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REVIEW



Magnetic iron oxide nanoparticles for drug delivery: applications and characteristics

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ABSTRACT

Introduction: For many years, the controlled delivery of therapeutic compounds has been a matter of great interest in the field of nanomedicine. Among the wide amount of drug nanocarriers, magnetic iron oxide nanoparticles (IONs) stand out from the crowd and constitute robust nanoplatforms since they can achieve high drug loading as well as targeting abilities stemming from their remarkable properties (magnetic and biological properties). These applications require precise design of the nanoparticles regarding several parameters which must be considered together in order to attain highest therapeutic efficacy.

Areas covered: This short review presents recent developments in the field of cancer targeted drug delivery using magnetic nanocarriers as drug delivery systems.

Expert opinion: The design of nanocarriers enabling efficient delivery of therapeutic compounds toward targeted locations is one of the major area of research in the targeted drug delivery field. By precisely shaping the structural properties of the iron oxide nanoparticles, drugs loaded onto the nanoparticles can be efficiently guided and selectively delivered toward targeted locations. With these goals in mind, special attention should be given to the pharmacokinetics and *in vivo* behavior of the developed nanocarriers.

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KEYWORDS

Magnetic iron oxide nanoparticles; targeted drug delivery; stimuli-responsive delivery; magnetically guided delivery; theranostics

1. Introduction

Over the past decades, nanotechnologies have emerged as new powerful tools in numerous technological applications. These applications have prompted increasing interest from researchers, which have produced outstanding results in the development of nanodevices and nanomaterials of different kinds (metal, oxide, semiconductors...). Among various types of nanomaterials that were investigated, magnetic iron oxide nanoparticles (IONs) have been widely studied due to their intrinsic magnetic properties (i.e. superparamagnetism) enabling them to be used in several scientific fields such as electronics or environment [1–4]. In addition to these remarkable magnetic properties, IONs biocompatibility, stability, and ecofriendliness have made them the ideal platform for biomedical applications [5]. Firstly, in the medical imaging field, iron oxide nanoparticles are known for their use as contrast agents (CAs) for magnetic resonance imaging (MRI). Some formulations (Resovist[®], Endorem[®]...) have been used previously in various clinical applications as T₂-weighted MRI CAs [6,7]. More recently, applications focusing on T₁-weighted MRI have been described and have given rise to promising results [8–12]. Besides their use for MRI, IONs also show great potential for applications with therapeutic purposes. They can be used to induce local heat enhancement when submitted to an alternative magnetic field, the so-called magnetic hyperthermia application. This property is particularly efficient for the elimination of cancer cells, which cannot survive in the temperature range of 42–49°C unlike healthy cells which are able to endure

such temperatures [13]. Other biomedical applications like tissue repair, cell labelling and magnetofection have also been described [14].

Beyond these applications, the delivery of therapeutic compounds by using IONs as carriers is a research field which has gained growing interest in the past years. Bounding or loading drugs onto iron oxide nanocarriers has proven to be an efficient way to improve the therapeutic effect of these drugs by taking advantage of the magnetic and biological properties of the IONs. Inappropriate properties (poor solubility, high toxicity, nonspecific delivery and short circulating half-lives) of most of the drugs can be overcome by their conjugation to iron oxide nanoparticles [15]. This ability to target specific sites can be triggered by two types of mechanisms called ‘passive targeting’ and ‘active targeting’. Passive targeting can occur via the ‘enhanced permeability and retention (EPR)’ effect. In the field of oncology, the growth of cancerous tumors is characterized by the development of leaky blood vessels, allowing the diffusion and the accumulation of IONs within the tumors. Even if this effect remains controversial and depends on the tumor type [16,17], such accumulation has been documented for various nanoparticles [18]. On the other hand, IONs can be actively targeted to the desired locations either by using an external magnetic field (magnetic targeting) [19] or by functionalizing their surface with vectors able to interact with given biomarkers.

IONs can be used in the field of drug delivery either as individual nanoparticles or as magnetic nanoassemblies, that is, nanoparticles encapsulated in macromolecular matrices. In

Article highlights

- IONs find applications in the biomedical field thanks to their magnetic and biocompatible properties making them powerful as, for example, contrast agents in MRI and drug delivery systems.
- Particle size and coating are two crucial parameters strongly impacting the behavior of the nanosystems in terms of therapeutic and/or diagnosis efficacy.
- Due to their strong magnetic properties, iron oxide nanoparticles can be guided by an external magnetic field toward targeted locations *in vivo* to enhance the delivery of therapeutic compounds in their site of action.
- Surface functionalization can be performed to render the drug release responsive to various stimulus such as temperature, redox state, or pH.
- Targeted drug delivery can also be attained by vectorizing the IONs with targeting agents able to specifically interact with disease markers.

This box summarizes key points contained in the article.

both cases, even if several ferrites have been recently described [20], the inorganic core is generally made of magnetite (Fe_3O_4) or maghemite ($\gamma\text{-Fe}_2\text{O}_3$) surrounded by an (in)organic coating [21]. For any of these types of applications, the properties of iron oxide nanoparticles strongly depend on their size and shape, these parameters being essential. Typically, biomedical applications require sizes (inorganic core) below 100 nm as well as narrow size distributions [22]. Particular attention must be devoted to the choice of the coating that must ensure the good stability and stealth of the nanoparticles in biological media. Besides, the coating can also be modified in such a way that the drug release become responsive to a stimulus (change in pH, temperature, or redox state) [23]. Finally, the drug release can be enhanced by the combination of the different properties abovementioned, for example, drug delivery combined with hyperthermia can work in a synergistic way toward optimum performance [24].

This review's aim is to cover recent applications of IONs for targeted drug delivery with a special emphasis on the delivery of chemotherapeutic compounds for cancer treatment considering the large amount of research done in that particular field. Design considerations and fabrication strategies for the development of magnetic nanocarriers based on IONs are discussed.

2. IONs preparation and surface modification

For biomedical applications, the most commonly used magnetic nanosystems are magnetite (Fe_3O_4) and maghemite ($\gamma\text{-Fe}_2\text{O}_3$) [25]. Various types of synthetic pathways leading to the formation of these types of iron oxides have thus been investigated. These synthetic processes can be either biological, physical, or chemical processes, each of which should all be optimized in order to obtain nanoparticles with the desired properties. Iron oxide nanoparticles prepared for the intended biomedical applications are mainly synthesized by chemical processes [26]. The chemical routes allowing the formation of iron oxide nanoparticles can be divided in two categories: the aqueous/hydrolytic routes and the non-aqueous/non-hydrolytic routes [27].

Among the hydrolytic routes, the coprecipitation method is known as the most conventional method for the synthesis of iron oxide nanoparticles. The coprecipitation process has several advantages over other methods, including its simplicity, its mild conditions, and its easy scale-up possibility [28]. Thanks to these advantages, the method has been widely used for the synthesis of Fe_3O_4 nanoparticles. Effectively, almost all the Food and Drug Administration (FDA) approved contrast agents for MRI, are obtained by this method. The method involves the simultaneous precipitation (coprecipitation) of ferric ions (Fe^{3+}) and ferrous ions (Fe^{2+}) in aqueous solution induced by a base, usually under inert atmosphere. Iron oxide nanoparticles obtained by this method are usually stabilized in basic or acidic media by a peptization process known as Massart's procedure [29] before further surface modification.

The thermal decomposition of an iron organometallic precursor at elevated temperatures in a nonpolar solvent has become the mainstream nonhydrolytic method for the preparation of highly monodisperse IONs, especially for nanoparticles with size below 30 nm characterized by very narrow size distributions and high crystallinity [30,31]. The presence of organic surfactants during the process guarantees the good dispersibility of the nanoparticles in apolar solvents but also ensures the control over the nucleation and growth steps leading to monodisperse distributions of nanoparticles.

To ensure their colloidal stability in physiological conditions, a surface post-modification is required [32]. The coating can be designed to (i) provide a reactive shell for grafting/bounding therapeutic compounds; (ii) improve biological behavior of the iron oxide nanoparticles by limiting nonspecific interactions and uptake by the mononuclear phagocyte system (MPS) and (iii) enhance the IONs internalization efficacy [33]. Particles coating can be performed by two different strategies:

- Adsorption: small organic molecules are grafted onto the nanoparticles surface thanks to anchoring moieties such as silanes, carboxylate or organophosphorus [34] showing a strong affinity with the metal oxide surface. Polymers such as polyethylene glycol (PEG), polyvinyl alcohol (PVA), polyvinylpyrrolidone (PVP), or natural molecules such as starch, sugar, albumin, cellulose have been reported as efficient stabilizers [35].
- Encapsulation: IONs are encapsulated in a self-assembled amphiphilic structure (lipids, polymers, vesicles) to form magnetic nanoassemblies [36,37] exhibiting good dispersibility and biocompatibility [38].

In both cases, the coating will dictate the pharmacodynamic behavior of the systems and subsequently their efficacy as drug delivery systems.

3. IONs-based targeted drug delivery in cancer theranostics

Cancers are defined as malignant diseases in which the uncontrolled development of abnormal cells leads to the formation of cancerous tumors able to spread throughout the body and consequently affecting the healthy cells and tissues. In the

United States, it is the second leading cause of death (cancer statistics, 2016) [39] and represents a major public health issue worldwide. The main treatments used to treat this kind of pathology are surgery, radiotherapy, and chemotherapy. While surgery and radiotherapy are rather local treatments for localized cancers eradication, the use of chemotherapeutic compounds suffers from a lack of specificity giving rise to severe side effects due to the simultaneous and uncontrolled destruction of cancerous and healthy cells [40]. Indeed, the anticancer activity of chemotherapeutic drugs arises from their ability to attack cells in a particular phase of the cell cycle, most of the time independently of the cell type [41]. In this context, targeted magnetic nanoparticles can provide a better tumor selectivity [42]. In the next sections of this paper, drug delivery applications of chemotherapeutics using magnetic nanocarriers are reviewed. Table 1 lists the mainly studied chemotherapeutic compounds and their related main effects on cells and DNA.

In the field of oncology, precise follow-up of the therapeutic response is highly attractive for monitoring the tumor evolution and managing subsequent treatments. Given their high efficacy as contrast agents for MRI and their ability to carry chemotherapeutic compounds for targeted delivery, IONs have been extensively studied for applications in tumor-targeted drug delivery assessed by MRI.

Table 1. Chemotherapeutic drugs used in targeted drug delivery with IONs and their related mechanisms of action.

Drugs	Action mechanism
Doxorubicin (DOX)	Intercalation into DNA and inhibition of topoisomerase II [43,44]
Paclitaxel (PTX)	Disruption of the normal tubule dynamics required for cell division [45,46]
Artemisinin	Generation of free radicals inducing cell damages [47,48]
Gemcitabine (GEM)	Inhibition of DNA polymerase [49]
Bortezomib	Inhibition of the proteasomal activity [50,51]
Cisplatin	Crosslinking with DNA purine bases inducing cell damages [52]
Docetaxel (Dtxl)	Disruption of microtubule dynamics [53]

Table 2 summarizes the characteristics and physicochemical properties (determined by the authors) of the different magnetic nanocarriers presented in this review.

3.1. MRI-assisted drug delivery using IONs

Xie et al. developed a dopamine-plus-human serum albumin (HSA) strategy to convert 15 nm oleate coated IONs (obtained by pyrolysis) into water-soluble IONs [54]. The pharmacokinetic properties of these HSA-coated IONs were studied by labelling them with ^{64}Cu -DOTA and Cy5.5. These nanoparticles tested in

Table 2. Characteristics of IONs applied as drug nanocarriers (LE = Loading Efficacy).

References	Loaded drug	Physicochemical characteristics	Zeta potential (pH 7.4)	Drug content	Coating
55	DOX	$D_H = 50.8 \pm 5.2$ nm $D \approx 15$ nm (TEM)	ND	DOX/Fe/HSA 1/2/20 (w/w/w)	Dopamine/Human serum albumin
58	DOX	$D_H \approx 67$ nm $D = 9-14$ nm (TEM)	ND	ND	Polyethylene glycol/ Polyethyleneimine
59	DOX	$D_H = 125 \pm 10$ nm $D = 10 \pm 2$ nm (TEM)	-35 ± 3 mV	ND	Heparin
62	Cisplatin	$D \approx 60-120$ nm (STEM)	ND	7.9×10^{-4} moles Pt/g Gold	Gold/Polyethylene glycol
66	Cisplatin	$D_H = 76.7 \pm 5.6$ nm $D = 4.3 \pm 0.9$ nm (TEM)	-45 ± 7.3 mV	LE = $43.2 \pm 3\%$	Dextran/Human serum albumin
70	DOX	$D \approx 10$ nm (TEM)	ND	ND	Polyvinyl alcohol
71	Mitoxantrone	$D_H = 72.7 \pm 0.23$ nm $D = 7.64 \pm 1.68$ nm (TEM)	-10.17 ± 0.80 mV	LE = $99.93 \pm 0.01\%$	Lauric acid/bovine serum albumin
73	Artemisinin	$D_H = 349.3$ to 445.9 nm	-9.33 to -33.3 mV	LE = 55 to 62 %	Chitosan
77	Poly-PTX	$D_H = 221.07 \pm 28.72$ $D = 3-10$ nm (TEM)	-28.10 ± 0.26 mV	ND	Thermally cross-linked polymers/ β -cyclodextrin
80	GEM	$D_H \approx 65.9$ nm $D \approx 10$ nm (TEM)	ND	570 GEM/NP	Amphiphilic polymer
82	PTX	$D_H \approx 30.2$ nm $D \approx 12$ nm (TEM)	Negative	274 PTX/NP	PEG/carboxymethylated β - cyclodextrin
83	PTX	$D_H = 15.74 \pm 0.74$ nm	-58.06 ± 1.72 mV	LE = $78.34 \pm 0.52\%$	Amphiphilic copolymer
84	DTXL	$D_H = 139.5 \pm 2.16$ nm $D = 8-10$ nm (TEM)	-10.9 mV	ND	Pluronic F127 polymer/ β -cyclodextrin
85	DOX	$D = 10$ nm (TEM)	ND	ND	Polymer
86	GEM	$D_H \approx 93$ nm	-41 mV	20 μmol GEM/g Fe	Dimercaptosuccinic acid
88	GEM	$D_H = 109 \pm 1$ nm $D = 12 \pm 3$ nm (TEM)	-45 ± 1 mV	2 μmol GEM/g Fe 34 GEM/NP	Dimercaptosuccinic acid
91	DOX	$D_H \approx 91$ nm $D \approx 12$ nm	-2.86 ± 6.80 mV	1089 \pm 21 DOX/NP	Polyethyleneimine
94	DOX	$D_H = 62.3 \pm 2.5$ nm $D = 10 \pm 2$ nm (TEM)	Neutral	$3.07 \pm 0.04\%$ DOX/iron oxide w/w	PEG
99	Bortezomib	$D = 5-7$ nm (TEM)	Positive	ND	Chitosan
101	DOX	$D_H \approx 100$ nm $D = 5-7$ nm (TEM)	ND	LE = 85 to 98 %	Chitosan
102	DOX	$D = 24-40$ nm (TEM)	Positive	LE = 72 %	Chitosan
103	DOX	$D_H \approx 120$ nm	ND	LE = 90 % 19 % w/w (PEG ₂₀₀₀)	Chitosan
104	DOX	$D_H \approx 30$ nm $D = 14$ nm (TEM)	Negative	14.5% w/w (PEG ₅₀₀₀)	Phospholipid-PEG

a U87MG xenograft model demonstrated a prolonged circulation half-time as well as accumulation in tumors attributed to the EPR effect and interaction of HSA with cell surface proteins. Later on, the same team encapsulated doxorubicin together with dopamine into the HSA matrices [55] to obtain tumor targeting IONs named 'D-HINPS' (Figure 1) having a hydrodynamic diameter (D_H) of 50.8 ± 5.2 nm.

In vitro assays using 4T1 cells (murine breast cancer cell line) demonstrated a better drug uptake for these systems (compared to free doxorubicin), which was explained by the inner polyamine coating potentially facilitating the cellular uptake [56]. These D-HINPS were then evaluated in a therapeutic study on a xenograft 4T1 murine breast cancer model and showed significantly higher tumor accumulation (evidenced by MRI) and higher tumor suppression effect than doxorubicin alone and Doxil® (FDA-approved liposomal doxorubicin [57]).

Huang et al. reported the development of IONs conjugated with folic acid for the diagnosis and treatment of breast cancer [58]. Dox was loaded onto these nanocarriers and their efficacy as drug delivery systems was tested in nude mice with xenograft MCF-7 breast cancer tumor. The authors monitored the accumulation of the nanocarriers in the tumor by MRI thanks to the high r_2 relaxivity of the IONs. Another work from Yang et al. focused on the preparation of DOX-loaded heparin-coated IONs for combined drug therapy and MRI [59]. These systems were characterized by slow release of the drug, better uptake efficiency compared to doxorubicin alone along with reduced cardiotoxic effect. T_2 -weighted phantom images demonstrated the contrast effect induced by these systems confirming their potential as theranostic tools for the treatment and diagnosis of cancerous cells.

3.2. Magnetically-guided drug delivery

Taking advantage of the magnetic properties of iron oxide nanoparticles, site-specific drug delivery can be achieved by guiding the IONs under the action of a localized external magnetic field. This approach has proven to be efficient for the accumulation of nanoparticles in particular pathologies such as tumor or inflamed sites [60]. The magnetic response of IONs is strongly dependent on their physicochemical properties, more specifically, the saturation magnetization of the fabricated nanosystems must be as high as possible in order to control the movement of the nanoparticles in the bloodstream and their accumulation toward the targeted sites [61].

This site-directed application has been studied by many groups developing magnetic nanocarriers with distinct structural

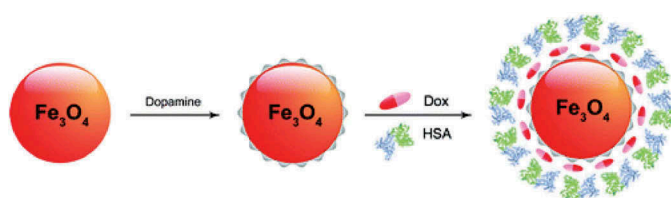


Figure 1. Schematic illustration of the dopamine-plus-HSA coated IONs loaded with doxorubicin (adapted with permission from 55 Copyright 2011 American Chemical Society).

features. For example, the group of Wagstaff et al. reported in 2012 the preparation of gold-coated iron oxide nanoparticles bearing a platinum anticancer drug (cisplatin) [62]. In this work, iron oxide nanoparticles were first synthesized by coprecipitation and oxidized to obtain maghemite. These nanoparticles were then coated with gold by using a method called 'iterative hydroxylamine seeding'[63]. Particle coating was then achieved by using thiolated compounds such as thiolated polyethylene glycol (PEG) linkers which were developed previously by the same team [64,65]. Finally, cisplatin was loaded onto the magnetic nanocarriers through strong coordination bonds with the PEG linker (Figure 2). The developed nanocarriers were then evaluated *in vitro* and exhibited a 110-fold increase in cytotoxicity on human ovarian carcinoma cell lines A2780 as well as a site-specific cell growth inhibition when attracting the nanoparticles with a bare magnet.

Cisplatin-bearing IONs were also developed by Unterweger et al. which developed dextran/hyaluronic acid coated IONs [66]. The use of hyaluronic acid (HA) allowed the incorporation of drugs such as cisplatin but also the targeting of overexpressed CD44 receptors in cancerous cells [67]. These IONs were then coated with low molar mass HA (obtained by enzymatic degradation of HA [68]) after amination of the dextran-coated IONs. Incorporation of cisplatin was achieved afterward through formation of a polymer-metal complex with HA, the final nanocarriers were characterized by efficient drug encapsulation ($43.2 \pm 0.2\%$). Authors highlighted a two stages drug release kinetics defined by an initial 30 min burst release followed by a continuous release during 48h which is typical for surface-bound drug. Moreover, in the presence of hyaluronidases (HA cleaving enzymes abundantly found in tumors [69]), significant increase of the drug release rate was observed, making these nanocarriers particularly promising for tumor targeted drug delivery, even more with their control by magnetic force which was also demonstrated by attraction of the nanoparticles with a neodymium magnet. The magnetic control of IONs for targeted drug delivery applications was also studied by Nadeem et al. whose work was focused on the development of PVA coated iron oxide nanoparticles loaded with doxorubicin [70]. By applying a magnetic field, these nanocarriers demonstrated decent control for magnetically guided delivering of the drug.

Zaloga et al. reported the synthesis of lauric acid (LA) and HSA coated iron oxide nanoparticles (with mean inorganic diameter of approximately 7 nm) with the antineoplastic

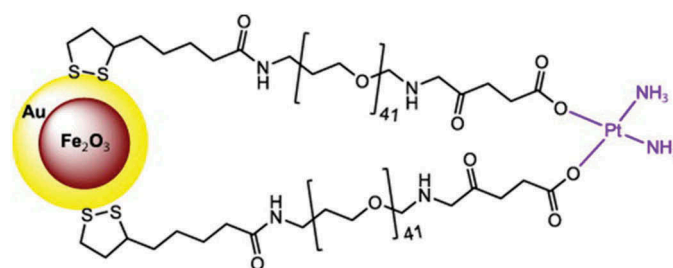


Figure 2. Schematic illustration of the gold-coated iron oxide nanoparticles loaded with cisplatin (adapted with permission from 62 Copyright 2012 Elsevier).

drug mitoxantrone adsorbed on the HSA shell [71]. These nanocarriers demonstrated enhanced stability as well as a linear drug release kinetics over 72 h. In another study, the same team was able to clearly evidence the site-specific therapeutic effect of these nanocarriers by means of an *in vitro* magneto-guided assay [72]. Natesan and co-workers developed chitosan-coated IONs formulated with artemisinin as anticancerous agent [73]. Chitosan is a natural polymer with a remarkable biodegradability along with the ability to encapsulate drugs making it an excellent coating for biomedical applications such as drug delivery [74]. The magnetic nanocarriers developed by Natesan et al. consisted in 10 nm iron oxide nanoparticles [75] coated with chitosan and artemisinin by the ionic gelation method [76]. The magnetic-assisted targeting, firstly assessed by attraction with an external magnet of the nanoparticles in a glass container, was then confirmed *in vivo* in a 4T1-breast tumor-bearing BALB/c mice model whereby it was demonstrated that higher amount of drug could be accumulated in the tumor. Another kind of drug delivery system was recently reported by Jeon et al. [77], which developed polymerized β -cyclodextrin-coated IONs able to load polymerized paclitaxel (anticancerous drug known for its low solubility in water [78]) by host-guest interaction. The obtained nanoassemblies exhibited high magnetism allowing their use as magnetically guided drug delivery system. *In vivo* studies on CT26-bearing mice showed the enhanced anticancer activity of these systems owing to magnetically induced targeting effect.

3.3. Vectorized magnetic nanocarriers

Functionalization of IONs with given targeting moieties like peptides, antibodies, or small organic molecules constitutes a promising strategy for the targeted delivery of therapeutic agents. The selection of targeting agents able to interact with disease markers via ligand-receptor or antigen-antibody interactions enable the IONs to specifically accumulate at diseased sites, therefore enhancing their specificity and their therapeutic effects [79].

Over the past few years, several research groups have focused their studies on the development of different kinds of vectorized magnetic nanocarriers and their evaluation as targeted drug delivery systems. Lee et al. reported gemcitabine (GEM)-loaded IONs modified with an amino-terminal fragment (ATF) peptide able to target urokinase plasminogen activator receptor (uPAR) [80]. This receptor is an excellent target as it is overexpressed in over than 86% of pancreatic cancer tissues [81]. These vectorized carriers exhibited increased receptor-mediated endocytosis allowing enhanced drug uptake in tumor cells. Moreover, the peptide linker used to conjugate gemcitabine on the magnetic carriers was chosen for its enzyme-sensitive properties enabling the controlled release of the drug via enzymatic cleavage in the intracellular components of the cancer cells. Nanocarriers accumulation in tumors was demonstrated by MRI as well, showing the combined diagnostic and therapeutic possibilities provided with such systems. The anti-HER2/neu peptide (AHNP) was used by the group of Mu et al. [82], for the treatment of breast cancer cells using paclitaxel-loaded iron oxide nanoparticles. Stable

iron oxide nanoparticles ($D_H \sim 30$ nm) conjugated with this small peptide and carboxymethylated- β -cyclodextrin to allow hydrophobic loading of paclitaxel were successfully prepared. *In vitro* evaluation of these nanocarriers showed their targeting ability toward breast cancer cells. More recently, Ahmed et al. [83], produced novel double-receptor-targeting magnetic nanocarriers for the diagnosis and treatment of prostate cancer. In this study, two peptides were used as vectors to target two overexpressed cell proteins on prostate cancer cells: luteinizing hormone-releasing hormone receptor (LHRH-R) and urokinase-type plasminogen activator receptor (uPAR). These peptides were conjugated onto iron oxide nanoparticles through formation of amide bonds with polymer-coated IONs. The final double-targeting nanocarriers were characterized by small hydrodynamic diameter, negative zeta potential and high loading of the drug paclitaxel (PTX). The authors showed that double-receptor-targeting nanocarriers allow a two-fold increase on the cancer cells cytotoxicity and a ten-fold reduction in the concentration of PTX required to have similar effect with the free drug.

Other vectors such as antibodies and aptamers are also found in the literature as vectorizing agents for targeted drug delivery using IONs. For instance, Nagesh et al. [84], developed IONs functionalized with J591 monoclonal antibodies targeting prostate specific membrane antigen (PSMA) which is highly overexpressed in prostate cancers. Iron oxide nanoparticles with average inorganic diameter of 8–10 nm were coated successively with β -cyclodextrin and pluronic F127 polymer to yield stable nanocarriers with the drug docetaxel incorporated in the hydrophobic cavity of β -cyclodextrin. *In vitro* experiments showed that this formulation of docetaxel-loaded IONs exhibited superior internalization into pancreas cancer cells thanks to optimal particle size and zeta potential. Anticancer efficacy was demonstrated through several pathways showing that this formulation can be highly useful for targeted prostate cancer therapy. PSMA-targeting nanocarriers were also developed by Leach et al. [85], which used a different kind of vector to target prostate cancer cells based on a hybridized aptamer (A10-3-J1) able to recognize the extracellular domain of PSMA. In this study, biotin-streptavidin coupling was used as conjugation method for the functionalization of the nanoparticles and doxorubicin was loaded through intercalation in the double helix of the aptamer. This different approach allowed the inhibition of nonspecific uptake and therefore the reduction of untargeted toxicity indicating that these platforms can yield statistically significant effectiveness. In another novel study, Aires et al. [86], coated IONs with antiCD44 antibodies capable of targeting CD44-positive pancreatic cancer cells and gemcitabine to induce cancer cells death. Disulfide bonds were employed for the multifunctionalization of the IONs, providing the nanocarriers with the ability to release the chemotherapeutic drug under high reducing conditions, such as the intracellular environment of the cancerous cells [87]. As expected, these nanocarriers showed a selective and rapid release in intracellular conditions as well as increased selectivity toward CD44-positive pancreatic cancer cells. The same group also grafted antiCD47 antibodies in a similar work using the same multifunctionalization

strategy [88]. Identical drug release behavior was observed along with efficient induction of apoptosis in pancreatic cancer cells, thus demonstrating that such formulations bear great potential for future therapeutic treatments.

3.4. Stimuli-responsive drug delivery

Other strategies allowing the increase of the drug release in specific locations consist in using stimuli-responsive coatings or functional groups. The first strategy is based on the variations of pH existing between the healthy tissues and the cancerous tissues. Indeed, tumors are characterized by a significantly lower extracellular pH than the surrounding healthy tissues. This slight difference in pH can be used to trigger the delivery of drugs grafted onto nanocarriers by means of pH-sensitive bonds or pH-sensitive coatings such as polymers or liposomes [89,90]. The ability of iron oxide nanoparticles to induce hyperthermia constitutes another way to increase the drug release rate when using drugs loaded onto the IONs by means of temperature-responsive polymers.

pH-responsive drug delivery systems based on iron oxide nanoparticles have been widely studied in the last years. Several strategies employing acid-sensitive functional groups can be found in the literature along with various types of nanocarriers based on iron oxide nanoparticles. In 2011, Kievit et al. [91]. reported the preparation of doxorubicin loaded IONs able to overcome the multidrug resistance (MDR) phenotype encountered in some drug-resistant cancers [92]. In this work, amine-terminated polyethylene glycol coated IONs (previously prepared by the same group [93]) were covalently conjugated with DOX via a pH sensitive hydrazone linkage (with polyethyleneimine as docking molecule for DOX). The nanocarriers were characterized by hydrodynamic diameter below 100 nm, high loading of drug (i.e. 1089 ± 21 DOX per nanoparticle) and slightly negative zeta potential which should facilitate the penetration of these systems into tumors. DOX release from nanoparticles showed to be more efficient at acidic pH due to the cleavage of the hydrazone linkage. It was also shown that these systems are less susceptible to MDR than the free drug, resulting in an increased therapeutic effect.

Gautier et al. reported the development of PEGylated IONs loaded with doxorubicin using a different loading approach by means of a pre-formed DOX-Fe²⁺ complex [94,95]. The DOX-Fe²⁺ complex can bind with hydroxyl groups on the surface of the nanoparticles and dissociate at acidic pH resulting in a pH-dependent drug release (Figure 3) [96]. Substantial increase in the drug release kinetics was observed at pH = 4, confirming the interesting potential of these nanocarriers.

Chitosan, besides its biocompatible properties, is also characterized by other properties such as antitumor activity [97] and increased solubility in dilute acidic solutions (due to the protonation of the amine groups in the polymeric chain) making it a particularly attractive choice for pH-responsive drug delivery applications [98]. The group of Unsoy et al. investigated chitosan-coated magnetic nanoparticles as pH-responsive nanosystems carrying bortezomib (FDA approved proteasome inhibitor drug) as anticancerous drug [99]. Iron

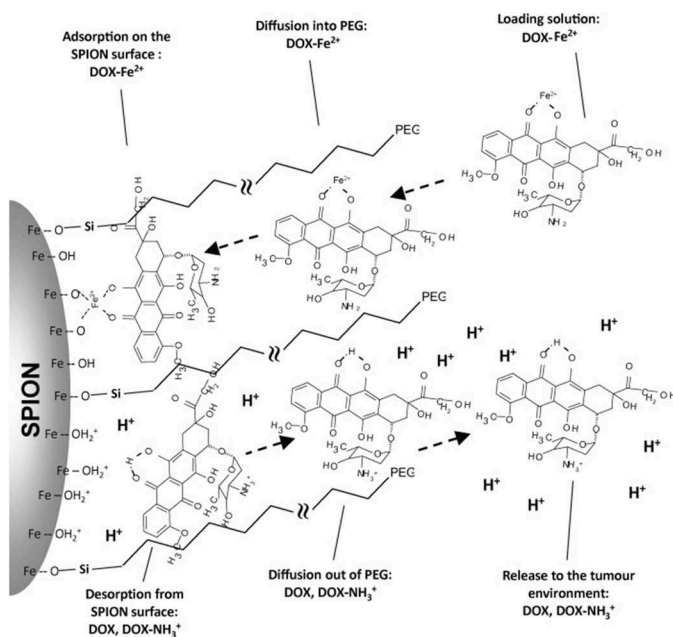


Figure 3. Schematic diagram of loading of pre-formed DOX-Fe²⁺ complex and of release of DOX from the nanoparticles (adapted with permission from 94 Copyright 2012 Elsevier).

SPION: Superparamagnetic iron oxide nanoparticles

oxide nanoparticles with average core size between 5–7 nm were synthesized by coprecipitation and coated *in situ* with chitosan by ionic crosslinking of triphosphosphate (TPP) [100]. Higher release of the drug was observed at pH = 4.2 as well as improved internalization of the bortezomib loaded nanoparticles by HeLa and SiHa cells. In another study, the same strategy was used to load doxorubicin on these chitosan-coated magnetic nanoparticles [101] where similar pH dependent release was observed. Accumulation of these nanocarriers around the nucleus was also evidenced and their cytotoxic effect on doxorubicin resistant MCF-7 cells was proven to be superior than the free drug. Amine functional groups, present on the polymeric chain of chitosan, are also possible grafting sites for the conjugation with drugs using pH-sensitive linkers. For instance, Adimoolam et al. [102]. recently reported chitosan-coated IONs with pH-sensitive glutaraldehyde linker for pH responsive delivery of doxorubicin. The introduction of the glutaraldehyde linker on the chitosan-coated nanoparticles allows the formation of imine bonds (with the amine groups of doxorubicin) which are sensitive at lower pH conditions (pH range of 4.4–6.4). It was demonstrated that these carriers could be used for specific delivery of doxorubicin in the intracellular components of human breast cancer (MCF-7) and ovarian cancer (SK-OV-3) cell lines.

Hyperthermia constitutes a second approach for the development of stimuli-responsive drug delivery using iron oxide nanoparticles. Several research groups developed magnetic nanocarriers coated with temperature-sensitive polymers showing enhanced drug release when the iron oxide nanoparticles are submitted to an alternative magnetic field. For instance, Zou et al. [103]. developed doxorubicin-loaded chitosan coated mesoporous IONs exhibiting enhanced therapeutic effect when they were submitted to an applied alternative current magnetic

field (ACMF). Another work from Quinto et al. focused on the preparation of phospholipid-polyethylene glycol coated iron oxide nanoparticles with a core size of 14 nm [104]. These nanocarriers could generate sufficient heat to raise the temperature to 43°C and could in the mean time release the doxorubicin in a sustained manner, demonstrating their potential for chemotherapy-hyperthermia combinatorial cancer treatment with increased efficacy.

4. Conclusion

The design of theranostic iron oxide nanoparticles able to combine imaging and targeted drug delivery is a promising way to treat cancers. In this short review, we presented an overview of recent developments made in the preparation of IONs-based drug delivery systems. Their physicochemical and their drug release properties were presented. To address the controlled drug release from magnetic nanocarriers, different strategies including the functionalization of the particle surface with stimuli-responsive (pH, temperature, magnetic field) or biological vectors are plentifully developed by different research groups. In the future, important developments in the design of such nanosystems should be performed toward the preparation of perfectly reproducible nanocarriers with optimal properties. Finally, by using all the aspects of iron oxide nanoparticles, more research should be devoted to the combination of drug delivery with other imaging modalities for preclinical and, eventually, clinical applications.

5. Expert opinion

Iron oxide nanoparticles have special characteristics, making them particularly attractive as magnetic drug delivery systems especially in the field of cancer therapy. The key factors determining the IONs behavior *in vivo* are their size (monocore or multicore, ...), the nature of the coating (neutral or charged, polymers or small molecules, ...) and consequently, their stability. Even if strong efforts are made in order to obtain highly sophisticated systems, one can notice that stability tests are not systematically applied or, in most of cases, are limited to water as the studied media. When considering biomedical applications, it should be emphasized that the agglomeration of nanosystems will impact their pharmaco-kinetic/dynamic behavior, influencing thus the efficacy of the targeting and/or delivery process. The study in other more complex body fluids (e.g. blood serum, blood plasma) should be envisaged. Indeed, nanoparticles flowing in these fluids are immediately covered by proteins forming what is called a 'protein corona'. This protein corona is a parameter which should be considered in the development of magnetic nanocarriers as it will directly govern the fate and behavior of the IONs in the body, and therefore affect the drug release and other properties of the developed formulations [105,106]. Similar remark can be done for *in vitro* studies since agglomeration can impact on the cell internalization kinetics. Prior to studying the efficacy of the formulations on cell cultures, the stability of the developed formulations should also be evaluated in culture media and compared to the controls. Besides, as

seen in Table 2, one can see noticeable discrepancies concerning the studied physicochemical properties of the developed nanocarriers.

Another important point that should be emphasized is that the way of expressing the total drug content differs significantly from one author to another. These differences make the comparison difficult between the described formulations. In our opinion, special attention should be made in the near future to propose guidelines for a standardized and systematic approach enabling the accurate characterization and evaluation of the developed nanocarriers.

In summary, magnetic nanocarriers based on iron oxide nanoparticles bear great potential for applications in drug delivery. The best potential probably being the use of drug-loaded stimuli-responsive nanomaterials enabling the targeted delivery of the drugs toward specific tumor sites. For the preparation of such nanosystems, several aspects such as synthetic processes, coating processes and drug loading should be considered together to clearly define their pharmacokinetics and *in vivo* fate. We expect that important sustained developments of targeted drug delivery systems and stimuli-responsive platforms should be performed in the near future by emphasizing on improved understanding of the interactions between drugs and particle coatings in order to be able to design efficient magnetic nanocarriers which meet the requirements for a potential clinical translation. For this to be possible, several issues have to be addressed in the near future: (i) provide optimized and easy scale-up IONs production methods, (ii) provide systematic and standardized protocols allowing the full characterization of the nanocarriers properties ranging from their physicochemical properties to their subsequent behavior and fate (toxicity, immunogenicity, clearance, and safety profiles). As of now, these issues are restraining the use of magnetic nanocarriers for the clinical use, these systematic investigations are necessary to make possible the practical translation into commercial human medicine.

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