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Review

Magnetic nanoparticles and targeted drug delivering

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ABSTRACT

Magnetic nanoparticles (MNPs) are being of great interest due to their unique purposes. Especially in medicine, application of MNPs is much promising. MNPs have been actively investigated as the next generation of targeted drug delivery for more than thirty years. The importance of targeted drug delivery and targeted drug therapy is to transport a drug directly to the centre of the disease under various conditions and thereby treat it deliberately, with no effects on the body. Usage of MNPs depends largely on the preparation processes to select optimal conditions and election agents to modify their surface. This review summarizes the most commonly used functionalization methods of the MNPs preparation methods and their use in targeted drug delivery and targeted therapy.

Contents

1. Introduction

Nanotechnologies are wide spread in medicine and pharmaceutical industries, namely in disease detection, controlled drug delivery, as biosensors, in tissue engineering and so on. Nanoparticles designed for drug delivery should be above all biodegradable and biocompatible [1,2]. Many various nanosystems for these purposes are mentioned in recent papers and the special interest is focused on MNPs, which are a major class of nanoscale materials with the potential to revolutionize current clinical diagnostic and therapeutic techniques [3–7]. Moreover, other applications of MNPs are widely studied including magnetically enhanced transfection, magnetically assisted gene therapy, magnetically induced hyperthermia and magnetic-force-based tissue engineering as mentioned in a review of Corchero and Villaverde [8].

Due to their unique physical properties and ability to function at the cellular and molecular level of biological interactions, MNPs have been actively investigated as the next generation of targeted drug delivery for more than thirty years [9,10]. The importance of targeted drug delivery and targeted drug therapy is to transport a drug directly to the centre of the disease under various conditions and thereby treat it deliberately, with no effects on the body. The greatest therapeutic potential is probably associated with applica-

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tions involving 'intelligent' particles with a magnetic core (to direct the particles to the vicinity of the target and also for hyperthermia or for temperature-enhanced release of the drug), a recognition layer (to which suitable receptors are attached), and a therapeutic load (adsorbed inside the pores or hosted within internal cavities of the particles).

The challenges are formidable, especially those related to the development of suitable recognition layers. Useful recognition moieties attached to the particles must be loaded to a high density while maintaining their desired characteristics [11,12]. The potential of drug delivery systems based on the use of nano- and microparticles stems from significant advantages such as: (i) the ability to target specific locations in the body; (ii) the reduction of the drug quantity needed to attain a particular concentration in the vicinity of the target; and (iii) the reduction of the concentration of the drug at nontarget sites minimizing severe side effects [11,13].

1.1. Tumor diseases and MNPs drug delivering

The major disadvantage of most chemotherapeutic approaches to cancer treatment is that most are non-specific. Therapeutic (generally cytotoxic) drugs are administered intravenously leading to general systemic distribution. The non-specific nature of this technique results in the well-known side effects of chemotherapy as the cytotoxic drug attacks normal, healthy cells in addition to its primary target, tumor cells [14,15]. To overcome this great disadvantage MNP can be used. Nanoparticles can be used to treat tumors in three different ways: (i) specific antibodies can be conjugated to the MNPs to selectively bind to related receptors and inhibit tumor growth; (ii) targeted MNPs can be used for hyperthermia for tumor therapy; and (iii) drugs can be loaded onto the MNPs for targeted therapy [16–18] (see Fig. 1). The targeted delivery of anti-tumor agents adsorbed on the surface of MNPs is a promising alternative to conventional chemotherapy. The particles, loaded with the drug, are concentrated at the target site with the aid of an external magnet. The drugs are then released on the desired area [17]. Magnetic particles smaller than 4 μm are eliminated by cells of the RES, mainly in the liver (60–90%) and spleen (3–10%). Particles larger than 200 nm are usually filtered to the spleen, whose cut-off point extends up to 250 nm, while particles up to 100 nm are mainly phagocytosed through liver cells. In general, the larger the particles are, the shorter their plasma half-life-period [11].

1.2. Magnetic targeting for gene delivery

Antisense and gene therapy have been areas of intense research in recent years due to their potential to generate a significant impact on medicine [15]. The true benefits of gene therapy are only realized if the limitations posed by insufficient gene transfer efficacy and specificity can be overcome [19]. There are several perspectives to the future use of magnetofection. For *in vitro* application, the three important features of magnetofection are (i) the drastically lowered vector dose; (ii) the considerably reduced incubation time required to achieve high transfection/transduction efficiency; and (iii) the possibility of gene delivery to otherwise nonpermissive cells [20].

2. Parameters influencing drug delivery efficiency

As mentioned above, the intended drug and a suitable magnetically active component are typically combined into a pharmacologically stable system with controlled releasing in the blood vessels. The rate of drug releasing can be controlled by directly modulating the magnetic field. Because the targeted therapy has the characteristics of driven magnetic accuracy, targeting, and high drug-capacity, it can be effective to lower toxic effects and to enhance the therapeutic effect [21,22].

The effective use of MNPs for biomedical applications such as targeted drug delivery depends on a number of factors related to the size and magnetism of the biocompatible nanoparticles. Parameters such as the physicochemical properties of the drug-loaded MNPs, field strength and geometry, depth of the target tissue, rate of blood flow, and vascular supply, all play a role in determining the effectiveness of this method of drug delivery [15].

Increasing the magnetization is advantageous to facilitate manipulation in drug delivery schemes [23]. The nanoparticles must be small so that they can be superparamagnetic in order to avoid agglomeration after stopping magnetic field and to remain in circulation without being removed by the body's natural filters such as the liver or the immune system [24]. Superparamagnetic nanosystem is preferred due to its ability to become magnetized upon exposure to a magnetic field but have no permanent magnetization (remanence) once the field is turned off (Fig. 2). Superparamagnetism is caused by thermal effects in material. In superparamagnetic particles, thermal fluctuations are strong enough to spontaneously demagnetize a previously saturated

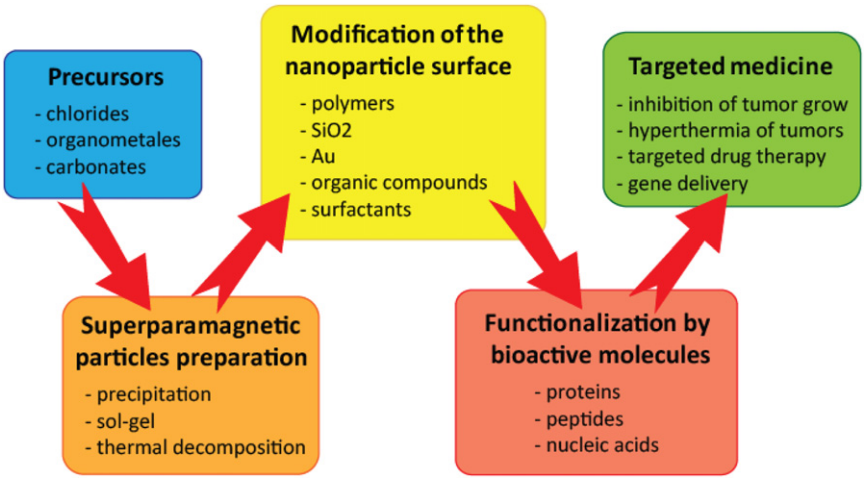

Fig. 1. Processes of magnetic particles preparation for drug delivery.

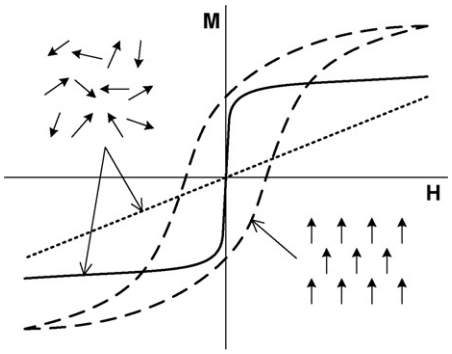

Fig. 2. Magnetization characteristics of superparamagnetic (solid line), paramagnetic (doted line) and ferromagnetic (dashed line) particles.

assembly, therefore these particles have zero coercivity and have no hysteresis (Fig. 2).

3. Functionalization of magnetic nanoparticles for drug delivery

Iron oxides with core/shell structure are the most widely used as sources of magnetic materials [25]. Iron oxides have several crystalline polymorphs known as α-Fe_2O_3 (hematite), β-Fe_2O_3, γ-Fe_2O_3 (maghemite), ε-Fe_2O_3, Fe_3O_4 (magnetite) and some others (amorphous and high pressure forms) [26]. Nevertheless, only maghemite and magnetite found the greatest interest of bioapplications [27]. Readily, carbonyl iron, which is well-known material with a unique form of elemental iron because of its small particle size, was also used as magnetic core [28].

In some reports, pure metals, such as Fe and Co were chosen as a magnetic material because they have several advantages over iron oxides, e.g., better magnetic properties, high saturation magnetization, and high specific loss of power [29,30]. Xing et al. fabricated α-Fe-incorporated nanoporous carbon with magnetic properties by a facile nanocasting process and employed it as tetracycline hydrochloride carriers [31]. However, Fe and Co have worse oxidative stability, compatibility in nonaqueous systems and toxicity then iron oxides.

Functionalization of MNPs with amino group, silica, polymer, various surfactans or other organic compounds (see Fig. 1) is usually provided in order to achieve better physical and chemical properties. Moreover, the core/shell structure of MNPs have the advantages of good dispersion, high stability against oxidation and appreciable amount of drug can be loaded to the polymer shell [32]. Furthermore, lots of functional groups from polymers on the surface can be used for further functionalization to get various properties [33]. It is favored that MNPs retain sufficient hydrophilicity and, with coating, do not exceed 100 nm in size to avoid rapid clearance by reticuloendothelial system (RES) [34]. It was found the surface functionalization plays also the key role in nanoparticle toxicity.

3.1. Polymer coating

Coating of MNPs with polymers used for drug delivery is the most commonly used way how to solve the stability of nanoparticles against oxidation, as demonstrated on several following examples [35,36]. Reshmi et al. reported the method how to prepare composite colloidal core/shell nanoparticles, consisting of magnetic core (carbonyl iron,) and biodegradable polymeric shell (cellulose acetate hydrogen phthalate) [28]. The polymeric shell could transport the drug and release it during its biodegradation [37].

MNPs tend to aggregate due to strong magnetic dipole-dipole attractions between particles. To avoid this difficulty, aqueous dispersion of the MNPs is attained by coating their surfaces with hydrophilic polymers such as starch or dextran and chitosan [38,39]. Kumar et al. suggested chitosan coated Fe_2O_3 MNPs and techniques for their safe transport and concentration in specific sites in the body that would constitute a powerful tool for gene/drug therapy *in vivo* [40]. Furthermore, drug delivery *in vitro* could be improved if the drugs were modified with antibodies, proteins, or ligands. For *in vivo* experiments, MNPs were conjugated with plasmid DNA expressing enhanced green fluorescent protein (EGFP) prior to coating with chitosan. Fe_2O_3 nanoparticles were synthesized in aqueous medium without surfactants using Fe(II)/Fe(III) aqueous solution with a molar ratio of 1:2. Colloidal magnetite suspensions were directly oxidized by aeration to form Fe_2O_3 nanoparticles. The other authors focused also on using chitosan coated iron oxide nanoparticles as a drug delivery system for targeting photodynamic therapy [41]. Photodynamic therapy involves administration of a tumor localizing photosensitizing agent, which may require metabolit synthesis (i.e., a prodrug), followed by activation of the agent by light of a specific wavelength [42,43].

Covalent bioconjugate of urokinase and dextran coated iron oxide nanoparticles were tested as magnetic drug carriers for targeted thrombolysis [44]. Dextran was also used in the study of Aviles et al., whose prepared dextran-coated magnetite seed particles system as the implant to increase the capture of magnetic drug carrier particles in capillary tissue [45].

In several reports, thermosensitive polymers were investigated. Purushotham and Ramanujan reported a study of a novel iron oxide–poly-(N-isopropylacrylamide) (PNIPAM) composite nanoparticles suitable for magnetic targeting followed by simultaneous magnetic hyperthermia and chemotherapeutic drug release [46]. The core of the nanoparticle consisted of iron oxide and PNIPAM was chosen as the thermosensitive polymer shell. Fe_3O_4 nanoparticles were synthesized by a reverse coprecipitation method adapted from Aono et al. [47], in which water solution of ferric chloride hexahydrate and ferrous chloride tetrahydrate were precipitated by NaOH solution. Composite nanoparticles were prepared in the presence of MNPs by free radical dispersion polymerization of NIPAM monomer in water with N,N-methylene(bis)acrylamide as the cross-linker N,N,N′,N′-tetramethylene diamine as the accelerator and ammonium persulfate as the initiator. Prepared iron oxide–polymer composite nanoparticles were mixed with the water-soluble anticancer drug doxorubicin.

Similarly, Hoare et al. prepared nanocomposite membranes using PNIPAM-based nanogels and magnetite nanoparticles [48]. Heat generated by magnetite induction heating was transferred to the adjacent thermosensitive nanogels, causing the nanogels to shrink and permit drug diffusion out of the device. If the magnetic field was turned off, the device cooled, causing the nanogels to reswell and refill the membrane pores. Koppolu et al. synthesized iron oxide MNPs for targeted and controlled drug delivery using the coprecipitation of ferrous and ferric salts in the presence of a basic solution and the surfactant docusate sodium salt (AOT) and finally coated them with two shells made up of PNIPAM and poly(D,L-lactide-co-glycolide) (PLGA) [49].

Sivudu and Rhee prepared magnetite nanocomposite by *in situ* development of magnetite iron oxide nanoparticles into the polyacrylamide hydrogel network via a coprecipitation reaction of ferrous chloride tetrahydrate and ferric chloride hexahydrate in the presence of ammonium hydroxide [50]. Liu and colleagues studied the temperature-responsive polymers for MNPs coating [51]. They were interested in the behavior of a polymer-water solution which is stable below the so-called lower critical solution temperature (LCST), above which the solution partitions into two phases: water

and a polymer-rich phase. For *in vivo* drug delivery, the temperatures should be a few degrees of centigrade above the physiological temperature.

Mahmoudi et al. tested polyvinyl alcohol as a coating material for superparamagnetic iron oxide nanoparticles (SPION) to probe the toxicity of these nanoparticles during the bio application [52]. They found that uncoated SPIONs can cause significant changes in the cell medium, such as denaturation of proteins, which in turn can cause toxicity. Häfeli et al. investigated the toxicity of MNPs coated with polyethylenoxide (PEO) triblock copolymers when used for intraocular targeting. They found that the PEO tail block length inversely correlates with toxicity [53].

Ciofani et al. proposed alginate MNPs prepared by an emulsion/reticulation technique for efficient drug release, targeting and thermotherapy in a single platform [54]. Arabic gum was also used as an alternative biopolymer for the coating and stabilization of iron oxide MNPs [55,56]. Interesting study of magnetic drug targeting was also performed with gelatin coated magnetic iron oxide nanoparticles [57]. Gelatin is a suitable candidate to bind with drug like doxorubicin forming drug–polymer conjugate due to presence of multifunctional groups, like $-NH_2$, –COOH in its chain. Arias and co-workers developed a diclofenac sodium-loaded magnetic nanomedicine, consisting of a magnetic core (iron) and a biocompatible polymeric shell (ethylcellulose) for parenteral administration [29].

Zhou et al. developed a facile synthesis of MNPs coated with poly((2-dimethylamino) ethyl methacrylate) (PDMAEMA) as a novel potential carriers for targeted drug delivery and controllable release [58]. The MNPs Fe_3O_4 were prepared by alkaline precipitation and modified by α-bromoisobutyric acid to link atom transfer radical polymerization initiators to the surface. The Fe_3O_4/PDMAEMA hybrid nanoparticles with core/shell structure are able to load drugs into the polymer shell. The release rate of drug is approximately steady going and can be effectively controlled by altering the pH value [58]. The same research group also reported a facile synthesis of hybrid nanoparticles with biodegradability, superparamagnetism and fluorescence as novel potential carriers for targeted drug delivery [59]. These Fe_3O_4 at poly(ε-caprolactone)-carbazole nanoparticles with core/shell structure are able to load drugs into the polymer shell, deliver them to the target by an external magnetic field, and the release rate is slow and steady going.

Abdalla et al. studied the drug loading efficiency of polylactide acid (PLLA) and poly(1-lactide acid-co-gylocolide) (PLGA) polymeric systems of various molecular weights [60]. They found that the molecular weight of the polymer plays a crucial role in the capacity of the drug loading on the polymer surface. Using a constant amount of polymer and Fe_3O_4 MNPs, both PLLA and PLGA at lower molecule weights showed higher loading efficiencies for the drug on their surfaces. Monodisperse Fe_3O_4 nanoparticles were made via the reaction of ferric acetylacetonate and a long-chain alcohol [61]. Previously, the same authors synthesized magnetite nanoparticles using iron acetylacetonate as precursor and phenyl ether as solvent [62]. These particles have been coated with oleic acid in hexane solution embedded in a porous silicon matrix. The porous silicon matrix was prepared by anodization of a highly n-doped silicon wafer in an aqueous hydrofluoric acid solution [63].

3.2. Protein coating

Skaat et al. described a novel method for selective marking of Amyloid-β (1–40) (Ab40 protein involved in Alzheimerĭs) fibrils by non-fluorescent or fluorescent-maghemite (γ-Fe_2O_3) nanoparticles, and the completely removal of the magnetized fibrils from the aqueous continuous phase by a magnetic field [64]. Non-fluorescent γ-Fe_2O_3 nanoparticles of narrow size distribution were synthesized by nucleation, followed by controlled growth of maghemite thin films onto gelatin–iron oxide nuclei [65].

3.3. Silane coating

Magnetite nanoparticles can be modified also with oleic acid, silane, or organosilane [66,67]. Silanes are commercially available with many amine groups, so forming an ideal system to tune the surface functionality of the Fe_3O_4 nanoparticles for protein conjugation. Xu et al. synthesized Fe_3O_4 nanoparticles coated with polyethylene glycol (PEG) by the alkaline coprecipitation method, ferrous chloride tetrahydrate and ferric chloride hexahydrate were used as iron sources [68]. Afterwards, these nanoparticles were modified with 3-aminopropyltriethoxysilane (3-APTES), providing a $-NH_2$ functional group, and applied in the immobilization of lysozyme. The attachment of PEG promotes water solubility, reduces toxicity, decreases enzymatic degradation [69], and increases the *in vivo* half-lives of small-molecule drugs. Balakrishnan et al synthesized MNPs by chemical reduction of ferrous chloride solution with sodium borohydride and coated them with amine-terminated PEG [70]. Cao and co-workers suggested using a nanocomposite consisting of superparamagnetic Fe_3O_4/aminosilane core/shell nanoparticles functionalized with cyclodextrine as potentially promising material in magnetic drug delivery technology and bioseparation [71]. These nanoparticles were synthesized via layer-by-layer method.

3.4. SiO_2 coating

Another drug delivery device was designed by Huang and colleagues who fabricated drug-carrying magnetic core/shell Fe_3O_4/SiO_2 nanoparticles using electrophoretic deposition onto an electrically conductive flexible PET substrate [72]. Superparamagnetic nanoparticles of Fe_3O_4 coated with SiO_2 layer were synthesized via conventional microemulsion and sol–gel technology and then associated with the encapsulated anti-epileptic drug, ethosuximide. The whole complex was created as the flexible chip which may offer advantages over conventional drug delivery devices by improvement of dosing precision, ease of operation, wider versatility of elution pattern, and better compliance. Wang and colleagues suggested the usage of superparamagnetic magnetite nanoparticles coated with SiO_2 and finally immobilized with polymer, 3-(triethoxysilyl)propyl isocyanate not only for drug delivery [73].

3.5. Other coating material

In some studies, other organic compounds and commercial products were applied for MNPs functionalization. Liu et al. used folate-mediated water-soluble superparamagnetic iron oxide incorporated into micelles and modified with Pluronic® F127 [74]. In another case, magnetic Fe_3O_4 nanoparticles were coated with tetraheptylammonium by the electrochemical deposition under oxidizing conditions (EDOC) method [75]. MNPs were used in the study of *in vitro* drug accumulation inside leukemia K562 cell lines. Lim at al. synthesized gold-coated iron oxide nanoparticles from ferric acetylacetone, oleic acid, oleylamine, hydrazine monohydrate and trioctyl amine. Prepared iron oxide nanoparticles were coated by gold via gold acetate [76].

4. Conclusions

In the last ten years, the synthesis of MNPs covering a wide range of compositions and tunable sizes has made substantial progress. Moreover, fabrication and surface engineering of iron oxide MNPs involves complex chemical, physical and physicochemical multiple

interactions. Controlled release of drugs from nanostructured functional materials, especially MNPs, is attracting increasing attention because of the opportunities in cancer therapy and the treatment of other ailments. The potential of MNPs stems from the intrinsic properties of their magnetic core combined with their drug loading capability and the biochemical properties that can be bestowed on them by means of a suitable coating. According to last published scientific papers, it seems the polymer acts as the most important material for modification of MNPs for drug delivery.

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