, simple to absorb and utilize and provides prolonged drug circulation in the blood and stable performance.[84,85]

(2) Chitosan

Chitosan is a polycationic biopolymer with wide biological applications due to its unique chemical nature, positive charge, presence of reactive hydroxyl, and amino group. Chitosan has excellent physiochemical properties such as biodegradable, biocompatible, and bioadhesive. Chitosan derivatives have increased tensile strength, swelling rate, water vapor permeability, and wettability of matrix. Synthesis of chitosan NPs via green engineering method is a major focus of modern nanotechnology research. Chitosan has several inherent properties such as wound healing potential, bactericidal, anticancer and fungicidal activity.[86]

(3) PVP

Polyvinylpyrrolidone, commonly called polyvidone or povidone, is a water-soluble polymer made from the monomer N-vinylpyrrolidone. Dry PVP is a light flaky hygroscopic powder and readily absorbs up to 40% of water by its weight. In solution, it has excellent wetting properties and readily forms films, which makes it good as a coating or an additive to coatings. It is used as an aid for increasing the solubility of drugs.[87]

(4) Polylactic glycolic acid

Polylactic glycolic acid (PLGA) has been among the most attractive polymeric candidates used to fabricate devices for drug delivery and tissue engineering applications. PLGA is biocompatible and biodegradable, exhibits a wide range of erosion times, has tunable mechanical properties and most importantly, is an FDA approved polymer. In particular, PLGA has been extensively studied for the development of devices for controlled delivery of small molecule drugs, proteins and other macromolecules in commercial use and in research.[88]

(5) Polyvinyl alcohol

Polyvinyl alcohol (PVA) is a vinyl polymer joined by only carbon–carbon linkages. It is water soluble, high biocompatibility, and biodegradable; hence, it is used to make water-soluble and biodegradable carriers, which may be useful in the manufacture of delivery systems. More interestingly, it is capable of self-cross-linking due to the high density of hydroxyl groups located on its side chains.[89]

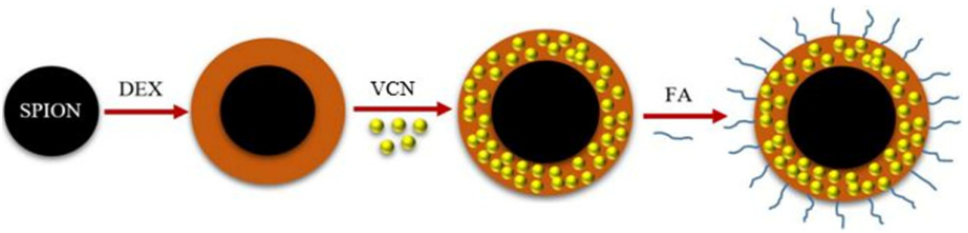

Fig. 5. The stages of the Fe_3O_4 nanoencapsulation process of the vincristine drug (VCN) and its folate functionalization.

Functionalized polymeric MNPs have a number of significant advantages over standard oral and intravenous drug administration modalities in terms of drug delivery.[90,91] NP interactions are influenced by the surface coating, as shown in Fig. 5, including its nature and structural organization, the surface coating controls the particle size and hydrodynamic parameters in the colloid.[31,92] Because every material has benefits and disadvantages, the choice of coating is largely governed by the intended application in terms of functionalization, stability, or size.[93] A targeted distribution with particle localization at a particular location is made possible by using a proper surface coating.[94]

6. Biomedical Applications of Fe_3O_4 Magnetic NPs

Over the last few decades, IONPs of various sizes have been synthesized and extensively studied for a variety of applications, especially biomedical applications including drug delivery, cell separation, MR imaging, cellular labeling, cancer therapy, tissue repair, etc.[95,96] The application of IONPs in biomedical applications is characterized by the way in which they coat the surface with different organic and inorganic coatings. IONPs can be encapsulated by proteins, surfactants, antibodies, nucleotide, drugs, etc.[97]

6.1. *Drug delivery*

Drug delivery technology is designed to improve drug release, absorption, circulation, and removal to enhance its efficacy, safety, and the convenience of the convenience of affected persons (Fig. 4). The idea of a drug delivery system (nanoencapsulation) has three elements: (i) the target material, (ii) the carrier, (iii) the curative drug.[98,99] Nanoencapsulation drugs are used for cancer treatment to avoid negative effects of chemotherapy by decreasing the distribution of drugs and decreasing the doses of cytotoxic substances.[100] It is possible to create a potent transport system for medications by conjugating MNPs. This transport system may even help reduce unwanted features of pharmaceuticals such as low solubility, toxicity, nonspecific delivery, and short circulation half-lives.[101] It has been shown that encapsulating the NP surface with polymers or conjugating the NPs with vector molecules can increase the selectivity of the drug in tumors while simultaneously decreasing systemic toxicity. This is effective in overcoming the drug resistance demonstrated by tumor cells.[102,103] These systems can deliver agents to the tumor location in a targeted manner, as shown in Fig. 6, which is advantageous. Such limited systems allow for the elimination of tumor cells while causing the least amount of damage to normal organs.[104] Khalkhali *et al.* prepared MNPs coated with DEX as a polymeric shell to load Curcumin (CU), an anticancer compound. The results revealed a high loading efficiency (13%) and a high encapsulation efficiency (95%). The results of an *in vitro* release study conducted in (PBS, pH = 7.4, 5.4) showed that the DEX coated MNPs exhibit sustained release behavior for at least four days, with a high degree of drug release in

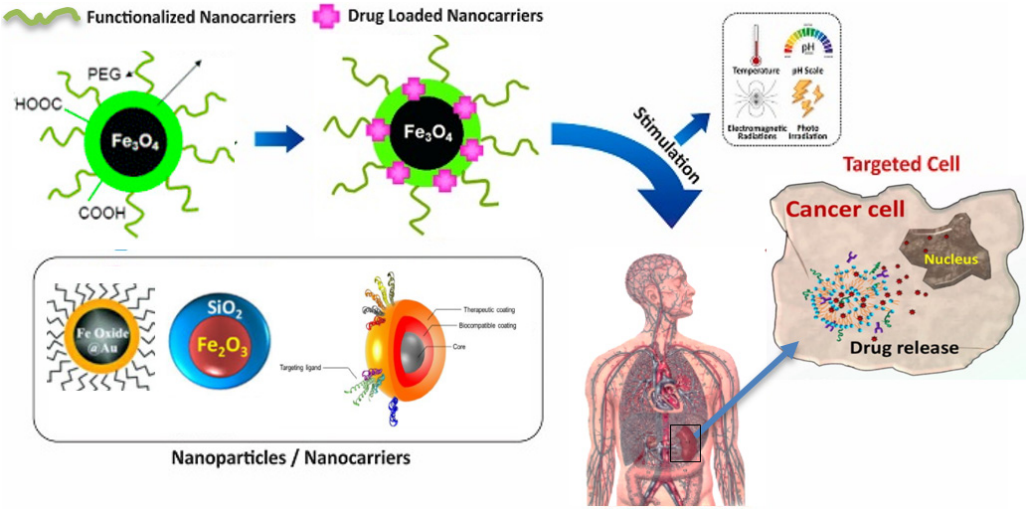

Fig. 6. Targeted drug delivery system.

acidic media.[105] Al-Musawi *et al.* synthesized superparamagnetic iron oxide nanoparticles (SPIONs) coated with Chitosan for loading of 5-fluorouracil (5-FU) anticancer, and folic acid was used as functionalized for targeted therapy of the bladder cancer. This nanosystem showed a significant cytotoxicity effect on the T24 cells cancer cells, while it has no significant cytotoxic effect on the human bladder epithelial cells HBlEpC normal cells.[106] Justin *et al.* constructed a core shell of IONPs coating with a biopolymer chitosan loaded with a CU anticancer were utilized for drug delivery into cervical cancer cell line-HeLa cells. The results showed IC 50 value of the CU loaded SPIONs against cancer HeLa cells was 30 μg/mL. These nanocarriers were able to release the drug after 6 h of incubation.[107]

6.2. *Cancer treatment*

Uncontrolled and uncoordinated cell division cell division results in cancer, which is a group of more than 100 diseases characterized by uncontrolled cell division. Cancer occurs when the primitive reproductive process loses its authority, producing harmful immature cells that invade and spread to other parts of the body, eventually entering the metastasis phase.[108] The fact that cancer is one of the most common causes of mortality throughout the world means that there is a continual desire for innovative solutions that may improve the efficacy of anticancer therapy. Targeted drug delivery systems are new applications in which the movement and distribution of a drug in the body are controlled and driven to specific locations where tumors are found; as a result, they are called targeted drug delivery systems.[109,110] The use of IONPs as a possible tool for the detection and eradication of cancer has the potential to bring about significant advances in the fields of nanomedicine and cancer treatment.[111] To be effective in tumor treatment, IONP must be administered to the tumor in sufficient quantities. This can be accomplished through one of two methods: (i) passive targeting, which involves the extravasation of IONP through the blood vessel irrigating the tumor and the enhanced permeability and retention (EPR) effect, or (ii) active targeting, which involves the binding of a ligand to IONP that specifically recognizes a cell receptor as shown in Fig. 7.[112,113] This type of ligand specifically binds to specific receptors in the target cells. The most investigated receptors include the transferrin receptor, folate receptor, glycoproteins, and epidermal growth factor receptor (EGFR).[114,115] For example, a highly selective tumor marker is the folate receptor, absent from normal tissues or inaccessible to circulating drugs due to its apical-polarized localization in normal endothelial cells. Although this receptor is completely accessible and overexpressed in many types of cancer cells, it is particularly prevalent in ovarian cancer and other malignancies of the brain, kidney, breast, and lung, which allows cancerous cells to efficiently capture folate, a form of water-soluble B vitamin that is required for growth and division,[116] magnetic drug targeting, which can be achieved if a drug delivery carrier has a strong magnetic moment and can be manipulated by a magnetic field.[117] Once effective targeting is

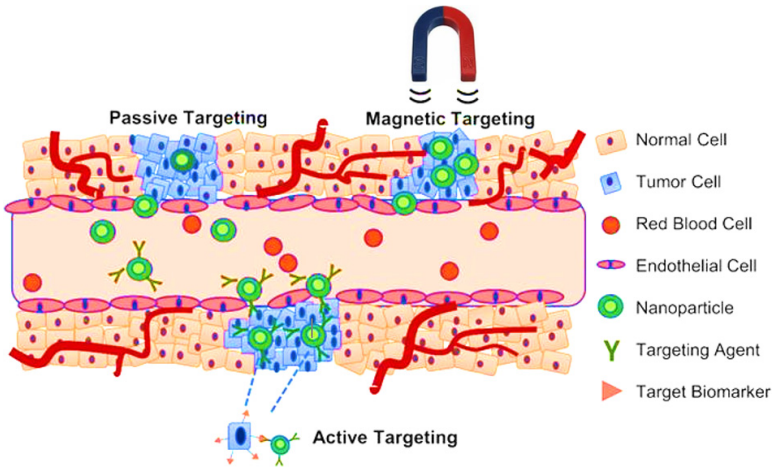

Fig. 7. NPs actively and passively target tumor cells.

Table 2. MNPs that have been used as nanoencapsulation for drug delivery to cancer treatment.

Author and year	NPs	Polymer Modification	Drug	Average size, nm	Cancer cell line	Conclusions	(Refs.)
Mangaiyarkarasi *et al.* (2016)	Fe_3O_4@LaF3:Ce3+	Chitosan	Paclitaxel (PTX)	19-37 nm	A549	The results from cell viability showed higher cytotoxic effect in A549 lung cancer cell lines compared with that of free PTX.	124
Situ *et al.* (2016)	SPION	Dextran (DEX), poly (lactic-co-glycolic acid) (PLGA) and micelle A54	Doxorubicin (DOX)	50 nm	BEL-7402	Effectively transported of the nanocarrier to the tumor tissue and has promising potential in special tumor targeting, efficient therapy for tumor.	125
Menon *et al.* (2017)	SPION	Chitosan and (PLGA)	—	289 ± 49 nm	A549, H460	The result confirmed that this nanocarrier demonstrated effective therapeutic efficacy by slowing tumor growth.	126
Feng *et al.* (2018)	SPION	PEG	-	10 nm	BALB/c mice	The nanocarrier showed strong cytotoxicity, high cellular uptake, fast clearance and low tumor distribution.	127
Albukhaty *et al.* (2020)	SPION	DEX	vinblastine (VBL)	74 ± 13 nm	PANC-1	The nanocarrier showed a sustainable release profile time and dose dependent targeted cancer cell cytotoxicity, and stronger inhibitory activity against tumor growth in PANC-1.	128
Mahdi *et al.* (2021)	SPION	DEX	5-fluorouracil (5-FU)	74 ± 13 nm	SNU-423	The nanocarrier exhibited high biocompatibility, controllability, penetrability, loading efficiency and inhibiting activity against tumor growth.	129
Al-Kinani *et al.* (2021)	Fe@Au	Chitosan (CS)	CU	63.65, 32.47, and 31.18 nm	T-47D	The results exhibited significant increases in amounts of apoptosis cause a decrease in T-47D cell viability and confirmed that the mean tumor size decrease in time until reach the negligible size.	61

Table 2. (*Continued*)

Author and year	NPs	Polymer Modification	Drug	Average size, nm	Cancer cell line	Conclusions	(Refs.)
Senturk *et al.* (2021)	SPION	PLGA-b-PEG	CU	5.6 ± 0.9 0.9 nm	GBM	Showed toxicity to T98G cells with cell viability less than 16%.The designed MNPs can release ~70% of their drug load during 72 h in a controlled manner.	130
Al-Musawi *et al.* (2021)	SPION@Au	Chitosan	DOX	102.6 ± 7 nm	SkBr3	*In vivo* data exhibited that the tumor development was significantly ($p < 0.01$) inhibited in the mice treated with this nanocarrier compared with those treated with free drug.	131
Adawiya *et al.* (2022)	Fe_3O_4@Au	Chitosan (CS)	CU	189.2 nm	MDA-MB-231	The nanocarrier has a noticeable enhancement effect in cell death and apoptosis induction compared to unloaded nanocarrier, and stimulates an increase in MDA-MB-231 cell death and leads to an 18.5% apoptosis rate.	62
Bahjat *et al.* (2022)	Fe_3O_4/TiO_2	—	DOX	170 nm	A549	The nanocarrier has higher cytotoxicity levels against lung cells (A549), as compared to the low cytotoxicity against normal cell line (WRL-68).	63

achieved, IONPs increase the value of medications in the treatment of cancer cells, allowing for a reduction in the total dose of the pharmaceuticals. Normally, malignant cells and bacteria have a net negative charge on their surface, but healthy cells do not. As a result of their interaction with pharmaceuticals (having a net surface positive charge), their growth rate can be reduced or hindered by being antiproliferative or cytotoxic, depending on the drug interaction and the dose level of the medication.[118] When subjected to an alternate magnetic field, IONs may be employed to generate local heat increase by converting electromagnetic energy into thermal energy. This procedure is known as magnetic hyperthermia therapy (MHT) in cancer treatment. It has the advantage of being highly effective in eradicating cancer cells since they cannot live in the temperature range of 42– 49°.[119,120] A second strategy for transporting and delivering drugs for cancer therapy is via PH-sensitive NPs. These NPs are integrated into the body through the process of endocytosis. The acidic environment of tumor tissue in comparison to normal tissue might cause the release of encapsulated/conjugated medicines from pH-sensitive nanocarriers when the pH of the tumor tissue is low. Due to cellular proliferation and angiogenesis (abnormal blood vessel formation), most solid tumors are characterized by hypoxia, which is characterized by a low oxygen concentration in solid tumors. In this case, the energy of the tumor cells is derived primarily from glycolysis, which makes the tumor microenvironment more acidic. Cancer cells have a high glycolysis rate, which is the fundamental cause of their low pH.[121,122]

The use of NP as a therapeutic target can increase treatment efficacy while decreasing systemic toxicity. To achieve passive targeting of NPs, it is necessary to take advantage of increased permeability and retention (EPR) effects. It uses cancer cells' enhanced vascular permeability and their impaired lymphatic outflow to allow NPs to target cancer cells passively. The interaction between the ligand and the receptor is what allows active targeting to take effect. Various cancer cell receptors have been identified, including the transferrin receptor, the folate receptor, the glycoprotein (such as lectin) and the EGFR.[123] The results on the research of employed nanoencapsulation for drug delivery to treatment cancer summaries are shown in Table 2.

6.3. *Fe_3O_4 NPs in agriculture*

In the last decade, efforts to use NPs in agriculture such as nanoformulations for efficient fertilization, nanosensors for early detection of stressors, or nanodevices for effective genetic manipulations have increased tremendously Iron-containing NPs. (iron oxides) are one of the most popular materials that have been proposed as potential fertilizers to treat iron-deficient soils. The low solubility of the iron ion (III) in soil limits iron uptake by plants, and therefore symptoms of iron deficiency occur in plants. This situation can also cause iron deficiency in animals and humans through nutrition.[132,133] Ghafariyan *et al.* examine the effect of SPION translocation and uptake in the soybean plant and change of chlorophyll in hydroponic environment. The result showed a translocation of SPIONs in soybean, and an increase in chlorophyll levels, without any toxic effect (Table 3). Furthermore, the result showed that the physicochemical properties of SPIONs had a significant impact on improving the chlorophyll content in the subapical leaves of soybean.[134] The NPs have a noticeable potential to transfer from one cell to another during plasmodesmata. In this pathway, the desmotubule, central rod and endoplasmic reticulum play an important role and contribute remarkably.[135]

Table 3. Studies representing the translocation of SPIONs in various plants.

Author and year	NPs	Average size	Plant	Translocation	Refs.
Ghafariyan *et al.* (2013)	SPIONs	18.9 nm	soybean	Yes	134
Ahmadov *et al.* (2014)	SPIONs	less than 50 nm.	elodea	Yes	136
Iannone *et al.* (2016)	SPIONs	10.9 ± 1.8 nm	wheat	Yes	137
Tombuloglu *et al.* (2018)	$MnFe_2O_4$	14.5 ± 0.5 nm	barley	Yes	138
Tombuloglu *et al.* (2019)	SPIONs	13 nm	barley	Yes	139
Al-Amri *et al.* (2020)	Fe_2O_3	20–40 nm	wheat	Yes	140
Tombuloglu *et al.* (2022)	Fe_3O_4, γ-Fe_2O_3	12, 14 nm	barley	Yes	141

7. Conclusions

This review sheds light on the importance of the SPIONs in biomedicine; we focused on the properties of these NPs, and we also shed light on the method that that that that that that generates them by PLAL as the best method to prepare nanoencapsulation use for tumor therapy. The application of NPs in the fields of biomedical engineering and agriculture has led to a new era of the development of novel drug, vehicles, which has the potential to revolutionize in the area of health care. The development of new drug delivery vehicles not only has reduced the payload of the drugs but has also improved the efficacy of the drug in the system due to improved biocompatibility and cytocompatibility along with increased circulation time. Thus, the advent of NPs has influenced all the spheres pertaining to medical biotechnology and biomedical engineering, improving and enhancing the already existing techniques along with the experimentation of new and advanced techniques for drug delivery and its monitoring.

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