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Review

Nanoparticles as drug delivery systems

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Abstract:
Controlled drug delivery systems (DDS) have several advantages compared to the traditional forms of drugs. A drug is transported to the place of action, hence, its influence on vital tissues and undesirable side effects can be minimized. Accumulation of therapeutic compounds in the target site increases and, consequently, the required doses of drugs are lower. This modern form of therapy is especially important when there is a discrepancy between the dose or the concentration of a drug and its therapeutic results or toxic effects. Cell-specific targeting can be accomplished by attaching drugs to specially designed carriers. Various nanostructures, including liposomes, polymers, dendrimers, silicon or carbon materials, and magnetic nanoparticles, have been tested as carriers in drug delivery systems. In this review, the aforementioned nanocarriers and their connections with drugs are analyzed. Special attention is paid to the functionalization of magnetic nanoparticles as carriers in DDS. Then, the advantages and disadvantages of using magnetic nanoparticles as DDS are discussed.

Key words:
drug delivery system, nanocarriers, nanoparticles, magnetic nanoparticles, targeting therapy

Introduction

Delivering therapeutic compound to the target site is a major problem in treatment of many diseases. A conventional application of drugs is characterized by limited effectiveness, poor biodistribution, and lack of selectivity [111]. These limitations and drawbacks can be overcome by controlling drug delivery. In controlled drug delivery systems (DDS) the drug is transported to the place of action, thus, its influence on vital tissues and undesirable side effects can be minimized. In addition, DDS protects the drug from rapid degradation or clearance and enhances drug concentration in target tissues, therefore, lower doses of drug are required [111]. This modern form of therapy is especially important when there is a discrepancy between a dose or concentration of a drug and its therapeutic results or toxic effects.

Cell-specific targeting can be achieved by attaching drugs to individually designed carriers. Recent developments in nanotechnology have shown that nanoparticles (structures smaller than 100 nm in at least one dimension) have a great potential as drug carriers. Due to their small sizes, the nanostructures exhibit unique physicochemical and biological properties (e.g., an enhanced reactive area as well as an ability to cross cell and tissue barriers) that make them a favorable material for biomedical applications.

Nanocarriers used in drug delivery system

According to the definition from NNI (*National Nanotechnology Initiative*), nanoparticles are structures of sizes ranging from 1 to 100 nm in at least one dimension. However, the prefix "nano" is commonly used for particles that are up to several hundred nanometers in size.

Nanocarriers with optimized physicochemical and biological properties are taken up by cells more easily than larger molecules, so they can be successfully used as delivery tools for currently available bioactive compounds [145]. Liposomes, solid lipids nanoparticles, dendrimers, polymers, silicon or carbon materials, and magnetic nanoparticles are the examples of nanocarriers that have been tested as drug delivery systems (Fig. 1).

The way of conjugating the drug to the nanocarrier and the strategy of its targeting is highly important for a targeted therapy. A drug may be adsorbed or covalently attached to the nanocarriers surface or else it can be encapsulated into it. Covalent linking has the advantage over other ways of attaching as it enables to control the number of drug molecules connected to the nanocarrier, i.e., a precise control of the amount of therapeutic compound delivered. Cell-specific targeting with nanocarriers may be accomplished by using active or passive mechanisms. The first strategy relies on the attraction of a drug – the nanocarriers conjugate to the affected site by using recognition ligands, attached to the surface of conjugates antibodies, low molecular ligands, e.g., folic acids, peptides, etc. The active strategy can be also achieved through a manipulation of physical stimuli (e.g., temperature, pH, magnetism). Passive targeting is a result of enhanced

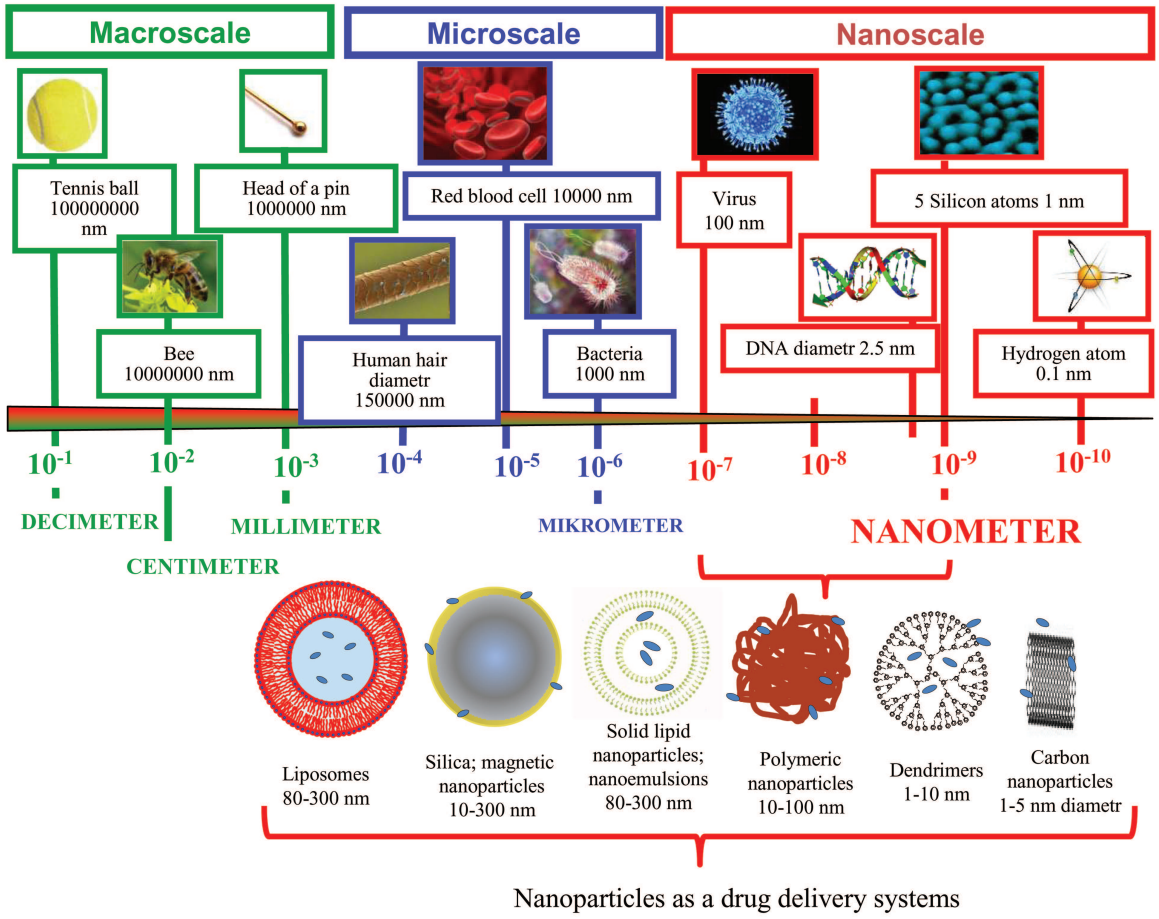

Fig. 1. Nanoparticle drug delivery systems with relation to other scales

vascular permeability and retention (EPR) which is characteristic of leaky tissues of tumors [111].

Once the drug-nanocarrier conjugates reach the diseased tissues, the therapeutic agents are released. A controlled release of drugs from nanocarriers can be achieved through changes in physiological environment such as temperature, pH, osmolality, or *via* an enzymatic activity.

Nanocarriers used for medical applications have to be biocompatible (able to integrate with a biological system without eliciting immune response or any negative effects) and nontoxic (harmless to a given biological system). Undesirable effects of nanoparticles strongly depend on their hydrodynamic size, shape, amount, surface chemistry, the route of administration, reaction of the immune system (especially a route of the uptake by macrophages and granulocytes) and residence time in the bloodstream. Due to a number of factors which may affect the toxicity of nanoparticles, their estimation is rather difficult and, thus, toxicological studies of each new DDS formulation are needed. However, with respect to their size, one can make some generalizations – smaller particles have a greater surface area, thus, they are more reactive and, in consequence, more toxic [5]. It is generally accepted that nanoparticles with a hydrodynamic diameter of 10–100 nm have optimal pharmacokinetic properties for *in vivo* applications. Smaller nanoparticles are subjects to tissue extravasations and renal clearance whereas larger are quickly opsonized and removed from the bloodstream *via* the macrophages of the reticuloendothelial system [35].

Liposomes

Liposomes have been the first to be investigated as drug carriers. They are nano/micro-particular or colloidal carriers, usually with 80–300 nm size range [144]. They are spherical vesicles composed of phospholipids and steroids (e.g., cholesterol), bilayers, or other surfactants and form spontaneously when certain lipids are dispersed in aqueous media where liposomes can be prepared, e.g., by sonication [139]. Liposomes have been reported to increase the solubility of drugs and improve their pharmacokinetic properties, such as the therapeutic index of chemotherapeutic agents, rapid metabolism, reduction of harmful side effects and increase of *in vitro* and *in vivo* anticancer activity [48]. A drug is incorporated in liposomes by the encapsulation process (Fig. 2). The release of a drug from liposomes depends on the liposome composition, pH, osmotic gradient, and the surrounding environment [48]. Additionally, a prolonged residence time increases the duration of action of such particles, but decreases their number. Interactions of liposomes with cells can be realized by: adsorption, fusion, endocytosis, and lipid transfer. There are a lot of drug examples in liposomal formulations, such as anticancer drugs [48], neurotransmitters (serotonin) [2], antibiotics [155, 175], anti-inflammatory [113], and antirheumatic drugs [158]. Recent studies have reported the clinical outcomes and side effects of photodynamic therapy (PDT) by means of intense pulsed light (IPL) and spray (liposome encapsulated 0.5% 5-aminolevulinic acid) which was used for the treatment of inflammatory facial acne [171]. Turkova et al. [155] compared the efficacy and safety of deoxycholate and lipid (liposomal) amphotericin B formulations (AMBF) in the treatment of invasive fungal disease (IFD) in neonates. The authors of the study have reported that deoxycholate amphotericin B is cheap and effective in treating neonatal IFD. The therapy appears to be safe for use as a first-line therapy if the underlying risk for nephrotoxicity is low [155]. Safdar and co-workers [130] conducted a meta-analysis in order to evaluate nephrotoxicity associated with amphotericin B lipid complex (ABLC) and liposomal amphotericin B (L-AmB). They showed that nephrotoxicity is generally similar for ABLC and L-AmB in patients receiving antifungal therapy and prophylaxis [130]. The unresolved problem of using drug delivery systems based on liposomes arises from their accumulation in cells (liver macrophages) outside the target tissues and the unpredictable effects dependent on the active agent they carry, such as cellular death [41].

Modified liposomes are an interesting type of such lipid structures. The multifunctional liposomes, containing the specific proteins, antigens, or other biological substances, can be used to design drugs which act selectively on a particular tissue. It is a promising approach for targeted delivery of therapeutics. Biswas et al. [22] presented hydrazine-functionalized poly-(ethylene glycol)-phosphatidylethanolamine (PEG-PE)-based amphiphilic polymer which can conjugate a variety of ligands. The researchers investigated the reversible model ligands monoclonal antinucleosome antibody 2C5 and antimyosin antibody 2G4, as well as glycoproteins concanavalin A (Con-A). The re-

versible attachment of homing devices is useful especially in modified liposomal systems, whereafter they successfully perform the function of targeting at the specific site. Ligands, such as antibodies, are cleaved off in response to an environmental stimulus, e.g., pH [22]. In addition, cationic liposomes (CLs) can be used as a gene delivery carrier [167]. They are better than natural or anionic liposomes for gene transfer [167]. Kim and co-workers [72] studied modified cationic liposomes either by polyethylene glycol (PEG)-grafting or PEG-adding methods as transfection complexes of plasmid DNA. In a recent study, Biswas et al. [21] have examined polyethylene glycol-phosphatidylethanolamine (PEG-PE) conjugate with the TPP group as drug carriers. They used paclitaxel (PTX) as a model drug and studied them for their toxicity, mitochondrial targeting, and efficacy in delivering. As a result, they suggested that TPP-PEG-PE can be used as non-toxic, mitochondria-targeted drug delivery systems [21].

Nanoparticles based on solid lipids

SLN (solid lipid nanoparticles), NLC (nanostructured lipid carriers) and LDC (lipid drug conjugates) are types of carrier systems based on solid lipid matrix, i.e., lipids solid at the body temperature [165]. They have been exploited for the dermal [1], peroral [100], parenteral [109], ocular [13], plumonary [83], and rectal [147] delivery.

SLN are particles made of solid lipids, e.g., highly purified triglycerides, complex glyceride mixtures or waxes stabilized by various surfactants [76]. The main characteristics of SLN include a good physical stability, protection of incorporated drugs from degradation, controlled drug release, and good tolerability. Additionally, some disadvantages have been observed, such as low loading capacity (limited by the solubility of drug in the lipid and the structure and polymorphic state of the lipid matrix), drug expulsion after crystallization, and a relatively high water content of the dispersions [104, 165].

NLC and LDC are modifications of lipid based nanoparticles that have been developed to overcome limitations of conventional SLN. NLC are produced by mixing solid lipids with liquid lipids, which leads to special nanostructure with increased payload and prevented drug expulsion. Three types of NLC have been introduced: imperfect type NLC (general imperfections in the matrix nanostructure form free spaces for the accommodation of the guest molecules), multiple type NLC (drugs are solved in oils and protected from degradation by the surrounding solid lipid) and amorphous type NLC (the crystallization that causes drug expulsion is avoided) [157]. NLC are mainly ex-

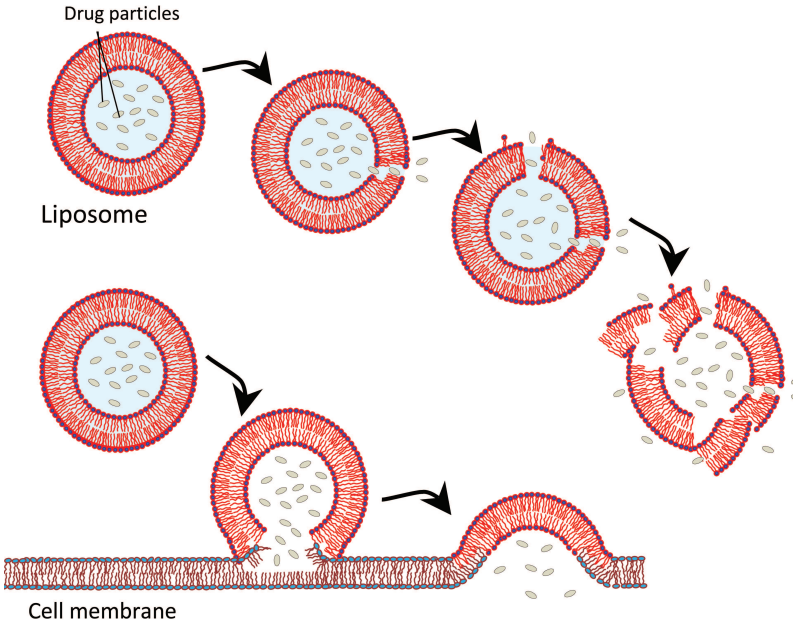

Fig. 2. Drug delivery by liposomes

ploited for dermal applications [103, 125]. LDC were developed in order to expand applicability of lipid based carriers to lipophobic drug molecules. These insoluble drug-lipid conjugates can be prepared by salt formation or by covalent linking followed by homogenization [102, 165].

Polymeric nanoparticles

Polymeric nanoparticles (PNPs) are structures with a diameter ranging from 10 to 100 nm. The PNPs are obtained from synthetic polymers, such as poly-ε-caprolactone [20], polyacrylamide [14] and polyacrylate [156], or natural polymers, e.g., albumin [94], DNA [93], chitosan [93, 128] gelatin [131]. Based on *in vivo* behavior, PNPs may be classified as biodegradable, i.e., poly(L-lactide) (PLA) [91], polyglycolide (PGA) [118], and non-biodegradable, e.g., polyurethane [55].

PNPs are usually coated with nonionic surfactants in order to reduce immunological interactions (e.g., opsonization or presentation PNPs to CD8 T-lymphocytes) as well as intermolecular interactions between the surface chemical groups of PNPs (e.g., van der Waals forces, hydrophobic interaction or hydrogen bonding) [152].

Drugs can be immobilized on PNPs surface after a polymerization reaction [87] or can be encapsulated on PNP structure during a polymerization step [99]. Moreover, drugs may be released by desorption, diffusion, or nanoparticle erosion in target tissue [152]. The examples of drug-polymeric nanocarrier conjugates used as drug delivery systems are shown in Table 1.

Among the aforementioned applications the one that is particularly interesting is the immobilization of retinyl acetate (RA) on ethyl cellulose (EC), which improves aqueous stability and photostability of a drug. In *ex vivo* tests on a skin tissue of mice, a 100% absorption of RA after 24 h has been demonstrated [8]. It is also worth to point out the biodegrad-

Tab. 1. Polymer nanocarriers as DDS

Drug	Therapeutic activity	Nanocarrier	Ref.
Carboplatin	Antineoplastic drug, ovarian, head, neck and lung cancer	Sodium alginate	106
5-Fluorouracil (5-FU)	Anticancer drug, colon cancer	CS-*g*-poly(*N*-vinyl caprolactam)	128
Doxorubicin	Antineoplastic agent, wide spectrum of tumors	PEGylatedPLGA	118
Capecitabine	Pro-drug of fluorouracil, metastatic colorectal and breast cancer	CS-poly(ethylene oxide-*g*-acrylamide)	3
Mitomycin C	Chemotherapeutic agent, bladder tumors	CS, CS-PCL, PLL-PCL	20
Rifampicin	Antitubercular drugs, latent M. tuberculosis infection in adults	Gelatin	131
Cyclosporine A	Cyclic polypeptide, immunosuppressant	GMO/poloxamer 407 cubic nanoparticles	79
Lamivudine	Anti-HIV drug	PLA/CS	43
Tacrine	Anti-Alzheimer drug	CS	164
Retinyl acetate	Photoaging, severe acne and skin inflammation	EC	8
Analogue of β-lactam	Antibiotic, infection G(+)bacteria	Polyacrylate	156
Clotrimazole	Antifungal drug	PLA-co-PLG	115

CS – chitosan; PEGylatedPLGA – PEGylated poly(lactic-*co*-glycolic acid); PCL – polycaprolactone; PLL – poly(L-lysine); GMO – glyceryl monooleate; EC – ethyl cellulose, PLA – polylactide; PLG – polyglycolide

able thermo-responsive chitosan-*g*-poly(*N*-vinylcaprolactam)-biopolymer used for the delivery of 5-fluorouracil to cancer cells. The hypothesized mechanism of 5-FU controlled release from this polymeric nanocarrier is swelling followed by conformational changes during a LCST (lower critical solution temperature) transition. The *in vitro* drug release showed a significant release above LCST. The high toxicity to cancer cells, comparatively lower to the normal ones, was observed [128].

The application of biodegradable nanosystems for the development of nanomedicines is one of the most successful ideas. Nanocarriers composed of biodegradable polymers undergo hydrolysis in the body, producing biodegradable metabolite monomers, such as lactic acid and glycolic acid. Kumari et al. [78] reported a minimal systemic toxicity associated with using of PLGA for drug delivery or biomaterial applications. Such nanoparticles are biocompatible with tissue and cells [116]. Drug-biodegradable polymeric nanocarrier conjugates used for drug delivery are stable in blood, non-toxic, and non-thrombogenic. They are also non-immunogenic as well as non-proinflammatory, and they neither activate neutrophils nor affect reticuloendothelial system [42].

Dendrimer nanocarriers

Dendrimers are unique polymers with well-defined size and structure. Dendritic architecture is one of the most popular structures observed throughout all biological systems. Some of the examples of nanometric molecules possessing dendritic structure include: glycogen, amylopectin, and proteoglycans [146].

In the structure of dendrimer, in contrast to the linear polymer, the following elements can be distinguished: a core, dendrons, and surface active groups. The core is a single atom or molecule (only if it has at least two identical functional groups) that dendrons are attached to. The dendrons (dendrimer arms) are molecules of monomer linked with the core, forming layers and building successive generations (their growth is spatially limited). Biocompatibility and physicochemical properties of dendrimers are determined by surface functional groups [23].

Selection of a core, type of a monomer and surface functional groups determine the usability of dendrimers in medical applications. Cytotoxicity of dendrimers and their so-called polyvalence is particularly relevant for biomedical purposes. Dendrimers cytotoxicity depends on the core material and is strongly influenced by the nature of the dendrimers surface. For example, changing the surface amine groups into hydroxyl ones may result in lower levels of cytotoxicity. The term *polyvalence* defines the number of active groups on a dendrimers surface. The presence of several surface functional groups enables a sumultanoeus interaction with a number of receptors, thus, it enhances biological activity.

There are a few ways of connecting biologically active compounds to dendrimers. The drug may be encapsulated in the internal structure of dendrimers [40] or it can be chemically attached or physically adsorbed on dendrimers surface [97]. The choice of the immobilization method depends on the drug properties. Encapsulation is used when drugs are labile, toxic, or poorly soluble. In turn, chemical attachment provides the possibility to control quantity of drugs on dendrimers surface by controlling the number of covalent bonds [140]. The selectivity of both methods may be enhanced by attaching on the dendrimers surface such targeting agents as folic acid [40, 140] or epidermal growth factor [173].

The surface of dendrimers provides an excellent platform for an attachment of specific ligands, which may include folic acid [140], antibodies [161], cyclic targeting peptides – arginine-glycine-aspartic acid (RGD) [159], selective A3 adenosine receptor [153], silver salts complexes antimicrobial agents [16], or poly(ethylene glycol) (PEG) [85]. The attached compounds can improve surface activity as well as the biological and physical properties of dendrimers.

Poly(amido amide) (PAMAM) is a dendrimer which is frequently used in biomedical applications. Both the structure of PAMAM dendrimers and the distribution of drugs [135] or genes [173] inside these molecules have been intensively investigated. PAMAM dendrimers grow through generations G = 1–10 and their size increases from 1.1 to 12.4 nm. The size of the respective generations of PAMAM is comparable to the size of selected proteins, e.g., dendrimer G3 with insulin and G7 with hemerythrin [150]. An example of a drug immobilization in PAMAM dendrimer is cisplatin. This complex compared with free cisplatin exhibits several advantages, such as slower rate of drug release, higher accumulation of the drug in solid tumors, and lower toxicity in all organs [40, 92]. Further examples of drug incorporation in

PAMAM dendrimers are anticancer drugs, including methotrexate [108], doxorubicin [59], 5-FU [140], and anti-inflammatory drugs, e.g., ibuprofen [149], piroxicam [122], or indomethacin [26].

The size and charge of PAMAM dendrimers influence their cytotoxicity. The higher-generation (G4-G8) PAMAM dendrimers exhibit toxicity due to their high cationic charge density [134]. Comparative toxicity studies on cationic and anionic dendrimers using Caco-2 cells have shown a significantly lower cytotoxicity of anionic compounds in comparison with the cationic ones [74]. Positively charged dendrimers introduced into the systemic circulation interact with blood components causing destabilization of cell membranes and cell lysis [63]. Roberts and coworkers [129] observed that cationic PAMAM dendrimers caused a decrease in cell viability, however, they found no evidence of their immunogenicity in rabbits. Additionally, they studied the toxicity of cationic PAMAM Starburst® in mice and they suggested that even high doses of low generation cationic dendrimers do not cause side effects. Recent studies have shown that G4 dendrimers, which have amino terminal groups, are toxic and impair the growth and development of zebrafish embryos. In turn, dendrimers with carboxylic acid functional groups did not exert adverse effect on zebrafish embryos [61]. Dendrimers can modulate cytokine and chemokine release. This property turned out to be helpful in therapy, but it can also cause serious toxic effects [49]. The PAMAM generation of 3,5-glucosamine dendrimers induces a synthesis of pro-inflammatory chemokines, such as MIP-1a, MIP-1h, and cytokines TNF-α, IL-1h, IL-6, IL-8 in human dendritic cells and macrophages, which exhibits an immunomodulatory effect. Chauhan et al. [27] studied *in vivo* toxicity profile of PAMAM dendrimers in mice. The researchers assessed the following parameters: the animal behavior, feed intake, body weight, carbohydrate, lipid and protein metabolism, hematological parameters, histopathology, and cell viability. They observed no effect on other hematological (excluding red blood cells, hematocrit value and hemoglobin) and biochemical parameters (excluding the decrease of glucose levels in the high-NH_2 dose) as well as on feed intake, body and organ weights. In addition, the histopathology showed a toxic effect on liver and kidneys [27]. PEGylation of dendritic systems is a way of lowering general toxicity. This process enables a long-lasting blood circulation and an avoidance of dendrimers accumulation in normal organs, such as kidneys and liver [75].

Silica materials

Silica materials used in controlled drug delivery systems are classified as xerogels [36] and mesoporous silica nanoparticles (MSNs), e.g., MCM-41 (Mobil Composition of Matter) and SBA-15 (Santa Barbara University mesoporous silica material) [163]. They exhibit several advantages as carrier systems, including biocompatibility, highly porous framework and an ease in terms of functionalization [7]. Among inorganic nanoparticles, silica materials are the carriers which most often are chosen for biological purposes [141].

Silica xerogels possess an amorphous structure with high porosity and enormous surface area. A porous structure (shape and pore dimensions) depends on synthesis parameters [50]. Sol-gel technique is frequently used to form silica xerogels loaded with drugs. A modification of the synthesis conditions, such as the ratio of reagents, temperature, concentration of the catalyst, and pressure of drying, allows to alter properties of xerogels used in controlled drug release [36, 126]. Phenytoin [52], doxorubicin [124], cisplatin [38], metronidazole [39], nifedipine [95], diclofenac [37], and heparin [4] are examples of drugs which have been loaded into xerogels using this technique.

The best known types of mesoporous silica nanomaterials are MCM-41 with a hexagonal arrangement of the mesopores and SBA-15 with a well-ordered hexagonal connected system of pores [163]. The MSNs, in comparison with xerogels, possess more homogenous structure, lower polydispersity and higher surface area for adsorption of therapeutic or diagnostic agents [46]. The mechanism of drug loading into mesoporous silica material is a chemical or physical adsorption [46]. By these processes, diverse types of drugs, including anticancer drugs [46, 60], antibiotics [81], and heart disease drugs [121], have been embedded into MNSs. The drug release is usually controlled by diffusion [81]. The silicalites and mesoporous silica nanoparticles potential application in photodynamic therapy has been also studied [62].

The MSNs properties make them an excellent material for various pharmaceutical and biomedical ap-

plications. The structure of MSNs enables the incorporation of both small [46] and large molecules [73], adsorption of DNA, and gene transfer [142]. This gives a possibility of using these nanomaterials in a combined therapy [60].

Some data indicate that nano-sized silica particles (SNPs) are biocompatible and have a great potential for a variety of diagnostic and therapeutic applications in medicine. However, recent studies have revealed *in vitro* and *in vivo* toxicity and certain hazards of using nanosilica. Most of the *in vitro* studies of silica nanoparticles show the adverse effect in investigated cells. The described effect depends on the cell type and nanoparticle size. Silica nanoparticles have an impact on a generation of oxidative stress in cells *via* formation of reactive oxygen species [84], elevated production of malondialdehyde [82], decreasing glutathione level [174], and induction of antioxidant enzymes, including superoxide dismutase (SOD) and heme oxygenase 1 (OH-1) [117]. All of these events are responsible for lipid peroxidation and cell membrane damage [82]. Previous work showed that exposure to silica nanoparticles at high concentrations caused activation of NF-κB in endothelial cells [84] or Nrf-2-ERK MAP kinase signaling pathway in human bronchial epithelial cells [51]. Pro-inflammatory response resulted in an induction of various chemokines (MCP-1 and MIP-2) [33, 84] and cytokines, such as interleukins IL-1 [121], IL-8, IL-6 [32, 87] and TNF-α [33, 121], CD54 and CD62E [32, 162]. Other researchers also reported that silica nanoparticles induced apoptosis *via* JNK/p53-dependent, mitochondrial pathways [84]. Chen et al. [29] suggested an absorption of SNPs in the nucleus generated aberrant clusters of topoisomerase I and protein aggregates in the nucleoplasm. The formation of nucleoplasmic aggregates impairs such nuclear functions as inhibiting replication and transcription [29]. Yang and coworkers implied that perturbation of intracellular free calcium homeostasis may be responsible for cytotoxic effect of silica nanoparticles [169]. A recent work by Zhao et al. [178] have demonstrated the effects of nanoparticles (depending on the surface properties, structure and size) on human red blood cells (RBCs). The uptake of large silica nanoparticles by RBCs showed a strong local membrane deformation leading to a spiculation of RBCs, internalization of the particles, and eventual hemolysis. On the contrary, adsorption of small particles occurred without affecting membrane or morphology of RBCs [178].

The size of nanoparticles plays a key role in their toxicity. Cho et al. [32] investigated the effect of the particle size on the pharmacokinetic parameters, such as tissue distribution and excretion *via* intravenously injected silica particles of different sizes in mice. They observed an occurrence of inflammatory response of the liver within 12 h after injection of 200 and 100 nm silica nanoparticles. However, this effect was not reported for the smaller particles (50 nm). All types of particles were excreted *via* urine and bile. These three types of nanoparticles were accumulated by macrophage in liver and spleen and remained there up to 4 weeks after the first injection of a single dose [32]. The authors then presented the effect of amorphous silica by intratracheal instillation. They observed significant increase of lung weights, total number of BAL cells and proteins concentration. The histopathological evaluation showed an inflammation, characterized by late neutrophils infiltration which resulted in the occurrence of symptoms of chronic granulomatous inflammation of the lung [33]. Other researchers reported that inhalation of silica nanoparticles caused the inflammation of pulmonary tract myocardial ischemic damage and atrio-ventricular blockage. In addition, they observed an increase of fibrinogen concentration in blood [30]. Although organically modified silica nanoparticles accumulate in all organs, there were no inducted signs of organ toxicity [77]. Nishimori et al. [112] evaluating the acute toxicity of amorphous silica particles observed a significant hepatotoxicity. During chronic administration nano-size materials cause liver fibrosis in mice [112].

Carbon nanomaterials

Carbon nanocarriers used in DDS are differentiated into nanotubes (CNTs) and nanohorns (CNH).

CNTs are characterized by unique architecture formed by rolling of single (SWNCTs – single walled carbon nanotubes) or multi (MWCNTs – multi walled carbon nanotubes) layers of graphite with an enormous surface area and an excellent electronic and thermal conductivity [17]. Biocompatibility of nanotubes may be improved by chemical modification of their surface [54]. Such adjustment can be implemented by covalent anchoring of PAMAM dendrimers [176], amphiphilic diblock copolymers [45],

or PEG layers [18] on CNTs surface or dispersion within a hyaluronic acid matrix [137]. Due to their mechanical strength, SWCNTs have been used as a support to improve properties of other carriers, e.g., polymeric or non-polymeric composites [137].

There are three ways of drug immobilization in carbon nanocarriers, which are: encapsulation of a drug in the carbon nanotube [11, 154], chemical adsorption on the surface or in the spaces between the nanotubes (by electrostatic, hydrophobic, π-π interactions and hydrogen bonds) [31, 177], and attachment of active agents to functionalized carbon nanotubes (f-CNTs). Encapsulation has the advantage over the two remaining methods as the drug is protected from degradation during its transport to the cells and is released only in specific conditions [119]. The examples of drugs that were attached to CNTs are listed in Table 2.

Drug release from carbon nanotubes can be electrically or chemically controlled. To prevent the unwanted release of the drug, the open ends of CNTs were sealed with polypyrrole (PPy) films [88]. Homing devices, i.e., folic acid [44] and epidermal growth factor [19], were attached to improve selectivity of such drug delivery systems.

Nanohorns – a type of the only single-wall nanotubes – exhibit similar properties to nanotubes [136]. Their formation process does not require a metal catalyst, thus, they can be easily prepared with very low cost and are of high purity [136]. The immobilization of drugs may rely on adsorption on nanohorns walls [105] or nanoprecipitation of drugs with nanohorns [6]. A comparison of these two paths of cisplatin incorporation into nanohorns showed that nanoprecipitation is much more effective (almost 3-fold increase in the number of molecules entrapped in nanohorns) than adsorption [6].

The toxicity of carbon nanomaterials also depends on their unique well-defined geometric structure [67]. The toxic potential of carbon nanotubes can result from the high length to diameter ratio and the toxicity of the sole material, which is graphite. In addition, some impurities, such as residual metal and amorphous carbon, contribute to the level increase of reactive oxygen species (ROS), thus, inducing the oxidative stress in cells [47]. Recent studies have pointed out the similarity in carcinogenic potential between CNT and asbestos. [120]. Carbon nanotubes have been shown to cause necrosis or apoptosis of macrophage cell lines and changes in cell morphology [67]. Radomski et al. [127] studied the effects of engineered carbon nanoparticles (MWCNT and SWCNT) on human platelet aggregation *in vitro* and rat vascular thrombosis *in vivo*. Incubation of platelets with carbon nanomaterials caused platelet aggregation with little or no granular release [127]. Incubation of bronchial epithelial cells and keratinocytes with high doses of SWCNT resulted in oxidative stress, including ROS generation, lipid peroxidation and mitochondrial dysfunction [133]. *In vivo* studies concerning intratracheal administration of nanotubes in rats revealed the induction of change in lung structures, such as granuloma formation and interstitial fibrosis

Tab. 2. Carbon nanotubes as DDS

Type of nanotubes	Drug	Method of immobilization	Ref.
MWCNTs	Cisplatin	Encapsulation *via* capillary forces	154
f-CNTs	Amphotericin B	Conjugated to carbon nanotubes	123
SWCNTs	Gemcitabine	Encapsulation	11
MWNTs	Epirubicin hydrochloride	Adsorption	32
MWCNTs@poly(ethylene glycol-*b*-propylene sulfide)	Doxorubicin	Adsorption	45
f-CNTs	Sulfamethoxazole	Adsorption	177
SWNTs-PL-PEG-NH_2	Pt(IV) prodrug-FA	Covalent amide linkages	44
SWNTs	Cisplatin – EGF	Attachment to carbon nanotubes *via* amide linkages	19
MWCNTs	Dexamethasone	Encapsulation	88

MWNTs multi walled nanotubes; f-CNTs functionalized carbon nanotubes; SWNTs-PL-PEG-NH_2 amine-functionalized single-walled carbon nanotubes

[80, 101]. Unmodified MWCNT caused pro-inflammatory response in keratinocytes cell lines, e.g., release of cytokine interleukin 8 and formation of cytoplasmic vacuoles [98].

Magnetic nanoparticles

Magnetic nanoparticles exhibit a wide variety of attributes, which make them highly promising carriers for drug delivery. In particular, these are: easy handling with the aid of an external magnetic field, the possibility of using passive and active drug delivery strategies, the ability of visualization (MNPs are used in MRI), and enhanced uptake by the target tissue resulting in effective treatment at the therapeutically optimal doses [10].

However, in most of the cases where magnetic nanocarriers have been used, difficulties in achieving these objectives appeared. It is most likely associated with inappropriate features of magnetic nanoparticles or inadequate magnet system. Magnetic nanoparticles, for instance, tend to aggregate into larger clusters loosing the specific properties connected with their small dimensions and making physical handling difficult. In turn, magnetic force may not be strong enough to overcome the force of blood flow and to accumulate magnetic drugs only at target site [110]. Therefore, designing magnetic drug delivery systems requires taking into consideration many factors, e.g., magnetic properties and size of particles, strength of magnetic field, drug loading capacity, the place of accessibility of target tissue, or the rate of blood flow [24].

Depending on magnetic properties, MNPs can be divided into pure metals (such as cobalt [96], nickel [69], manganese [132], and iron [143]), their alloys and oxides. However, narrowing the area of MNPs applications only to biomedicine reduces significantly the choice of magnetic material. Such a restriction results from the lack of knowledge of the negative effects which the majority of these nanomaterials have on the human body.

Iron oxide nanoparticles, due to the favorable features they exhibit, are the only type of MNPs approved for clinical use by Food and Drug Administration. These attributes are: facile single step synthesis by alkaline co-precipitation of Fe^{2+} and Fe^{3+} [53], chemical stability in physiological conditions [12] and possibility of chemical modification by coating the iron oxide cores with various shells, i.e., golden [148], polymeric [34], silane [25], or dendrimeric [114] (Fig. 3). In addition, iron oxides – magnetite and maghemite – occur naturally in human heart, spleen and liver [57], which indicates their biocompatibility and non-toxicity at a physiological concentration. It is essential to estimate a safe upper limit of MNPs for biomedical use.

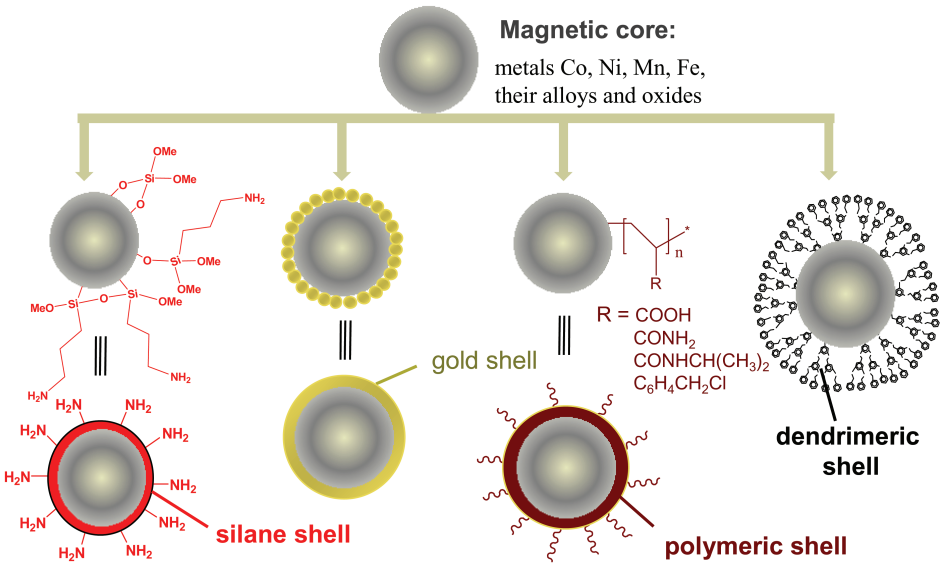

Fig. 3. Magnetic nanoparticles with various shells

Connecting a drug with MNP may be achieved by covalent binding [53], electrostatic interactions [53], adsorption [168], or encapsulation process [166]. Targeting of drug-MNPs conjugates to diseased tissues (magnetic targeted drug delivery systems – MTDDS), depending on their size and surface chemistry, can be carried out by passive or active mechanism. Passive targeting is a result of enhanced vascular permeability and retention (EPR) of tumor tissues. Active strategy relies on the attraction of nanoparticle to the affected site by using recognition ligands (e.g., antibodies) attached to the surface of MNPs and by handling of an external magnetic field [53].

Therapeutic activity of diverse drugs incorporated into iron oxide nanocarriers have been tested and reported (Tab. 3). MNPs have been examined for multitasking treatment as biosensors (diagnosis) and drug carriers (therapy) simultaneously. Concomitant use of magnetic resonance or magnetofluorescent imaging and targeted therapy (*via* conjugation of targeting moieties) can enhance effectiveness of cancer therapy [34].

MNPs have been also tested as carriers for the treatment of in-stent thrombosis. Traditional thrombolytic therapy is associated with severe side effects, such as hemorrhagic complications. In order to eliminate these issues, a tissue plasminogen activator (tPA) – a protein involved in dissolving blood clots – was covalently coupled to silanized [71] and chitosan-modified [28] magnetic nanoparticles. The preliminary studies indicate that such conjugates can be useful in magnetically targeted lysis of in-stent thrombosis and can improve clinical aspects of thrombolytic therapy.

The influence of iron oxide NPs on cellular function and toxicity has been investigated and reported. MNPs, depending on the way of their administration, may interact with extracellular components or/and with the cell membranes of macrophages, endothelial cells, skin epithelium, and respiratory or gastrointestinal tracts [35, 86, 89]. After inhalation, MNPs accumulate in the brain which indicates their ability to cross the blood-brain barrier. Mechanisms of internalization and overall biodistribution of MNPs are closely associated with their surface chemistry and hydrodynamic sizes [172]. Magnetic nanoparticles can be quickly opsonized by plasma proteins, recognized and subsequently removed from the bloodstream by macrophages of the reticuloendothelial system [138]. The greatest overall uptake of nanoparticles can be observed in liver and spleen [160].

Investigations concerning the deformation of cells upon their exposure to nanoparticles have revealed that the toxicity of MNPs (at the same molarity) increases

Tab. 3. Magnetic nanoparticles as DDS

Drug	Therapeutic activity	Nanocarrier (core@shell)	Ref.
Ciprofloxacin	Anti-infective agents (antibiotic)	Fe_3O_4@poly(vinyl alcohol)-*g*-poly(methyl methacrylate)	15
Gemcitabine	Antimetabolites, cancer chemotherapy	Fe_3O_4@poly(ethylene glycol)	151
Doxorubicin	Antineoplastic agent	Fe_3O_4@gelatin	56
5-Fluorouracil	Antimetabolites, anticancer drug	Fe_3O_4@ethylcellulose	9
Daunorubicin	Chemotherapeutic leukemia drug	Fe_3O_4	166
Anti-β-HCG monoclonal antibody	Choriocarcinoma-specific gene vector	Fe_3O_4@dextran	68
Cisplatin	Chemotherapeutic drug	Fe_3O_4@poly ε-caprolactone	170
Paclitaxel	Mitotic inhibitor used in cancer chemotherapy	Fe_3O_4@poly[aniline-co-sodium *N*-(1-butyric acid)	65
1,3-Bis(2-chloroethyl)-1-nitrosourea (BCNU)	Anti-cancer chemotherapy drug	Fe_3O_4@poly[aniline-co-*N*-(1-butyric acid) aniline]	64
t-PA	Tissue plasminogen activator, thrombolytic therapy	Fe_3O_4@tetraethyl orthosilicate	71
		Fe_3O_4@chitosan	28
Dopamine	Catecholamine neurotransmitter, Parkinson's disease	Fe_3O_4@silica (diatom)	86

rd@ – functionalization

in the following order: from nanobeads, to nanoworms and nanospheres [90]. MNPs coated with long-chain polymers are less cell toxic (slightly lower cell viability in relation to the control probe in MTT assay) than MNPs coated with shorter polymer chain of the same type (with a significantly reduced viability) [58].

Magnetic nanoparticles promote activation of phagocytotic and cytokine-release functions of macrophages [47]. Gas vesicles were observed in MNPs-treated cells with increased granularity of the cells [89]. Magnetite nanoparticles have the potency of causing oxidative DNA lesions in cultured A549 cells (the human lung epithelial cell line) [70]. They also cause transient increase of ALT (serum alanine aminotransferase), AST (aspartate aminotransferase), and ALP (alkaline phosphatase) levels [66]. In several reports iron oxide was found to accumulate in tissues but without significant histological changes in vital organs [166].

It is known that iron oxide NPs can induce oxidative stress by excess of ROS production. The response of defense elements leads to increased expression of antioxidant enzymes, such as heme oxygenase 1 and superoxide dismutase. This stage is followed by pro-inflammatory response, i.e., cytokine, chemokine, and matrix metalloproteinase (MMP) release, leading to apoptosis and mutagenesis. An increase in the activity of MMP in the nervous system can enlarge BBB permeability and cause neuronal damages. Oxidative stress-induced cell injury and death may be avoided using appropriate dose of MNPs [107].

Conclusion

Nanocarriers as drug delivery systems are designed to improve the pharmacological and therapeutic properties of conventional drugs. The incorporation of drug molecules into nanocarrier can protect a drug against degradation as well as offers possibilities of targeting and controlled release. Due to small dimensions, nanocarriers are able to cross the blood-brain-barrier (BBB) and operate on cellular level. In comparison with the traditional form of drugs, nanocarrier-drug conjugates are more effective and selective. They can reduce the toxicity and other adverse side effects in normal tissues by accumulating drugs in target sites. In consequence, the required doses of drugs are lower.

Although there are several nanoparticle-based therapeutic agents which are currently being developed and are under preclinical evaluation, only a handful of nanoparticle drugs are available on the pharmaceutical market, e.g., liposomal conjugates: Doxil® (doxorubicin) or DaunoXome® (daunorubicin). It is due to the fact that nanoparticle based drug delivery systems do have a lot of drawbacks and limitations. Some of them arise from scaling up problems. For instance, small size and large surface area of nanoparticle-based targeting system can lead to an aggregation, making physical handling difficult. Nanocarrier-drug conjugates can be phagocytosed by cells whereas their intracellular degradation may cause cytotoxic effects. Other issues include low drug loading capacity, low loading efficiency, and poor ability to control the size distribution of carriers. Furthermore, there is a lack of technological methods, which will lead to nanodevices of approvable quality.

Despite all the limitations and shortcomings, nanoparticle DDS which respond to slight changes in the local cellular environment have a potential to resolve many of the current drug delivery problems. However, before the ongoing research will bring a clinically useful drug delivery system, challenges which include developing toxicity testing protocols, improving biocompatibility, drug loading, targeting, transport and release, controlling interaction with biological barriers, detecting and monitoring exposure level and assessing the impact on the environment have to be met.

Due to a number of functional groups on the surface of nanoparticles, the drug can be attached to the carrier only in a stoichiometric ratio. The oxidative stress and inflammation in different cell types have been often reported as toxic mechanisms of various types of nanoparticles. Nanoparticles of diameter 10 nm can remain in cells and induct chronic inflammatory response and fibrosis of tissue. An additional problem is the lack of knowledge concerning the distribution of drug carriers and the unpredictability of the process. Thus, in our opinion, the magnetic targeted drug delivery system is one of the most attractive strategy target therapy. Magnetic nanoparticles have their unique magnetic properties and they can be attracted by magnetic fields, thus, acting as drug carriers in a target therapy. In addition, inorganic magnetic nanoparticles containing the iron and gadolinium serve as an excellent contrast enhancing agents in MRI (approved by FDA – Food and Drug Administration).

A real therapeutic breakthrough can be achieved solely by carrying out painstaking studies in the field of nano-therapy. Using nanosystems in therapies of diseases may contribute to achieving an effective cancer treatment. Moreover, immobilization of homing devices, such as folic acid, epidermal growth factor or antibodies, to the surface of nanoparticles, improves selectivity of drug carriers. The key applications of nanoparticles in medicine are diagnosis and target therapy, however, their wider use is still the future.

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