Magnetic Nanoparticles in Medicine: Progress, Problems, and Advances

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Received July 20, 2021; revised August 4, 2021; accepted August 11, 2021

Abstract — The review presents an analysis of the current state of research related to the design, development, and practical application of methods for biomedical radioelectronics and nanomedicine, including the use of magnetic nanoparticles. The important role of rational scientific physical approaches and experimental methods in the design of efficient and safe magnetic nanoparticle-based agents for therapy, controlled targeted drug delivery, and diagnostics, including spatial imaging, is emphasized. Examples of successful practical application of magnetic nanoparticles in medicine based on these methods are given, and an analysis of the main problems and prospects of this area of science is conducted.

DOI: 10.1134/S1064226922020073

INTRODUCTION

The development of new highly effective diagnostic and therapeutic agents is currently of strategic importance, which, in particular, has been shown by the ongoing coronavirus pandemic. The increase in the efficiency of traditional medicine is associated with the creation and implementation of new approaches to diagnostics and therapy, including, along with biochemical methods, various physical effects and diagnostic tools. The introduction of colloidal nanoparticles and functional nanostructured systems into the body can provide such imaging and diagnostic capabilities. In addition, it can make it possible to implement selective remote external physical effects in local areas of the body and provide a direct therapeutic effect (for example, hyperthermia) or controlled targeted drug delivery and release in the target area. The use of functional nanoparticles and other colloidal nanoobjects and nanostructures (systems consisting of nanoobjects) in medicine is a complex multidisciplinary scientific and practical task the solution of which is far from complete. This review focuses on the medical applications of magnetic nanoparticles (MNPs). Despite the obvious and often impressive successes of fundamental research in this area (see, for example, reviews and monographs, as well as original articles [1–54]), in the real practical biomedical application of MNPs and compositions based on them, the same problems arise, as when using other types of medicinal nanopreparations. The main problems that determine the slow introduction of nanodrugs into real clinical practice are primarily associated with the complexity and multifactorial nature of the processes of interaction of inorganic nanoparticles with various biological structures of the human body. These interactions and their consequences cannot always be predicted by conducting preclinical studies (in vitro and in animal models). Recently, it has become obvious that for further progress in studying the behavior of magnetic nanoparticles directly in the human body, the development and implementation of new radioelectronic technologies for their spatial visualization are especially necessary.

The relatively slow progress of nanomedicine has already begun to raise doubts about the fundamental possibility of overcoming the existing problems of nanomedicine in the foreseeable future [7, 55–66]. The disadvantages of practically oriented medical methods using nanoparticles and other nanoobjects and nanostructures are caused, in particular, by the great complexity of such methods [7], their insufficient reliability (irreproducibility of results) [67], and their efficiency much less than expected [57, 60, 66, 68], and other reasons [69]. So, from 1995 to 2018, only 15 “passive” anticancer drug nanocarriers were approved for practical use, and not a single “active” nanocarrier has successfully passed clinical trials required for widespread medical use [61, 66, 70]. In the period from 1985 to 2005, about 3 million scientific articles on oncological nanomedicine were published, but only 3% of the declared techniques reached the stage of clinical trials [59]. As a result, the National
Cancer Institute (NCI), a large US scientific foundation, which enthusiastically began funding the 10-year Cancer Nanotechnology Plan in 2005, stopped funding the Centers of Cancer Nanotechnology Excellence (CCNEs) program in 2019 [65].

All of the above applies in full measure to the methods using MNPs [71–76]. MNPs and magnetic colloidal systems based on them differ from other types of medicinal colloidal nanocarriers by the expanded possibilities of controlled delivery to the diseased organ (using an external magnetic field [1, 77–85]), as well as the possibility of their independent use as therapeutic agents (for example, in the method of hyperthermia [1, 77–85]), diagnostic agents (for example, in magnetic resonance imaging [94–99]), and multifunctional (theranostic) agents [100–102]. However, chemical, biological, and medical problems arising in the way of practical application are similar for all types of colloidal nanocarriers [103].

The question arises why, despite the obvious advances in understanding the fundamental principles of nanomedicine [31, 41, 104, 105] and various modern high-precision experimental methods for studying nanoobjects [26, 106–109], is its practical application inhibited? In this review, we tried to answer this question, and discuss the possible future of nanomedicine, paying special attention to the features and prospects of the medical use of magnetic nanoparticles, which are functional objects of a number of methods of biomedical radioelectronics.

1. GENERAL INFORMATION ABOUT NANOMEDICINE

At present, nanomedicine has reached a level of development where it is beginning to be considered as a separate area of life sciences [110, 111]. The origins of nanomedicine are usually attributed to the work of German physician and researcher P. Ehrlich, who expressed the idea of creating a drug that selectively and specifically acts on a diseased organ and does not affect healthy tissues. Ehrlich called such an ideal remedy the “magic bullet” [112]. Now this approach to designing medicinal agents for the treatment of cancer is commonly called selective toxicity [113]; in this case, a selective effect is assumed at the cellular or even intracellular level [114]. Ehrlich created the first drug for chemotherapy (and proposed this term) [115] and introduced the important concept of the therapeutic index (the ratio of the minimum already active and maximum still safe drug concentration) (Fig. 1 [116]), which is still used to quantify the relative drug safety [116]. Ehrlich believed that the effect of a drug on a cell is explained by a sequence of ordinary chemical reactions, and the most efficient drugs should have a low molecular weight [113]. The latter assumption was subsequently fully confirmed for artificial chemically synthesized drugs, which include the majority (more than 80%) of modern pharmaceuticals [114].

For any medicinal agent, the issue of dose is important. In order for the drug to work, its concentration in the blood must be for a long time within the limits that set the therapeutic index (see Fig. 1). If a drug is not encapsulated in a carrier (does not have a protective membrane separating it from the liquid biological environment of the body), its concentration in the blood after introduction into the body first rapidly increases and then rapidly decreases (see Fig. 1a) due to metabolism and excretion from the body [116]. Such pharmacokinetic dependence leads, as a rule, to the need to increase the administered dose of the drug and, as a consequence, to an excess of the maximum nontoxic concentration (see Fig. 1a). The gradual release of therapeutic molecules from the drug carrier due to a special coating avoids this problem (see Fig. 1b).

The idea of delayed drug delivery into the blood has played an important role in the history of nanomedicine [117]. In the 1960s, macroscopic drug carriers emerged; they slowly release the contents to the outside due to their shell. The first materials for such car-
Carriers were paraffin wax (Spansules technology [118]), silicone rubber [119], and polyethylene vinyl acetate copolymer [120]). They have been used in particular for the treatment of cataracts (Ocusert®) and contraception (Norplant®). Biodegradable polymers such as poly(lactic-co-glycolic) acid (PLGA) appeared in the 1980s; porous microparticles containing a therapeutic substance began to be made on their basis. For example, anticancer agent Decapeptyl® was developed according to this principle and was approved in Europe in 1986. Another biodegradable polymer, polyethylene glycol tetraphthalate (PEG-T), became the basis of Locteron® for the delivery of α-interferon, which has been used since the mid-1990s until now. A further decrease in the size of medicinal nanocarriers occurred when conjugates of polymers, in particular poly(N-(2-hydroxypropyl)methacrylamide) (PHPMA) and styrene maleic anhydride (SMA), with therapeutic molecules, such as doxorubicin, were synthesized [121, 122].

Another important event for nanomedicine was the discovery by H. Maeda in 1984 of the effect of enhanced penetration and retention (EPR) of colloidal particles in actively growing tumors [123]. The polymer–drug conjugate (SMA conjugated to the anticancer peptide drug, neocarcinostatin), which Maeda called “SMANCS,” was additionally “labeled” with a dye molecule. It turned out that the dye is accumulated in tumor tissue to a much greater extent than in healthy tissue. Maeda suggested that rapidly forming vasculature in tumors has larger pores (about 800 nm) than normal, and the lymphatic drainage system is not able to work efficiently (Fig. 2). This leads to an increased concentration of the colloidal nanodrug in the tumor tissue.

Until now, the EPR effect is the basis of almost all “passive” drug delivery techniques. One of the disadvantages of the EPR effect from the point of view of application in nanomedicine is the difficulty in removing nanocarriers that have already released the drug from the tumor in order to make room for new drug carriers [124]. The search for new polymer conjugates led to the discovery and subsequent active use of nanocarriers based on polymer micelles [125–127]. It is well known that amphiphilic block copolymers spontaneously assemble into polymer micelles several tens of nanometers in diameter in aqueous media. Such polymer micelles have a unique core–shell structure, in which the inner part can serve as a nanocarrier for drugs, including hydrophobic ones. The outer shell of the micelle is formed by hydrophilic polymers such as, for example, polyethylene glycol (PEG). Polymeric micelles have several advantages, such as ease of preparation, efficient drug loading without chemical modification of the parent drug, controlled drug release, and increased circulation time in the bloodstream. The EPR effect is also characteristic of polymer micelles.

Interest in biomimetic vesicles, liposomes as possible nanocarriers of drugs, increased simultaneously with the creation of polymer micelles. Liposomes have been actively studied since the 1960s, as they were considered quite adequate artificial models of cell membranes [128]. Liposomes are small spherical artificial vesicles with a membrane consisting of phospholipid bilayers [2, 17, 129–132]. They can be made from natural nontoxic phospholipids and cholesterol in the form of one or more concentric bilayers capable of encapsulating hydrophilic and hydrophobic drugs. The size of liposomes depends on their composition and preparation method and varies from ≈10 nm to ≈2.5 μm [133]. It is liposomes that are used in many nanomedical techniques approved for practical use [134, 135]. This is due, in particular, to the possibility of obtaining liposomes with different sizes, their biocompatibility, biodegradability, low toxicity, and immunogenicity [128, 136]. Nanocomposite liposomes, the membranes of which contain superparamagnetic nanoparticles of iron oxides, are of great interest and have prospects from the point of view of selective controlled release of an encapsulated drug by external remote physical radioelectronic impacts (alternating electromagnetic fields [51, 52], and electric field pulses [53]).

Currently, in addition to liposomes and polymer micelles, nanomedicine uses dendrimers, nanogels, inorganic nanoparticles (including magnetic ones), and biomimetic particles, as well as various complex nanostructures based on them, to create nanocarriers for drugs [23, 137–139]. Let us list some features of nanoobjects (Fig. 3), which are most typical and useful for medical applications [17, 21, 140].

Inorganic nanoparticles (including magnetic ones) increase the rate and solubility limit of drugs, their bioavailability; they are relatively low toxic; magnetic
nanoparticles can be controlled by an external magnetic field.

**Polymer-based nanoparticles** are multifunctional, they increase the stability of the drug and improve drug penetration into tissues and cells.

**Liposomes and micelles** significantly increase the amount of the transferred medicinal agent and reduce its toxicity, protect the transferred drug from degradation, and increase the circulation time of the drug in the circulatory system.

**Biomimetics** are characterized by increased biocompatibility and low immunogenicity.

**Dendrimers** increase the uniformity of the nanodrug in size and shape.

**Nanogels** have a high payload; they allow for different control over the drug release process.

Note that the listed features of individual nanoobjects are, to one degree or another, inherent in all other types. In this review, we will dwell in detail on the medical application of MNPs, which belong to inorganic nanoparticles.

2. FEATURES OF MEDICAL APPLICATION OF MAGNETIC NANOPARTICLES

The main physicochemical properties of MNPs are described in detail in the literature (see, for example, [80–82, 100, 141]). The key feature that distinguishes MNPs from other types of drug nanocarriers is the possibility to act on them with an external electromagnetic field and to use them in various methods and approaches of biomedical radioelectronics. This effect can ensure the control of the movement of nanoparticles and their accumulation in target local areas of the body, and, if necessary, significant heating (in the hyperthermia method). From the point of view of the classification of magnetic properties, MNPs are ferro- or ferrimagnets exhibiting superparamagnetic properties due to single-domain properties at sufficiently high temperatures (above the so-called blocking temperature) [142]. MNPs based on iron oxides, magnetite (Fe₃O₄) and maghemite (γ-Fe₂O₃) [143–145], are most suitable for medical applications, since nanophase iron oxides are low toxic, they are widespread in living systems and can be metabolized by the cells [145]. Biogenic magnetic nanoparticles of iron oxide (magnetite and maghemite) are currently found in a variety of living organisms and play an important physiological role, allowing the body to navigate in the Earth’s magnetic field (magnetosomes in bacteria, insects, fish, birds, etc.), and are also the consequence and manifestation of pathologies, in particular, in humans, their presence correlates with neurodegenerative diseases [17].

In the literature, MNPs based on iron oxides are often called superparamagnetic iron oxide nanoparticles (SPIONs), meaning the characteristic property of these nanoparticles is superparamagnetism [141, 146]. In recent decades, SPIONs have become increasingly popular due to their numerous biomedical applications, such as cancer therapy with magnetic field-
mediated hyperthermia, targeted drug delivery, iron replacement therapy, and MRI [147–149]. Although SPIONs are generally considered biocompatible and have a low cytotoxic potential [150], it is clear that these particles are still foreign bodies in the human organism and can have various effects on the immune system, which lead to hypersensitivity, immunosuppression, or, conversely, immune stimulation [151, 152].

The goals of searching for new drugs using nanotechnology, the main or auxiliary element of which are MNPs, are diverse. They include [153–155]:

— Improving the so-called therapeutic index by increasing efficiency and/or reducing toxicity.

— Targeted drug delivery, specific to the tissue type, or even at the cellular or subcellular level.

— Improving the pharmaceutical properties of therapeutic molecules such as stability, solubility, and circulation time in the body; increasing the drug concentration in the diseased organ.

— The possibility of controlled drug release [156].

— The possibility of targeted intracellular delivery of therapeutic agents based on biological macromolecules, DNA, small interfering RNA, mRNA, etc. [157].

— Simultaneous delivery (co-delivery) of complex therapeutic agents to increase the efficiency and overcome drug resistance; the possibility of a more accurate selection of the ratio of the components of a complex drug taking into account a specific patient (the so-called personalized medicine) [158].

— The possibility of successful transcytosis of drugs, i.e., overcoming endothelial (for example, blood-brain) and epithelial (gastroenterological) barriers.

— The possibility of more accurate diagnostic (visualization) methods.

— The possibility of simultaneous diagnosis and therapy, including in real time, so-called theranostics.

— The possibility of using the intrinsic specific properties of nanocarriers for therapy, for example, hyperthermia using MNPs.

Usually, the medical application of MNPs is considered either therapeutic or diagnostic (Fig. 4) [159]. However, MNPs can also be multifunctional, i.e., both diagnostic and therapeutic (i.e., theranostic) agents [100, 160–162]. For each specific practical medical task, MNPs are modified to improve existing ones or to obtain special specific properties, i.e., they are functionalized. This is necessary, in particular, because the drug nanocarrier, before reaching the “target,” must be freely present in biological fluids of complex chemical composition (blood, lymph, cytoplasm, etc.). Upon reaching the target, the carrier must specifically interact with it, which also requires modification of MNPs. If MNPs are used for diagnostic purposes, radioactive or fluorescent molecules must be pre-attached to the MNP surface. Figure 5 schematically shows possible types of MNP functionalization [163, 164].

An important task is the controlled release of the drug from the protective shell or vesicle when the nanocarrier has reached the target [117, 165]. Ideally, the functionalization of MNPs should allow controlling the drug release process using various types of stimulation [166] and, in addition, make it possible to take into account the individual characteristics of the
3. PROGRESS IN MEDICAL APPLICATION OF MAGNETIC NANOPARTICLES

Examples of successful medical application of MNPs can be conditionally divided into two groups: (1) introduction of the method using MNPs into real medical practice; (2) the development of a method or a separate part of it, which promises advantages over similar methods used in medical practice but has not yet been approved for clinical use. There are much fewer examples of the first kind than the second [42, 134, 168–172]. The reasons for this are discussed in the next section, but here we note that one of the main reasons for the slow introduction of MNPs into medical practice is the strict criteria for the admission of new drugs and techniques, which are becoming more stringent every year. The most prominent organizations that accept or reject new drugs are the US Food and Drug Administration (FDA) and the European Medical Agency (EMA) [134, 106, 107, 162, 173]. In addition, many aspects of medical devices and instruments are regulated by the International Organization for Standardization (ISO) (www.iso.org). To reach the final stage of real medical use, a new drug must go through several stages [69, 174, 175]. The first stage includes fundamental research, culminating in a detailed development of the scientific foundations of all elements of the new method. In the process of implementing the second stage (preclinical trials), it is necessary to determine many characteristics of a new drug method in vitro and in vivo (on an animal model that is adequate for the proposed human organ for treatment), for example, the peculiarities of drug metabolism, its relative efficacy in comparison with other drugs, optimum dose, optimal delivery method, side effects, in particular cytotoxicity, and possible interactions with other drugs. The organization and conduct of preclinical trials should be in accordance with the Good Laboratory Practice guidelines [176–178]. Clinical trials include four phases. Phase 1 usually involves fewer than 20 healthy volunteers, lasts several months, and has the primary goal of finding a safe dose. Phase 2 clinical trials involve volunteer patients (usually several hundred) and have the main goal of finding the optimal dose. Phase 3 largely duplicates phase 2, but the number of volunteers can reach several thousand. The goal of phase 3 is to confirm the results of the previous two phases and to identify as many side effects as possible. Based on the results of phase 3, a new drug is registered. In phase 4 (post-registration), the number of volunteers increases even more, the statistical reliability of the efficacy and safety data obtained at the previous phases of clinical trials is verified. Phases 2, 3, and 4 of clinical trials can last for several years. It often takes 10–20 years from the birth of a concept of a new medicinal agent to its commercialization [140]. Throughout the clinical trial process and after its completion, the results of all studies, as well as patent information and information about the intended manufacturer, are transferred to an organization authorized to grant approval for practical use, for example, the FDA. After the completion of clinical trials, if approved after a thorough examination, in particular, comparing the efficacy and safety of existing pharmaceuticals and methods with those proposed, a new drug or method can be produced as a commercial product. But even after the start of actual use of this product, the FDA or a similar organization inspects the manufacturers’ factories, identifies cases of previ-
Although Ferumoxytol nanoparticles are superparamagnetic, this property is not used in any way in the treatment of anemia. However, for MRI purposes, it is the superparamagnetic nanoparticles that are needed. Therefore, Ferumoxytol began to be investigated to test the possibility of its use as a contrast agent in MRI diagnostics of a wide range of diseases: multiple sclerosis, pancreatitis, cardiovascular and tumor diseases, etc. [169, 193, 194]. On the International Clinical Trials Registry website of the US National Institutes of Health, www.clinicaltrials.gov, some of these studies are marked as completed (in early phases). The question of whether these studies will continue and whether Ferumoxytol will be used as an MRI contrast agent remains open. A drug similar to Ferumoxytol, Ferumoxtran-10 (another name Ferrotran, commercial names Sinerem® and Combidex®), in which the magnetite nanoparticle shell is formed by the polysaccharide dextran, was originally intended for use in MRI diagnostics of lymph node cancer and was approved for use in some European countries [169]. However, applications were withdrawn by the FDA in 2005 and by the EMA in 2007 due to reports of side effects. Currently, various gadolinium compounds are used in almost half of all MRIs using contrast agents [97, 99]. However, due to the accumulation of gadolinium ions in tissues (including the brain), these compounds can be unsafe, especially if they are used repeatedly [195]. Therefore, the likelihood of using Ferumoxytol and other types of SPIONs as a substitute for gadolinium-containing agents in MRI remains rather high [196–199], even despite reports of possible side effects when using Ferumoxytol as an anti-anemic agent [200] and, in general, not entirely a clear situation with the degree of toxicity of iron oxide-based MNPs [201]. Here, apparently, a choice must be made, either to abandon the use of SPIONs altogether due to possible side effects [202], or still use SPIONs in the MRI method for certain types of tumors, where other types of contrast agents are unacceptable [203, 204]. The second solution, from our point of view, looks preferable.

MNPs have a unique property that distinguishes them from other types of nanopreparations, namely, they can be controlled using an external magnetic field, which makes them indispensable in the “targeted drug delivery” methods. However, the success of the clinical application of MNPs in this area is still very moderate [171, 205]. To date, the only example of targeted drug delivery using MNPs is [1, 77], which, however, did not go beyond phase 2 of clinical trials. This is due, in particular, to the limited applicability of the method [1, 77] only to superficial tumors. This deliberately reduces the number of volunteer patients and prevents statistically reliable clinical trials with a sufficiently large number of participants to be fully carried out, which is required for the approval of the method by the regulator. In [1, 77], SPIONs with a diameter of about 100 nm, chemically bound to epiru-
bicin [206], were injected into blood vessels near the tumor on the surface of the patient’s face or neck. A permanent magnet creating a magnetic field with an induction of 0.8 T was placed near the tumor so that it would attract MNPs with a drug to it. The procedure was applied to 14 patients for whom the previous stages of treatment according to traditional schemes did not lead to noticeable success. In addition, all tumors were inoperable. Although the application of the method of targeted doxorubicin delivery using MNPs has achieved some success in the treatment of superficial tumors, in general, the results obtained are not yet completely convincing [1].

In the literature, we can find numerous examples of studies on MNPs, which are potentially interesting for practical medical use, but have not reached clinical trials, i.e., studies were carried out either in tissue culture or in animals (see, for example, a recent review [159]).

When using MNPs in therapeutic or diagnostic medical methods, it is extremely important to directly control the spatial arrangement of nanoparticles inside the patient’s body. This is especially true in methods with controlled drug release in the target area of the body, which should be produced only after the MNP reaches the target organ. An experimental radio-electronic technique that solves this problem, called magnetic particle imaging (MPI), was proposed in 2005 [207]. The method is based on such specific property of MNPs as superparamagnetism. In contrast to macroscopic ferromagnets and paramagnets, the saturation magnetization of which at room temperature occurs in very low (~1 Oe) and very high (~1 MOe) magnetic fields, respectively, the magnetization of superparamagnets reaches a plateau in external magnetic fields with a strength of about 1 kOe easily achievable with conventional laboratory magnetic field sources. Figure 6 shows the dependence of magnetization \( M \) on strength \( H \) of the external magnetic field, which is characterized by saturation regions, in which the magnetization practically is not changed. The MPI scanner contains a system of six coils that create quasi-static magnetic fields orthogonal to each other, the sum of which provides a displacement (i.e., scanning) in the space of the field-free point (FFP) region, on which a harmonically varying alternating magnetic field with amplitude that allows passing the nonlinear part of the magnetization curve (left panel in Fig. 6). The receiving coil of the scanner registers the time dependence of magnetization, which will be nonlinear only if MNPs fall into the FFP region. In this case, the Fourier transform of the receiving coil signal will give noticeable amplitudes of harmonics at frequencies that are multiples of the frequency of the alternating magnetic field. If MNPs are outside the FFP region, the corresponding signal of the receiving coil will be almost constant, and the amplitude of the Fourier harmonics will be small (right panel in Fig. 6).

The MPI method was further developed in [208, 209]. A pilot facility that allows MPI to be applied to studies on the human brain was described in [209]. The state of the theory and technique of the MPI experiment for 2021 was described in detail in the review [186].

At the end of this section, on the whole, it can be concluded that the use of MNPs in medicine does not yet meet the expectations that were placed on them at the initial stages of the development of nanomedicine [210–213]. Nevertheless, over the past 20 years, it has been possible to prove the fundamental possibility of the practical implementation of magnetic hyperthermia [181], magnetically controlled targeted drug delivery and thereby reducing their toxicity [1, 77], and the ability of MNPs to play the role of contrast agents in MRI [191]. Thus, the special physical properties of MNPs, which can be considered as their advantages in
MAGNETIC NANOPARTICLES IN MEDICINE

4. PROBLEMS OF MEDICAL APPLICATION OF MAGNETIC NANOPARTICLES

As noted above, the main problem of the medical use of MNPs, like other nanodrugs, is their extremely slow practical implementation [111, 168, 214–216]. This problem is inherent in nanotechnology in general [217]. The fact that the problem is broader and very urgent is indicated by the introduction of the terms “crisis of translation” [218], reproducibility crisis [219, 220], and other similar phrases expressing concern about the slow progress in this area, into scientific circulation.

The reasons hindering the widespread practical use (“translation”) of MNPs can be conditionally divided into three groups [66, 103, 111, 221]: (I) scientific (fundamental and technical), (II) clinical (medical and social), and (III) marketing (commercial).

Group I includes: (1) insufficient understanding of the mechanisms of interaction of MNPs with biological components and structures of the body during drug delivery to a diseased organ [222], as well as (2) mechanisms of accumulation of MNPs with drugs in the organ itself; (3) different behavior of MNPs in in vitro and in vivo experiments; (4) technical difficulties in the implementation of the method (or its individual parts) using MNPs, preventing their use anywhere other than individual high-tech laboratories [223]; (5) poor knowledge of the pharmacokinetic processes involving MNPs; (6) the ambiguity of the data on biosafety [224, 225]; and (7) the possible inadequacy of the animal models used to the analogs in the human body [153, 226].

Group II includes: (1) the high cost of clinical trials, which is unacceptable for many research teams (hundreds of millions of dollars [227]); (2) an incorrectly chosen target (for example, the type of malignant tumor) for this method; (3) errors in choosing the dosage and duration of treatment; (4) poor reproducibility of results due to insufficiently strict control over the synthesis and characterization of the used MNPs (i.e., the absence of sufficiently stringent standards for MNPs); (5) a possible change in the properties of MNPs during the transition from laboratory synthesis to industrial (scaling problem); (6) the variety and unpredictability of possible side effects during phases 3 and 4 clinical trials on a large sample of volunteers.

The problems of group III (marketing) of MNP-based nanodrugs are varied; but the main one is the amount of competition, including that due to emerging new traditional (not “nano”) drugs, which are less toxic and more effective than their predecessors.

One can schematically depict the main obstacles in the way of introducing nanopreparations into medical practice in the form of a “mountain range” (Fig. 7).

The term “biological barriers” (see Fig. 7) summarizes a large number of different factors [54]. As mentioned above, one of the fundamental principles of nanomedicine is the requirement that a drug does not affect healthy tissues of the body, which leads to the task of drug “encapsulating” (creating protective membranes). At the same time, the biological environment affecting the drug during its delivery to the diseased organ should not change its therapeutic properties. However, when even encapsulated or surface-modified MNPs enter the blood, due to opsonization, their surface is quickly covered with a “biocorona” consisting mainly of protein and lipid molecules, which significantly affects their stability, involvement in metabolism, including the time of excretion from the body, and its immune response [114, 228, 229]. The details of the interaction of MNP-containing medicinal agents injected into the patient’s body and various biological structures may significantly depend on the individual characteristics of the organism and, therefore, should be carefully studied in clinical trials.
on a significant number of volunteers. The biomedical heterogeneity of potential consumers of nanodrugs is a serious obstacle to its practical implementation.

The problem of developing uniform quality standards for MNPs intended for use in medicine also remains unresolved so far [230]. Although, in general, laboratory synthesis of nanoparticles has reached a high level of perfection [231], “irreproducibility” remains a problem; i.e., a situation when the published results of a scientific study cannot be reproduced in other laboratories (or, worse, even in the one where the research was carried out) [232]. It is especially important to have accurate information on the toxicity of MNPs if their medical use is expected. Among the most important and most general issues that need to be resolved are the following [233]:

(1) Will nanoparticles exhibit similar properties and interactions in various organs and cells? Do these properties and interactions depend on the person’s age? Does the history of particle movement in the body have any influence on these interactions?

(2) How do the results of in vivo and in vitro studies of nanoparticles in cell cultures depend on the properties (and origin) of these cultures? The results of studies on the same (formally) cell cultures can vary greatly even when using the same nanomaterials.

(3) Can the rate of in vivo introduction of particles affect the rate of particle aggregation leading to their locally increased concentration and, as a consequence, sedimentation, thrombus formation, and similar effects? How does the rate of injection affect the uptake of nanoparticles and metabolism in key filtration organs such as the liver, spleen, capillaries of the lungs and kidneys, and will there not be toxic byproducts?

(4) How does functionalization of nanoparticles change their toxicity in vivo?

Up to this point we have listed the problems in the medical use of nanoparticles that are common to all types of nanodrugs. However, the magnetic properties of MNPs also cause some specific problems [41]. The first of these problems is of fundamental nature. Thus, targeted drug delivery using a static magnetic field is possible only at a minimum, but not a maximum. It follows from Thomson’s theorem that superparamagnetic nanoparticles cannot be in stable equilibrium under the action of only magnetostatic forces.

This introduces difficulties when using MNPs in methods of targeted drug delivery [235, 236]. Obviously, it is convenient to use the static magnetic field created by permanent magnets or solenoids for targeted drug delivery using MNPs [85]. It is the permanent magnets that have been used in clinical trials for the treatment of superficial tumors [77].

The problem can, in principle, be solved by applying dynamic control of MNPs using a magnetic field slowly alternating according to a certain algorithm [235, 237]. However, this greatly complicates the already technically difficult magnetic method of targeted drug delivery. Another way to solve this problem is to use a miniature ferromagnetic stent that is inserted into the tumor and becomes the center of attraction for MNPs [238]. However, in this case, an important advantage of the magnetic method of drug delivery, non-invasiveness is lost.

There are other specific problems of the medical use of MNPs: an increased tendency to aggregate due to magnetic dipole–dipole interactions [239] and the need to create a significant degree of inhomogeneity of magnetic fields [240]. The first of these problems can be solved in principle by the appropriate modification of the MNP surface by choosing the correct concentration and magnetic parameters of the particles; the second problem is technical; it can be solved by the correct spatial configuration of the magnetic field sources.

5. PROSPECTS FOR MEDICAL APPLICATION OF MAGNETIC NANOPARTICLES

Currently, nanomedicine, part of which are methods using MNPs, namely, magnetic field-controlled hyperthermia, targeted delivery and controlled release of drugs, and magnetic resonance diagnostic methods, face complex tasks [103, 111, 172, 241]. The essence of these tasks is to overcome the many problems described in the previous sections. To successfully resolve these problems, it is necessary, among other things, to eliminate some imbalances in the organization of scientific research. Until now, most research has been carried out by teams of chemists, physicists, biologists, materials scientists, engineers, and only occasionally medical practitioners. Thus, already at the beginning of the research process, the final task, the creation of a novel medicinal nanopreparation, is postponed to the future; and most attention is paid to obtaining nanostructures with very good physicochemical properties, the quality criterion for which, however, may in no way be related to the ultimate goal.
This feature of modern works on nanomedicine has been called “the invisible gorilla effect” [63]. In Russian, the content of this effect can be expressed by the proverb “not to see the forest for the trees.”

Another negative feature of scientific studies on nanomedicine of the last 20–30 years, which needs to be overcome, is called “publication bias” or “the file drawer problem” in English language literature [242, 243]. It consists in the fact that the overwhelming majority of research articles report only positive results, not mentioning negative ones. The same is true for most review articles on nanomedicine, which focus on successes and to a much lesser extent discuss failures or pitfalls. In the case of the search for new medicinal agents and the development of new methods of diagnosis and therapy, knowledge about negative results is no less important than positive ones.

Another important problem, without which progress of nanomedicine is impossible, is the standardization of the characteristics of nanoobjects in order to be able to compare both preclinical research results and, more importantly, the results of clinical trials [92, 233]. It is necessary to introduce a list of standard physicochemical characteristics of MNPs that are mandatory for measuring, in particular, polydispersity degree (variation in size), degrees of toxicity, pathogenicity, and biodegradability, tendency to aggregation, basic magnetic properties (for MNPs), etc. All the most important characteristics affecting toxicity, bioavailability, and immunogenicity must be experimentally measured (determined) and described in detail in order to correctly and fully interpret the results of the study and allow their comparison with previously published data. Of course, such standardization should take into account the specifics of individual sections of nanomedicine and the characteristics of various diseases.

Research groups that create biomedical methods using MNPs may not synthesize them themselves but use ready-made ones. Currently, 14 commercial firms offer research-level MNPs [92]. One type of such particles (Ferrotran) is undergoing clinical trials, and several more types VivoTrax™, VivoTrax Plus™, FeraSpin™, RCL-01, Nanomag®, Perimag®, and Synomag® are ready for them.

The success of future medical applications of magnetic nanoparticles depends largely on the development of radio-electronic MPI technology for visualizing magnetic nanoparticles inside the body [186, 207]. It is impossible to control the action of a drug delivered to a diseased organ using MNPs without direct information about the success of this delivery. Moreover, with the use of MPI technology, the theranostic approach has been recently applied in an animal model; visualization of MNPs was accompanied by the process of hyperthermia [244]. The striving for multifunctionality and a combination of therapeutic and diagnostic effects will, apparently, be the main trend in future studies related to the use of MNPs in medicine [245–247].

CONCLUSIONS

Our analysis of the progress and problems of biomedical applications of MNPs and methods of biomedical radioelectronics using such nanoparticles shows that their potentialities in this area have not yet been fully disclosed. The methods of magnetic hyperthermia and controlled targeted drug delivery have been implemented in practice only in isolated cases and in a limited form. Although the practical application of MNPs for diagnostic purposes is more successful, there are many problems associated with inevitable side effects. The understanding of the need for changes both in the very approach to scientific research in this area and in the content of this research is gradually maturing in the scientific community. The multidisciplinary character of the research should be expanded with experts in medicine and physiology. In addition to continuing research on optimization of the processes of targeted delivery and controlled release of drugs, hyperthermia, it is especially important to develop physical methods for visualizing magnetic nanoparticles in a living organism, as well as multifunctional methods and approaches that effectively and simultaneously solve several diagnostic and therapeutic tasks.

FUNDING

The work was carried out within state assignment no. AAAA-A19-119041590070-1 and was supported by the Russian Foundation for Basic Research, project no. 20-12-50280.

CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest.

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Translated by G. Levit