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Original
Design and fabrication of magnetically responsive nanocarriers for drug delivery / Kralj, S., Potrč, T., Kocbek, P., Marchesan, S., Makovec, D.. - In: CURRENT MEDICINAL CHEMISTRY. - ISSN 0929-8673. - 24:5(2017), pp. 454-469. [10.2174/0929867323666160813211736]

Availability:
This version is available at: 11368/2897553 since: 2017-09-02T11:41:50Z
Publisher:

Published
DOI:10.2174/0929867323666160813211736
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09 October 2026

Design and Fabrication of Magnetically Responsive Nanocarriers for Drug Delivery

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Abstract

Magnetically-assisted delivery of therapeutic agents to the site of interest, which is referred to as *magnetic drug targeting*, has proven to be a promising strategy in a number of studies. One of the key advantages over other targeting strategies is the possibility to control remotely the distribution and accumulation of the nanocarriers after parenteral administration. However, preparation of effective and robust magnetically responsive nanocarriers based on superparamagnetic iron oxide nanocrystals (SPIONs) still represents a great scientific challenge, since spatial guidance of individual SPIONs is ineffective despite the presence of high magnetic field gradient. A strategy to overcome this issue is the clustering of SPIONs to achieve sufficient magnetic responsiveness. In this mini-review, we address current and future strategies for the design and fabrication of magnetically responsive nanocarriers based on SPIONs for magnetically-targeted drug delivery, including the underlying physical requirements, the possibility of drug loading, and the control of drug release at the targeted site.

Introduction

Nanotechnology is advancing at a fast pace and holds promise to overcome many of current therapeutic limits through the advent of nanomedicine [1, 2]. Many drug candidates never undergo translation from pre-clinical trials to market due to their specific physicochemical properties (e.g. poor water solubility), which hinder their efficacy and/or safety when administered in traditional formulations, such as tablets, capsules, and solutions for injections [3]. Proper design and development of novel nanocarrier systems can revitalize such drug candidates and bring them back into further translational studies. Drug adverse effects can be diminished or avoided by drug incorporation into advanced nanodelivery systems, which enable passive or active drug targeting, including smart external guiding of the nanocarriers in the body, and controlled drug release at the target site [4].

Nanomaterials in the form of nanoparticles, nanotubes, nanorods, and other self-assembled nanostructures can be transformed into advanced nanocarriers, which are particularly suited for biomedical applications [1]. A key feature is their nanoscale size, which correlates with the size of biological macromolecules and subcellular structures. They can be used for advanced diagnostics and treatment of various diseases as well as in tissue regeneration [5]. Nanodelivery systems based solely

on organic materials are nowadays approaching a mature stage, meaning their entry to the market, upon a few decades of development. For example, nanomedicines in form of liposomes (DaunoXome®, Myocet®, Doxil®) and albumin nanoparticles (Abraxane®) have already reached clinical use in cancer treatment [6, 7]. Despite the extensive development of diverse nanocarriers, poor stability, low drug loading, and lack of external guidance for efficient targeting, are often limiting factors for successful translation from preclinical to clinical use [8- 11].

Recently, inorganic nanomaterials have attracted increasing attention due to their unique advantages. They display notably higher thermal, chemical, and biological stability in physiological conditions relative to organic materials [12]. Among inorganic nanomaterials, which have been proven to be safe and efficient in the treatment of human pathologies, iron oxide nanocrystals play an elected role, being either in paramagnetic form (akaganeit; β-FeOOH) or exhibiting ferromagnetic or superparamagnetic properties (maghemite; γ-Fe_2O_3 and magnetite; Fe_3O_4) [13-15]. Superparamagnetic iron oxide nanocrystals (SPIONs) have been synthesized by a variety of approaches ranging from traditional low-cost coprecipitation methods to more sophisticated techniques such as sonolysis, electrochemical methods, laser pyrolysis or chemical vapour deposition [16, 17], resulting in commercial manufacture of different magnetic particles for research and clinical use by different well-known companies and start-ups (Table 1).

Table **1**. List of some companies selling products based on iron oxides for research and development as well as clinical use.

Company	Application	Website
AMAG Pharmaceuticals Inc.	Anemia treatment, MRI contrast agents	www.amagpharma.com
Chemicell GmbH	DNA and RNA purification, bioseparations, gene transfection, drug delivery	www.chemicell.com
EMD Millipore (Merck KGaA)	Immunoassays, magnetic bioseparations , protein purification	www.emdmillipore.com
Endomagnetics Ltd.	*In vivo* cancer diagnostics, hyperthermia	www.endomagnetics.com
Invitrogen Inc.	Immunoassays, DNA and RNA isolation, protein purification, cell separations	www.thermofisher.com
MagForce Nanotechnologies AG	Hyperthermia	www.magforce.de
MagnaMedics GmbH	*In vitro* diagnostics, DNA isolation, immunoassays	www.magnamedics.com
Mikromod GmbH	Nucleic acid purification, magnetic separations, drug delivery	www.micromod.de
Nanos SCI	Drug delivery, magnetic bioseparations, cell sorting, fluorescent cytometry, microfluidics	www.nanos-sci.com
nanoTherics Ltd.	Bioseparations, gene transfection	www.nanotherics.com

Sirtex Medical Ltd.	Radiation therapy	www.sirtex.com
Spherotech Inc.	Enzyme immunoassay, cell sorting, fluorescent cytometry, cell separations	www.spherotech.com

A promising strategy for magnetic drug targeting typically involves the concomitant use of different nanotechnological approaches. It is useful only in case the disease is localized to a specific part of the body and it is advantageous over other targeting strategies due to the ability to remotely control the distribution and accumulation of the parenterally administered nanocarriers in the body. The most frequently used magnetic component of magnetically responsive nanocarriers (MNCs) are iron oxide nanocrystals, which are incorporated together with a therapeutic component (drug) into a single MNC, such as liposomes, micelles, polymeric matrix type or inorganic core-shell nanoparticles [12, 18]. MNCs can also be prepared with other types of magnetic nanoparticles such as metallic Fe, Co, and FePt exhibiting superior magnetic properties but lacking biocompatibility because they can be readily oxidized and are intrinsically toxic. SPIONs can be manipulated by an external magnetic field gradient if properly assembled into MNCs. Their feature of remote responsiveness combined with the intrinsic penetrability of magnetic fields into the human body, opens up great opportunities for many applications involving external guidance and retention of the MNCs at a desired site. Due to their unique physical properties, SPIONs can play a role also for other biomedical applications. Key examples include: contrast agents in magnetic resonance imaging (MRI) for medical diagnostics [19] or magnetic particle imaging [20]; heat-producing agents when exposed to radio frequency alternating magnetic field (AMF) in magnetic hyperthermia for cancer treatment, or for controlled drug release from MNCs [21, 22]; building blocks of magneto-mechanical actuation-associated nanomedicines in low and super-low frequency AMF [23-26], and many others [27].

Despite numerous examples of application of SPIONs in biomedicine, preparation of effective and robust MNCs based on SPIONs still represents a great scientific challenge. Many approaches exist to improve an important physical limit of individual SPIONs, namely the too small magnetic force (F_M) acting on individual nanocrystals exposed to magnetic field gradient [28-30]. In general, magnetic drug targeting involves (i) the incorporation or attachment of a drug in/onto the biocompatible MNC, (ii) intravenous injection of the nanocarrier in the form of colloidal suspension, (iii) application of magnetic field gradient to direct the carrier to the pathological site, and (iv) release of the payloads from the carrier at the target site (Figure 1).

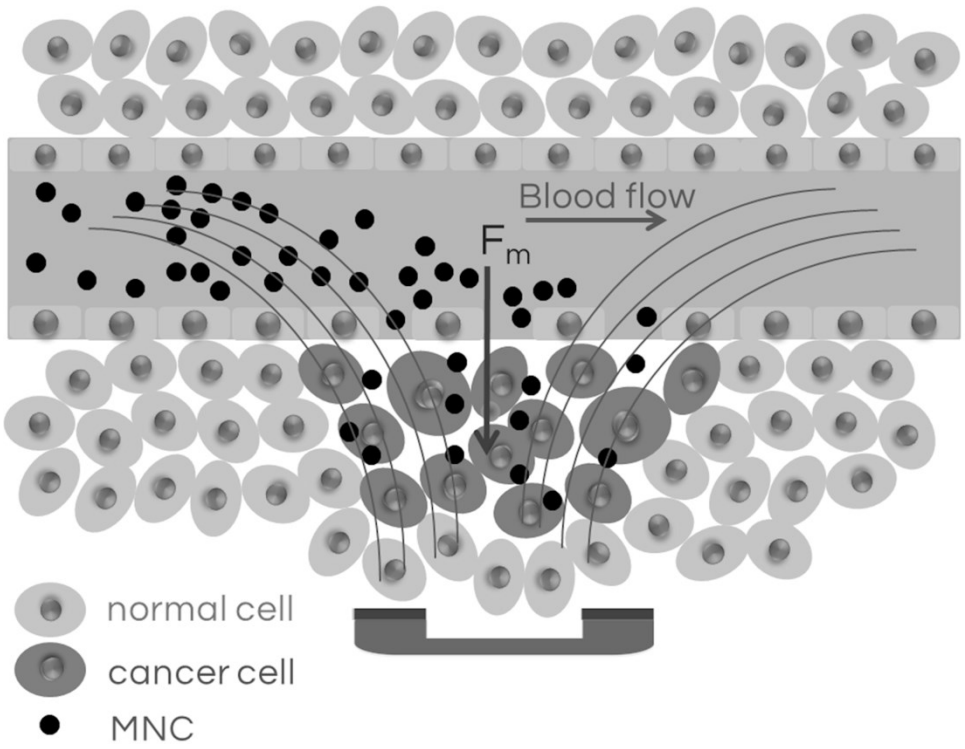

Figure 1. Scheme representing magnetic drug targeting. Magnetic field is focused to the target site (e.g. tumor). The magnetic force acting on the nanocarriers, as they enter the field, reinforces extravasation and accumulation of magnetically responsive nanocarriers (MNCs) at the target site.

Key parameters that determine the effectiveness of this drug delivery method include: the physicochemical properties of the nanocarrier, the field strength and geometry, the depth of the target tissue, the blood flow rate, and the extent of vascular supply to the site [31, 32]. The idea of drug delivery in the form of "magic bullet" was envisaged by Paul Ehrlich (Nobel Prize in 1908) who proposed selective targeting of a toxin to a pathogen by co-delivery with an agent of selectivity that targets specific receptors. In 1960, Freeman and co-workers suggested that magnetic carriers could be concentrated in a specific part of the body with the aid of a magnetic field [33]. The first magnetically responsive carriers for targeted drug delivery have been designed in the form of micron-sized particles in the 1970s [34-36]. In the last two decades, the design and development of nanoscale drug carriers have been challenging tasks that offer plenty of space for further improvement [37-41].

In this mini-review we primarily address current and future strategies for the design and fabrication of MNCs based on SPIONs for magnetically targeted drug delivery, including the underlying physical requirements for their magnetic responsiveness. We do not analyse in detail other aspects such as the techniques for the synthesis of SPIONs, or the interactions of the nanocarrier systems with the biological environment. An important emphasis of the mini-review will also be devoted to the drug loading possibilities into a nanocarrier and the controlled release of the payloads at the targeted site. For an in-depth discussion of other targeting strategies, such as passive targeting based solely on enhanced permeation and retention (EPR) effect, and a number of active targeting strategies which

rely on binding of the targeting ligands (affinity moieties) to the nanocarrier surface and their nanotoxicity assessments, please refer to existing comprehensive reviews [42-46].

1) Physical requirements for effective magnetic targeting

The key feature of magnetically responsive carriers is their ability to be efficiently (i) isolated from complex fluids, such as blood flowing through the target region, and (ii) retained at a desired site for prolonged time, if exposed to a magnetic field gradient generated by a strong permanent magnet such as Nd-Fe-B (Neodymium Iron Boron alloy). The magnet can be placed outside the body over the target site or implanted internally using minimally invasive surgery [32, 47, 48]. It is crucial to understand that a magnetic field gradient is required to exert magnetic force (F_M) at a distance; a uniform field gives rise to a magnetic torque, but no translational action. For successful magnetic targeting, the F_M should prevail over the thermal energy (k_BT), causing a Brownian motion, and over the hydrodynamic drag in the blood. The F_M acting on the nanocrystal is proportional to its magnetization (M), volume (V), and magnetic field gradient (∇H), i.e., $F_M = \mu_0 M V \nabla H$ (where μ_0 is the permeability of free space), with M being mainly defined by the type of magnetic material and magnetic field strength. Particle size (d) has only a minor effect on the M of nanocrystals, while it has a much larger impact on the F_M, since F_M increases with d^3. The size of individual SPIONs should not be increased over ~15 nm because at that size limit the SPIONs lose their superparamagnetic properties and thus they are not suitable for the preparation of colloidal suspensions, due to magnetic dipole-dipole interactions resulting in undesired aggregation [49]. On the other hand, the individual SPIONs, unfortunately, cannot be effectively guided within the body despite the presence of high magnetic field, due to the too small F_M acting on each individual SPION [50]. Thus, the most beneficial way to effectively increase F_M acting on a nanocarrier in a stable suspension exposed to a magnetic-field gradient, whilst maintaining the superparamagnetic state, is to increase its volume [28, 51]. This objective could be achieved by assembly of numerous individual SPIONs into well-defined clusters that is the basis for nanocarriers' magnetic responsiveness [29]. The common feature of these clusters is that multiple SPIONs are physically held together in a small spatial compartment. We have recently published innovative nanotechnological approaches for the preparation of highly magneto-responsive SPIONs clusters with a size range of 50-150 nm, optimal for further development into magnetically responsive drug delivery systems [29, 30, 52]. Indeed, a great challenge still remains in the efficient incorporation of a drug into a nanocarrier, especially preparation of MNCs with spatially separated compartments for drug and magnetic nanocrystals, with advantages in terms of improved drug stability [12, 53].

To achieve magnetic targeting, the magnetic force acting on individual magnetic carriers needs to overcome the hydrodynamic drag force (F_D), which enables the carrier to evade the magnetically targeted site. The F_D is linearly dependent on the viscosity of the fluid medium (e.g. blood), the diameter of the carrier, and the difference in velocities of the carrier and the fluid. The motion of the carrier towards high magnetic gradient is affected also by buoyancy force, which depends on the difference between the densities of the carrier and of the fluid medium. After taking into an account all the above-mentioned forces, we come to the parameter known as magnetophoretic mobility of the carrier, *i.e.* a parameter that describes the carrier's magnetic responsiveness [49]. Since the magnetophoretic mobility depends on the carrier size, it is significantly greater in case of micron-

sized particles or microspheres (~ 1 μm in diameter) compared to nanoscale carriers (~ 100 nm in diameter) and the individual nanocrystals (~ 10 nm in diameter). This "guiding" feature of microspheres is already widely applied in bioseparations, which exploit the same physical principles for magnetic manipulation [32]. Thus, such relatively big microspheres can be efficiently used in cell and other types of bioseparations where the biomolecules and cells coupled with microspheres can be isolated from the complex mixtures in the shortest possible time [49]. However, the magnetically responsive micro-sized carriers are too big for the intravenous or intra-arterial applications because they can cause embolism. Moreover, the majority of solid tumors exhibit a porous vasculature with the pore size between 380 nm and 780 nm, depending on the tumor type and its microenvironment [54]. Therefore, the optimal particle size for preparation of magnetically responsive drug carriers should be a compromise between the biomedical size restrictions, giving preference to smaller particle sizes, and the particle magnetophoretic mobility parameter, being greater in case of larger particles. Some studies on magnetic targeting, where the hydrodynamics of the magnetic carriers have been investigated, revealed that the magnetic field gradients should be at least 8 Tm^{-1} and 100 Tm^{-1} for effective targeting of the femoral and carotid arteries, respectively [55]. In fact, the magnetic drug targeting is likely to be most effective in body regions where the blood flow is slow and in the regions close to the permanent magnet, due to both lower F_D and larger magnetic field gradients [56]. The minimum size of the magnetic carriers based on SPIONs dispersed in an aqueous suspension to be efficiently attracted in a magnetic field gradient in a reasonable time is approximately 50 nm [28]. There are various terms used in literature for such assembled particles with size from 50 to 300 nm, *i.e.* magnetic nanobeads, multi-core nanoparticles, nanocomposite particles, nanospheres, nanoclusters, nanoparticle clusters, and SPION clusters. However, we use the general term of MNCs, as the optimal size of drug delivery system based on SPIONs for intravenous application is in the "nano" range.

2) Structural types of magnetically responsive nanocarriers in drug delivery

The syntheses of the magnetic component as well as the design of the nanocarrier are key steps to achieve a magnetically-responsive nanodelivery system capable of efficient targeting as discussed above. Drugs may be coupled to the carrier surface by means of electrostatic or covalent bonding. Although this approach is straightforward, it has some drawbacks. Surface-bound drug molecules may impair colloidal stability of the nanodelivery system; drug release may be hampered due to strong binding; alternatively, extensive burst release can occur in case the drug is weakly bound. Drug attachment to the nanocarrier surface is also limited by the specific surface area of the nanocarrier. Therefore, when the nanocarrier size is increased for improved magnetic responsiveness, there will be an overall reduced surface area, and thus a relatively smaller amount of binding sites for the drug. An interesting alternative to surface attachment is drug incorporation into an organic and/or inorganic matrix, which physically holds the SPIONs together in a defined spatial compartment whilst allowing drug loading and release [12]. The drug loading capacity of such delivery systems is often enhanced compared to the drug attachment to the nanocarrier surface. In addition, the majority of drugs are low-molecular-weight molecules often associated with challenging physicochemical properties, such as poor water solubility. Therefore, the design and fabrication of a suitable nanocarrier system for delivery of such drugs requires additional attention.

2.1) Magnetoliposomes

Liposomes are biocompatible, biodegradable, and generally non-toxic nanodelivery systems that enable transport of both (i) hydrophilic drugs in the aqueous interior and (ii) hydrophobic/amphiphilic drugs embedded in the liposome membrane [57]. However, the applicability of liposomes for the delivery of poorly soluble compounds is limited, since only small drug amounts can be incorporated into the hydrophobic liposomal bilayer; besides, this approach can impair the bilayer stability. Currently, large unilamellar liposomes with a diameter ranging from 100 to 200 nm represent the most successful nanodelivery systems in clinical use. Besides surface properties, the size of the carrier is indeed a crucial parameter affecting circulation half-time in the bloodstream [58].

Magnetoliposomes can be prepared by incorporation of SPIONs into the liposomes. They represent a novel and very promising multi-purpose tool for imaging and magnetic targeting, which can be non-invasively controlled [57]. Importantly, both liposome components and SPIONs are FDA-approved, thus their combination may proceed to the clinical practice with minimal safety concerns [59]. The magnetic responsiveness can be achieved by incorporation of either hydrophilic or hydrophobic SPIONs in the aqueous liposome interior or in the liposome membrane, respectively (Figure 2). Several examples have been reported in the literature thus proving the versatility of this approach. Nappini *et al.* have described incorporation of up to 30 SPIONs with the size from 10 to 16 nm per individual magnetoliposome [60]. Garnier *et al.* prepared magnetoliposomes with high iron content by incorporation of up to 77 citrate-coated SPIONs with a size of ~7 nm into a single liposome [58]. Thermosensitive magnetoliposomes containing citrate-coated SPIONs and paclitaxel for the treatment of various solid tumors were described by Kulshrestha *et al.* [61]. A similar system with entrapped dextran-coated SPIONs and a fluorescent dye was prepared by Tai *et al.* [59]. Bothun *et al.* designed folate-targeted cationic magnetoliposomes with encapsulated doxorubicin and anionic SPIONs [62]. Guo *et al.* developed monodisperse dextran-coated magnetoliposomes with the size of ~120 nm where SPIONs and doxorubicin were encapsulated in the liposome interior. This formulation demonstrated excellent stability in serum and good magnetic responsiveness. The release of doxorubicin was triggered by exposure to the low frequency AMF [63]. Undesired interaction between drug and SPION (*i.e.*, drug complexation with surface iron atoms) can be avoided with spatial separation of the two components; for example, magnetoliposomes may have hydrophobic SPIONs in the liposomal bilayer, so that the aqueous liposome interior will be available for incorporation of sensitive drugs. The research group of Babincova prepared large unilamellar magnetoliposomes with spatial separation of doxorubicin and SPIONs that were encapsulated into the liposome interior and lipid bilayer, respectively [64]. Chen *et al.* described MNC in the form of 100 nm-sized unilamellar magnetoliposomes with embedded 5 nm-sized oleate-coated SPIONs in the liposome membrane, and carboxyfluorescein in the aqueous interior. The drug release was triggered by hyperthermia, thanks to heat generation by SPIONs exposed to AMF [65]. Bixner and Reimhult presented vesicles with hydrophobic, monodisperse 3.5 nm *N*-palmityl-6-nitrodopamide-coated SPIONs embedded in the membrane. In this study the effectiveness of SPION incorporation into the liposomes was dependant on the size and surface coating of SPIONs and it was significantly improved compared to other previously reported methods, *i.e.*, 26 SPIONs per 100 nm-sized vesicle. However, SPION loading decreased and the polidispersity and lamellarity of vesicles increased, when oleate-

coated SPIONs were embedded in the liposome membrane [57]. Magnetoresponsive hybrid liposomes with incorporated thermosensitive polymers and SPIONs were designed by Katagiri and co-workers. In this case, oleate-coated SPIONs were incorporated in the lipid bilayer, while the water-soluble fluorescent dye pyranine was loaded in the liposome interior. Remote control of pyranine release was achieved by exposure to AMF; the release rate was affected by the amount of incorporated SPIONs and the type of thermosensitive polymers used [66].

Peiris *et al.* described a multi-component nanocarrier system for doxorubicin delivery with SPIONs in the form of short nanochains being attached to the drug-loaded liposomes. This delivery system coupled with AMF-triggered drug release showed improved penetration and deposition at micrometastatic sites. As a result, a low dose of cytotoxic drug proved effective for cancer treatment, indicating great potential for application in all types of cancer that exhibit aggressive and metastatic phenotypes [67-70].

Magnetoliposomes are frequently studied MNCs for the delivery of hydrophilic biomacromolecules, such as therapeutic proteins. Ye *et al.* developed magnetoliposomes loaded with recombinant human interferon-α_2b and hydrophilic 10 nm-sized SPIONs. Cell experiments and animal studies demonstrated that magnetoliposomes delivered by magnetic targeting significantly inhibited cancer cell growth, and notably reduced tumor size in nude mice, indicating improved therapeutic efficacy and reduced side effects to non-target organs [71]. Meier *et al*. developed immuno-magnetoliposomes with a high amount of entrapped hydrophilic SPIONs for MRI [72]. They showed that liposome PEGylation up to a certain degree had a positive influence on both the amount of entrapped SPIONs and the stability of magnetoliposomes. Furthermore, Martins *et al.* tested the application of surface-modified magnetoliposomes for the affinity adsorption of antibodies, with the antigen being either embedded in the phospholipid bilayer or covalently coupled to the surface of the magnetoliposome [73]. This system displayed good properties for further development into immunodiagnostics or drug delivery formulations.

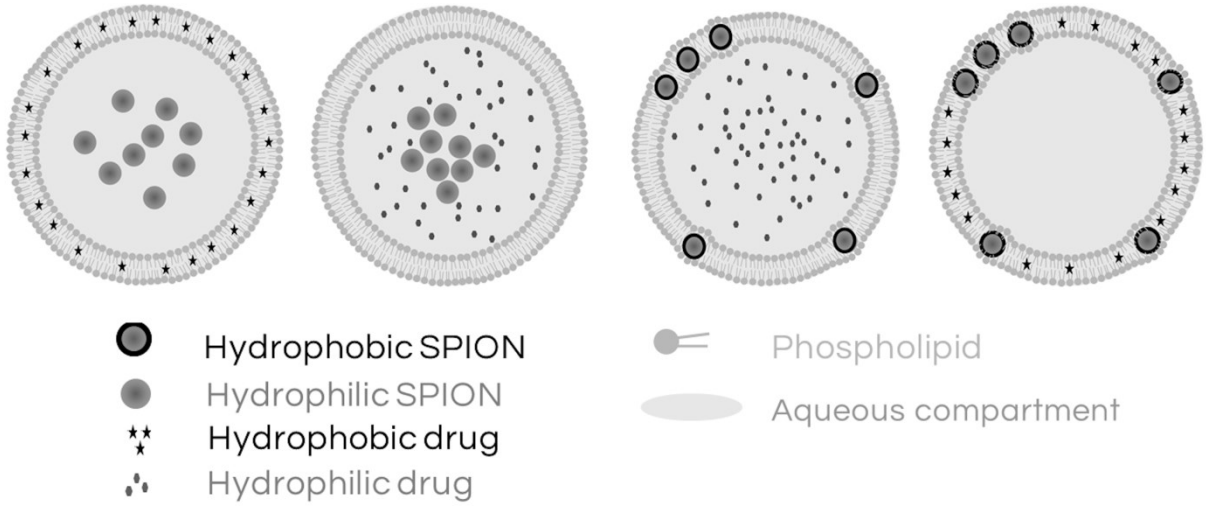

Figure 2. Schematic representation of the most frequent types of drug-loaded magnetoliposomes. Hydrophilic SPIONs and drugs can be encapsulated into the inner aqueous compartment, while hydrophobic SPIONs and drugs can be incorporated into the phospholipid bilayer.

2.2) Polymeric magnetically-responsive nanocarriers

Nanocarriers based on polymer matrices are nowadays widely investigated for various applications in biomedicine. The polymer matrix can be either hydrophilic or hydrophobic; therefore, hydrophilic as well as hydrophobic drugs can be loaded. Drug release from the polymer matrix can be either diffusion- or erosion-controlled. Additional incorporation of SPIONs makes such nanocarriers magnetically-responsive.

In 1994, Häfeli and co-workers successfully synthesized biodegradable poly(lactic acid) microparticles containing magnetite nanocrystals and the beta-emitter ^{90}Y for targeted radiotherapy of subcutaneous tumors [74]. This initial study was based on micro-sized carriers, while further developments mostly focused on the design of nanosized polymeric carriers. Hu and co-workers designed 200 nm-sized tamoxifen-loaded poly(L-lactic acid) nanocarrier containing 6 nm-sized SPIONs [75]. Similar polymeric nanocarriers were obtained from poly(lactic-co-glycolic acid) loaded with 10 nm-sized hydrophobic SPIONs for the targeting of intracellular compartments (Figure 3) [76]. The nanoparticles have the potential to be evolved into magnetically-responsive drug nanocarriers for relatively hydrophobic anticancer drugs. Burnand *et al.* used the catechol-modified poly(vinyl alcohol) as a coating polymer for monodispersed SPION clusters. The clusters with size between 40 and 80 nm showed potential applicability in biomedicine [77].

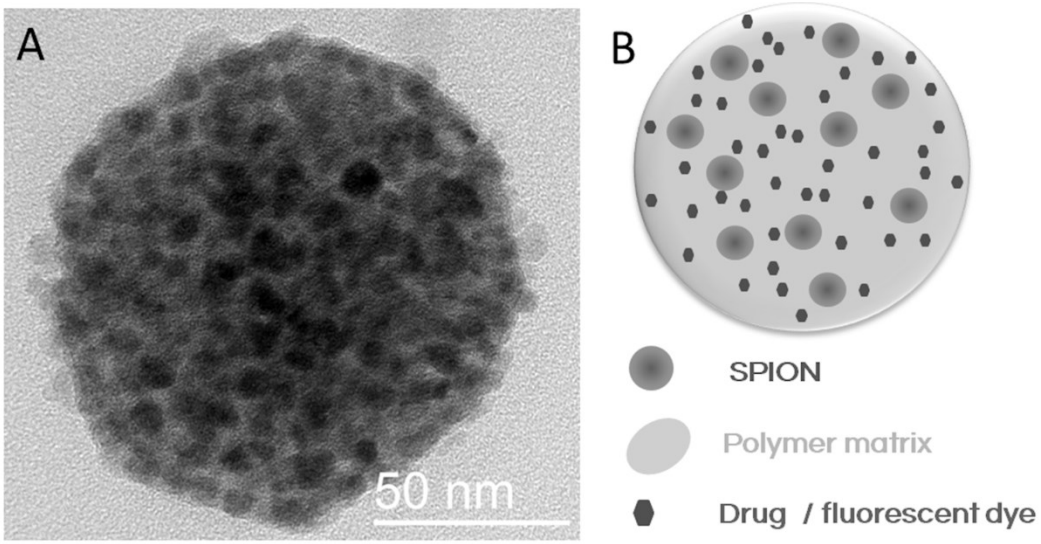

Figure 3. (A) TEM image and (B) schematic representation of a polymeric nanoparticle with the diameter of approximately 100 nm. Multiple hydrophobic SPIONs were incorporated in the polymer matrix together with sparingly water-soluble drug or fluorescent dye.

Fang *et al.* successfully prepared SPION clusters with an average diameter of approximately 140 nm and coated with chitosan for detection and identification of low abundant glycopeptides in glycoproteome analysis. Aberrant glycosylation of some important proteins is highly associated with various disease states including cancer. The presented formulation showed great potential for the design of relevant drug delivery systems [78].

There is vast literature on drug delivery applications of polymer-based nanocarriers containing SPIONs, especially for cancer treatment, but also for diagnostic use. For instance, Chertok and co-workers presented starch-coated SPIONs with a hydrodynamic diameter of 110 nm [79]. The particles were composed of multiple individual SPIONs and a 5-fold increase in *in vivo* accumulation was seen for glioma sites that were magnetically-targeted, relative to non-targeted tumors. Yang and co-workers developed cisplatin- and gemcitabine-loaded 250 nm-sized magnetic poly(ethyl-2-cyanoacrylate) particles [80]. The nanocarrier was successfully loaded with hydrophobic SPIONs and cisplatin whereas incorporation efficiency of relatively hydrophilic gemcitabine was much lower. Thus, cisplatin exhibited sustained release, whereas gemcitabine displayed rapid release. Another magnetically-responsive polymeric nanocarrier was reported by Di Corato and co-workers [81]. They designed 100 nm-sized poly(maleic anhydride-*alt*-1-octadecene) nanoparticles loaded with multiple SPIONs and quantum dots. The nanosystem demonstrated good magnetic responsiveness that was confirmed by magnetic cell sorting. The magnetic particles could be loaded with hydrophobic drugs and applied in drug delivery. Li *et al*. developed a promising multifunctional theranostic nanodelivery system based on polyethylene glycol functionalized SPIONs, which were loaded with chlorin e6, a widely used photosensitizer in photodynamic therapy. Due to the greatly accelerated cellular uptake, such magnetic nanoparticles showed a much stronger cancer cell eradication in comparison to free chlorin e6, therefore indicating a good potential for application in magnetically-targeted, photodynamic cancer treatment [82]. SPION clusters coated with poly(dopamine) with an average diameter of 80 nm were developed as a magnetic field-directed theranostic agent by Wu *et al.* The SPION clusters enabled ultrasensitive MRI imaging whereas the poly(dopamine) coating induced cancer cell death under near-infrared laser irritation, due to the photothermal conversion ability of poly(dopamine) [83]. Oka *et al.* described preparation of composite particles based on biodegradable polymer polyhydroxyalkanoate and SPIONs. A model drug pyrene was incorporated into the polymer matrix and released upon biodegradation, indicating applicability of the system in magnetically-guided drug delivery [84]. Release can be triggered *also via* magnetic hyperthermia when the matrix is prepared from thermo-responsive polymer and loaded with SPIONs [85]. Drug release occurs through nanoscale cracks formed within the matrix, due to the local heat generated by SPIONs exposed to high frequency AMF [21, 86-88]. Another possibility is drug release triggered by formation of openings that are induced by a magneto-mechanical force [89].

Shortcomings of polymer matrix nanocarriers include: relatively high polydispersity, limited mechanical and microbiological stability, and high cost [43], therefore inorganic nanocarriers represent an interesting alternative and are currently widely investigated.

2.3) Silica-based core-shell magnetically-responsive nanocarriers

Core-shell particles have attracted considerable attention in the field of drug delivery, due to many unprecedented advantages [90]. Silica-based shell structures are especially interesting [91]. Research in the field has been intensively focused on the development of facile and versatile synthesis methods for the fabrication of mesoporous silica shells on various types of magnetic core particles, since high surface area, high pore volume, and large pore channels are advantageous properties of mesoporous silica [92]. Furthermore, it is highly desirable that mesopore channels in the shell are open to the surface in order to achieve loading and release of various guest molecules. However,

these core-shell particles can also be transformed into hollow carriers to enable enhanced drug loading in the interior and preserved magnetic responsiveness [93].

Silica is a product of sol-gel process that involves alkoxide precursors (tetraethyl orthosilicate; TEOS), which undergo hydrolysis upon reaction with water and catalyst. Subsequent condensation results in the formation of either homogeneous spherical particles or defined layers (*i.e.*, shell) on the surface of core particles. In the late 1960s, Stöber reported the preparation of colloidal silica particles as a result of sol-gel chemistry [94]. Since the classical Stöber process yields only non-porous silica with low surface area, new approaches have been developed for the preparation of mesostructured silica [95-98]. Deng *et al.* have reported magnetically-responsive silica-coated particles with perpendicularly aligned channels inside the silica shell [99]. The highly ordered channels are formed upon addition of cetyltrimethylammonium bromide (CTAB), and subsequent refluxing in acetone. The Shi group proposed a similar carrier system composed of a non-magnetic hematite core that was transformed into a magnetic core, upon silica coating and reductive thermal treatment [93]. These hollow nanostructures were further evolved into drug delivery system with high-loading of ibuprofen (~ 12 % w/w) and prolonged drug release in a simulated body fluid. Liong and co-workers have prepared multifunctional nanocarriers composed of multiple 20 nm-sized SPIONs and then coated them with a 100–200 nm-thick mesoporous and fluorescent silica shell [100]. Hydrophobic anticancer drugs such as camptothecin and paclitaxel were loaded into silica pores *via* incubation of the empty nanocarrier in a concentrated DMSO solution of the anticancer drug. The authors observed that only 4 % w/w of the loaded drug was released into aqueous medium, while the total drug amount came out of the mesopores when the nanocarrier was incubated in DMSO or methanol.

Our group has recently developed novel magnetically-responsive SPION clusters based on chemically-directed assembly of individual silica-coated SPIONs in aqueous suspension [30]. The SPION clusters have a diameter of approximately 50 nm, and display a “raspberry-like” morphology that show high surface area and a large fraction of iron oxide (~ 46 emu g^{-1}). These SPION clusters are readily functionalized for further conjugation or attachment of drug molecules. More recently, we have synthesized core-shell particles with a SPIONs core of ~ 100 nm in diameter and a silica shell of variable thickness (5 – 30 nm) by means of phase-transfer of SPIONs assisted by poly(acrylic acid) and polyvinylpyrrolidone (Figure 4) [29, 52]. The particles show excellent magnetic responsiveness and redispersibility as well as good potential to be evolved into drug delivery systems.

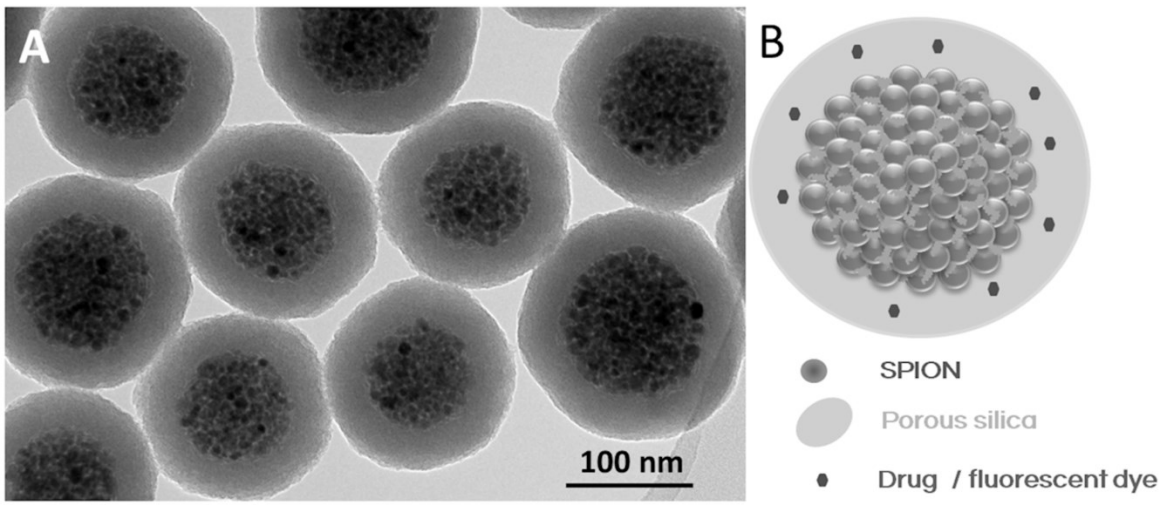

Figure 4. TEM image (A) and schematic representation (B) of magnetic core-shell nanostructures. The SPIONs cluster composed of ~ 80 SPIONs represents the “core”, which ensures effective magnetic responsiveness, and the silica coating represents the “shell”, which enables drug loading into its pores or drug attachment onto its surface.

2.4) Magnetically-responsive nanocarriers assembled with layer-by-layer (LbL) deposition methods

The first LbL self-assembly approaches have been presented in the 1990s [101]. Since 1998, when they were first applied for drug delivery, they proved to be a promising nanotechnological platform [102-105]. Polyelectrolyte capsules are the most studied type of LbL carrier for the delivery of low-molecular-weight compounds, as well as therapeutic proteins and peptides. They present very important advantages such as: (i) precise control of the capsule wall thickness and pore size; (ii) broad selection of capsule’s wall material; (iii) preparation in absence of organic solvents; (iv) good control over drug loading and release; and (v) easy fabrication process [106]. The drug molecules and SPIONs can be loaded onto such nanocapsules using three general methods presented in Figure 5.

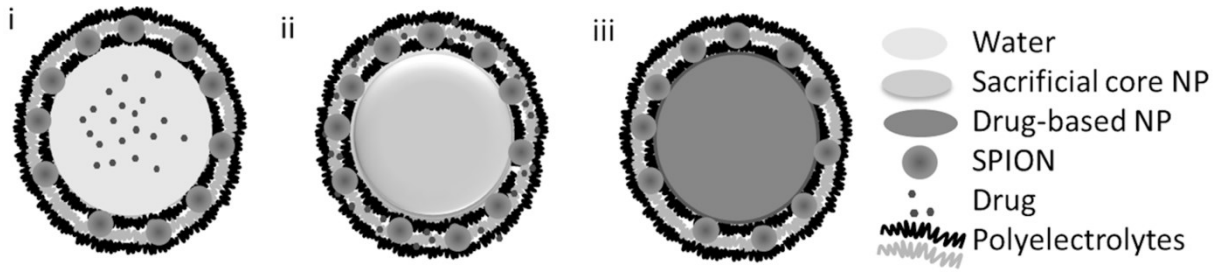

Figure 5. Scheme representing the most common approaches for preparation of magnetic drug-loaded capsules based on SPIONs with the use of layer-by-layer (LbL) assembly technique: (i) loading of low-molecular-weight compounds into preformed polyelectrolyte nanocapsules; (ii) direct incorporation of drug and SPIONs into capsule’s wall during deposition of oppositely charged polyelectrolytes onto sacrificial template core particles; and (iii) deposition of oppositely charged polyelectrolytes and SPIONs onto drug-based core nanoparticles.

Design and fabrication of the LbL nanocapsules is usually based on co-incubation of sacrificial templates with excessive amounts of oppositely charged polyelectrolytes. By repeating both polymers deposition, multilayers form of well-defined thickness and molecular structure. Electrostatic interactions are certainly the most exploited forces in LbL; however, also others can be used, such as: hydrophobic forces, hydrogen bonding, inclusion complexes, affinity binding (e.g., biotin-streptavidin recognition), coordination polyelectrolyte, block polymer micelles, and protein nanocapsules assembled via isobutyramide grafts can be used for preparation of nanocapsules [107-115].

The simplest method to obtain magnetic LbL nanocapsules carrying SPIONs is to self-assemble charged SPIONs and polyelectrolytes in the capsule multi-layered wall [116-118]. The distribution of SPIONs and their inter-particle distance within the capsule wall can be controlled by varying LbL conditions, such as ionic strength, pH, and the presence of unbound polyelectrolytes. Higher ionic strength can lead to denser SPIONs “packing” inside the capsule wall due to decreased absolute value of zeta potential that results in lower electrostatic repulsion among neighbouring SPIONs during deposition [119]. The presence of free polyelectrolytes results in significantly lower SPIONs

density in the capsule wall. Alternatively, SPIONs can also be loaded inside capsules core [120, 121]. Polyelectrolytes can also be conjugated with drugs prior LbL assembly to achieve magnetically-responsive drug delivery systems. For instance, paclitaxel and hyaluronic acid have been successfully conjugated to polyelectrolytes and have already entered clinical studies for cancer therapy [122, 123]. Katagiri and co-workers described magnetically-responsive capsules synthesized by a colloid-templating technique showing controlled release of low-molecular-weight compounds [124]. Melamine-formaldehyde sacrificial core particles were decorated with polyelectrolytes and magnetite using LbL assembly. After removal of the organic core, the outermost wall was decorated with an additional lipid bilayer and, at the same time, a dye was encapsulated into the capsule interior and used as a model drug. Dye release was triggered on-demand by exposing the nanocarrier to radiofrequency AMF, which caused heating of the SPIONs-containing shell, thus increasing the lipid bilayer permeability.

2.5) Colloidosome as magnetically-responsive nanocarriers

Colloidosomes are a special type of assembled nanostructures where the liquid interior compartment is enclosed by a layer of relatively tightly packed nanoparticles or nanocrystals, assuring the robustness of the whole structure [125]. A number of studies describe micron-sized (> 1 μm) colloidosomes composed of iron oxide nanocrystals, however, such systems are not appropriate for drug delivery due to the carrier oversize [126, 127]. Recently, Bollhorst and co-workers have described an innovative approach for the synthesis of submicron (< 1 μm) bifunctional colloidosomes that allowed the simultaneous incorporation of SPIONs and fluorescent silica nanoparticles in a single submicron colloidosome (Figure 6) [128]. Such colloidosomes represent a promising platform for their use in magnetically responsive drug delivery. Their few-hundred-nanometers large aqueous interior can be used for delivering hydrophilic cargo that can be a small molecule or even a large biomacromolecule, such as a therapeutic protein or gene. Preparation of colloidosomes is based on water-in-oil mini-emulsions stabilized by oil-soluble surfactants; therefore, hydrophilic cargo is not in contact with the surfactants. That could be advantageous for the delivery of enzymes and other therapeutic proteins that may be very sensitive to the composition of the formulation.

Drug release from colloidosomes can occur via diffusion through the nanopores among the packed nanocrystals in the colloidosome shell. Shell porosity can be affected by the heat produced due to exposure of colloidosomes to radiofrequency AMF, or due to potential mechanical actuation generated by low-frequency AMF as proposed by Golovin *et al.* [26]. However, drug release from colloidosomes can also be achieved by light-triggered disassembly of the colloidosome shell as it has recently been proposed by Li *et al.* [129].

An innovative colloidosome-like delivery system was reported by Gong *et al.* [130]. The magnetic carrier was fabricated by using a microfluidic flow-focusing approach. The liquid interior was loaded with acetylsalicylic acid, while the shell was composed of SPIONs embedded into crosslinked chitosan. Drug release was mechanically-controlled by compression-extension of the magneto-elastic shell induced by AMF and was shown to be dependent on frequency and magnitude of the applied magnetic field.

Despite the rapid progress and great promise of colloidosome systems, further research and optimization is needed to achieve optimal size for drug delivery applications.

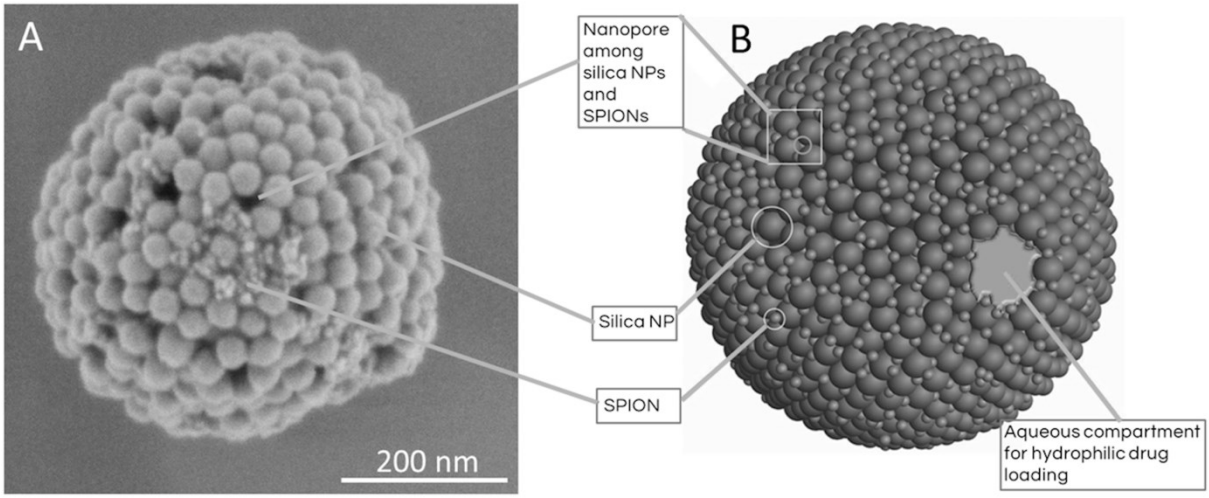

Figure 6. (A) SEM micrograph and (B) schematic representation of magnetic colloidosome composed of SPIONs and fluorescent silica NPs.

3) Perspectives and future challenges

Magnetic targeting was presented as a promising strategy in a number of studies, but it was tested only in a few clinical trials to date [37, 131]. Lubbe and co-workers [132, 133] have performed the first clinical trial of magnetically-targeted drug delivery where 14 patients were treated with epidoxorubicin that was electrostatically-conjugated to the surface of a magnetic carrier. The carrier was effectively targeted to the tumor site in 6 patients. A second clinical trial was performed by Koda and co-workers on 32 patients with hepatocellular carcinoma [134]. The doxorubicin-coupled magnetic carrier was successfully targeted in 30 patients using an external magnetic field. In another clinical trial, Wilson and co-workers conjugated doxorubicin to the magnetic carrier, which was selectively delivered to hepatocellular carcinoma by using an external magnetic field [135]. The results showed that the magnetic carriers were effectively targeted to the tumor site and up to 91% of the tumor volume was affected by the drug. It is thus apparent that, despite of the slow progress in the clinical translation of magnetically-responsive carriers, their potential remains great for targeted drug delivery.

In general, the techniques used for the syntheses of various types of high-quality nanocrystals with well-defined magnetic properties are nowadays known and well-optimized [16]. However, strategies for the assembly of individual nanocrystals into multifunctional hierarchical structures such as MNCs are rather less developed, and not yet prepared for industrial scale-up. Currently available magnetic targeting is likely to be ineffective in case the target site is located deep in the body, due to insufficient magnetic force exerted on a distant MNC, thus resulting in poor magnetic capturing [49, 56, 136]. Therefore, it is an urgent need to design new highly magneto-responsive nanomaterials with high drug loading. Nanoscale size, high magnetic responsiveness, and high drug loading are unfortunately incompatible features. Therefore, such a challenge should be solved with the development of efficient delivery systems that find an optimal balance in terms of how much magnetic responsiveness can be sacrificed to take advantage of a smaller carrier size and higher drug loading.

Since SPIONs in the form of magnetite and maghemite are recognized as safe and biocompatible, the development of new MNCs is expected to be primarily based on SPIONs assemblies. The future design of nanocarriers and magnetically actuated nanomedicines leads to the synthesis of novel superparamagnetic structures with anisotropic shapes such as nanorods, nanodiscs, nanotubes, nanoworms, and nanochains [23, 29, 137-140]. These materials may have larger magnetic moment and better magnetic responsiveness in a magnetic field gradient compared to spherical particles of the comparable cross-section. Recently, we reported a new approach for the magnetically-assisted synthesis of anisotropically shaped nanostructures, namely superparamagnetic nanochains, with the length of ~ 500 nm and diameter of only ~ 100 nm (Figure 7) [29] . Such nanochains can easily be magnetically guided with low magnetic field gradients, whilst having the potential to be transformed into an effective MNC. Besides magnetic targeting, the superparamagnetic nanocarriers with anisotropic shapes also show great promise in magneto-mechanical actuation of nanomedicines by low frequency AMF. However, the major challenge remains in the advancement of scale-up approaches for the synthesis of such anisotropic nanostructures.

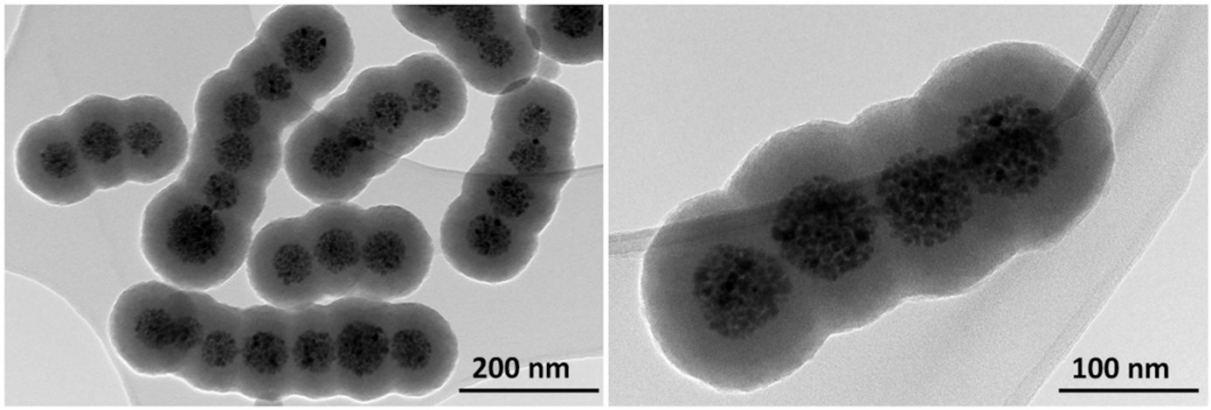

Figure 7. TEM images showing the magnetic nanochains prepared by facile sol-gel synthesis in a magnetic field using SPION clusters as primary building blocks. Superparamagnetic nanochains form stable colloidal suspensions, express excellent magnetic responsiveness, and hold great potential to be evolved towards a magnetic drug-delivery system.

We shall note that a very important difference between magnetic and active targeting lies in the design of the nanocarrier. In contrast with active targeting, MNCs do not need affinity ligands on their surface to be targeted to a specific site in the body [141]. Furthermore, such affinity ligands bound on the surface of the nanocarriers often impair the colloidal stability of the delivery system in a complex medium such as blood. Therefore, the design of MNCs allows more freedom for the optimization of the nanocarrier surface to avoid undesired interactions with blood components, such as formation of protein corona leading to a premature elimination of the nanocarrier by the reticuloendothelial system [142, 143].

The MNCs of the future should respond to magnetic guidance to perform several tasks, including: controlled release of the payload, selective targeting, and eventually other actions at the disease site. Often researchers attempt to use chemical cues to trigger drug release at the desired site in the body, such as reductive intracellular environment, specific enzymes overexpressed by cancer cells (cathepsins), acidic pH in the tumors, and low endosomal pH [8]. Despite all such efforts, these types

of triggered drug release systems lack the required precision and robustness and might not be sufficient to achieve the desired goals by itself. The drug release from the MNCs at the target site can be triggered remotely by magnetic heating in a radio frequency AMF or with the help of low frequency AMF magneto-mechanical actuation [26, 89]. However, in the near future it can be expected that a combination of various chemical and physical cues of triggering means will be integrated into an individual MNC in order to achieve more selective drug release at the target site.

ACKNOWLEDGEMENTS

The support of the Ministry of Higher Education, Science and Technology of the Republic of Slovenia within the National Programs P2-0089 and P1-0189, and Research Project J1-7302 is gratefully acknowledged. SK is grateful to the European Social Found, Operational Programme 2014-2020 (Axis 3 – Education and Training, Specific Programme n.26 – TALENTS^3 Fellowship Programme – "MAGIC SPY"). The authors thank Dr Tobias Bollhorst for SEM micrograph of magnetic colloidosome.

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