ACADEMIA ROMÂNĂ
*Revue Roumaine de Chimie*
http://web.icf.ro/rrch/

*Rev. Roum. Chim.*,
**2012**, *57*(12), 1003-1011

*REVIEW*

# HYBRID POLYMER PARTICLES WITH MAGNETIC PROPERTIES FOR DRUG DELIVERY

Lăcrămioara BĂLĂIȚĂ* and Marcel POPA

"Gheorghe Asachi" Technical University of Iași, Faculty of Chemical Engineering and Protection of the Environment, Department of Natural and Synthetic Polymers, 73 Prof. dr. docent Dimitrie Mangeron Street, 700050, Iași, Roumania, tel.: +40232/278683/2271

*Received August 1, 2012*

For more than thirty years, the preparation of magnetic nano- and microparticles has been actively investigated for technology and biomedical applications. In medicine and therapy, magnetic particles are used in catabolism of tumors in hyperthermia, as contrast enhancement agents in magnetic resonance imaging, as therapeutic drug, gene and radionuclide delivery in bioseparation including cell sorting.
Magnetic particles present important properties, but low stability in biological fluids, because of the tendency of proteins adsorption. The coating of magnetic particles with biocompatible polymers may stabilize the particles and increase the blood circulation half-life. In addition, the polymers present chemical groups able to functionalize the magnetic particles and capacity to blend therapeutic agents.
This review is focused on the main properties of the magnetic particles and on the characteristics of the magnetic polymer particles used as the next generation of targeted drug delivery.

## INTRODUCTION

Magnetic particles are very interesting materials for researchers in different areas like biomedicine and biotechnology, magnetic resonance imaging, data storage, catalysis, environmental remediation, sensing devices, immunomagnetic separations, targeted drug delivery, cell labeling, bio-imaging.[1-16] The large density and easy oxidation of the magnetic particles can limit some of the above-mentioned applications. To improve the potential applications of the magnetic particles, it is important to associate these inorganic materials with organic ones. The organic substances have low density, good processability and chemical stability, so inorganic particles can be integrated with suitable organic substances (usually polymers), leading to a new class of materials, usually known as inorganic–organic hybrid materials.[16] Hybrid materials can have special characteristics derived from the entrapped inorganic particles together with the organic substance and can provide new properties generated by synergistic effects due to the interaction between them. If the polymers or the monomers contain functional groups, such as amino, phosphates, carboxylic acids, and sulfates, surface coating not only provide a protection for magnetic nanoparticles from aggregation or oxidation, but also could be used for certain functional applications, for example, drugs, enzymes or protein binding.

## PROPERTIES OF MAGNETIC MATERIALS

Most used magnetic materials are iron oxides. There are several types of iron oxides: magnetite ($Fe_3O_4$) and four crystalline polymorphs of $Fe_2O_3$, $\alpha$-$Fe_2O_3$ (hematite) $\beta$-$Fe_2O_3$, $\gamma$-$Fe_2O_3$ (maghemite)

* Corresponding author: lbalaita@yahoo.com

and ε-$Fe_2O_3$ which can be prepared in the laboratory.[17] Of them, only maghemite and magnetite fulfill the necessary requirements for biomedical applications. These requirements include low toxicity, chemical stability in physiological conditions, sufficiently high magnetic moments, also the easy and economical procedures for the preparation of these materials[18]. The size and the shape of the nanoparticles are also parameters that affect the performance in therapeutic and diagnostic techniques, such as hyperthermia or magnetic resonance imaging. All these parameters are strongly influenced by the preparation techniques.[6,7]

Magnetic particles have notable properties as superparamagnetism and biocompatibility. Magnetic materials present magnetic dipoles generated by the spinning of some of their electrons. These polarized electrons can be aligned in a parallel or antiparallel way with respect to the neighboring ones and this type of interaction gives rise to the macroscopic magnetic effect that can be measured. The magnetic materials can be classified, depending on their magnetic response observed, as paramagnets, ferromagnets, ferrimagnets or antiferromagnets. The magnetic properties are dependent on the size of particles, so at a certain temperature, the magnetic behavior of any material can be modified by adjusting its size.[6]

The paramagnetic materials have randomly oriented (or uncoupled) magnetic dipoles, which can be aligned only in the presence of an external magnetic field and along its direction. The paramagnetic material has no coercivity or remanence, it means that when the external magnetic field is turned off, the internal magnetic dipoles randomize again, see Fig. 1. The nanoparticles with such magnetic behavior are **superparamagnetic** (SPM). The nanoparticles must have smaller sizes (of the order of tens of nanometers or less) so that they can be superparamagnetic in order to avoid agglomeration after turned off magnetic field and to remain in blood circulation without being removed by the body's natural filters such as the liver or the immune system.[2,7]

The **ferromagnetic** material present the individual magnetic dipoles that can align parallel one to the other, even in the absence of an external magnetic field. Some metals such as Fe, Co or Ni and some of their alloys (Fe-Pt, Fe-Co) are ferromagnetic materials. The strength and the magnetization of the material can be described by three parameters: the coercive field, $H_C$, the saturation magnetization, $M_S$ and the remanent magnetization, $M_R$. $H_C$ represents the minimum energy required for the reversal of the magnetization of the material. $M_S$ indicates the maximum value of magnetization that the material can reach under the effect of sufficiently high magnetic fields. $M_R$ is the residual magnetization at zero applied fields. These parameters are presented in the hysteresis loop generated in magnetization measurements (Fig. 1).

The Ms value measured for magnetite (92 emu/g) is higher than those for maghemite (78 emu/g) for a similar particle size.[19]

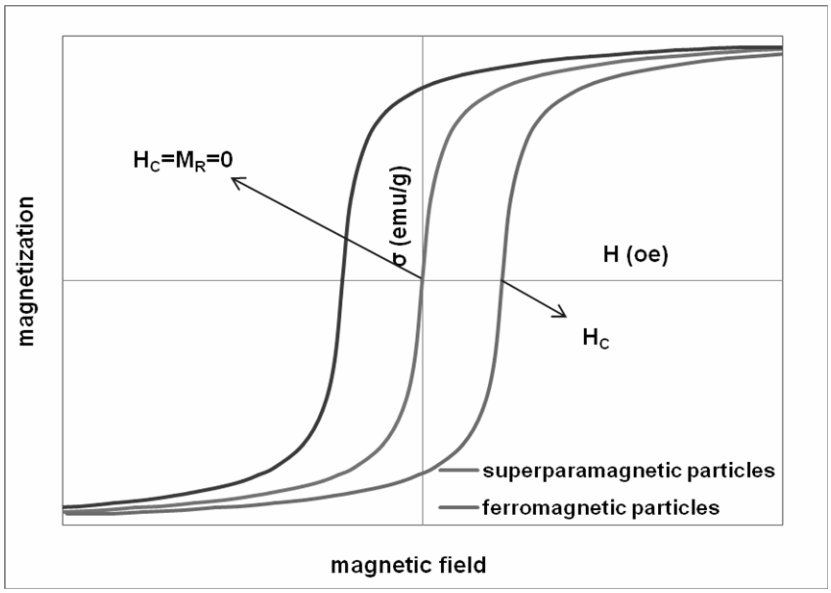


Fig. 1 – Magnetization curves for superparamagnetic and ferromagnetic particles.

Another situation, contrasting to the ferromagnetism, is when neighboring magnetic dipoles can align antiparallel, so that they will cancel each other (magnetic dipoles repulsion). This type of magnetic exchange can lead to two different situations: **antiferromagnetism** (the magnetic dipoles have the same value so the material shows a net zero magnetization) and **ferrimagnetism** (the opposing dipoles are unequal values and in that case a magnetization remains, even in the absence of an external magnetic field).

The latter case is interesting for biomedical applications and actually iron oxide (both magnetite and maghemite) belongs to the **ferrimagnetic** class of materials.

The reduction of size magnetic particles has some advantages that make them more suitable for therapeutic and diagnostic techniques. First of all, the decreasing of particles' size allows the control of magnetic parameters, such as coercivity. Therefore, the biomedical performance of the magnetic material can be optimized to the practical requirements. The decrease of the particle size below a certain radius (named 'superparamagnetic radius') causes a magnetic transition so the ferromagnetic particles become superparamagnetic. For the superparamagnetic particles, high magnetic moments are observed under the effect of a magnetic field, but once the external magnetic field is turned off no permanent magnetization (remanence) will be present. This property is a significant advantage for *in vivo* experiments, because after ending the therapy or the diagnostic measurement, the absence of coercivity, or in other words the zero net magnetic moment of the nanoparticles will prevent the aggregation of the particles. In this way the formation of embolisms in the blood vessels is avoided. The property direct associated with nanostructured magnetic materials is the superparamagetism and we can talk about it when the thermal energy is sufficiently high to overcome the magnetic stabilization energy of the particle.

## Biocompatibility

Basic requirements of nanocarriers are to have long blood circulation times and avoid the reticuloendothelial system (RES) in order to accumulate in target tissues.[20]

Also, the physicochemical properties of magnetic particles, such as size, morphology, charge, polymer coating determine their *in vivo* behavior, especially the blood half-life.[21] Particles smaller than 10 nm are rapidly removed by the renal clearance process.[22] Particles with sizes situated in the range 10-100 nm have the optimum size for longer time *in vivo* circulation. Particles bigger than 150 nm are sequestrated by reticuloendotelial system either by macrophage cells present in blood or by phagocyte cells of the spleen[23] or of the liver.[11]

Magnetic particles less than 4 μm are eliminated by cells of the RES, mostly in the spleen (3–10%) and liver (60–90%). Overall, the larger the particles, the lower their plasma half-life-period are.[11]

The shape is another factor which contributes at the stability and biodistribution of magnetic nanoparticles.[24] The circulation time for the oblate spheroid was found via simulation much longer than for spherical nanoparticles.[25] Some more recent studies have confirmed this theoretical result. By comparing the biostability of elliptical discs with various size spheres, was found that elliptical discs have longer circulation times[26] and the cell uptake is three times higher for spherical nanoparticles. As it has been mentioned before, spherical particles smaller than 200 nm pass through the spleen, unlike elliptical discs with sizes larger than 1,000 nm can pass through. This surprising behavior is explained by auto-organization (alignment or tumbling) of non-spherical nanoparticles under the influence of flow.[25] At this time the role of the particles shape on biodistribution is not fully understood or explained.[23]

The nanoparticle surface charge (zeta-potential) plays also an important role on stability in biological media: the adsorption of plasma protein increases with the growing of surface charge density (Increasing the surface change density increases the plasma protein adsorption). The amount of protein adsorption depends on the protein structure and by the hydrophobicity of the polymer used for coating. The nanoparticles with negative surface charge are related with proteins having isoelectric points higher than 5.5, while positively charged particles adsorb proteins having isoelectric points less than 5.5.[27] Nanoparticles with hydrophobic surfaces, unlike those with hydrophilic surfaces, exhibit more susceptibility to opsonization. The surface of hydrophilic particles is relatively strongly antifouling, binding only to albumin, while hydrophobic surfaces are able to bind, besides albumin, other proteins, such as, IgG, a poliproteins and fibrinogen.[28]

So, the biocirculation of nanoparticles can be negatively affected by specific protein binding. At the same time, in some cases, the binding of specific proteins on nanoparticle surfaces can be useful for easy passage through biological barriers. For instance, the polipoprotein on nanoparticles surface, may facilitate passage through the blood–brain barrier.[29]

The stability of the nanoparticles introduced in the body can be compromised by several aspects. One of them is related to the differences between the ionic strength of the physiological media and ultrapure water usually used in laboratory for preparation of particles. The change of ionic strength of aqueous solution in terms of its growth can result in the loss of electric double layer surrounding the charged particles, that fact inducing an aggregation of the system, unwanted situation, for the reason given above. A similar behavior could be observed when particles enter specific body compartments, due to a variation in pH with respect to the media in which the nanoparticles are initially dispersed. Also, by injection of the nanoparticles in the blood, it may be a nonspecific adsorption of plasma proteins onto nanoparticles surface, phenomenon named 'opsonization'. The opsonization is more pronounced for particles with nanometer size, because of the high surface-to-volume ratio as well as the attractive forces between the magnetic nanoparticles. When this phenomenon occurs, a fast clearance of the nanoparticles is observed.[6]

Those effects can be prevented by introducing polymers, natural or synthetic, to the nanoparticle surface such as dextran,[30] poly(ethylene glycol),[31,32] polyvinyl alcohol,[33] poly(L-lactic acid),[34] chitosan,[35-37] alginate,[38] starch,[39] gum Arabic,[40] carrageenan,[41] pullulan,[42] gelatin.[43] The polymers have been used to coat magnetic nano and micro-particles prepared by non hydrolytic methods, or in alternative they may be used during the synthesis by co-precipitation methods.[44]

The stable polymer layer often enhances the long term biocompatibility of magnetic nanoparticles-based systems. Also, the polymer improves dispersal and increases surface functionality, which creates the possibility to obtain multifunctional magnetic particles.[45] With this new feature the magnetic nanoparticles are suitable for tracking experiments that require monitoring and imaging magnetic-stained cells over long periods.

The stability of nanoparticles depends on the coating, on one hand, and on the interaction with the biological environment on the other hand. The agglomeration of particles in contact with proteins may provoke changes regarding cell internalisation or attachment and cytotoxicity. The examination of the agglomeration of nanoparticles coated with vinyl alcohol/vinyl amine copolymer or poly(vinyl alcohol) or poly(ethylenimine) was realized with turbidity measurement and photon correlation spectroscopy. Uncoated magnetic particles agglomerate immediately in phosphate buffer solution (PBS) and biological fluids, but the above polymer coated magnetic particles were stable in water and in PBS for months and in a pH range of 3–11 without any signs of agglomeration.

The use of these particles for *in vivo* application is conditioned by the nanoparticles agglomeration behavior in simulated body fluids and by the cytotoxicity (cell viability) for different cells.[46]

Iron oxide magnetic particles unlike other types of nanoparticles, such as those based on cobalt or nickel, are more biocompatible because iron cell homeostasis is better managed upon physiological uptake.[45]

## Toxicity

All substances used in humans and animals require extensively testing for toxic side effects. Besides the acute toxicity of the particles, it must to be considered the degradation products toxicity, the stimulation of cells with subsequent release of inflammatory mediators and toxic effects throughout the particulate system.

As it is well known, the cytotoxicity is usually much higher *in vitro* then *in* vivo.[47] A possible explanation is that the degradation compounds which determine the toxicity are naturally eliminated *in vivo*. Thus, toxicity tests conducted *in vitro* may have certain limitations.

The particles should be degraded and eliminated by the body without keeping residues; otherwise they may accumulate in certain cells. One of the most used toxicity tests *in vivo* is the intraperitoneal injection of nanoparticles in mice that allows studying the $LD_{50}$ ($LD_{50}$ is the amount of a material, given all at once, which causes the death of 50% of a group of test animals), the mitotic index and the effect of particles on macrophages and other cells (spleen, kidney, liver) by means of histology. Magnetic particles degrade into $Fe^{2+}$ and $Fe^{3+}$ so they generally show low toxicity.[48] Magnetite can degrade via the Fenton reaction:

$$Fe^{2+} + H_2O_2 \rightarrow Fe^{3+} + HO^- + HO\bullet^-$$

This degradation process is generating a reactive free radical, so it has been found to display cytotoxicity. Gupta found that magnetite and maghemite nanoparticles show different toxicities.[31] Magnetic particles are relatively safe because they do not accumulate in the vital organs and are rapidly eliminated from the body as it was demonstrated by *in vivo* studies. In addition, the presence of a polymer coating can also reduce magnetic particles toxicity.[49]

### Advantages and limits

These magnetic particles present several advantages. The size of the magnetic particles is very small varying between a few nm and a few tens of nm. A possible consequence here is the higher surface per volume ratio, which is expected to provide higher sensitivity, by comparation with nanoparticles-based on the encapsulation of the different building blocks.[6]

The wide surface of the particles assures higher loading capacity of the drug that could be attached at the particles, so that the dose of the nanostructures used as shuttle for the delivery is improved. Also, a larger number of targeting biomolecules could be associated with the surface of the nanoparticles, which provide a more efficient system for the recognition for targeted cells or tissues. As well, the small size suggests the improvement of the colloidal stability of the nanostructures. Also, it could be possible the merging of different inorganic nanoparticles at the interface of the particles, preparing thus the materials with interesting features, which might lead to new applications.

The use of magnetic particles is limited due to insufficient characterization of particles, the inhomogenous morphology and fast elimination through the RES.[47]

## POLYMER MAGNETIC PARTICLES

Magnetic polymer particles are composed of magnetic nanoparticles embedded in a polymer matrix. The morphologies or structures of the obtained particles are different and depend on the relative position of the magnetic nanoparticles.[50] The possible morphologies or structures of the obtained nanosystems are schematically illustrated in Fig. 2.

One kind of spheres present the magnetic particles homogeneously distributed in the volume of polymer matrix (Fig. 2a). Another type of spheres is characterized by core–shell structure which can be polymer core–magnetic shell (Fig. 2b) or magnetic core–polymer shell (Fig. 2c). Also, mixed systems can be obtained, where the core–shell particles are homogeneously dispersed in polymer matrix. Polymer particles with heterogeneous magnetic nanoparticles distributed in the polymer matrix are preferentially obtained in some techniques, such as miniemulsion polymerization.[1]

The use of polymers for the coating of magnetic particles provides *in vivo* an interface with biological media and has different tasks to fulfill: a) assuring colloidal stability for magnetic particles through steric stabilization in a biological suspension with pH around 7.4 and a high concentration; b) providing functional groups on particle surface for further derivatization, which allows the possibility of designing hybrid particles with capacity for multimodal tracking, targeting, delivery and stimulated release of therapeutic agents such as peptides, proteins and drugs; c) delaying immediate removal by the reticuloendothelial; d) assuring biocompatibility and cell uptake of the magnetic particles; e) protecting layer for the core: the presence of the shell prevents the oxidation of the iron core.[6,51,52]

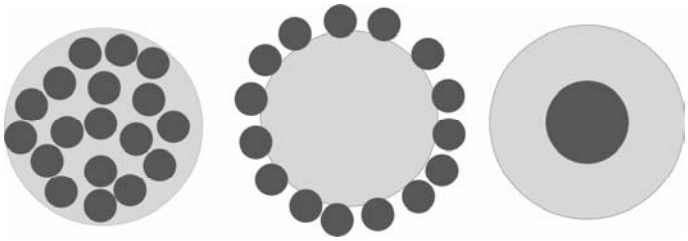

Fig. 2 – Schematic representation of the possible morphologies of magnetic polymer particles (cross section): a) magnetic nanoparticles distributed in polymer matrix; b) magnetic nanoparticles distributed on the polymer particle surface; c) magnetic core-polymer shell.

For many applications in medicine, a polymer coating on the magnetic particles is preferred over simple functionalization with small organic compounds.[53]

The main advantage of the core-shell structure of magnetic particles is good dispersion, high stability against oxidation and appreciable amount of drug which can be loaded to the polymer shell.[34] Moreover, many of functional groups from polymers surface can be used for further functionalization to obtain different properties.[54] It is very important that with coating, the magnetic nanoparticulate system does not exceed 100 nm in size to avoid rapid clearance by reticuloendothelial system (RES).[10] Also, it must be taking into account that the surface functionalization has important contribution in change in nanoparticle toxicity. Another precaution before use *in vivo* or *in vitro*: after crosslinking the polymer shell, exhaustive purification is required to ensure complete elimination of the reactants.[7]

Particle size and morphology determine the mode of *in vivo* application. For administration of drug through intravenous injection of drug delivery system, coated particles must have a diameter less than 100 nm and sufficient hydrophilic groups on the surface to allow the particle to evade the RES.[30] Hydrophilic character of polymer has the capacity to diminish the coating by plasma components and allows coated particles to remain in the flow blood for longer periods of time.

Some of the natural polymers used as coating materials are water soluble and their mechanical strength is missing. To prevent them from breaking down in water, crosslinking is performed.[55] Even so, they still have not appreciable strength and their structure is porous. Synthetic polymers seem to be a solution, because they have better mechanical strength than many natural polymers but, some coating formed from synthetic polymers are still porous on molecular scales, so the protection of magnetic core is not that efficient, because the corrosion of magnetic is probable.[13]

Many methods have been described to prepare magnetic polymer particles, either through in-situ or post-syntesis: first of all polymerization is realized in different ways, as a) emulsion, in presence of magnetic nanoparticles,[56,57] b) dispersion,[58] c) micro-suspension,[59] d) miniemulsion.[60] Other methods are encapsulation, hyperbranching, end-grafting,[45] nano-precipitation,[61] emulsion crosslinking,[36,55] suspension crosslinking,[62,63] emulsion solvent evaporation.[64]

## TARGETED DRUG DELIVERY

The conventional administration routes used to deliver drugs to the body include oral (gastric, enteric and colonic), injections, implants, transdermal, mucosal (ophthalmic, nasal, vaginal, anal and sub-lingual). Also, the classic administration of drugs includes periodic dosages and the spread of drug throughout the body not only in the affected area.

It is very important to target the drugs directly to the site of the diseases, under various conditions and thereby with limiting the secondary effects on the body. This goal is realized by targeted drug delivery using a drug loaded polymer magnetic particle system.

The main advantages of using polymeric coated nanoparticles over traditional oral administration of drugs are the stabilization of the bioactive agent by the polymer matrix and lower exposure to degradation during the delivery, thus conferring longer circulation lifetime and minimizing any side effects.[45]

The polymeric shell includes the intended drug and a suitable magnetically active component with which could also transport the drug at the target site and release it during its biodegradation.[64]

A promising alternative to conventional chemotherapy is the targeted delivery of anti-tumor drugs included in the polymer matrix or adsorbed on the polymer surface of magnetic polymer particles. The particles, loaded with the drug, are injected at the target site and maintained in that aria with the aid of an external magnet. So, the active component is then released on the disease area,[15] (Fig. 3). The direct modulation of the magnetic field can determine the control of the drug releasing rate. In this way, the targeted therapy can be effective by decreasing of toxic effects and can enhance the therapeutic effect of the drug.[35]

Such systems increase the efficiency of the drug, maximizing patient compliance and enhancing the ability to use highly toxic, poorly soluble or relatively unstable drugs.[1,18]

The successful use of the magnetic polymer particles for biomedical applications, especially for targeted drug delivery, is conditioned by some factors related to the magnetization, size and biocompatibility of the nanoparticles. To determine the effectiveness of the drug targeting some physicochemical factors related to drug delivery magnetic polymer nanosystems, must be taken into account such as field strength and geometry, depth of the target tissue, rate of blood flow, and vascular supply.[9] Adjusting the external magnetic field facilitates handling of the magnetic drug delivery systems.[14]

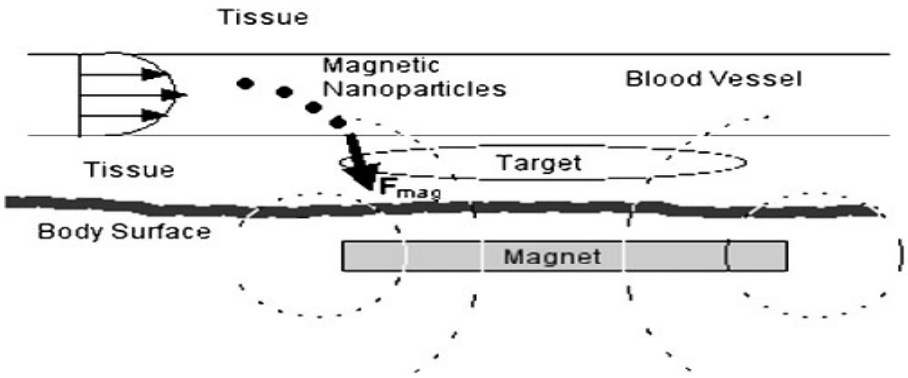


Fig. 3 – Magnetic targeting principle using polymer covered and drug complexed nanoparticles. Magnetic particles are introduced injectably with a cathetus in the interest area and later are retained with the magnetic field.[2]

Long blood-circulation time is necessary for accumulation of nanoparticles smaller than 500 nm in tumors and infection sites due to the enhanced permeability and retention effect. The vascular system close to tumor sites is an increased permeability and an inefficient lymphatic drainage, which causes the enhanced permeability and the retention effect.[65]

The effect of nanoparticle size on accumulation at tumor sites was studied and the conclusion was that the accumulation of the particles with sizes between 40 and 100 nm depends only on the blood residence half-life, being at the same time independent of nanoparticle size.[66]

The accumulation of particles with sizes around 20 nm depends on both factors. Small nanoparticles arrive rapidly at the tumor site, but have a relatively short residence time, compared with particles larger than 40 nm which arrive later at the tumor sites, but reside longer in the blood. The residence time at the affected site is a very important feature for therapeutic efficiency, considering that the nanoparticles, after injection, are transported by blood, followed by diffusion from the blood vessel to the vicinity of tumor.

The distribution and the targeting efficiency of the nanoparticles depend on size and also on residence time at the site of the tumor.[66]

The main challenge in this area is to obtain, with all these components (therapeutic agent, magnetic particles and polymer), a nanometer scale particle system.[13]

Magnetic drug targeting is a promising cancer treatment avoiding the side effects of conventional chemotherapy[67] due to precise targeted delivery. For example, a strong magnetic field gradient at the tumor location induces accumulation of the magnetic nanoparticles covered by starch derivatives, which bound mitoxantrone.[5] The success of drug delivery via magnetic particles was proved by administration of magnetic polymer particles loaded with oxantrazole, when it was measured in the brain, 100–400 times higher oxantrazole levels than those when it was obtained after the solution dosage form.[68]

## CONCLUSION

The superparamagnetic nanoparticles are favorites for medical applications due to its property to be magnetized by exposure to an external magnetic field and to have no remanence (permanent magnetization) after the magnetic field is shut down. Also, they have high surface to volume ratios, low toxicity and they are easy to prepare.

According to many scientific papers published lately, it seems the polymer is an important material for features improving of magnetic particles used in drug delivery. Nevertheless, some issues must be considered for the perspective of production at a large scale for application in humans: storage stability, control particles size distribution, colloidal stability, cost of sale, possibilities of administration at home, less chemicals used for preparation of magnetic polymer particles.

Drug delivery from nanostructured systems, especially magnetic polymer particles, is attracting considerable attention due to the opportunities in cancer therapy and the other diseases treatment.

*Acknowledgements:* This paper was supported by the project PERFORM-ERA "Postdoctoral Performance for Integration in the European Research Area" (ID-57649), financed by the European Social Fund and the Roumanian Government.

## REFERENCES


1. S.F. Medeiros, A.M. Santos, H. Fessi and A. Elaissari, *Int. J. Pharm*., **2011**, *403*, 139-161.
2. Q.A. Pankhurst, J. Connolly, S.K. Jones and J. Dobson, *J. Phys. D: Appl. Phys.*, **2003**, *36*, R167-R181.
3. T.K. Jain, M.A. Morales, S.K. Sahoo, D.L. Leslie-Pelecky and V. Labhasetwar, *Mol. Pharm.*, **2005**, *2*, 194-205.
4. I. Chourpa, L. Douziech-Eyrolles, L. Ngaboni-Okassa, J.F. Fouquenet, S. Cohen-Jonathan, M. Souce, H. Marchais and P. Dubois, *Analyst*, **2005**, *130*, 1395-1403.
5. C. Alexiou, R.J. Schmid, R. Jurgons, M. Kremer, G. Wanner, C. Bergemann, E. Huenges, T. Nawroth, W. Arnold and F.G. Parak, *Eur. Biophys. J.*, **2006**, *35*, 446-450.
6. A. Figuerola, R. Di Corato, L. Manna and T. Pellegrino, *Pharmacol. Res.*, **2010**, *62*, 126-143.
7. J. Chomoucka, J. Drbohlavova, D. Huska, V. Adam, R. Kizek and J. Hubalek, *Pharmacol. Res.*, **2010**, *62*, 144-149.
8. M. Hofmann-Amtenbrink, B. von Rechenberg, H. Hofmann, Superparamagnetic nanoparticles for biomedical applications, in: "Nanostructured Materials for Biomedical Applications", 2009, Editors: M. C. Tan, G.M. Chow, L. Ren, 119-149.
9. C. Sun, J.S.H. Lee and M.Q. Zhang, *Adv. Drug. Deliv. Rev.*, **2008**, *60*, 1252-1265.
10. V.I. Shubayev, T.R. Pisanic and S.H. Jin, *Adv. Drug Deliv. Rev.*, **2009**, *61*, 467-477.
11. M. Arruebo, R. Fernandez-Pacheco, M.R. Ibarra and J. Santamaria, *Nano Today,* **2007**, *2*, 22–32.
12. K. Schulze, A. Koch, B. Schopf, A. Petri, B. Steitz, M. Chastellain, M. Hofmann, H. Hofmman, and B. von Rechenberg, *J. Magn. Magn. Mater.*, **2005**, *293*, 419-432.
13. S.C. McBain, H.H.P. Yiu and J. Dobson, *Int. J. Nanomedicine*, **2008**, *3*, 169-180.
14. A. Jordan, R. Scholz, P. Wust, H. Fahling and R. Felix, *J. Magn. Magn. Mater.,* **1999**, *201*, 413-419.
15. R. Fernandez-Pacheco, J.G. Valdivia, M. Gutierrez and R. Ibbara, Magnetic nanoparticles for local drug delivery using magnetic implants, in: "Micro and Nano Technologies in Bioanalysis, Methods and Protocols", vol. *544*, Oak Ridge, **2009**, 559-569.
16. L. Stanciu, Y.-H. Won, M. Ganesana and S. Andreescu, *Sensors*, **2009**, *9*, 2976-2999.
17. R. Zboril, M. Mashlan and D. Petridis, *Chem. Mater.*, **2002**, *14*, 969-982.
18. A.S. Lubbe, C. Bergemann, J. Brock and D.G. McClure, *J. Magn. Magn. Mater.*, **1999**, *194(1)*, 149–155.
19. A. K. Gupta and M. Gupta, *Biomaterials,* **2005**, *26*, 3995-4021.
20. S.M. Moghimi, A.C. Hunter and J.C. Murray, *Pharmacol. Rev.*, **2001**, *53*, 283-318.
21. F. Alexis, E. Pridgen, L.K. Molnar and O.C. Farokhzad, *Mol. Pharmaceutics*, **2008**, *5*, 505-515.
22. H.S. Choi, W. Liu, P. Misra, E. Tanaka, J.P. Zimmer, B.I. Ipe, M.G. Bawendi and J.V. Frangioni, *Nat. Biotechnol*., **2007**, *25*, 1165-1170.
23. C. Boyer, M.R. Whittaker, V. Bulmus, J. Liu and T.P. Davis, *NPG Asia Mater*., **2010**, *2*, 23-30.
24. S. Mitragotri, *Pharm. Res.*, **2009**, *26*, 232-234.
25. P. Decuzzi and M. Ferrari, *Biomaterials*, **2006**, *27*, 5307-5314.
26. S. Muro, C. Garnacho, J.A. Champion, J. Leferovich, C. Gajewski, E.H. Schuchman, S. Mitragotri and V.R. Muzykantov, *Mol. Therap.*, **2008**, *16*, 1450-1458.
27. P. Aggarwal, J.B. Hall, C.B. McLeland, M.A. Dobrovolskaia and S.E. McNeil, *Adv. Drug Deliv. Rev.*, **2009**, *61*, 428-437.
28. T. Cedervall, I. Lynch, M. Foy, T. Berggad, S.C. Donnelly, G. Cagney, S. Linse and K.A. Dawson, *Angew. Chem. Int. Ed*., **2007**, *46*, 5754-5756.
29. T.M. Göppert and R.H. Müller, *J. Drug Target.*, **2005**, *13*, 179-187.
30. C.C. Berry, S. Wells, S. Charles, G. Aitchison and A.S.G. Curtis, *Biomaterials*, **2004**, *25*, 5405–5413.
31. A.K. Gupta and A.S.G. Curtis, *J. Mater. Sci.: Mater. Med.*, **2004**, *15*, 493-496.
32. N. Kohler, C. Sun, A. Fichtenholtz, J. Gunn, C. Fang and M. Zhang, *Small*, **2006,** *2*, 785-792.
33. K. Schulze, A. Koch, A. Petri-Fink, B. Steitz, S. Kamau, M. Hottiger, M. Hilbe, L. Vaughan, M. Hofmann, H. Hofmann and B. Von Rechenberg, *J. Nanosci. Nanotechno.*, **2006**, *6*, 2829-2840.
34. F.X. Hu, K.G. Neoh and E.T. Kang, *Biomaterials*, **2006**, *27*, 5725-5733.
35. D. Wang, J. Li, H. Li and F. Tang, *T. Nonferr. Metal. Soc.*, **2009**, *19*, 1232-1236.
36. L.E. Udrea, D. Hritcu, M.I. Popa and O. Rotariu, J. *Magn. Magn. Mater.*, **2011,** *323*, 7-13.
37. X. Huang, J. Zhuang, D. Chen, H. Liu, F. Tang, X. Yan, X. Meng, L. Zhang and J. Ren, *Langmuir*, **2009**, *25*, 11657-11663.
38. V. Badescu, L.E. Udrea, O. Rotariu, R. Badescu and G. Apreotesei, *Rev. Roum. Chim*., **2009**, *54(3)*, 201-204.
39. T. Dung, T. Danh, L. Hoa, D. Chien and N. Due, *J. Exp. Nanosci.*, **2009**, *4*, 259-267.
40. A.C.A. Roque, A. Bicho, I.L. Batalha, A.S. Cardoso and A. Hussain, *J. Biotechnol.*, **2009**, *144*, 313-320.
41. A.L. Daniel-da-Silva, S. Fateixa, A.J. Guiomar, B.F.O. Costa, N.J.O. Silva, T. Trindade, B.J. Goodfellow and A.M. Gil, *Nanotechnology*, **2009**, *20*, 355-602.
42. F. Gao, Y. Cai, J. Zhou, X. Xie, W. Ouyang, Y. Zhang, X. Wang, X. Zhang, X. Wang, L. Zhao and J. Tang, *Nano Res.*, **2010**, *3*, 23-31.
43. B. Gaihre, M. S. Khil, D. R. Lee and H. Y. Kim, *Int. J. Pharm*., **2009**, *365*, 180-189.
44. S.R. Wan, J.S. Huang, H.S. Yan and K.L. Liu, *J. Mater. Chem.*, **2006**, *16*, 298-303.
45. A.M.G.C. Dias, A. Hussain, A.S. Marcos and A.C.A. Roque, *Biotechnol. Adv.*, **2011**, *29*, 142-155.
46. A. Petri-Fink, B. Steitz, A. Finka, J. Salaklang and H. Hofmann, *Eur. J. Pharm. Biopharm.*, **2008**, *68*, 129-137.
47. T. Neuberger, B. Schopf, H. Hofmann, M. Hofmann and B. von Rechenberg, *J. Magn. Magn. Mater.*, **2005**, *293*, 483-496.
48. A. Nel, T. Xia, L. Mädler and N. Li, *Science*, **2006**, *311*, 622-627.
49. Y. Wang, Y.W. Ng, Y. Chen, B. Shuter, J. Yi, J. Ding, S.-c. Wang and S.S. Feng, *Adv. Funct. Mater*., **2008**, *18*, 308-318.
50. O. Philippova, A. Barabanova, V. Molchanov and A. Khokhlov, *Eur. Polym. J.*, **2011**, *47*, 542-559.
51. R. Singh and J.W. Lillard, *Exp. Mol. Pathol*., **2009**, *86*, 215-23.
52. A. Faraji and P. Wipf, *Bioorg. Med. Chem.*, **2009**, *17*, 2950-2962.
53. L. Balaita and M. Popa, *Rev. Roum. Chim*., **2009**, *54(3)*, 185-199.
54. Parvin S, Matsui J, Sato E and Miyashita T., *J. Colloid Interf. Sci.*, **2007**, *313*, 128-134.

55. G. Tataru, M. Popa and J. Desbrieres, *Int. J. Pharm*., **2011,** *404,* 83-93.
56. S. Braconnot, C. Hoang, H. Fessi, A. Elaissari, *Mater. Sci. Eng. C*, **2009**, *29*, 624-630.
57. G.G. Utkan, F. Sayar, P. Batat, S. Ide, M. Kriechbaum and E. Piskin, *J. Colloid Interf. Sci.*, **2011**, *353*, 372-379.
58. H. Mackova, D. Kralova and D. Horak, *J. Polym. Sci. Pol. Chem.*, **2007**, *45*, 5884-5898.
59. M. Lu, S. Bai, K. Yang and Y. Sun, *China Particuology*, **2007**, *5*, 180-185.
60. W. Zheng, F. Gao and H. Gu, *J. Magn. Magn. Mater*., **2005**, *293*, 199-205.
61. A. Jurikova, K. Csach, M. Koneracka, V. Zavisova, M. Muckova, N. Tomasovicova, G. Lancz, P. Kopcansky, M. Timko and J. Miskuf, *J. Phys. Conf. Ser.*, **2010**, *200*, 122004.
62. E.B. Denkbas, E. Kilicay, C.Birlikseven and E. Ozturk, *React. Funct. Polym.*, **2002**, *50*, 225-232.
63. D.S. Jiang, S.Y. Long, J. Huang, H.Y. Xiao and J.Y. Zhou, *Biochem. Eng. J.*, **2005***, 25(1)*, 15-23.
64. J.L. Arias, M. Lopez-Viota, M.A. Ruiz, J. Lopez-Viota and A.V. Delgado, *Int. J. Pharm.*, **2007**, *339*, 237-245.
65. D. Peer, J. Karp, S. Hong, O. Farokhzad, R. Margalit and R. Langer, *Nature Nanotech.*, **2007**, *2*, 751-760.
66. S.D. Perrault, C. Walkey, T. Jennings, H.C. Fischer and W.C.W. Chan, *Nano Lett.*, **2009**, *9*, 1909-1915.
67. R. Asmatulu, M.A. Zalich, R.O. Claus and J.S. Riffle, *J. Magn. Magn. Mater.*, **2005**, *292*, 108-119.
68. J.M. Gallo, P. Varkonyi, E.E. Hassan and D.R. Groothius, *J. Pharmacokinet Biop.*, **1993**, *21(5)*, 575-592.