Drug Development and Industrial Pharmacy

ISSN: 0363-9045 (Print) 1520-5762 (Online) Journal homepage: http://www.tandfonline.com/loi/iddi20

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To cite this article: Fei Xiong, Shengxin Huang & Ning Gu (2018): Magnetic nanoparticles: recent developments in drug delivery system, Drug Development and Industrial Pharmacy, DOI: 10.1080/03639045.2017.1421961

To link to this article: https://doi.org/10.1080/03639045.2017.1421961

Published online: 25 Jan 2018.

DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY, 2018
https://doi.org/10.1080/03639045.2017.1421961

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REVIEW ARTICLE

Magnetic nanoparticles: recent developments in drug delivery system

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ABSTRACT

Nanostructured functional materials have demonstrated their great potentials in medical applications, attracting increasing attention because of the opportunities in cancer therapy and the treatment of other ailments. This article reviews the problems and recent advances in the development of magnetic NPs for drug delivery.

ARTICLE HISTORY
Received 8 October 2017
Revised 21 December 2017
Accepted 22 December 2017

KEYWORDS
Magnetic nanoparticles; drug delivery system; pharmacokinetics; biodistribution; drug loading

Introduction

Magnetic nanoparticles (MNPs) have attracted considerable attention in the past, because of their unique optical, electronic, magnetic and physicochemical properties. The dimensions of MNPs make them ideal candidates for nano-engineering of surfaces and the production of functional nanostructures. The modifications of MNPs make them form the basis for a huge variety of pharmaceutical and medical applications, including diagnostics and drug delivery, and have special potential in cancer therapy [1,2]. Currently, a variety of MNPs are in early clinical trials and some formulations have been clinically approved for medical imaging and therapeutic applications. Some of them include Lumiren® and Gastromark® for bowel imaging; and Feridex I.V.® and Endorem® for liver and spleen imaging, among others [3,4]. Meanwhile, MNPs as a drug delivery system (DDS) have received considerable attention, in order to solve the lack of efficient transport system in the body to deliver drug to the nidus.

Magnetic DDS works on the delivery of MNPs loaded with drug to the tumor site under the influence of external magnetic field (Figure 1). Nanoparticles within the size range of less than 10 nm, due to the presence of single domain state [5], which is called superparamagnetism, behave magnetic only under the influence of external magnetic field and are rendered inactive once removed. This behavior of superparamagnetic materials results in potential advantages to deliver therapeutics onto specific sites under the influence of external magnetic field and can be reverted to their nonmagnetic states by removing external magnetic field to allow them to be excreted [6].

A variety of MNPs and microparticle carriers have been developed to deliver drugs to specific target sites *in vivo* for more than 30 years [7–9]. Various kinds of MNPs have been used, including iron oxide (e.g. Fe_3O_4 and MFe_2O_4 (M = Mn, Co and Zn)), alloys (e.g. FePt, PtCo and Fecor), and multifunctional MNPs with core/shell, dumbbell or multicomponent hybrid structures. The optimization of these carriers continues today with the objectives (i) to reduce the amount of systemic distribution of the cytotoxic drug, thus reducing the associated side effects, and (ii) to reduce the dosage required by more efficient, localized targeting of the drug. In the last decade we have made great progress in the research about the MNPs to meet the common criteria for DDS including (i) avoiding captured by cell of reticule-endothelial system (RES), (ii) low toxicity with reduced adverse reactions and easy-elimination after function, (iii) transporting drug to the site in high yield while keeping safety, and (iv) targeting accurately and releasing effective quantities of drugs to achieve a desired concentration.

However, despite the large efforts to prepare MNPs for biomedical applications, the number of MNP used in clinical is few. Most of the FDA-approved MNPs are used for MRI and some for treatment of anemia. The part for MNPs-based tumor targeting nanosystem, according to the researches, has not been utilized in clinical fields. To find out and improve the clinical applications of MNPs in DDS and other clinical fields, in this review, we focus on the recent development of MNPs for clinical drug delivery and overview the key points that affect the properties and clinical applications of the MNPs.

Drug loading system

As one of the most important factors restrains MNPs from clinical application, drug loading has attracted much attention recently. It still remains a significant challenge and a major barrier to their clinical application that fabrication of reproducible and consistent formulations with controlled drug loading profiles [10]. Therefore, developing a multifunctional DDS with high drug loading capability, magnetic resonance imaging (MRI) property, good biocompatibility has become significant and desirable. The key parameters in the behavior of MNPs are related to drug-loaded methods, surface

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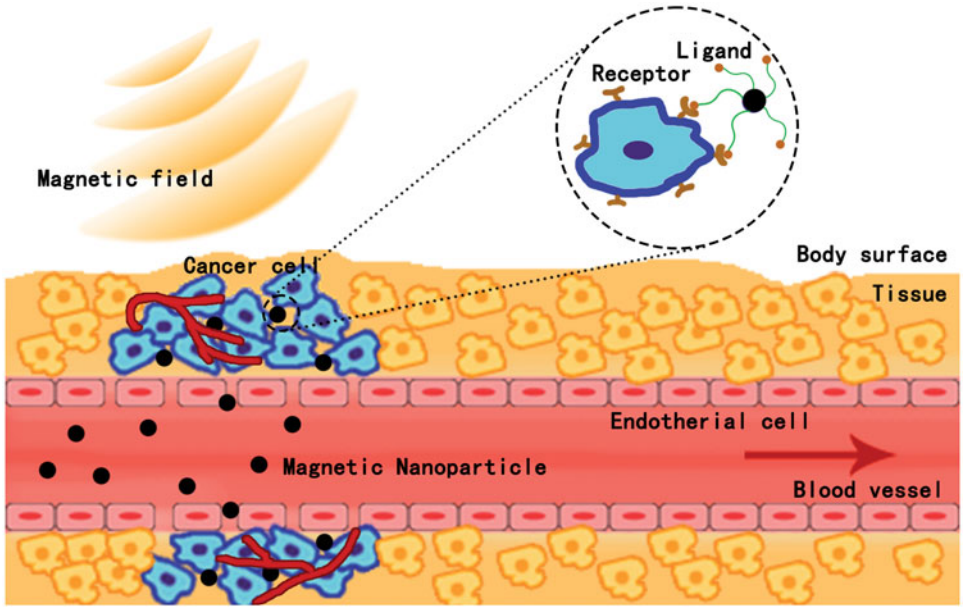


Figure 1. Schematic representation of magnetic drug delivery system under the influence of external magnetic field.

chemistry, size (magnetic core, hydrodynamic volume and size distribution) and shape and materials [11].

Drug loading method

In general, drug-loaded methods are categorized into two major types, chemical linkages and physical interactions, both of which have a strong influence on MNPs' drug loading behavior. The choice of chemistry is dictated, in part, by the chemical properties and functional groups found on the Superparamagnetic Iron Oxide Nanoparticle (SPION) coating and ligand to be linked [4].

Chemical linkages

Covalent linkages are strong and stable bonds, which can be specifically formed between functional groups, typically amino, carboxylic acid and thiol groups found on the MNP surface and conjugated ligands. MNP surfaces functionalized with amine, sulfhydryl, aldehyde and active hydrogen functional groups can be targeted. These strategies are particularly suitable for small molecule conjugation. Usually, these functional groups are added to the MNP surface via its polymer coating, which can dictate both the type and number of functional groups on each MNP. These chemical handles are found either on the body of the polymer (chitosan, polyetherimide and dextran) or at their terminal ends (polyethylene glycol (PEG)). More binding sites can be added per polymer chain, on its body, thus affecting the total number of reactive groups available. These same chemical groups are also found on the targeting, optical or therapeutic agent to be covalently attached. To control polymer conformation and provide stable covalent linkages to the surface of iron oxide nanoparticles, Kohler et al. [12] developed a trifluoroethyl ester-terminal PEG silanes capable of forming self-assembled monolayer's (SAMs) and increasing the packing density of the polymer chains onto the nanoparticles surface. In addition, terminal amine or carboxyl groups extending out from the nanoparticle surface provide sites for conjugation of functional legends for a number of biomedical applications, as demonstrated by the attachment of folic acid in this study. However, the strong and stable bonds cannot easily release drugs when reaching the target position, which more studies should be engaged to improve.

In the recent years, graphene-IO hybrids have been extensively used for drug release in tumor cells and tissues. Graphene- IO hybrids benefit the drug delivery in terms of higher loading and controlled deliveries over grapheme or IONPs alone, thus improving the efficiency of the final system [13]. The future of the combination of graphene, the new material, with MNPs is well worth looking forward to.

Physical interactions

Physical interactions include electrostatic, hydrophilic/hydrophobic and affinity interactions. There are several unique advantages of this interaction including rapid speed of binding, high efficiencies and no need for intermediate modification steps [4]. On the contrary, the physical interactions are not stable enough to avoid the drug revealing during the delivery travel (Figure 2).

Electrostatic interactions. Electrostatic interactions have been particularly proved useful in the assembly of plasmid DNA onto MNPs. Severalresearch groups have demonstrated this utility by creating MNPs coated with cationic polymers of polyetherimide (PEI), which are then complexed with negatively-charged plasmid DNA molecules [14–16]. Kim et al. [17] reported that SPION were used to transfer gene into umbilical cord blood-derived mesenchymal stem cells (UCB-MSCs). This novel transfection method using SPION is safe and effective to UCB-MSCs and would be a tool for genetic optimization with a significant potential for cell tracing.

Hydrophobic/hydrophilic interactions. It has been proved that hydrophobic/hydrophilic interactions are highly useful when adsorbing hydrophobic drugs onto MNPs. For this application, MNPs are engineered with hydrophobic layers that can adsorb hydrophobic drugs that then being triggered for release intracellularly when the coating degrades [18,19]. Singh et al. [20] prepared and characterized MNPs embedded in polylactide-co-glycolide matrixes (PLGA-MNPs) as a dual drug delivery and imaging system capable of encapsulating both hydrophilic and hydrophobic drugs in a 2:1 ratio. This study demonstrated the dual usable purpose of

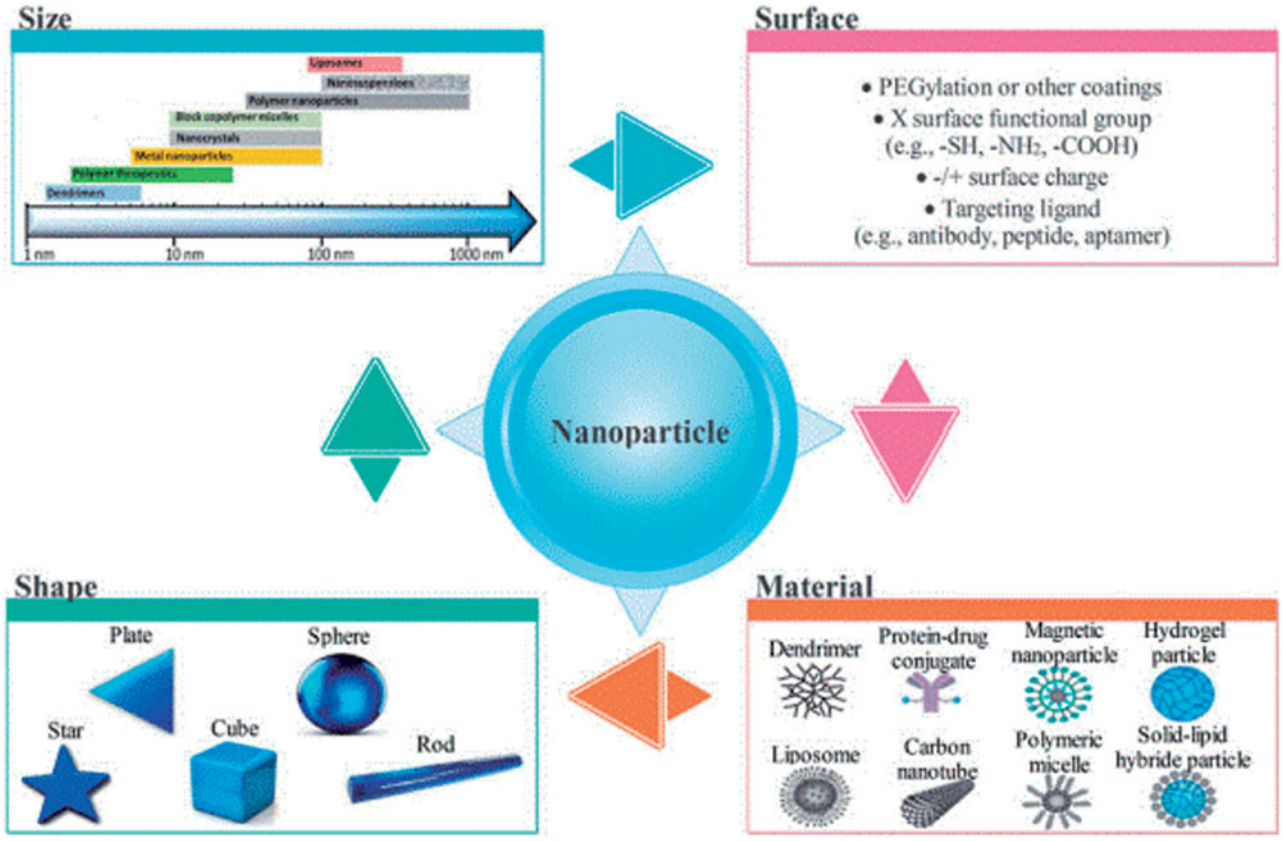


Figure 2. Some nanotechnology-based drug delivery platforms with illustrations of biophysicochemical properties.

formulated PLGA-MNPs toward either, in therapeutics by delivering different hydrophobic or hydrophilic drugs individually or in combination and imaging for cancer therapeutics in the near future. This strategy has drawbacks, including MNPs sensitivity to environmental conditions and low control over molecular orientation of bound ligands. Thus while suitable for drug delivery applications where the attached molecule is released for functionality, attachment of targeting ligands through these strategies are unattractive.

Affinity interactions. Affinity interactions, on the other hand, have shown to be very effective for bio-conjugation of targeting ligands to MNPs [21,22]. The linkage formed is highly stable and the strongest of all non-covalent linkages chemistries. Unlike hydrophobic and electrostatic interactions, affinity binding is insensitive to environmental conditions such as changes of pH salinity or hydrophilicity. Using this strategy Gunn et al. produced high-affinity multivalent display of targeted MNPs for immunotherapy applications [21]. Table 1 shows the similarities and differences of different DDS.

The surface chemistry

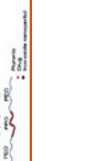
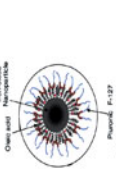
The surface chemistry is also a key parameter to the drug loading capability. It has been reported that MNPs covered with a layer of biodegradable polymer shell or evenly distributed in the matrix of polymer nanoparticles can be effective magnetic drug carrier [23]. Presence of multifunctional groups, like –NH2, –COOH, in the gelatin chain makes it a suitable candidate to bind with drug like doxorubicin (DXR) forming drug–polymer conjugate [24] or poly(-ethylene glycol) to form RES evading conjugate [6].

The molecular weight of the polymer on MNPs' surface has an effect on the *in vivo* performance of MNPs. We synthesized paclitaxel (PTX)-loaded MNPs modified with methoxy PEG-lysine-oleic acid2 (PTX-MNPs-PLO) with three different PEG molecular weights (1000, 2000 and 4000 Da), which is expected to act as an MRI contrast agent and meanwhile for cancer therapy. As the pharmacokinetics (PKs) and distribution *in vivo* processed, the results of which exhibited that PTX-MNPs-PLO2000 had the longer circulation lifetime compared with Taxol, PTX-MNPs-PLO1000 and PTX-MNPs-PLO4000. And results of magnetic targeting in kidneys suggested that deep buried or ultrasmall magnet is likely to be more preferable. PTX-MNPs-PLO2000 holds great promise in the application of magnetic accumulation, target drug delivery and thermal therapy [25] (Figure 3).

As known, the tumor cells grow in acidic environment. In the past years, various pH and magnetic dual-responsive nanoparticles have been developed to combine pH-triggered drug release with magnetic targeting, thermotherapy and imaging [6]. A dually responsive nanocarrier with multilayer core-shell architecture was prepared based on Fe_3O_4@SiO_2 nanoparticles coated with mPEG-poly (l-Asparagine). The Fe_3O_4@SiO_2, poly(l-Asparagine) and mPEG segments, respectively, serve as a super-paramagnetic core, a pH-sensitive shell and a hydrophilic corona. An antitumor agent, doxorubicin (DOX), was successfully loaded into the nanocarrier via combined actions of hydrophobic interaction and hydrogen bonding [26].

Functionalized core/shell MNPs with antimicrobial properties, surface-engineered manganese iron oxide MNPs, coated with two different polymers and loaded with usnic acid (UA) were developed to be used for the prevention and treatment of medical device-related infections. Between the two polymer coatings, the one based on an intrinsically antimicrobial cationic polyacrylamide

Table 1. Similarities and differences of different drug delivery system.

Drug delivery system	Drug carrier	Drug loading method	Interaction between drug and MNPs	Requirement of MNPs for Drug property	Multifunction: Targeting: Long circulation (anti-passive targeting)	Multifunction: Targeting: Magnetic targeting (physical targeting)	Multifunction: Targeting: Active targeting	Multifunction: Magnetism thermal therapy	Multifunction: MRI	Schematic diagram of drug delivery system	Reference
Magnetic lipid carriers	Liposome	Phospholipid surrounded drug and MNPs	No direct interaction	None	√	√	√	×	√		[77]
	Solid lipid nano particle				√	√	√	√	×		[78,79]
Biological conjugate	MNPs	Chemical reaction	Chemical bond	Specify chemical bond	√	×	×	×	√		[80–82]
		Physical interactions	Electrostatic interactions	Strong and different charge from MNPs surface	√	×	×	×	√		[83]
			Similar compatibility	Hydrophobicity	×	√	×	×	×		[84]

√: reported; ×: none reported.

(pAcDED) resulted to be able to provide MNPs with proper magnetic properties and basic groups for UA loading. Thanks to the establishment of acid-base interactions, pAcDED coated MNPs were able to load and release significant drug amounts resulting in good antimicrobial properties versus *Staphylococcus epidermidis* (MIC = 0.1 mg/mL). The use of pAcDED having intrinsic antimicrobial activity as MNP coating in combination with UA likely contributed to obtain an enhanced antimicrobial effect [27]. Kai Cheng et al. synthesized Fe_3O_4@C nanocapsules via a sacrificial-template method by coating SiO_2 nanospheres with an Fe_3O_4@C double-shell structure, which showed a loading capacity as high as 1300 mg/g for doxorubicin (DOX), and the DOX-loaded on the surface of the carbon shells displays pH-sensitive release behavior [28].

Size and shape

MNPs display unique physical and chemical properties due to their size, which is in the same range as antibodies, receptors, nucleic acids, proteins and other biological macromolecules. In all of the applications involving the use of MNPs, the particle size remained as the most important parameter as many of the chemical and physical properties associated to MNPs are strongly dependent upon the nanoparticle diameter. It is suggested that NPs ranging from approximately 10–100 nm, preferentially accumulate in the tumors as opposed to normal tissues [4]. In regard to shape, in our study, superparamagnetic anisotropic nano-assemblies (SANs) were fabricated and loaded with vincristine (VCR) to form VCR-SANs. SANs were found to be more promising than isotropic nano-assemblies via our *in vivo* and *in vitro* examinations [29]. Recent advances in the designed synthesis and assembly of uniformly sized iron oxide nanoparticles have brought innovation in the field of nanomedicine. Size-dependent magnetic characteristics of uniform-sized iron oxide nanoparticles are able to develop various kinds of MRI contrast agents and drug delivery vehicles [30].

Chemical and colloidal stability

Independent of their specific biological functionality, all the MNP formulations must retain their chemical and colloidal stability *in vivo* under the applied magnetic field. It is known that the naked MNPs are both chemically and colloidally unstable in biological fluids even in the absence of magnetic field. Without a coating, MNPs have hydrophobic surfaces with large surface area to volume ratios and a propensity to agglomerate. A proper surface coating can render them chemically stable via passivation of the magnetic core [31] and provide enhanced colloidal stability by way of increasing electrostatic and/or steric repulsion between the MNPs, allowing iron oxide MNPs to be dispersed into homogenous ferrofluids and improve MNP stability [32].

It was reported that amphiphilic comblike polymers can enhance the colloidal stability of Fe_3O_4 nanoparticles. With the inclusion of an amphiphilic comblike PEG derivative (CL-PEG) as an amphiphilic polymeric surfactant, stable colloidal dispersions of Fe_3O_4 MNPs were obtained. The flexible, hydrophilic side chains of CL-PEG-modified MNPs prevented the approach of adjacent nanoparticles, thereby resisting aggregation and resulting in a stable aqueous colloid [33]. And, MNP surface modification was carried out with oleate ions as coating shell able to ensure colloidal MNP stability and also allowing further adding of secondary organic shell for conferring hydrophilicity or possibility of grafting various biomolecules [34].

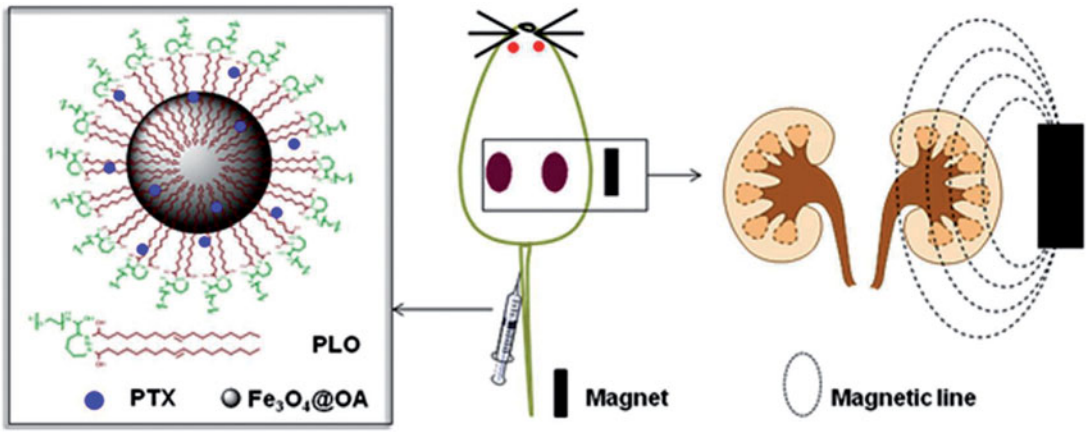


Figure 3. Schematic of PTX-loaded Fe_3O_4@OA modified by PLO and its kidney targeting application.

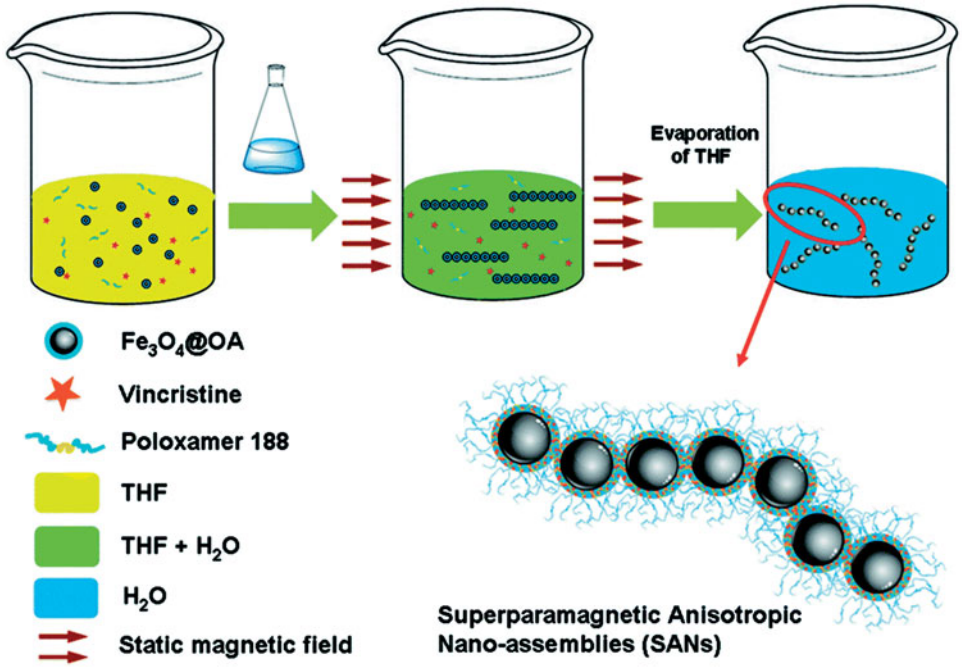


Figure 4. The fabrication process and ideal structure of the vincristine-loaded superparamagnetic anisotropic nano-assemblies (VCR-SANs).

Specific targeting

Specific targeting is one of the crucial factors in the administration of drugs and therapeutic biomolecules. There are two main categories of targeting mechanisms, passive and active targeting.

Passive targeting refers to the accumulation of drug or drug-carrier system at a particular site due to physiochemical or pharmacological factors [35]. Drug or drug carrier nanosystems can be passively targeted making use of the pathophysiological and anatomical opportunities [35,36] such as spontaneous penetration (Figure 4).

The development of long-circulating nanoparticles has allowed for many MNP platforms to exploit structural abnormalities in the vasculature of particular pathologies, such as tumors, inflammatory and infectious sites. This phenomenon, known as the enhance permeability and retention (EPR) effect, is based on the mechanism that these tissues possess 'leaky' vasculature which allows macromolecules and nanoparticles to extravagate and accumulate more readily. This nonspecific accumulation, or passive targeting, has been demonstrated with nanoparticles ranging from 10 to 500 nm in diameter [23]. Removal of MNPs depend on size is a common occurrence in healthy capillaries, as well. The residence time of MNPs in the bloodstream is the main limitation. Thus, drug delivery using conventional MNPs by passive targeting would be limited to tumors in mononuclear phagocyte system (MPS) organs (liver, spleen and bone marrow) [37].

Active targeting involves the selective modification of a drug or drug-carrier nanosystem with active agents, which have a selective affinity for recognizing and interacting with certain types of cells, like tissue or organ cells in the body [38–41]. These interactions include antigen–antibody and ligand–receptor binding, and physical signals such as magnetic fields and temperatures that are externally applied to the target sites [42].

Active targeting is based on the over or exclusive expression of different epitopes or receptors in tumor cells, and on specific physical characteristics. Thus, nanocarriers sensitive to physical stimuli (e.g. temperature, pH, electric charge, light, sound and magnetism) have been developed and conjugated to drugs.

Alternatively, active targeting may be based on over-expressed species such as low molecular weight ligands (folic acid, thiamin and sugars), peptides (RGD and LHRD), proteins (transferrin, antibodies and lectins), polysaccharides (hyaluronic acid), polyunsaturated fatty acids, peptides, DNA, etc. [37]. One example of specific binding on tumor cells is the approach of Shevtsov et al. using heat shock protein HSP 70 linked to the surface of SPIONs that are able to attach to the CD 40 receptor which is expressed on glioma cells [43]. The specific overexpression of Endoglin (CD105) receptors in actively proliferating cells was utilized in a concept for an antibody-labeled iron-tagged single-walled carbon nanotube that is additionally attributed with doxorubicin as a chemotherapeutic agent. The application in a murine breast cancer model yielded significantly increased cell death [44].

Biodistribution

Controlled release

Controlled release also plays a significant role in the clinical applications of the MNPs. Although MNPs have great biocompatibility and strong magnetic response ability, their biological dispersion is poor and they are easy to reunite and be cleared by macrophages or RES, due to its magnetic properties and smaller particle size. For drug delivery, MNPs may bring the problem of low utilization of drugs and the large side effect, which will affect the clinical efficacy. Taking Doxil as an example, Andresen et al. [45] found that although it is an effective carrier for delivering doxorubicin to the tumor tissue, only a modest increase in antitumor activity was observed. The major reason is the low rate of release of the drug from Doxil both in the blood circulation and in the tumor tissue. High-level tumor accumulation of nanoparticle formulation does not directly correlate to the bioavailability of the drug to the tumor, which is more dependent on the rate of drug release.

Thus, an increased level of attention has been paid to designing a formulation with a triggered-release mechanism, in which a nanoparticle formulation can release the encapsulated drug after accumulating in the target tissue. A controlled release of drugs from nanocarriers can be achieved through changes in temperature, pH, osmolality or via enzymatic activity. There are three approaches to control the rate of release of drug from the nanoparticles to match the PK profile of the nanoparticles and pharmacodynamic profile of the drug: (i) Increasing the rate of intracellular delivery by conjugating a targeting ligand on the surface of nanoparticles. (ii) Increasing the rate of escape of drug from the endosome/lysosome to improve bioavailability. And (iii) Increasing the rate of drug release locally at the target tissue by a physical method. Li et al. constructed a light controlled release prochelator using MNPs as a therapeutic agent with high selectivity toward metal ions that can efficiently inhibit Ab aggregation and decrease cellular reactive oxygen species, thereby protecting cells from different neurogenetic disorders [46].

Novel macro- to nano-scale systems that utilize remote-controlled drug release due to actuation of MNPs by static or alternating magnetic fields and magnetic field guidance of MNPs for drug delivery applications have attracted more and more attention [47]. The Food and Drug Administration (FDA) has established that the magnets inducing fields up to 8 T do not present any significant physiological risk for the adults. Fields $\approx$1 T can be readily obtained using external devices with electromagnets or powerful permanent magnets based on neodymium – iron (Nd – Fe) alloys (for $\sim$15 cm depths in the body) or by implanting the magnets internally by minimal invasive surgery (for larger depths) [48]. The SPIO conjugated thermo-sensitive polymers not only has magnetic targeting, but can realize the function of the release of drugs in specific parts after induction of magneto thermal phenomena in the alternating magnetic field [49].

Wu et al. [50] prepared thermo-sensitive SPIO with poly(N-isopropyl acrylamide) as enclosure. The particle size is about 100 nm at room temperature environment, while shrinking to 80 nm at 40 $\sim$ 45 °C. Under body temperature (37 °C) the MNP system is stable and releases drug slowly, and after it to the target site, magnetic particles generated magnetic heat in the alternating magnetic field environment, raising the temperature to above the critical temperature, so that the shell shrinks and drug releases quickly.

Pharmacokinetics and tissue distribution

The PKs and tissue distribution of the nanoparticles largely define their therapeutic effect and toxicity. It is reasonable to split all possible applications into three major categories (vascular system; hollow organs; soft tissues). It is very important to monitor the PK and biodistribution of nanoparticles to understand and predict their efficacy and side effects, because the PK profiles of the parent drug and the drug encapsulated in the nanoparticles are often different.

PK study involves measuring drug concentrations in all major tissues after drug administration over a period of time until the elimination phase. It is necessary to monitor the drug concentration long enough to fully describe the behavior of the drug or nanoparticles *in vivo* (usually 3 $\times$ half-life). The PK profile in the blood can be fitted using various programs to obtain key PK parameters, including maximum concentration (Cmax), half-life (t1/2), clearance (Cl), area under the curve (AUC) and mean resident time (MRT, average time that a molecule of a drug stays in the body), that quantitatively describe how the body handles the drug or nanoparticles. PK data not only can help describe but also can help predict the behavior or profile of the drug or nanoparticles. They are often used to decide the dose and dose regimen for maintaining desirable blood concentration for improved therapeutics with minimal side effects.

Unlike small molecule drugs that can diffuse through the capillary wall into the tissue, nanoparticles rely on the gaps between the endothelium to pass through the barrier. Tissues with a leaky endothelial wall, including tumor, liver, spleen, and bone marrow, usually contribute significant uptake of nanoparticles, which is based on a phenomenon called the 'enhanced permeability and retention' (EPR) effect due to the increased capillary permeability in the tumor tissue.

The PK and biodistribution of the nanoparticles are mainly determined by their chemical and physical properties, including size, surface charge and surface chemistry. Approaches for improving the PK of nanoparticles include maintaining the size around 100 nm, keeping the ζ potential within 10 mV, and grafting PEG onto the surface of nanoparticles. In investigating the effects of NP shape on biodistribution, a limited number of comparative studies have been performed evaluating the biodistribution of non-spherical and rod-shaped NPs [4]. It has been suggested that anisotropically shaped NPs can avoid bioelimination better than spherical NPs. In one notable study by Geng et al., the authors demonstrated a relationship by which an increase in the length-to-width aspect ratio of the nanostructure correlated with increased *in vivo* blood circulation time of nanostructures [51]. High aspect ratio shaped MNPs have also been evaluated *in vivo* and found to have similarly enhanced blood circulation times over the spherical counterparts.

The major drawback for the slow development of effectively targeted nanocarriers could be the lack of knowledge about the distribution and location of targeted nanoparticles after oral or intravenous administrations. Most studies have not examined the targeting efficiency of nanoparticles real time *in vivo*, thus precise bio-distribution and subsequently therapeutic effects are not well known. Therefore, detecting cancer (malignant) cells in the body and monitoring treatment efficacy in real time is a challenge that needs to be overcome to develop efficient targeted nanocarrier system for cancer therapy [52].

Safety and toxicity

As the applications of MNPs increasing, the public, scientific and regulatory authorities have given many concerns about their toxicological properties and long-term impact on human health [37,39,53]. To ensure a developed MNP system poses no threat to the patient after administration, toxicity of the individual components and NP as a whole must be evaluated. Hence, in the past decades, many studies have been done for the *in vivo* behaviors and toxicology of MNPs for the safe design [38,40–42,53,54].

In vitro *toxicity of MNPs*

Among the MNPs safety issues, *in vitro* toxicity research is an important subject as it is simple, inexpensive and easy to control [55]. The techniques usually used to assess toxicity of MNPs include (1) *in vitro* assays for cell viability/proliferation/differentiation (the MTT assay of mitochondrial function [38], the LDH assay of cell membrane integrity and immunochemistry markers for apoptosis/necrosis); (2) microscopic analysis of intracellular localization (electron microscopy and atomic force microscopy); (3) *in vitro* hemolysis and (4) gene express analysis/genotoxicity [56–59]. The methods above are extremely useful for initially evaluating the expected biocompatibility of new MNPs.

Generally, MNPs toxicity issues are related to dose-dependent effects and a higher number of MNPs will increase the risk for any toxic effects [60,61]. It is important to link cytotoxicity data both with the amount of iron oxide nanoparticles incubated as well as with the internalized number of nanoparticles over time. Nanoparticle-mediated cellular response is size-dependent [62] and in the study by Kunzmann et al. [63] size-dependent toxicity of silica-coated iron oxide nanoparticles was observed for primary monocyte-derived dendritic cells.

In vivo *toxicity of MNPs*

The *in vivo* interaction of MNPs and biological system is quite complicated and dynamic [64–66]. Once MNPs enter into the body, absorption occurs through interactions with biological components, for instance, proteins and cells; then they are distributed into different organs, in which they may remain in the same nanostructure or become metabolized [67]. In order to improve in design of biocompatible MNPs have a better understanding of nanoparticle nonspecific toward tissues and cell types, and assess basic distribution and clearance that serve as the basis to understand their activity and potential toxicity, a systematic and thorough quantitative analysis of the PKs (i.e. absorption, distribution, metabolism and excretion) of MNPs need to be perform [68,69].

Blood compatibility is an essential property for the *in vivo* functions of most nanoparticles [56,70]. Low of blood compatibility can lead to coagulation and the blood contact properties of MNPs should always be evaluated before clinical trials to for the safety concern. Several routine and widely available clinical assays can determine the coagulation properties of MNPs (i.e. prothrombin time, activated clotting time, activated partial thromboplastin time and thrombin time). The surfaces of MNPs are rapidly covered by selective sets of blood plasma proteins after injection. Generally, nanoparticle size, surface chemical, shape and stability are the key factors, which determine the interaction of the MNPs with proteins. MNPs fate and biodistribution inside the body are strongly influenced by the protein adsorption. For instance, adsorption of human serum albumin was demonstrated to prolong circulation time in blood [68,71].

The variability in manufacturing methods to produce uniform MNPs are required to make cross comparisons between the PK results obtained from different research groups [69,72]. Functional MNPs are typically coated with stabilizing molecules and/or biological molecules. It is easily achieved traditional radiolabeling of the surface molecules, but the PK results using this labeling method can be misleading. Multi-indicator techniques, such as multimodality imaging methods (PET-MRI), would provide a complete picture of metabolic processes. In order to achieve more effective correlation between MNPs properties and *in vitro* cytotoxicity and metabolism data, it is necessary to increase the resolution of *in vivo* distribution to the cellular level. The clear mapping of the fate, kinetics, clearance, metabolism, immune response and MNPs would allow the development of predictive models of nanotoxicity [73].

Perspectives and future challenges

A search of the Web of Science that stipulated 'magnetic nanoparticles' and 'drug delivery systems' as two keywords produced 805 hits, and the total cited frequency was 21,184 hits [74]. Focusing on the current research on the MNPs is aim to find the way to improve the MNPs performance in DDS. One area of special interest is the development of strategies able to increase the circulation time of MNPs in the blood. Another area of recent interest is the development of nano-attractors able to concentrate MNPs in a desired region [75]. This is highly depended on the physicochemical properties of MNPs. Size, shape and surface chemistry dictate *in vivo* behavior, including biodistribution, biocompatibility and PKs. As such, these parameters can be tuned to achieve enhanced targeting via passive, active and magnetic targeting mechanisms. Find the balance between size and magnetism, proper surface linking way with drug, and the ideal shape of MNPs, then high drug-loading and maximum drug releasing rate at the targeting position MNPs can be obtained.

An important issue needs to be considered when selecting SPIONs for drug delivery: the fate of the SPIONs after the drug delivery, i.e. elimination route or retention time in the body system if they are biodegradable and the relevant side effects. For example, silica-coated SPIONs could be biocompatible; however, if the iron oxide core is exposed, it can cause an oxidative stress which could be associated with neurological disorders. Similarly poly(methyl methacrylate) is biocompatible but its biodegradable products, such as methacrylate monomer, could be reactive and toxic. The selection of SPIONs for specific drug loading should be carefully judged based on how the drug and shell materials complement each other; otherwise a burst effect could produce toxic chemicals by combination of drug and shell materials.

Practice shows that targeted drugs in clinical application are only effective in some patients. It was pointed out that we must firstly screen patients who are appropriate to a sort of targeted drug, to judge whether she/he can obtained efficacy through

drug. In addition, we should monitor whether the targeted drug fail or not during treatment, if it is found that efficacy significantly reduced, can be promptly disable or switch to other drugs, the traditional pathology biopsy specimens were obtained from tumor tissue before treatment, various target molecules' growth and decline situation cannot be reflected during treatment. To solve these problems, the composite functional nanoparticles a set of angiography and treatment or imaging nanoparticles and treatment nanoparticles can be prepared, to use imaging nanoparticles for targeted localization of the disease, and then use nanoparticles for targeted therapy treatment [76].

As technology developing, we will know the *in vivo* behavior of MNPs better, at the same time more elaborate and functional MNPs can be made. We may remark here that even if increase in efficiency is marginal it may lead to further investigations and improvement of the method which in turn prove helpful for healthcare and environment.

Disclosure statement

No potential conflict of interest was reported by the authors.

Funding

This work was financially supported by The National Key Research and Development Program of China [2017YFA0205502, 2017YFA0104301], The National Natural Science Foundation of China for Key Project of International Cooperation [61420106012], National Natural Science Foundation of China (81473160), the Basic Research Program of Jiangsu Province (Natural Science Foundation, No. BK20151422), Fundamental Research Funds for the Central Universities (2242014R30013 and 2242016K40033), National High Technology Research and Development Program of China (No. 2013AA032205), and Qing Lan Project. This work is supported by Collaborative Innovation Center of Suzhou Nano Science and Technology.

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