



Magnetic Nanoparticles and Their Biomedical Applications

Manyetik Nano Partiküller ve Biyomedikal Uygulamaları

Kemal Çetin¹, Fatma Denizli², Handan Yavuz², Tahira Qureshi², Deniz Türkmen² and Adil Denizli^{2*}

¹Necmettin Erbakan University, Faculty of Science, Department of Chemistry, Konya, Turkey.

²Hacettepe University, Department of Chemistry, Ankara, Turkey.

ABSTRACT

The combination of magnetism and nanotechnology has presented promising materials: magnetic nanoparticles. These materials have been getting more attention due to their “size-dependent functionality”. There is a critical size for nanoparticles that their properties change. Materials with various functions can be synthesized with the desired properties since a wide range of polymers including natural and synthetic polymers can be utilized in the production of the magnetic nanoparticles. Furthermore, they can be more selective and specific with the conjugation target-specific ligands. This structural and functional diversity enables these materials to be used in a wide range of areas. In this review, we discuss the main components of the magnetic nanoparticles and their examples in biomedical applications. They can be used as contrast agents in magnetic resonance imaging; delivery systems in the controlled release of therapeutic agents; supporting materials for separation, isolation, and purification of biomolecules. They can be also functioned in hyperthermia and magnetofection for gene therapy. However, even though their increasing research interest, magnetic nanoparticles still need to be improved to be more popular in the commercial area. We hope that these functional materials will present promising possibilities in nanotechnology and biomedicine in near future.

Key Words

Biomedical applications, bioseparation, drug delivery, hyperthermia, magnetic nanoparticles.

ÖZ

Manyetizma ve nanoteknolojinin birleşimi umut vaat eden malzemeler sundu: manyetik nanopartiküller. Bu malzemeler “boyuta bağlı fonksiyonellik” özellikleri sayesinde ilgi çekmektedir. Nanopartiküller için makro ölçekteki çeşitli özelliklerinin nano ölçekte değiştiği kritik bir boyut vardır. Manyetik nanopartiküllerin üretiminde doğal ve sentetik polimerler dahil çok çeşitli polimerler kullanılabilirdiğinden farklı işlevlere sahip malzemeler istenen özelliklerle sentezlenebilir. Ayrıca, hedefe özgü ligandların konjugasyonu sayesinde daha seçici ve özgül olabilirler. Bu yapısal ve işlevsel çeşitlilik, bu malzemelerin geniş bir alanda kullanılmasının önünü açmaktadır. Bu derlemede manyetik nanopartiküllerin ana bileşenleri ve biyomedikal uygulamalardaki örnekleri tartışılmaktadır. Manyetik rezonans görüntüleme kontrast madde; terapötik ajanların kontrollü salımında dağıtım sistemleri; biyomoleküllerin ayrılması, izolasyonu ve saflaştırılması için destek malzemeleri olarak kullanılabilirler. Gen tedavisi için manyetofeksiyonda ve hipertermide de işlev görebilirler. Öte yandan, manyetik nanopartiküllerin araştırılması konusunda artan ilgiye rağmen ticari alanda daha popüler olması için hala geliştirilmeleri gerekmektedir. Bu fonksiyonel malzemelerin yakın gelecekte nanoteknoloji ve biyotıp konusunda umut verici olanaklar sunacağı düşünülmektedir.

Anahtar Kelimeler

Biyomedikal uygulamalar, biyoayırma, ilaç taşıma, hipertermi, manyetik nanopartiküller.

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Correspondence to: A. Denizli, Hacettepe University, Department of Chemistry, Ankara, Turkey.

E-Mail: denizli@hacettepe.edu.tr

INTRODUCTION

By means of its unique features, nanotechnology has been one of the tremendous fields of science and technology in the recent era. Substances in nanosize act differently compared with the ones in bulk size. There is a critical size for nanoparticles (NPs), and the characteristics such as surface energy of NPs change beyond this size [1]. Because of increase in surface energy, interfacial reactivity of NPs change [1]. This ‘size-dependent functionality’ of NPs has led to revolutionary progress in material processing and their applications. Magnetic nanoparticles (MNPs) are gaining interest owing to their functionalities in a wide range of scientific areas including magnetic resonance imaging, bioseparation, drug delivery and controlled release systems, magnetofection, catalysis, biosensors, data storage, environmental remediation and hyperthermia [2–7] excellent biocompatibility as well as multi-purpose biomedical potential (e.g., applications in cancer therapy and general drug delivery).

Because MNPs have large surface area, high surface energy, and efficient magnetic interactions, organic/inorganic layers may be used to stabilize MNPs [8]. They can be coated with functional components such as synthetic polymers, biomolecules entities, and inorganic substances based on designable interactions for biomedical applications.

In the literature, there have been many publications and ongoing researches about “magnetic nanoparticles”. As results shown in Figure 1, an exponential increase in number of publications was observed between the years 2000 and 2017. The growth in MNPs fabricated for various goals has usually increased rapidly over the last eighteen years. This review attempts to present general properties of MNPs and their recent improvements and applications in biomedical area.

Magnetism And Magnetic Nanoparticles

In general, the magnetic characteristics of the materials occurred due to the motion or spin of the electrons of atoms. Materials can act the following magnetism features:

- Diamagnetism
- Paramagnetism
- Ferromagnetism
- Ferrimagnetism
- Antiferromagnetism

Other than the ones mentioned above, superparamagnetism and metamagnetism are also types of the magnetisms.

Recently, various types of magnetic nanoparticles have been produced. One of the main and the most popular ones are iron, nickel and cobalt metals and their oxides.

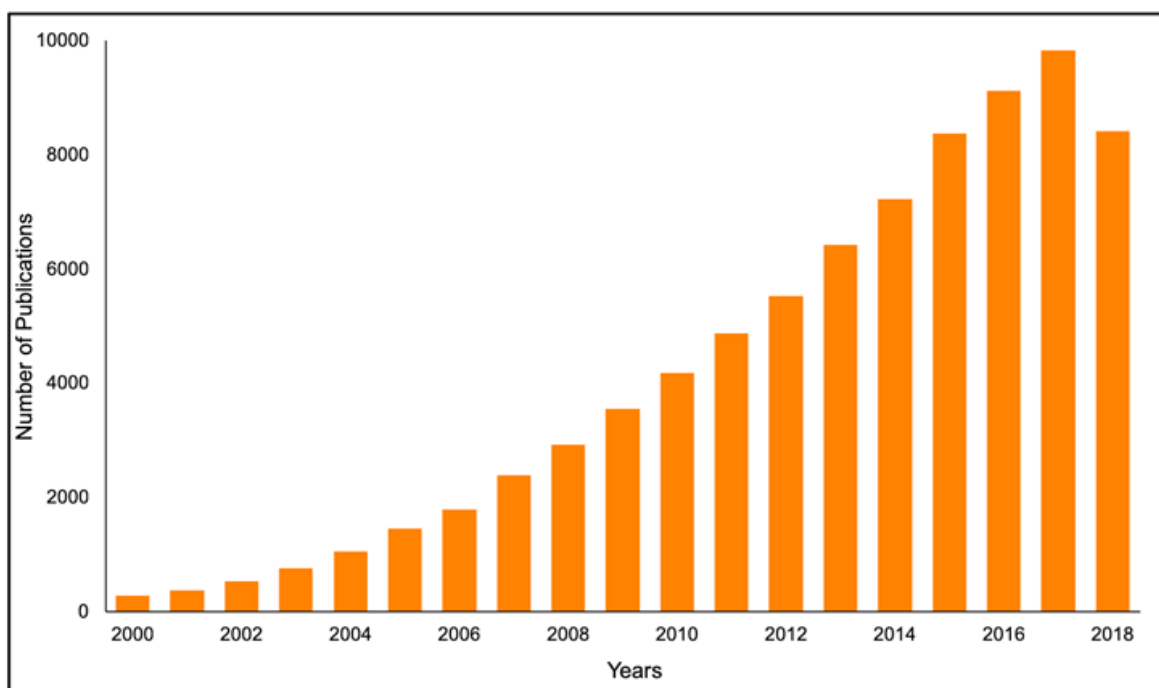


Figure 1. Increase in the number of scientific papers published involving magnetic nanoparticles. (Source: ISI Web of Knowledge © The Thomson Corporation. Search term: ‘magnetic nanoparticles’. Date of search: November 2018.)

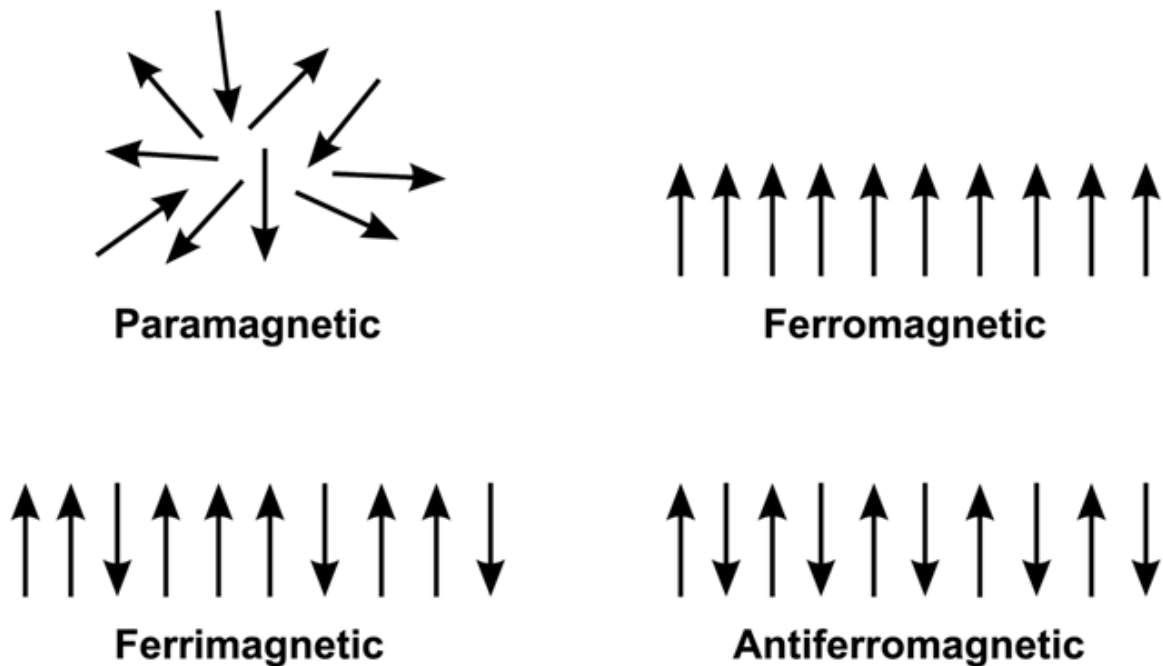


Figure 2. Paramagnetic, ferromagnetic, ferrimagnetic and antiferromagnetic arrangement of the magnetic moments.

MNPs produced using oxides, hydroxides, and oxide-hydroxides of iron are gaining interest in biomedical applications [7,9–11]. Ferrite NPs which is smaller than 128 nm exhibit superparamagnetic behavior and self-agglomeration is prevented [12]. Various applications of these MNPs, so-called superparamagnetic iron oxide nanoparticles (SPIONs), are presented in biomedical science [13–15].

Another type of magnetic materials is polymer (plastic) magnets produced using organic polymers. [16,17]. Because these non-metallic magnets might be more biocompatible when compared with metallic ones, they might be useful for various biomedical applications including drug delivery, magnetic resonance imaging, hyperthermia etc. Dilute magnetic semiconductors (DMSs) are also a class of magnetic materials. DMSs are a kind of semiconductors doped with transition metals such as TiO_2 , SnO_2 , ZnO , Eu , Dy and they show characteristics of both semiconductors and magnetic materials [18–21].

MATERIALS and METHODS

MNPs are produced from iron, nickel cobalt, and their alloys with some other metals including copper, zinc, strontium and barium [22]. Various techniques are used for the production of MNPs; they can be classified as:

Top-down approach: In this physical method, size of magnetic materials is reduced and they are dispersed in an aqueous medium with colloidal agents [23]. However, in top-down approach, it is hard to produce NPs with the desired shape and size [24] Solid phase techniques

including mechanical attrition are the main processes for top-down NP synthesis [24]. Recently, laser ablation is also used for this approach [25]

Bottom-up approach: This approach consists of vapor phase methods (e.g. aerosolbased processes, chemical vapor deposition, gas condensation, arc discharge generation, laser ablation), liquid phase techniques (e.g. sol-gel, solvothermal and sonochemical methods) [24]

Nanolithography: Nanostructures, nanocatalysts, semiconductors and so on can be produced using nanolithographic techniques. Template fabrication and scanning probe microscopy based nanolithography methods are popular types of nanolithography [24]

Microbial methods: In this methods MNPs are produced via a biomineralization process. Magnetotactic bacteria having organelles called magnetosomes which contain magnetic crystals may produce MNPs in a fluid with microelectromagnets [26]. They can synthesize a chain of MNPs inside their bodies [26].

After synthesizing of MNPs, surface modification processes including post-synthesis adsorption, in situ coating and post-synthesis grafting may be applied for the aimed application areas [27].

Biomedical Applications

MNPs can be utilized in a wide range of biomedical applications such as magnetic resonance (MR) imaging, targeted drug delivery systems, tissue engineering, magnetofection, hyperthermia/ablation of tissues and separation, isolation and purification of biomolecules.

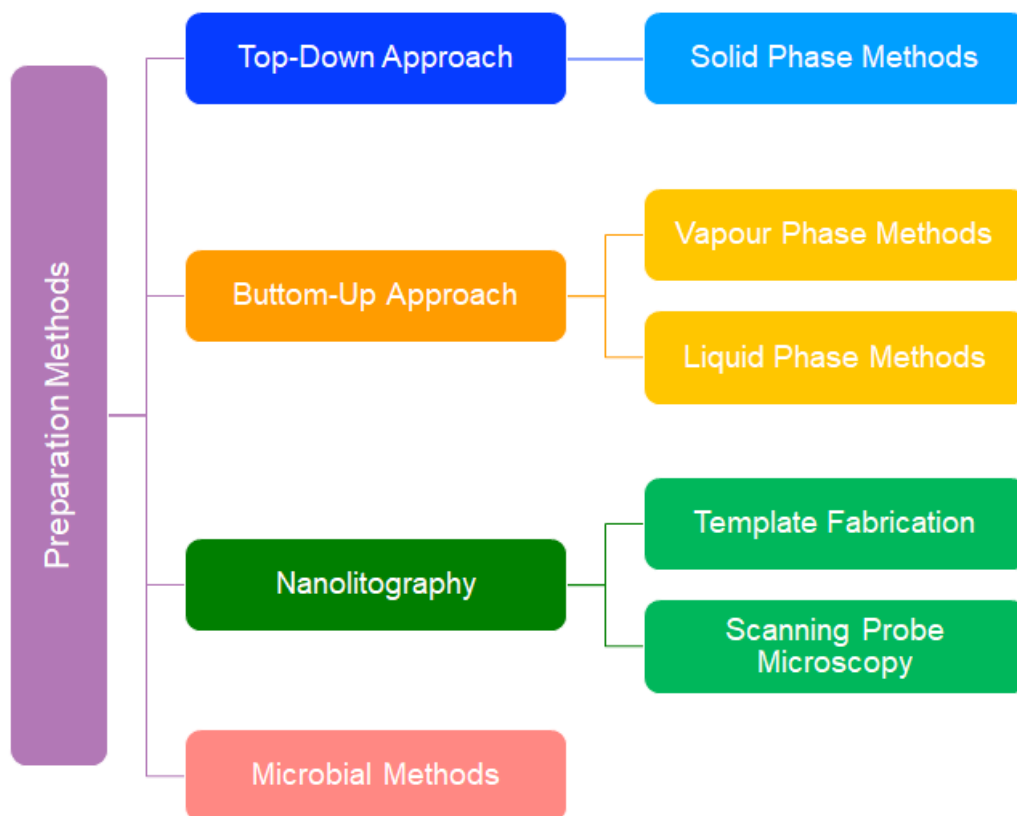


Figure 3. General preparation methods for magnetic nanoparticles.

Magnetic Resonance Imaging

Magnetic resonance imaging (MRI) is a method used for detection of diseases, diagnosis and to lead the treatment. MNPs have been used as contrast agents for MRI. For instance, MNPs were prepared by the adsorption of a chitosan layer on the surface of magnetic NPs to form a core-shell. [28]. Then, these MNPs were conjugated with targeting ligand, fluorescent dye for targeted delivery and MRI contrast agent. Drug release profile, cytotoxicity, receptor mediated internalization character of the MPNPs were investigated. The MNPs exhibited stronger contrast enhancements towards cancer cells, which they can be used as an MRI contrast agent.

Lee et al. described a magnetism-engineered iron oxide (MEIO) nanoprobe for molecular imaging [29]. They prepared conjugated MEIO with antibodies and obtained an enhanced MRI sensitivity for the detection of cancer markers compared with probes currently available. In another study, MRI-enhancing NPs containing internal gadolinium [Gd(III)] ions for T1 imaging contrast were improved [30]. The system has a multilayered geometry and Gd(III) ions are located between an inner core and outer Au layer. Relaxivity enhancement of this new systems were found to be higher compared with the traditional chelating agents.

Targeted Drug Delivery

One of the main drawbacks of the chemotherapy is that the most of the anticancer drugs are nonselective, which means they can kill not only malignant cells but also healthy cells [31]. Therefore, researchers have been improving various drug delivery systems to carry drug molecules to the target site with reducing the adverse effects of the drug on the rest of the body [32–35]. MNPs are promising candidates as target-specific drug carriers. Hence, they can carry antineoplastic agents to the tumor site and help healthy tissues not to be affected. Furthermore, because MNPs can lead local administration of the therapeutic agent, volume of drug used decreases leading to a decrement in side effects of the drugs. MNPs are used for delivery of not only antineoplastic agents but also other therapeutic agents including antibodies, peptides, proteins, genes etc.

Magnetic CoFe_2O_4 nanostructures (MCFO) with the size of 9.72 nm in diameter was synthesized via a coprecipitation method using caffeine to alkalize the medium [36]. Ionic cross-linked magnetic hydrogel beads based on CoFe_2O_4 nanoparticles and sodium alginate (Alg) were produced and chlorpheniramine maleate is used as a model drug. Hydrogel beads containing

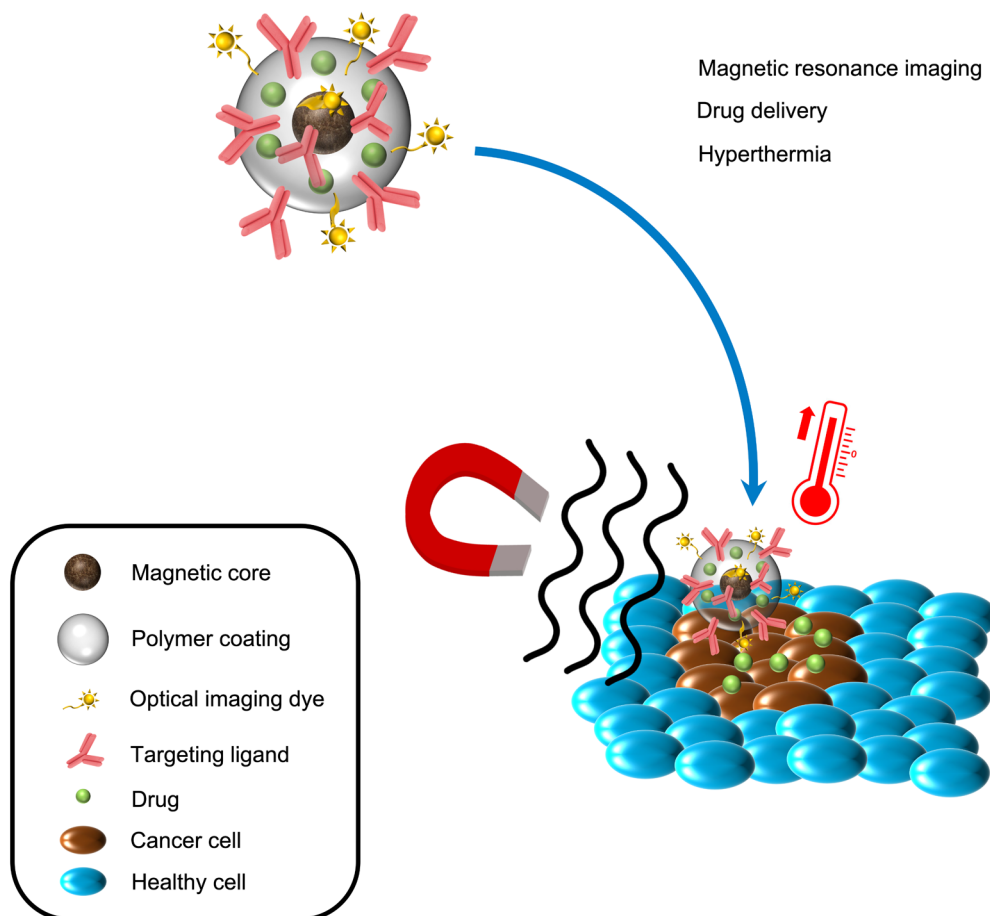


Figure 4. MNPs are good candidates for magnetic resonance imaging, drug delivery and hyperthermia.

magnetic nanostructures showed a pH-dependent drug release. According to cytotoxicity test using MTT assay on U87 cell lines, CFO nanoparticles and MCFO/Alg beads are biocompatible products. Drug encapsulation efficiency (EE) and *in vitro* release profile were determined using high-performance liquid chromatography (HPLC). Methoxy poly(ethylene glycol)-poly(lactide) copolymer (MPEG-PLA) was synthesized in order to prepare NPs with size less than 100 nm for controlled delivery of Paclitaxel (PAX) [37]. Biphasic release profile consists of firstly a fast release rate and then a slow one was observed. Multimodal magnetic poly(D,L-lactide-co-glycolide) NPs were developed for detection and treatment of breast cancer [38]. DOX was incorporated into poly(D,L-lactide-co-glycolide) NPs via nano-emulsion method. The antibody Herceptin1 (HER) used for targeting breast cancer was conjugated to these MNPs. The MNPs exhibited high cancer cell affinity and DOX from MNPs was released and sustained for three weeks. Lipid-polymer hybrid MNPs were improved for remote

radio frequency (RF) magnetic field-controlled camptothecin (CPT) release [39]. Stimuli-responsive MNPs exhibited a great reduction in MT2 mouse breast cancer cell growth *in vitro* by a remote RF field.

For the treatment of gliomas, MNPs were prepared as poly[aniline-co-N-(1-one-butyric acid) aniline] coated on Fe_3O_4 cores [40]. 1,3-bis(2-chloroethyl)-1-nitrosourea (BCNU), a compound used to treat brain tumors, was immobilized onto these MNPs. Results showed that bound-BCNU-3 was more stable than free-BCNU when they are stored at various temperature values. Results showed that this MPNP system leads tumor treatment more effectively using lower doses and potentially reduces the side-effects. Alexiou et al. used magnetic NPs covered by starch polymers for local chemotherapy after intraarterial infusion and magnetic drug targeting [41]. The MNPs with the diameter around 250 nm are studied using a rabbit model with a VX2 squamous cell carcinoma. Biodistribution of

MNPs can be visualized via X-ray imaging and histologically confirmed. Lellouche et al. “all-in-one” MNPs by incorporating PEI into poly(D,L-lactide-co-glycolide)-poly(ethylene glycol) particles for the delivery of siRNA as a gene therapy [42]. They also encapsulated magnetic NPs as an MR imaging contrast agent. They observed the delivery of siRNA to reduce the PLK1 expression in pancreatic cancer cells, and cause subsequent cell cycle arrest and induction of cell apoptosis. Furthermore, no acute toxicity was observed according to *in vivo* studies. Hence, this new system has a great potential to be used for cancer therapy. Abed et al. investigated the effects of ultrasound irradiation on the drug (i.e., 5-fluorouracil, F-FU) release from magnetic PLGA nanocapsules [43]. The release profile of nanocapsules irradiated by various ultrasound parameters (1 or 3 MHz; 0.3-1W/cm²; 5-10 minutes) was analyzed for 14 days and they observed that the ultrasound expedited the rate of F-FU release from the nanocapsules. According to mathematical analysis, an erosion-controlled release mechanism was valid for these nanocapsules.

Spherical shaped magnetic poly ϵ -caprolactone (PCL) NPs with the size of 160 ± 5 nm were produced by the o/w emulsion method as magnetic drug carrier [44]. Anticancer drugs, i.e. cisplatin and gemcitabine, was encapsulated during preparation of PCL magnetic NPs and drug loading amounts were 24.6 and 7.6 wt.% for cisplatin and gemcitabine, respectively. After characterization of PCL magnetic NPs, drug release was observed for 30 days. *In vitro* study of magnetic susceptibility under external magnetic field also showed that PCL magnetic NPs are good candidate for targeted drug delivery as a magnetic drug carrier. Layer-by-layer assembled milk protein coated magnetic NPs were developed for oral drug delivery using DOX and indocyanine green (ICG) as model drug molecules [45] which were incorporated into the inner polymeric layer, and subsequently coated with casein. The resulting casein coated iron oxide nanoparticles (CN-DOX/ICG-IO). Drugs were incorporated into the inner polymeric layer of the MNPs and then magnetic NPs were also covered with casein. While casein coated MNPs showed stability in the gastric condition supplied by gastric protease, drugs were released from MNPs in intestine condition because casein layer was degraded due to intestinal protease. Moreover, MNPs supplied MR imaging capability for *in vivo* imaging guided drug delivery.

Transferrin (Tf) is a glycoprotein which transports iron into the cells. Since transferrin receptor (TfR) is expres-

sed at higher level on membrane of malignant cells than the normal cells, transferrin can be used for the selective cancer therapy. Because TfR is expressed by brain capillary endothelial cells, Transferrin also can be used to deliver across blood brain barrier (BBB) [46]. Capecitabine loaded magnetic dextran-spermine NPs were produced via ionic gelation and then Tf was conjugated on to these MNPs for targeted delivery across BBB [46]. Cytotoxicity tests were applied using U87MG and pH-responsive release from the MNPs was observed with enhanced cytotoxicity against these cells. Results of *in vivo* histological studies showed that an important increase in Fe concentrations in brain after 1 and 7 days of post-injection.

Magnetofection and Gene Therapy

Magnetofection is a transfection method using MNPs and external magnetic field to carry nucleic acids into the target cells [47]. Nanocomposites are formed by coating MNPs with the cationic compounds such as surfactants and lipids [48]. These nanocomposites containing nucleic acids are carried to the target cells by means of external magnetic field. Magnetofection can be used for transfection of various nucleic acids including DNA, mRNA, siRNA, shRNA, dsRNA. Magnetofection is a promising way to be used in gene therapy by introducing exogenous DNA to repair the mutation causing a disease [49]. Gene therapy has a remarkable potential for treatment of various genetic disorders, neurodegenerative diseases, cardiovascular diseases and even cancer [50,51]. Magnetofection is used for not only transfection of nucleic acids but also some viruses, e.g. retrovirus and adenovirus, into the cells [52]. MNPs-based gene therapy has many advantages such as low vector doses, short incubation time with high efficiency, potential of precise targeting *in vivo* and ability to carry the genes to non-permissive cells [53].

Hyperthermia

The term “hyperthermia” is from Greek words hyper, meaning “rise”, and, thermos, meaning “heat” and hyperthermia means elevated body temperature [54]. Hyperthermia was used as a treatment method in ancient times by various civilizations including Egyptians, Indians and Greeks [55–57]

Sun energy, hot water and hot mud from thermal springs, steam from volcanic caves have been used as a hyperthermia method to cure the diseases [54]. Greek philosopher Parmenides (BC 515 - BC 460) said that

“Give me the power to produce fever and I will cure all diseases” for the hyperthermia treatments [57]. Nowadays, hyperthermia is used for some diseases including cancer.

When MNPs are exposed to an external high-frequency magnetic field, an increase in temperature of the MNPs are observed [58]. This outstanding feature of MNPs makes them promising materials for hyperthermia since MPNs can provide local hyperthermia treatment including intracellular treatment, leading minimal damage to the tissues around the target area. Moreover, hyperthermia with MNPs also enables reaching the inaccessible tumors by conventional methods.

Water dispersible and biocompatible $\text{La}_{0.7}\text{Sr}_{0.3}\text{MnO}_3$ (LSMO) magnetic NPs were reported to be used in

hyperthermia cancer therapy [59]. After LSMO magnetic NPs were prepared, they are functionalized using oleic acid (OA). OA-LSMO magnetic NPs were then interacted with betaine HCl to change their apolar character to polar one. According to results, OA-LSMO magnetic NPs exhibited high magnetization with satisfying self-heating capacity when an external AC magnetic field is applied. In addition, they exhibit colloidal stability and biocompatibility. In another study, chitosan magnetic NPs with three different ferrofluid concentrations were prepared by ionically crosslinked with tripolyphosphate salts [60]. After applying hyperthermia using these chitosan magnetic NPs, cell viability of A-172 cells was 67-75% while cell viability of fibroblasts was not reduced significantly.

Bioseparation

Bioseparation is an important topic in biomedical

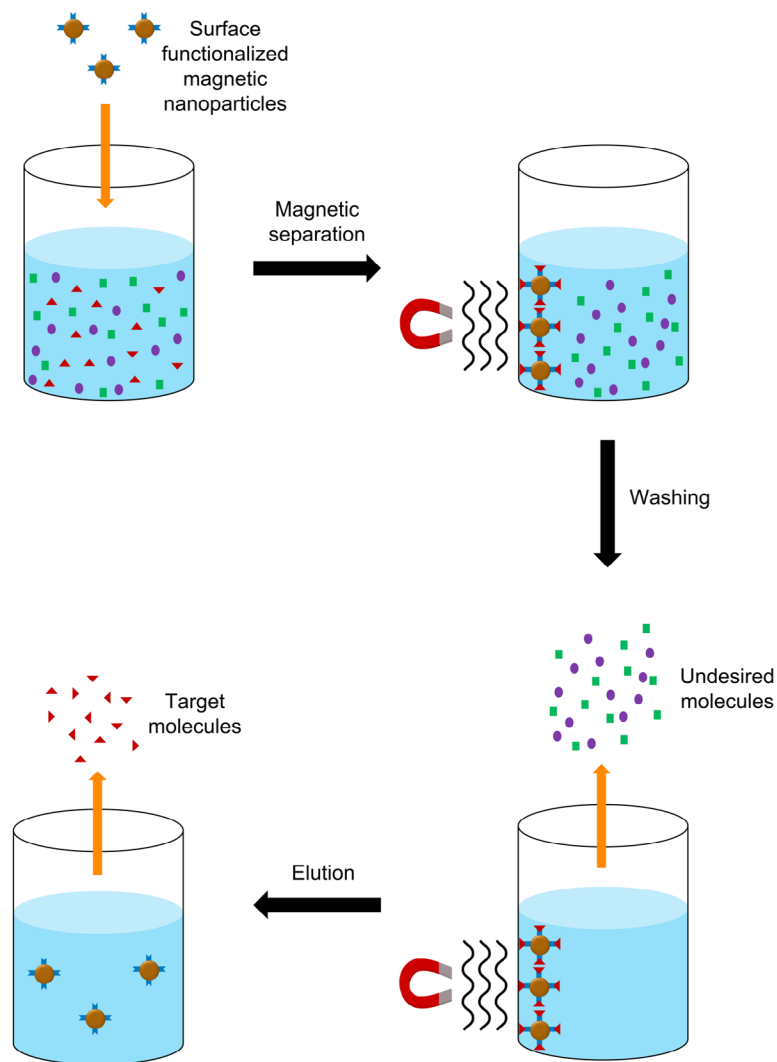


Figure 5. Schematic representation of bioseparation by magnetic nanoparticles.

studies since isolated and purified biomolecules are used in a wide variety of areas, from diagnosis and treatment of diseases to the discovery of new therapeutic agents. Some attractive features of MNPs such as low-cost production, satisfying efficiency, high dispersibility, and effective separation mood enable them handy materials in the separation and purification of biomolecules. Besides these, because MPNs are prone to modification with polymers, biomolecules entities, organic or inorganic substances etc., target-specific and selective MNPs can be fabricated by surface modification techniques. Proteins, nucleic acids (i.e., DNAs, RNAs), cells, bacteria and so on can be separated, isolated and purified by a well-designed MNP systems. A magnetic selective sorbent was prepared by combining of Fe₃O₄ magnetic NPs and Aliquat®336 thiosalicylate, a thiol-containing task specific ionic liquid for the solid-phase extraction (SPE) of cadmium ion from water and fruit samples [61]. After the characterization studies, optimum conditions were determined by examining extraction and desorption parameters such as pH and sorbent dosage. The analyte showed a good linearity in the range of 2.5–260 ng/mL with correlation coefficient of R²> 0.996. Furthermore, limit of detection (LOD) and enrichment factor (EF) were found to be 0.5 ng/mL and 50, respectively. Researchers improved uranyl-imprinted amino functionalized silica coated Fe₃O₄ magnetic NPs surface imprinting method combined with a sol–gel process in order to extract uranyl ions [62]. Non-imprinted ones were also synthesized as a control group. Adsorption-extraction studies were examined in batch mode and optimum conditions were determined by examining the effects of medium pH, sample volume, contact time weight of the adsorbent and of other ions. maximum adsorption capacities of the imprinted and non-imprinted adsorbents for uranyl ions were found to be 25.8 and 9.7 µmol/g, respectively. In another study, 2-hydroxyethyl methacrylate (HEMA)-based hydrophobic magnetic NPs containing N-methacryloyl-(L)-alanine (MAAL) were prepared by microemulsion polymerization to be used in immobilization of amyloglucosidase (AMG), an enzyme hydrolyzing α-(1 → 4) and α-(1 → 6) glucosidic bonds of starch [63]. Average diameter of the hydrophobic magnetic NPs was determined as 79 nm. Maximum AMG adsorption capacity was obtained at pH 3.0 (Q_{max} = 294.42 mg/g) It was also observed that adsorption capacity of magnetic NPs was increased by increasing the temperature due to the fact that the dominant interaction was hydrophobic ones. Relative activity of

the immobilized and free AMGs were maximum at pH 5.0. The authors also claimed that immobilized AMG exhibited important resistance at high temperatures and also lost only 40% of activity, while free AMG lost its all activity at the same time.

CONCLUSION

MNPs have exciting superiorities such as large surface area, size- and shape-dependent functionalities, low-cost preparation and so on. They are also convenient for surface modification processes. They can be modified by a wide range of materials from synthetic polymers to biomolecules and inorganic substances according to the target and the intended purpose. Hence, MNPs are promising materials for the applications in biomedical research area. In literature, there are publications about MNPs improved for MRI, targeted drug delivery, magnetofection, hyperthermia and bioseparation. However, MNPs are still need to be improved to be more demanding in biomedical market but MNPs-based biomedical materials will be increasingly encountered in near future because of the development of synthesis and characterization methods and advanced computational modeling.

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