Chapter 1

Advances in Cancer Treatment: Role of Nanoparticles

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Additional information is available at the end of the chapter

Abstract

This chapter is devoted to the advances in the field of nanoparticles-mediated cancer treatment. A special attention is devoted to the use of magnetite and silver nanoparticles. The synthesis and properties of Fe_3O_4 and Ag nanoparticles as contrast or antitumoral agents as monolith or component of more complex systems such as polymer matrix composite materials based on: polymers (chitosan, collagen, polyethylene glycol, polyacrylates, and polymethacrylates, polylactic acid, etc.) and various antitumoral agents (cytostatics, natural agents and even nanoparticles-magnetite, silver, or gold) are discussed. Special attention is paid for the benefits and risks of using silver and magnetite nanoparticles. In both cases, the discussion focuses on aspects related to diagnosis and treatment of cancer. The influence of size and shape [1-3] is important from the materials characteristics as well as from the biological points of view. The role of magnetite is also analyzed from the point of view of its influence on the delivery of different components of interests (antitumoral components, analgesics/anti-inflammatory agents, etc.). The potentiating effect of the nanoparticles over the cytostatics and natural components is highlighted.

Keywords: cancer, magnetite, silver nanoparticles, diagnosis and treatment, hyperthermia, drug delivery

1. Introduction

Cancer is a real problem of our century and one of the leading causes of death, accounting for one of eight deaths occurring worldwide [4, 5]. Based on the actual data, the International Agency for Research on Cancer (IARC) estimates ~13.1 million deaths associated to cancer by

2030. It is becoming clear for many researchers that the low survival rate is due to the lack of adequate drug delivery systems and not due to the lack of potent, natural, or synthetic antitumoral agents. Therefore, there is a real need to develop carriers and delivery systems which would be able to deliver the chemotherapeutic agents only at the specific target site and improve the efficiency of treatment and consequently limiting the unwanted systemic side effects [6]. Cancer is characterized by rapid, uncontrolled cell differentiation. Due to the fast cell differentiations, the tumor grows fast but the angiogenesis is slower and consequently nonmatured or formative vasculature is characteristic for these tumoral tissues. This is why nanoparticles are able to penetrate the cancer tissue through the leaky vasculature, whereas tight junctions between endothelial cells in healthy tissue do not allow the penetration [7]. Furthermore, cancer tissue lacks a well-formed lymphatic circulation which is responsible for tissue homeostasis. This leads to enhanced retention of particles in cancer tissue. This phenomenon in cancer is called enhanced permeation and retention (EPR) effect. The size of the drug carrier system plays an important role in retention process [8, 9]. Consequently, the use of nanoparticles could be a great opportunity for the treatment of cancer.

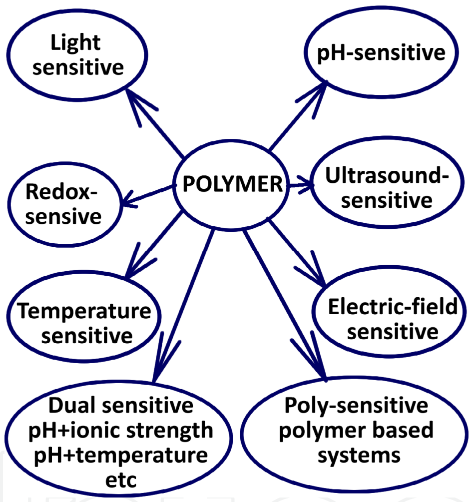
Cancer that begins in bone tissue is rare in adults and increases in importance in young people. Bone cancer treatment is a real challenge in this century. It affects especially children and young people/teenagers (10–20 years) – up to 4-7% of all cancers – and rarely appears in old people (less than 0.2% of all cancers) [10-12]. Malignant primary bone tumors are usually associated with an aggressive growth [12]. One of the most common forms of primary bone cancer is osteosarcoma (which counts for ~35.1% of primary bone cancer). In many cases, bone cancer treatment involves surgery, radio- and chemotherapy, even if many unconventional therapies are available; some of the most studied being hyperthermia and photothermia as well as the use of different nanoparticles due too their intrinsic antitumoral activity. Some of our previous works proved the possibility of combining surgery with hyperthermia [13], surgery with chemotherapy [14, 15], as well as surgery with hyperthermia and with antitumoral nanoparticles [16]. The use of these nanoparticles is beneficial because it can lead to a decrease in the amount of cytostatics and consequently lower systemic toxicity due to the use of cytostatics. Beside the treatment, special attention is paid to pain management. In all phases of cancer, the management of pain is present, the analgesics used being gradually changed from mild analgesics to even opioids, especially in the advanced forms of cancer when the treatment is shifted from cure to palliation [17].

Bone cancer treatment involves a different approach compared to other types of cancer especially due to the particularities of the bony tissue. The most important characteristic of the bone tissue, which affects bone cancer treatment, is the low diffusivity of the antitumoral agents inside the tumoral tissue as well as the low penetration ability of different radiations into the bony tissue [18].

Over the past decades, developments in polymer as well as in nanoparticles chemistry have allowed synthesis and conjugation of functionalities which can respond to stimuli. This is an important advance in the field of cancer treatment because it allows not only a passive targeting strategy but also an active targeting strategy by using carrier–monoclonal antibody conjugates and carrier–ligand conjugates, which can be activated at desired moment/site. The stimuli-responsive polymers can be used in order to design various carrier systems such as micelles, vesicles, liposomes, gels, micro- and nanospheres, micro- and nanoparticles, and core–shell structures [5, 19].

Nanoscience and nanotechnologies are of high interest for researchers from all fields of science allowing exciting opportunities from industry to (nano)medicine, but also unsuspected menace. In most fields, the researches in the field of nanomaterials and nanotechnologies are of increasing importance, the most scientific database revealing increasing number of publications (papers, reviews or even patents) [20, 21], especially increasing market share of the nanotechnology products of thousands of billion Euros [22]. A rational use of the nanotechnologies/nanomaterials must be laid down in order to optimize the opportunities/risks ratio. In the case of cancer and other deadly diseases, higher risks can be assumed in their treatment.

It is well known that there are a lot of “smart polymers” which are stimuli-responsive polymers. They can be “activated” by pH, temperature, light, electric field or even by dual stimuli like pH and ionic strength, pH and redox, pH and temperature, etc. [5, 23], as presented in Scheme 1.



Temperature-responsive polymers:
- Poly(N-isopropylacrylamide);
- Poly(N-vinylcaprolactam);
- Polylactic acid

pH-responsive polymers:
- Poly(acrylic acid);
- Poly(methacrylic acid);
- Poly(lactic-co-glycolic)–polyethylene glycol
- Poly(acetoacetoxyethyl methacrylate);
- Poly[2-(diisopropylamino)ethyl methacrylate];
- Poly(hexyl methacrylate);
- Poly[2-(dimethylamine)ethyl methacrylate)
- poly(methacrylic acid–co-acrylic acid)-co-polyvinyl-pyrrolidone;
- 2-(N,N-diethylamino)ethyl methacrylate;

Light-responsive polymers:
- Poly(N,N-dimethylacrylamide-co-4-phenyl-azophenyl acrylate);
- Poly(N,N-dimethyl acrylamide-co-4-phenyl-azophenyl acrylamide);

Electric field-responsive polymers:
- Poly(dimethylsiloxane);
- Poly[2-(methacryloyloxy)ethyl phosphorylcholine];
- Poly(ethylenediamine-co-1,10-bis(chloro-carbonyl)decane);

Dual-responsive polymers:
- Poly(acrylic acid-graft-vinylidenefluoride) – pH and ionic strength.

Sheme 1. Classes of stimuli-responsive polymers and some of their major representative polymers

However, in most cases, the delivery mechanism is very complex; the contribution of several mechanisms has to be considered. The influence of the temperature, for instance, is important. For instance, even for the non-thermo-sensitive systems the temperature plays an important role, the delivery being influenced. Usually, the temperature can influence the solubility of the drug (usually increasing temperature leads to increased solubility) as well as the mobility/ diffusion of the drug (usually these properties increase with the temperature). Similarly, the pH can influence the solubility of the drugs and consequently influence the delivery rate of the active components.

2. Role of magnetite in cancer treatment

Magnetite is widely used in the medical field, being recommended due its native magnetic properties – magnetically guiding possibility, hyperthermia generating property, high loading capacity of many biological active agents, etc. Magnetic systems offer attractive diagnostic and treatment possibilities and consequently there are increasingly studied for a lot of biomedical applications. Superparamagnetic iron oxide nanoparticles (the so-called SPIONs) are usually used for inducing magnetic-field-responsive functionality of drug delivery systems. For this purpose, magnetite and/or maghemite can be further coated with a proper hydrophilic shell. The presence of the shell can dramatically change the properties of the magnetite, making it suitable for a wide range of medical and nonmedical applications. The main applications of magnetite and magnetite-based materials are presented in Scheme 2.

Applications of magnetite and magnetite-based materials

Biomedical applications

- Magnetic resonance imaging (MRI) [24-26]
- Biosensor and bioseparation, including DNA separation and isolation [26, 27]
- Magnetic manipulation of biomolecules [25]
- Drug and gene delivery [28]
- Drug transport [11, 29]
- Cancer therapy by hyperthermia [26] magnetocytolysis
- Tissue engineering [26]

Nonmedical applications

- Permanent magnets
- Ferrofluids for mechano-electrical applications
- Environmental contaminant (organic and inorganic) removal [30, 31]
- Magnetic sealing [32]
- Dampening and cooling mechanisms in loudspeakers

Sheme 2. Applications of magnetite

2.1. Magnetic materials as contrast agents

Iron oxide nanoparticles have been extensively studied as contrast agents for cancer detection and monitoring by MRI. They generally produce enhanced proton relaxation rates at significantly lower doses than paramagnetic ions (Gd^{3+}, for instance) because of their larger magnetic moment, and they provide negative (dark) contrast by enhancing T_2 relaxivity of water protons.

(Ultrasmall) Super Paramagnetic Iron Oxides are often used for magnetic resonance imaging – MRI. They consist of iron oxide cores, covered by different hydrophilic macromolecules, for example, dextran. Their synthesis is generally realized in one step alkaline precipitation starting from Fe^{2+} and Fe^{3+} aqueous precursors. The shell has three main roles: limit the magnetic core growth during the synthesis, limit the agglomeration due to the sterical repulsion due to the charged nature of the shell, and reduce the *in vivo* opsonization process. In fact, usually these core–shell structures consist of several magnetic cores, more or less aggregated, embedded into a hydrophilic macromolecules, which are sometimes cross-linked in a second step for enhancing the mechanical entrapment [33, 34].

2.2. Magnetic supports for drug delivery systems

Magnetite is widely used for obtaining drug delivery systems because it is a good sorbent; it can be functionalized; and can bind by covalent bonds different drugs, but also because it can be guided in magnetic field into the tumor (tumoral tissue/organ). The magnetically targeted drug delivery involves the loading of the magnetic nanoparticles with the antitumoral drug and the implanting of these magnetite-based nanoparticles into or in the proximity of the tumor or to inject these nanoparticles in the patient body via the circulatory system. Then, the magnetic nanoparticles are concentrated into the tumor by using adequate magnetic field. In this case, the delivery will occur mainly into the tumor and, consequently, the systemic toxicity will be low [35].

The mechanism of delivery can function differently, depending on the internal and external factors, as schematically represented in Scheme 3. These delivery mechanisms can be generally considered for any delivery system as also for magnetic drug delivery systems.

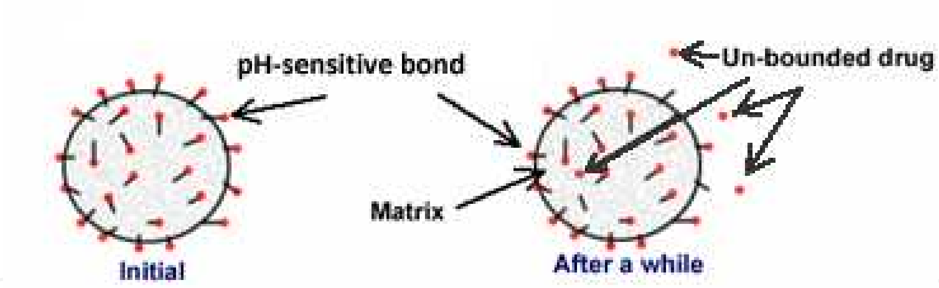
pH-triggered delivery is an essential issue in many medical applications because in many diseases pH changes occur, or once introduced into the body, the delivery must happen at a certain pH which corresponds to the pH of the desired tissue/organ. As presented in Scheme 1, there are a lot of pH-sensitive polymers.

Core–shell structures are often used as drug delivery systems. In the case of magnetite, the extensive use of core–shell structures is explained based on the low chemical stability of the magnetite as well as due to the nonspecific adsorption of plasma proteins and a rapid clearance of the particles by the immune system. The presence of different shells can lead to a strong modification of the surface properties of these micro- and nanostructured particles, which makes these materials suitable for biomedical applications. Both organic and inorganic coatings are extensively studied [41, 42].

Chitosan-based magnetic materials are often used as drug delivery systems of different drugs, including cytostatics. The polycationic structure of chitosan is proved to be effective as an antimicrobial agent as well as carrier and delivery systems. Many chitosan-based magnetic drug delivery systems for cancer treatment were developed during the time. Chitosan-coated magnetite for camptothecin release was obtained via typical precipitation/absorption route.

Delivery mechanism	
Factors affecting the delivery [5, 16, 35-40]	
Osmotic-controlled delivery	The osmotic-controlled delivery is the simplest mechanism of delivery, the drugs being delivered due to the different osmotic concentrations between the drug delivery system and the surrounding environment. Most of the drug delivery systems involve this mechanism, its share in the overall release process being variable.
Enzymatic-triggered delivery	This mechanism is especially important in the case of covalently bonded drugs. In this case, existent enzyme must recognize the support-drug bond and once the bond is broken the drug is free and can manifest its specific antitumoral activity. Proteases, hydrolyses, as well as other enzymes can be involved in the support-drug bond breaking. In certain conditions, the enzyme can be also introduced into the body, since the magnetic materials is accumulated into the desired organ/tissue.
pH-triggered delivery	pH-triggered delivery is often essential for medical applications, especially when the targeted application is related to the digestive tract, including the treatment of different forms of digestive-tube-associated cancers. The pH of the digestive tract is between 1 and 3 (in stomach) and over 8–9. In these conditions, the targeted delivery in stomach or intestines can be induced by designing drug delivery systems with pH-sensitive polymers. Such systems are also used for orally administered cytostatics delivery when protective measures have to be taken because of sensitive cytostatics (proteases from stomach could destroy the antitumoral agent).
Temperature-triggered delivery (including magnetic control due to the produced hyperthermia)	Temperature is an essential factor that influences the delivery of biological active agents, including cytostatics. Many formulations were proposed and tested at preclinical and clinical levels. In cancer, temperature can be considered as an internal factor because the tumor cells are in continuous replication and proliferation and consequently energy release is happen, even if the temperature increase is not very high. Also, especially in cancer treatment, the temperature can be considered external factor/stimuli because the intentionally produced temperature/hyperthermia leads to cancer cells death. In these conditions, the produced temperature is not enough for temperature-responsive systems to be developed. However, under hyperthermia conditions (an increase of 4–8^{o}C) as well as along with the implantation or injection of temperature-sensitive systems (the temperature increase can be upto 20^{o}C), the temperature increase is enough to develop temperature-triggered delivery systems.
Electromagnetic-triggered delivery	External electromagnetic field is applied and, due to the produced hyperthermia, the delivery rate is increased. Lipid matrices containing dispersed superparamagnetic iron oxide (SPIO) or other magnetite-based systems were investigated as magnetic field responsive drug delivery systems. Yi et al. [37] showed that lipid matrices based on myristic alcohol, oleic acid-coated SPIO particles, and umbelliferone, was able to deliver umbelliferone when external magnetic field was applied. The delivery is an indirect process which is due to the heating process and not directly due to the applied alternating magnetic field [38, 39]. In the case of lipid matrices containing dispersed superparamagnetic iron oxide, once heated the delivered heat leads to phase change in the lipid matrix and, along with melting, drug release is dramatically increased. When composite materials based on magnetite and cytostatics are obtained, the delivery is assured by the increasing diffusion induced by the increasing temperature. It was showed that once the alternating electromagnetic field was applied, the delivery rate increased [16].
Dual or poly-sensitive delivery	There are a lot of complex systems able to respond to two or even more factors. Usually, the increasing number of components can lead to an increasing number of factors of controlling the delivery. Usually, combining polymers from two independent classes allows a dual delivery control. The same observation is correct when using magnetic nanoparticles and polymers from certain classes. Magnetic control is very important because can assure "targeted delivery: as well as can be used to intensify the delivery rate.

Sheme 3. Delivery mechanism of magnetite or magnetite-based drug delivery systems of cytostatic drugs



Sheme 4. Schematic representation of the delivery mechanism in pH-sensitive mechanism

Basically, the synthesis consists in magnetite preparation by precipitation followed by chitosan and camptothecin adsorption from aqueous solution. The thus obtained camptothecin-loaded magnetic chitosan nanoparticles have spherical shape and a hydrodynamic radius of 65–280nm and exhibit low cytotoxicity against 7721 liver cancer cells. The in vitro drug release from these polysaccharide modified magnetic nanoparticles exhibited a steady and sustained release profile, after 12 h the overall release of camptothecin being ~20% (in 0.001M PBS, pH = 7.4, temperature or 37^{o}C) [43-46].

Zhang and Misra [47] developed a novel magnetic drug targeting carrier consisting of magnetic nanoparticles encapsulated in dextran-g-poly(N-isopropylacrylamide-co-N,N-dimethylacrylamide). This nanostructured system was obtained by functionalization of the magnetic nanoparticles with 3-mercaptopropionic acid hydrazide ($HSCH_2CH_2CONHNH_2$) via Fe–S covalent bonds. The anticancer therapeutic drug, doxorubicin, was attached to the surface of the functionalized magnetic nanoparticles through an acid-labile hydrazone bond, formed by the reaction of hydrazide group of 3-mercaptopropionic acid hydrazide with the carbonyl group of doxorubicin (see Scheme 5).

The developed system is pH-sensitive and could be a valuable system for cancer treatment when considering the normal pH of the blood (pH=7.4) and the pH of the endosomes of some cancer cells (pH =~5.0–5.5), since the delivery is faster under acidic conditions. This means that targeted delivery will be obtained in the acidic regions corresponding to the tumor sites. Furthermore, due to the presence of magnetite, the magnetic system can be concentrated at the desired tissue/organ and local hyperthermia can be produced. In these conditions, additional temperature control can be applied; once the temperature increases, the cumulative doxorubicin release increases by almost 20%, reaching ~90% after 48 h [47]. The thus designed stimuli-responsive magnetic system has a lower critical solution temperature (LCST) of ~38^{o}C, which makes it suitable as carrier system in cancer treatments of humans.

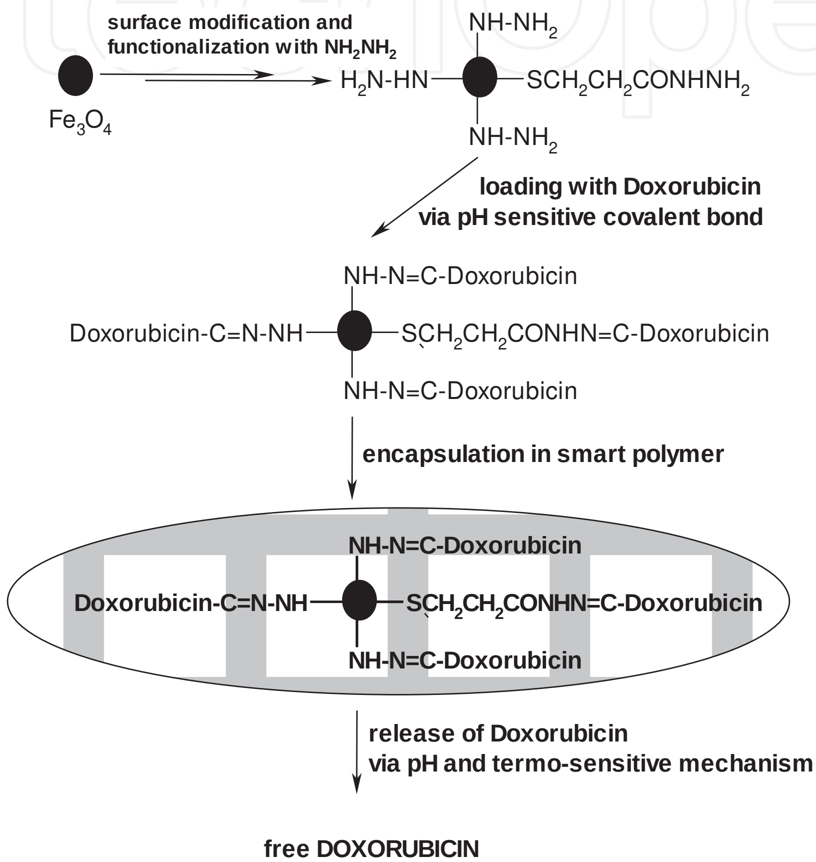
Drug delivery system	**Active component**	**Delivery mechanism**
Polyethylene glycol (linker hydrazone)	Doxorubicin	**pH-sensitive mechanism** of delivery induced by drug–polymer bond breaking (polymer/active component is realized via a third agent called linker)
Poly(amidoamine) dendrimer (linker hydrazone)		
Hyaluronic acid (linker hydrazone)		
Melanolactone– polycaprolactone (linker hydrazone)		

Drug delivery system	**Active component**	**Delivery mechanism**
N-(2-hydroxypropyl) methacrylamide (linker hydrazone)		
Poly(amidoamine) dendrimer (linker cis-aconityl)		
Polyacetal (linker acetal)		
Pullalan (amide linker		
Poly(aspartate hydrazide) (linker hydrazone)	Paclitaxel	
Polyethylene glycol (linker hydrazone)		
Dextran (linker hydrazone)	Streptomycin	
Alginate (linker cis-aconityl)	Daunomycin	
Polyethylene glycol and poly(lactic acid)	Paclitaxel	**redox-responsive drug delivery mechanism** via disulfuric bond breaking
Polyethylene glycol and oligocholic acids		
Gold nanoparticle-pluronic		
Poly(*ε*-caprolactone) and poly(ethyl ethylene phosphate)	Doxorubicin	
Poly(*ε* -caprolactone), poly(2,4-dinitrophenylthioethyl ethylene phosphate), and polyethylene glycol		
Polyethylene glycol and poly(*ε* -caprolactone)		
Dextran-lipoic acid derivatives		
Methoxy polyethylene glycol and poly(*ε*-caprolactone)		
Methacrylic acid and *N*,*N*-bis(acryloyl)cystamine		
Polyethylene glycol and oligocholic acids	Vincristine	
Polyethylene glycol, poly(L-lysine), and poly(L-phenylalanine)	Methotrexate	
Poly(*N*-isopropylacrylamide)	5-Fluorouracil	**Temperature-triggered delivery mechanism**
Poly(*N*-vinylcaprolactum)		
Pluronic F-127-chitosan	Curcumin	
Hydroxypropyl cellulose		
Poly(*N*-isopropylacrylamide-co-*N*,*N*-dimethylacrylamide), poly(D,L-lactide-co-glycolide), poly(*ε* -caprolactone)	Doxorubicn	
Poly(*N*-isopropylacrylamide-co-acrylamide)-b-poly(D,L-lactide)	Docetaxel	
Poly(*N*-isopropylacrylamide-co-*N*,*N*-dimethylacrylamide)-bpoly(D,L-lactide-co-glycolide)	Paclitaxel	
Poly(*N*-isopropylacrylamide-co-*N*,*N*dimethylacrylamide- co-10-undecenoic acid) nanoparticles	Doxorubicin	**Complex, dual pH/ temperature-responsive** drug delivery **mechanism**
Poly(*N*-isopropylacrylamide-co-acrylic acid)-b-polycaprolactone nanoparticles	Paclitaxel	

Drug delivery system	Active component	Delivery mechanism
Methoxy polyethylene glycol-b-P(*N*-(2-hydroxypropyl) methacrylamide dilactate)-co-(*N*-(2-hydroxypropyl) methacrylamide-co-histidine, methoxy polyethylene glycol-b-poly(lactic acid)	Doxorubicin	
Poly(D,L-lactide)-g-poly(*N*-isopropylacrylamide-comethacrylic acid) nanoparticles	5-Flourouracil	
Methacrylic acid and *N*,*N*-bis(acryloyl)cystamine nanogels	Doxorubicin	**Complex, dual pH/redox responsive** drug delivery **mechanism**
Polyethylene glycol-SS-poly(2,4,6-trimethoxybenzylidene-pentaerythritol carbonate) micelle	Doxorubicin	
Methoxy polyethylene glycol-2-mercaptoethylamine-grafted-poly(L-aspartic acid)-2-(diisopropylamino) ethylamine-graftedpoly(L-aspartic acid) micelles	Doxorubicin	
Polyethylene glycol- Fe_3O_4 nanoparticles	Doxorubicin	**Complex, dual pH/ magnetic-responsive** drug delivery **mechanism**
Methoxy polyethylene glycol-b-poly(methacrylic acid)-b-poly(glycerol monomethacrylate) coated Fe_3O_4 nanoparticles	Adriamycin	
Methoxy polyethylene glycol-b-(*N*,*N*-dimethylamino)ethyl methacrylate-b-polyglycidyl methacrylate coated Fe_3O_4 nanoparticles	Chlorambucil and Indomethacin	
Polyethylene glycol-poly(imidazole L-aspartamide)-2-vinylpyridine coated Fe_3O_4-SiO_2 nanoparticles	Doxorubicin	
1,3,5-Triazaadamantane Fe_3O_4 capped mesoporous silica nanoparticles	Doxorubicin	
Pluronic with Fe_3O_4 nanoparticles	Doxorubicin	**Complex, dual temperature/ magnetic-responsive** drug delivery **mechanism**
Poly(*N*-isopropylacrylamide-acrylamide-allylamine) coated Fe_3O_4 nanoparticles		
DNA-capped MSNs	CPT, floxuridine	**Complex, dual temperature/ enzyme-responsive** drug delivery **mechanism**
Poly(oligo(ethylene glycol) acrylate-co-2-(5,5-dimethyl-1,3-dioxan-2-yloxy)ethyl acrylate) (P(OEGA-co-DMDEA)) nanogels containing bis(2-acryloyloxyethyl) disulfide	Doxorubicin, Paclitaxel	**Complex, ternary temperature/pH/ redox-responsive** drug delivery **mechanism**
Poly(*N*-isopropylacrylamide-co-methacrylic acid) (P(NIPAM-co-MAA)) coated magnetic mesoporous silica nanoparticles	Doxorubicin	**Complex, ternary temperature/pH/ magnetic-responsive** drug delivery **mechanism**
Poly(*N*-isopropylacrylamide)-chitosan magnetic nanohydrogels		

Drug delivery system	Active component	Delivery mechanism
Fe(II) loaded poly(methacrylic acid) microcontainers crosslinked by *N*,*N*-methylene-bisacrylamide and *N*,*N*-bis(acryloyl)-cystamine	Daunorubicin	**Complex, ternary pH/redox/magnetic-responsive** drug delivery **mechanism**

Table 1. Most important delivery mechanism of antitumoral agents and some of their most important representatives (based on [5, 48])



Scheme 5. Synthesis and dual-sensitive magnetic drug delivery system

Bhatnagar and Venuganti [5] realized a very complex review based on stimuli responsive drug delivery systems of over 70 smart delivery systems, classifying them function of the delivery mechanism and active components. Some of the most representative drug delivery systems are presented in Table 1. It can be seen that the mechanism of delivery is very important because it can allow a tighter control of release, which is essential in cancer treatment due to the high toxicity of the cytostatics.

2.3. Magnetic materials as hyperthermia generator

Hyperthermia is an interesting effect of some materials and appears to be of great importance in cancer treatment. Since discovered, over 4000 years ago [49], magnetite was tested for the treatment of different types of cancer from primary (breast, colon, bladder, toque, bone, etc.)

to metastatic cancer [50-56]. The high attractiveness of these materials is related to the easy targeted hyperthermia, these nanoparticles being easy to move using an adequate magnetic field to the desired tissue or organ.

Hyperthermia is a technique of the Ancient Egyptians. Records related to the use of hyperthermia in the treatment of (breast) cancer were reported around 2600 BC and later in 2000 BC and was rediscovered in the late 19th century [53, 57]. In the treatment of cancer, the high expectations of the use of hyperthermia can be justified taking into account the following issues. Cancer cells generally perish above 43^{o}C because the oxygen demand is high while the oxygen transported via the blood is not sufficient (due to incomplete angiogenesis) whereas normal cells are less affected even at higher temperatures. In addition, tumors are more easily heated than the surrounding normal tissues, since the blood vessels and nervous system are poorly developed in the tumor. In fact, the beneficial heat effect is well known and used for a long time. Different heating techniques of heating of tumors were attempted, including heating with hot water, infrared waves, ultrasound, as well as microwaves. In the case of deep-seated tumors, these techniques are not effective and consequently ferromagnetic microspheres have to be used to generate hyperthermia [58].

Magnetic composite materials are often obtained by combining the useful properties of magnetic nanoparticles and different organic or inorganic components, the most used being polymers: collagen, chitosan, chitin, dextran, as well as inorganic oxides like ZnO, SiO_2, TiO_2, and titanates [56, 59].

Ferrimagnetic glass ceramic microspheres as well as magnetite microspheres were produced by different researchers and were reviewed by Kawashita et al. [58]. Magnetite microspheres of ~20-30 μm were already prepared by Kawashita et al. [58]. Also, glass-ceramics containing magnetite in a wolastonite and bioglass matrix was proved to be effective in cancer treatment. The cancer cells were transplanted in rabbit tibiae by inserting into the medullary canal as a glass ceramic pin. The hyperthermia is generated by placing it into an alternating magnetic field. Based on these data, it can be assumed that glass-ceramic microspheres (20-30 μm in diameter) could be easier applied because the cancer cells might be scattered around and consequently a larger area must be covered. Comparing magnetite and glass-ceramic microspheres it can be concluded that magnetite exhibits a higher heat generation capacity (41W/g) compared with the glass-ceramic-loaded magnetite microspheres (10W/g), which is consistent with the lower magnetite content. Under these conditions, the maximum coercive force corresponds to a crystallite size of ~40nm.

Muzquiz-Ramos et al. [55] have obtained biomimetic apatite coatings on magnetite particles for bone cancer treatment. For this purpose, firstly, they obtained magnetite nanoparticles of ~12nm by coprecipitation and, then, by immersing magnetite nanoparticles into simulated body fluid – SBF or 1.5 SBF (50% more concentrated SBF than human blood plasma – see concentrations in Table 2) – for certain period of time they deposited HA coating onto the magnetite nanoparticles. Hydroxyapatite formation is strongly dependent on the composition and immersion time in SBF. It was found that, the immersion in SBF does not alter the superparamagnetic behavior of the magnetite core and consequently it can be used as potential candidates for the treatment of solid bone tumors.

	Na^+	K^+	Ca^{2+}	Mg^{2+}	Cl^-	HCO_3^-	HPO_4^{2-}	SO_4^{2-}
Human blood plasma	142.00	5.00	2.50	1.50	148.80	4.20	1.00	0.50
SBF	213.00	7.50	3.75	2.25	223.20	6.30	1.50	0.75
1.5SBF	142.00	5.00	2.50	1.50	103.00	27.00	1.00	0.50

Table 2. Composition of human blood plasma, SBF, and 1.5SBF

In 2010, Andronescu et al. [13] proposed to slightly change the existent protocol of bone cancer treatment. In short, the protocol involves the combination of surgery and chemotherapy in the treatment of bone cancer. Depending on several facts, the chemotherapeutic drugs can precede and/or follow the surgery (Figure 1). During the surgical resection of the tumoral bony tissue, the surgeon can introduce into the newly resulted defect(s) multifunctional materials. Two main roles can be identified and have to be noted. First of all, the material can act as a scaffold contributing to a faster healing and, secondly, it can assure a supplementary, antitumoral activity based on the delivered components, interactions with the tumoral cells, or produced hyperthermia.

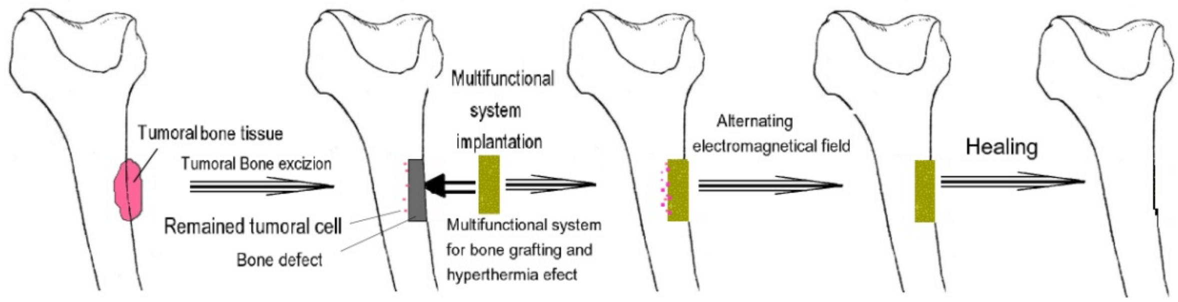


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Figure 1. Bone cancer treatment of osteosarcoma

3. Role of metal nanoparticles in cancer diagnostics and treatment

Metal nanoparticles (silver and gold) are widely used in cell imaging, DNA hybridization detection, proteins interaction, and photothermal therapy due to their extremely strong absorption and light scattering in the plasmon resonance [60]. In principle, the high attractiveness for using gold and silver nanoparticles in the cancer diagnosis and therapy is due to the unique optical properties, facile surface chemistry, and appropriate size scale. The tumor detection and treatment can be further improved by controlling size and shape or by conjugation of these nanoparticles with specific ligands/biomarkers [61]. The selective delivery of the metal nanoparticles is crucial for *in vivo* imaging and/or therapy. There are several strategies for delivery of these nanoparticles into the tumor: topical application for the skin tumors; direct injection or intraoperative application for the accessible deep tumors, or intravascular injection for the inaccessible tumors. In the case of tumors localized in hard tissues, the low diffusion of the body fluids does not assure the necessary flow through these tissues and consequently through the tumoral tissue and therefore direct, intraoperative application is necessary.

PEGylated gold or silver nanoparticles can also act as carrier of anticancer chemotherapeutics. PEG coating assures high biocompatibility, lower agglomeration tendency, and masking against immune systems. When intravenously injected into the body, it exhibits high retention time especially in solid tumors. After retention in the tumor, NIR irradiation can be applied and selective ablation of the nanoparticles-enhanced tumor occurs [62-64]. Molecular specific imaging and therapy of cancer is easily achieved by the synthetic conjugation of the nanoparticles with antibodies targeted to receptors overexpressed on the cancer cells.

Silver-based nanostructured materials can be used as bioimaging labels for human lung cancer H1299 cells as proved by Guo et al.

Xu et al. [65] reported the synthesis of silver and gold spherical metal nanoparticles of various sizes for IR-sensitive antitumoral activity. Silver nanoparticles (AgNPs) of 10, 20, and 40nm as well as gold nanoparticles (AuNPs) of 20, 50, and 100nm were prepared and modified with Fetal Bovine Serum. Also, AgNPs with 12nm diameter were obtained and functionalized with meso-2,3-dimercaptosuccinic acid and silanes bearing various functional groups including amino group, short chain PEG and carboxylic group. The thus obtained nanoparticles were tested on three lines of C6 glioma cells (originated from mouse), U251, and SHG-44 cells (originated from human GBM). They found that the antitumoral ability of these nanoparticles is dependent on concentration, IR dose, and nanoparticle size. In short, the smaller nanoparticles have higher efficiency; the higher irradiation dose leads to higher killing ability; and the higher concentration leads to lower survival cells. The used capping agent is also important, even if, the mathematical quantification is more difficult. The tests highlighted that meso-2,3-dimercaptosuccinic acid and PEGylated silane modified nanoparticles do not affect the cell sensitivity to radiation but, carboxy- and amino-silane bearing nanoparticles drastically decrease the cell survival.

Gold nanocages were synthesized by galvanic replacement reaction between Ag template and $HAuCl_4$. In short, silver nanoparticles of 30–200nm nanocubes are transformed in Au nanoboxes and nanocages (nanoboxes with porous walls) with tunable optical properties from blue (400nm) to near-infrared (1200nm). In order to obtain deeper penetration, near-infrared light is necessary. At present, three strategies of shifting the surface plasmon resonance from visible to near-infrared are known:

- form agglomerates from spherical Au nanoparticles;
- by elongating the nanoparticles from spherical gold nanoparticles to nanorods/whiskers;
- by emptying the interiors of spherical nanoparticles to form hollow gold nanostructures.

Most of these structures can be designed by using adequate capping agents or changing synthesis route.

4. Silicate-based materials as vectors against tumor cells

Targeted action is many a time necessary for both diagnosis and therapy. Complex systems based on magnetic core, different shells, and tumoral receptors are of great importance. The locoregional drug delivery systems are well known to be beneficial because the systemic toxicity can be reduced compared with the other administration routes [4, 10, 14]. The targeted delivery is very useful especially when local administration is not possible. In most cancer treatment protocols, active components must be administrated that, due to their high toxicity, are desired to be delivered at a certain site without spreading to other tissues or organs. Silicates are interesting materials for industrial and medical field. Montmorillonite was largely exploited in biomedical field because it is pH-sensitive and can be loaded with large amount of drugs into its layered structure. The pH-sensitiveness is determined by the ability of this material to modify its characteristic interlayer spacing. In acid solutions, the interlayer spacing is minimal and increases in basic conditions. This property is exploited in medicine, montmorillonite being used, for instance, to deliver active components in neutral/basic media like colon or intestines. It is also important to mention that montmorillonite-based formulations can be used for oral administration of different active components that are unstable in stomach conditions because of the protective role of the silicate (proteic drugs, for instance, cannot be administrated orally; the stomach environment will destroy them). For this purpose, montmorillonite was tested for oral administration of cytostatics [66-68]. Schematically, the targeted delivery of cytostatics form silicates are presented and discussed in Figure 2.

In oral delivery, the contact of the DDS with the digestive tract is the most important factor which has to be considered when designing orally administrated DDS. It is important to mention that the contact of the DDS with gastric acid can destroy the active component(s). There are a lot of active components which, under the action of gastric acid, became inactive (inactivation due to the action of pepsin and/or hydrochloric acid), and amongst these active components there are also many cytostatics which can be inactivated by gastric acid. In these conditions, some drugs cannot be orally administrated or different protective measures must be taken. One of the most common protective way is the entrapping of the drug into organic or inorganic matrix, which, if correctly selected, can release the drug or its complexes at the intestine/colon level [66]. At this level, different scenarios are possible: free active component(s) acts locally fighting against colon cancer or, can be absorbed into the blood and enter the blood circulatory system. At this moment targeted or nontargeted delivery can occur. In the case of targeted delivery, the active component/complex is predominantly delivered at the desired tissue/organs due to the presence of recognizing agents linked on the complex or simply, due to the intratumoral microenvironment, as we presented in Figure 2.

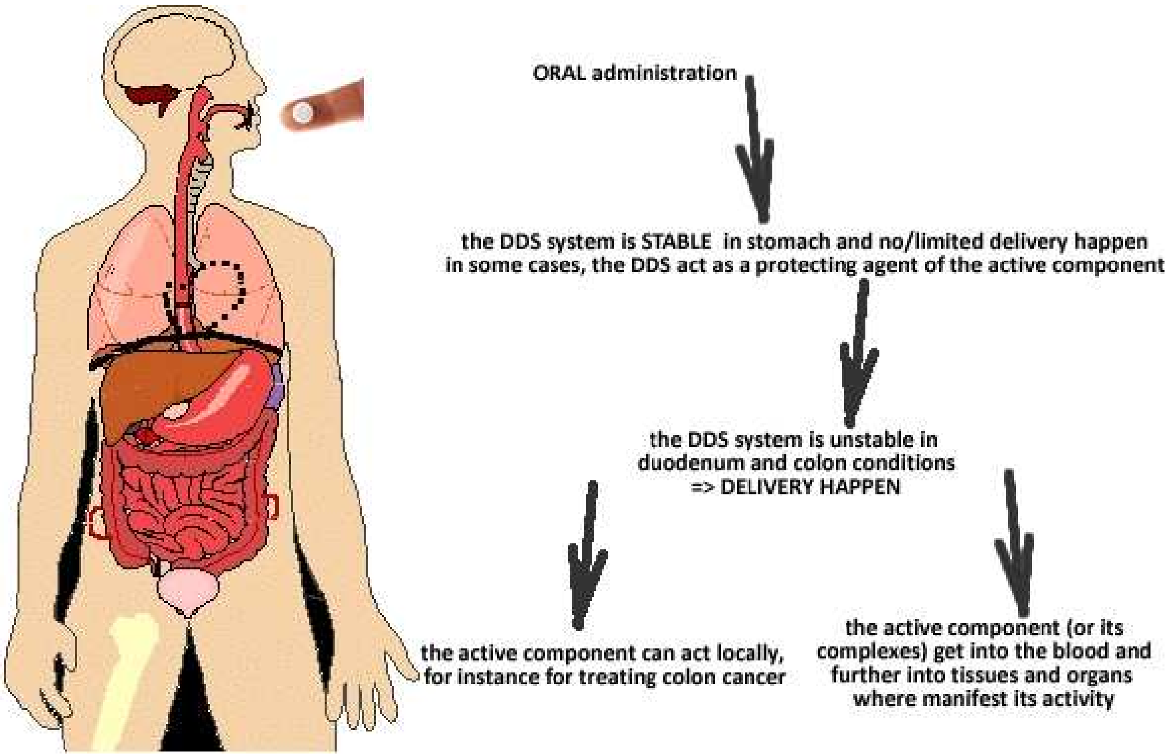

Figure 2. Schematic representation of cytostatics targeted delivery for oral administration

5. Conclusions

Metal and metal oxide nanoparticles are of great interest for medical and industrial applications. Magnetite is an important metal oxide with many potential applications in nanomedicine. Hyperthermia, targeted drug delivery system, and carrier and contrast agents are the most known medical applications with proved applicability in cancer diagnosis and treatment. The properties of magnetite nanoparticles are dependent on size and shape as well as composition and synthesis route. The bare magnetite is usually not recommended for biomedical applications because the host body recognizes it as a “foreign body” and consequently core–shell structures are usually obtained and tested for these applications.

Even if long-term toxicity of the nanoparticles is the subject of controversies, the use of gold and silver nanoparticles bring many advantages compared with other actual alternatives (like cytostatics). Further studies related to the influence of shape and size, capping agents, receptors immobilization onto the metal nanoparticles are still necessary. Surface plasmon resonance can be designed by size and shape and surface functionalization of both silver and gold nanoparticles. The surface plasmon resonance shift from blue to near-infrared is important because it allows a better/deeper penetration of the radiation into the body.

Mesoporous silicates are intensively studied for drug delivery and especially for cancer treatment, alone or in combination with other organic or inorganic polymers. Mesoporous silicates can be used for targeted delivery systems. These DDSs can be administrated orally, the delivery being intensified in neutral/basic conditions from intestines/colon.

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