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Magnetic hyperthermia prospects in modern approach to cancer treatment

Perspektywy hipertermii magnetycznej w nowoczesnym podejściu do leczenia nowotworów

Abstract

The rising incidence of cancer poses a constitutes a civilization (social) threat, leading to an increase in deaths worldwide. Current cancer treatments exhibit certain limitations, which necessitates the search for new, safer solutions. The main challenge is the need to achieve a more selective effect on cancer cells to minimize side effects and increase the effectiveness of treatment. The use of magnetic hyperthermia is a promising alternative to conventional treatments. Magnetic hyperthermia (MH) is based on the phenomenon of heat generation by nanoparticles under the influence of an alternating magnetic field at the tumor site. This review will provide a detailed discussion of the physical basis of hyperthermia and the properties of nanoparticles used in MH, with a focus on iron oxides, analyzing their potential in the context of cancer treatment. The paper also presents practical applications of MH at various stages of research, covering laboratory, preclinical and clinical studies. The paper aims to provide a broader understanding of the role of magnetic hyperthermia as an innovative therapeutic method in cancer treatment. Noteworthy, the research and improvement of technology are aimed at maximizing the clinical benefits resulting from the use of MH.

Key words: magnetic hyperthermia, magnetic nanoparticle, cancer, iron oxide, anti-cancer therapy.

Streszczenie

W ostatnich latach obserwuje się rosnącą zachorowalność na nowotwory, co ma bezpośredni wpływ na wzrost liczby zgonów na całym świecie. Obecne metody leczenia nowotworów wykazują pewne ograniczenia, co stawia przed nami konieczność poszukiwania nowych, bezpieczniejszych rozwiązań. Głównym wyzwaniem jest konieczność uzyskania bardziej selektywnego oddziaływania na komórki nowotworowe, aby zminimalizować skutki uboczne i zwiększyć skuteczność terapii. Wykorzystanie hipertermii magnetycznej stanowi obiecującą alternatywę dla konwencjonalnych metod leczenia. Hipertermia magnetyczna (MH) opiera się na zjawisku generowania ciepła przez nanocząsteczki będące pod wpływem zmiennego pola magnetycznego w miejscu nowotworu. W ramach tego przeglądu zostaną szczegółowe omówienie podstawy fizyczne hipertermii oraz właściwości nanocząstek używanych w MH, ze szczególnym uwzględnieniem tlenków żelaza, analizując ich potencjał w kontekście leczenia nowotworów. Artykuł prezentuje również praktyczne wykorzystanie MH na różnych etapach badań, obejmując badania laboratoryjne, przedkliniczne i kliniczne. Niniejsza praca ma na celu szersze zrozumienie roli hipertermii magnetycznej jako innowacyjnej metody terapeutycznej w leczeniu nowotworów, podkreślając konieczność kontynuacji badań i doskonalenia technologii w celu maksymalnego wykorzystania jej klinicznych korzyści.

Słowa kluczowe: hipertermia magnetyczna, nanocząstki magnetyczne, nowotwory, tlenki żelaza, terapia przeciwnowotworowa.

Introduction

The rising occurrence of cancer represents a notable public health concern, conspicuously impacting worldwide epidemiological statistics. According to the World Health Organization (WHO), there will be 19.3 million new cases of cancer worldwide in 2020, and 9.96 million deaths from it. Cancer ranks first or second in causes of death before age 70 in 112 of 183 countries, and third or fourth in another 23 countries. In addition, the number of cases is steadily rising. An almost 50% increase is predicted over the next 20 years (Sung et al., 2021). Despite advances in oncology and the availability of traditional treatments such as chemotherapy and radiation therapy, the disease poses a significant threat to humanity. Limitations in the efficacy of these therapies and their potential side effects provide the impetus for further research into innovative therapeutic strategies that are more effective, precise and less invasive. The main challenge is the need to develop cancer treatments that act selectively on cancer cells while minimizing damage to healthy tissues. In this context, it becomes necessary to develop innovative approaches such as magnetic fluid hyperthermia (MFH) (Wlodarczyk, 2022).

Magnetic hyperthermia is a treatment method that relies on generating heat at the tumor site through the application of an alternating magnetic field. This process leads to changes in the physiology of cancer cells, ultimately resulting in their apoptosis. The key element is the precise delivery of heat to the targeted sites, maintaining the temperature in the range of 41 ºC to 46 ºC, which induces intracellular and extracellular degradation processes, such as protein denaturation and aggregation (Durak, 2017). Cancer cells are more sensitive to the elevated temperature, dying when exceeding 42 ºC, while healthy cells can survive. During hyperthermia therapy, heat is generated by introducing magnetic nanoparticles (MNPs) into the tumor area. Most commonly, these are iron oxides with superparamagnetic properties. In addition, through chemical manipulation on the nanometer scale, the magnetic nanoparticles can be configured with bio-particles, including antibodies (Miaskowski et al., 2016). This process enables optimized therapy or precision targeting inside the body. MNPs can act as drug carriers, provide contrast during magnetic resonance imaging (MRI), or act as magnetic heating sources. This multifunctional approach allows nanoparticles to be widely used in the areas of diagnostics, therapy and monitoring, representing a significant step forward in the field of nanomedicine (Perigo et al., 2015).

Introduction

Hyperthermia comes in three main varieties: local, regional and whole-body. In local hyperthermia, the action of high temperature covers a small area such as a single tumor. The regional variety covers larger areas, such as entire organs or tissues. Usually, whole-body hyperthermia is used to combat metastatic cancer cells spreading throughout the body. However, this therapy can become more complicated and potentially harmful, sometimes resulting in damage to healthy tissues.

Today, there are several techniques for inducing hyperthermia, such as exposure to microwaves, the use of high-frequency currents, lasers, and immersing the patient in heated water baths (Durak, 2017). Unfortunately, these methods are characterized by a lack of selectivity for the target tissue, which can lead to side effects. To improve therapeutic efficacy, the use of more specific heat sources is being pursued. A breakthrough in this aspect is magnetic hyperthermia, during which the heat released from magnetic nanoparticles covers only the tumor area, without damaging healthy tissue (Peiravi et al., 2022; Pucci et al., 2022; Vilas-Boas et al., 2020). Figure 1 shows the differences in the temperature distribution in the patient's body during treatment with classical hyperthermia and hyperthermia with MNPs. In the case of MFH, a selective increase in temperature is observed in the tumor area to which MNPs were previously delivered. In practice, the numerical modeling of temperature distribution in the breast tumor area with MFH was discussed in detail in a study conducted by Sawicki and Miaskowski (Sawicki and Miaskowski, 2013).

Magnetic Fluid Hyperthermia is a therapeutic procedure in which fluid containing magnetic nanoparticles (ferrofluid) is injected into tissue containing tumor cells and then exposed to an alternating radiofrequency magnetic field. Introduced MNPs administered intravenously, accumulate in the tumor area due to the effect of increased permeability and retention (EPR) of blood vessels (Clark, 2016). Tumors are often characterized by blood vessels that are more permeable than those in healthy tissues. This phenomenon allows nanoparticles to leak from the blood into the tumor tissue. In addition, blood vessels in the tumor area often

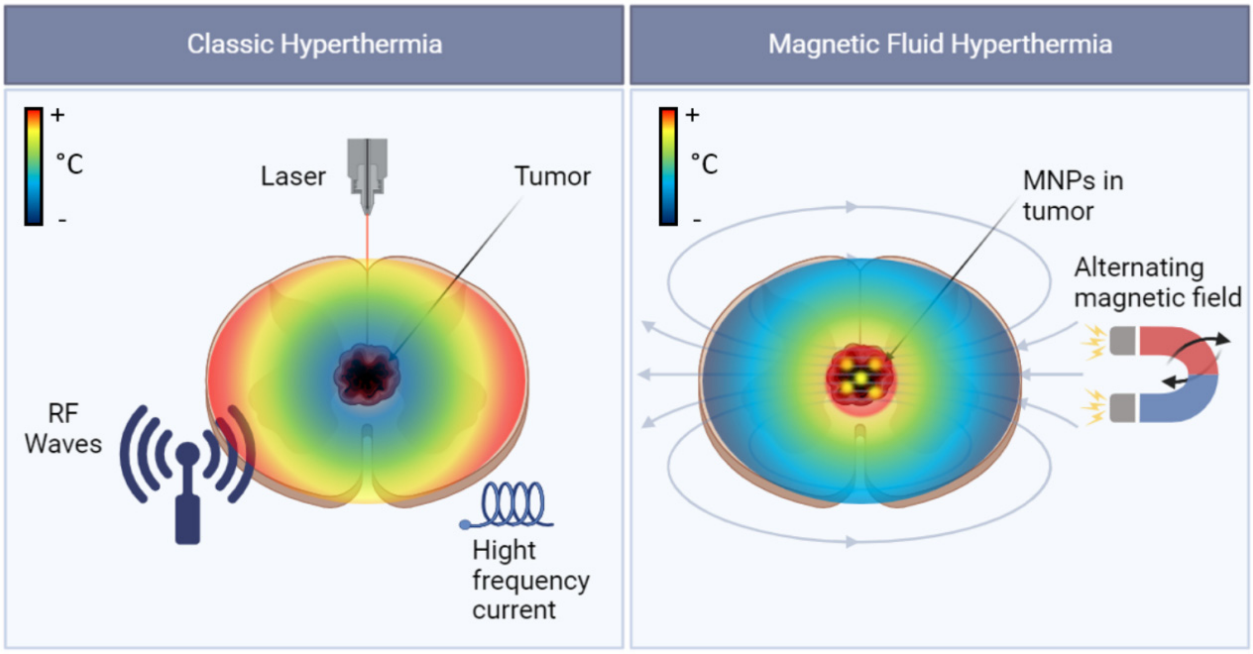

FIGURE 1. Temperature distribution inside the patient's body during classical hyperthermia and with magnetic liquid hyperthermia (own elaboration).

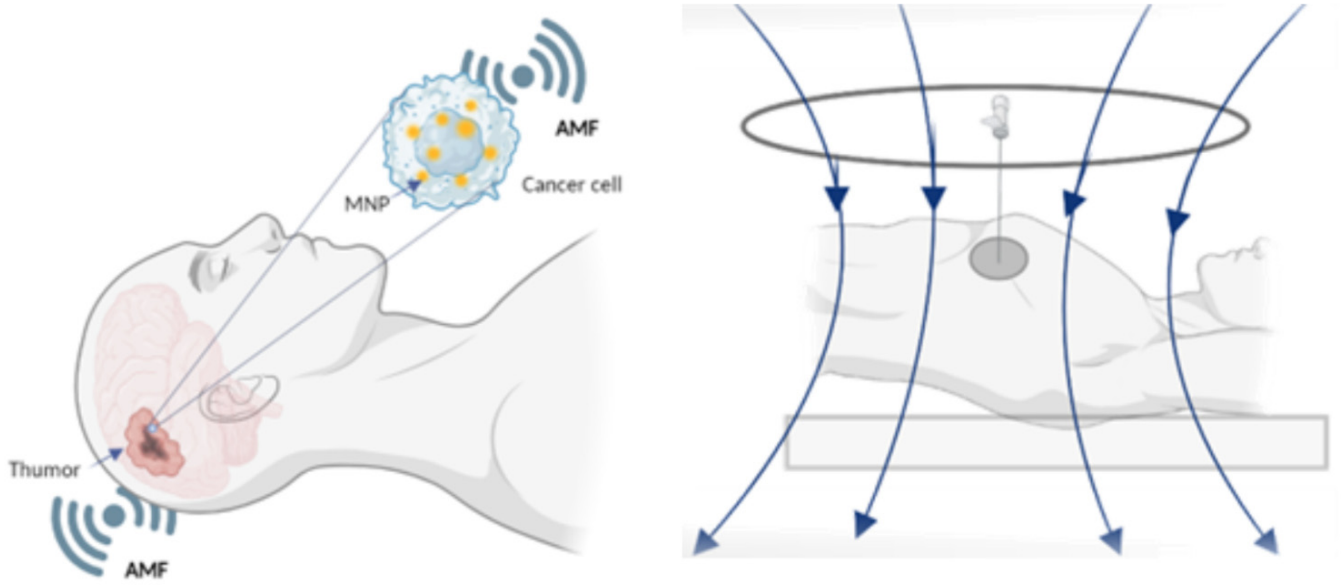

FIGURE 2. Schemes of action of magnetic hyperthermia (own elaboration).

have impaired structure and functions, causing nanoparticles to stay longer in the tumor area than in healthy tissues. To further accelerate the rate of accumulation of MNPs, one can focus on targeted delivery to cancer cells using antibodies or other ligands. Cancer cells have characteristic receptors that can be targeted with specific functional groups present on the surface of MNPs. These receptors are the result of the mutant genotype of cancer cells, which allows them to be distinguished from healthy cells. Identification of tumor cell-specific receptors is crucial for targeted hyperthermia therapy. This makes it possible to treat tumors with minimized toxicity. Basically, MNPs are introduced into the human body by injecting a solution containing a calculated amount of MNPs. An external alternating magnetic field, generated by radiofrequency (RF) induction coils, causes a temperature rise in the magnetic material, in this case magnetic nanoparticles introduced selectively into the tumor area. This approach results in heating only the target area of the tumor. The temperature difference between tumor cells and non-tumor cells can reach 2 to 3 °C (Dutz, 2014). The magnetic field generated by the induction heating coils penetrates deep into tissues, such as subcutaneous adipose tissue, without unduly damaging healthy tissues (Hervault, 2014). In this way, MFH therapy creates a state-of-the-art strategy for treating hard-to-treat tumors located deep in the body or located at sensitive structures. The AMF frequency

range used in MFH ranges from a few kHz to 10 MHz, with sufficient penetration deep into tissues (Sohail, 2016; Vilas-Boas, 2020). The schemes depicting the principle of magnetic hyperthermia is shown in Figure 2.

MFH exploits the biological differences between cancer cells and healthy cells, increases its effectiveness in the field of cancer therapy. Rapid growth and frequent divisions of cancer cells are associated with reduced blood flow due to progressive degradation of vascular beds. As a result, heat dissipation through the bloodstream in cancer cells is delayed compared to normal tissues. In addition, a lower heat capacity is observed in cancer cells compared to their healthy counterparts. As a result, under conditions of limited energy dissipation and lower heat capacity of the tumor area, the temperature of tumor cells is higher than that of normal tissues (Song, 1984). Above 41 °C, DNA double-strand break repair mechanisms are blocked, making cells more susceptible to therapeutic agents. Especially during the S-phase of cell division, hyperthermia can increase their sensitivity to cytostatic drugs. Hyperthermia can also modulate blood flow in tumor tissue, increasing the amount of cytostatic drugs and oxygen, which enhances the effects of chemotherapy and radiotherapy. Further temperature increases above 42 °C lead to blood vessel damage, local hypoxia, tumor acidification and eventual necrosis of tumor cells, minimizing the effects on healthy tissue. In addition, hyperthermia can activate the immune system in the tumor environment, mobilizing it to recognize and fight cancer cells (Wlodarczyk, 2022). Healthy human somatic cells, except neurons, can survive at 44 °C for at least 1 hour (Dutz, 2013). Thus, hyperthermia does not damage healthy tissues unless the temperature exceeds the above value.

Physical aspects of magnetic hyperthermia

Particles with sizes on the order of tens of nanometers, unlike ferromagnetic solid materials (with sizes of micrometers and larger), exist as single magnetic domains. The transition to a single-domain state results in an increase in the coercivity field, the cause of which is a change in the magnetization mechanism. In the case of multi-domain particles, the remagnetization occurs through the movement of the domain walls, and in the case of single-domain particles through fluctuation processes. An interesting variety of magnetism resulting from the reduction in size of ferromagnetic materials is superparamagnetism. To understand the essence of this phenomenon, it is worth noting that for such a single-domain superparamagnetic particle, the energy can be written as: $E_a(\theta)=KV\sin^2\theta$,
where E_a is the anisotropy energy, θ is the angle contained between the easy magnetization axis and the magnetization vector, V is the volume of the particle, and K is the magnetic anisotropy constant (Fock et al., 2018). Since the magnetic moment of a nanoparticle can be directed parallel or antiparallel to the easy magnetization axis, the above expression reaches two energy minima for $\theta = 0$ and $\theta = \pi$. When the thermal energy is comparable or higher than the anisotropy energy of the superparamagnetic nanoparticle, spontaneous fluctuations between the two minima can occur. The KV product, on the other hand, determines the height of the energy barrier separating the two minima. The height of the energy barrier depends on the volume of the nanoparticle and decreases with decreasing size (Huang and Hainfeld, 2013).

Related to superparamagnetic fluctuations is the concept of relaxation time, i.e. time it takes for the magnetization vector to rotate between two energy minima. For the first time, this term was used by Néel when describing relaxation for a particle with uniaxial anisotropy (Néel relaxation). It involves the reorientation of magnetic moments in the same direction as the applied alternating magnetic field. Under the influence of an external alternating magnetic field, the relaxation of the magnetic moments is forced, which leads to the generation of heat. Heat generation in such single-domain nanoparticles occurs mainly through two processes: Néel relaxation and Brownian relaxation. The former mechanism involves the reorientation of magnetic moments in the same direction as the applied oscillating magnetic field. This type of relaxation is strongly dependent on the size of the nanoparticles. It is dominant in the case of systems of small, well-separated particles, in which the interactions are neglected. For nanoparticles dispersed in a liquid, a second one - Brownian relaxation - is also present. Brownian relaxation is caused by the friction created by the rotation of the entire particle in the carrier liquid. The Brownian relaxation mechanism takes into account environmental parameters such as the viscosity of the medium and the hydrodynamic volume of the nanoparticle. In the case of ferrofluid, that is, liquid with magnetic nanoparticles suspended in it, both types of relaxation processes occur (Vallejo-Fernandez et al., 2013) (Figure 3). In a hyperthermia procedure, both mechanisms have an important impact on heat generation, since nanoparticles are usually dispersed in a liquid medium such as blood or other body fluids.

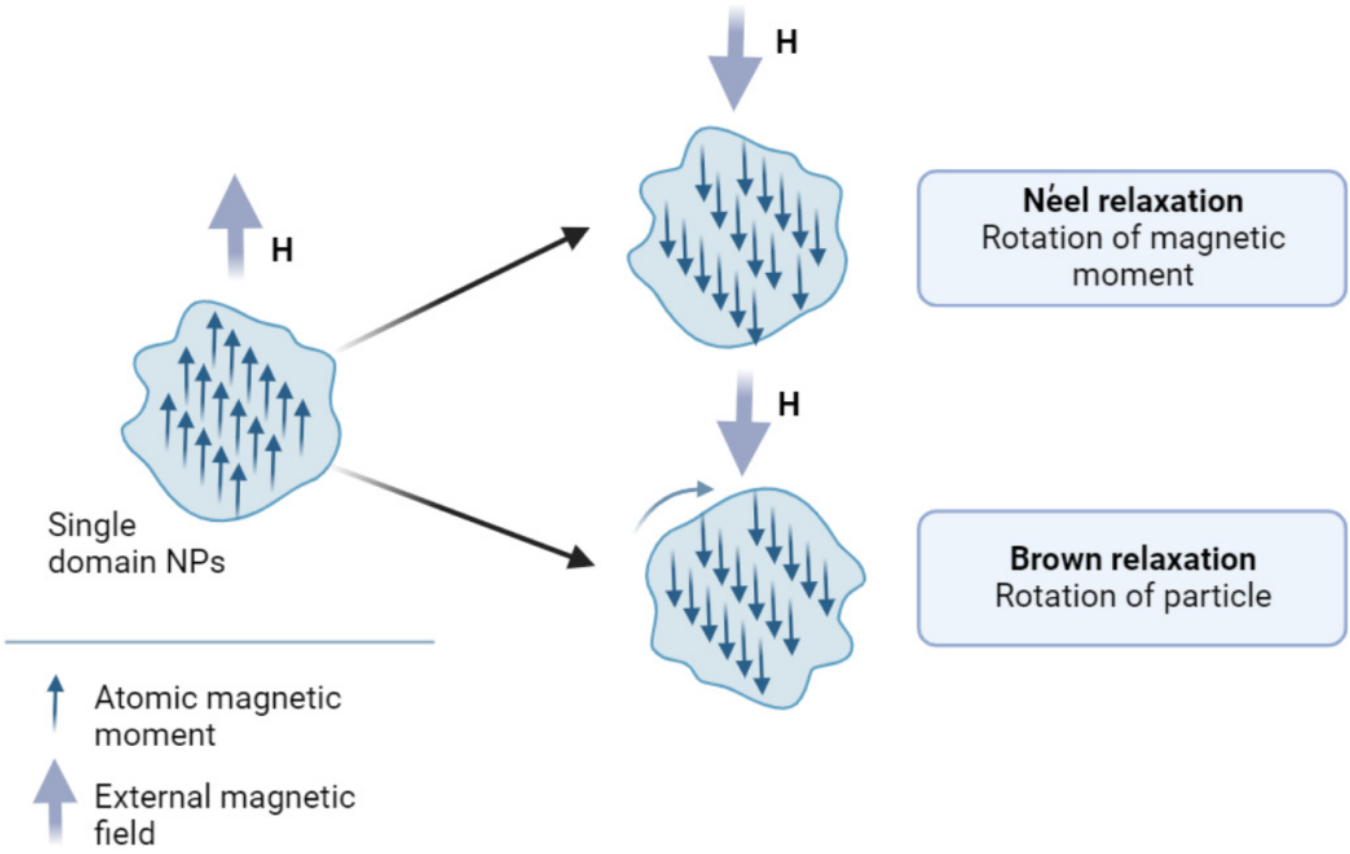

Figure 3. Schemes of Néel and Brownian relaxation in superparamagnetic materials (own study).

Iron oxide nanoparticles

Magnetic nanoparticles are solid particles between 10 and 1000 nm in size that are susceptible to magnetic fields. They can have a variety of shapes such as spheres, rods or tubes. In the biomedical field, nanoparticles serve not only as potential anticancer agents, but also as antimicrobial agents, such as in the form of layers on medical implants, and as tools for sensitive tests to detect various diseases. Their versatility stems from their unique properties and highly reactive surface, which, however, brings with it challenges related to their stability. By coating nanoparticles with polymers, they become carriers of bioactive substances such as cytotoxic drugs. Through precise targeting and activation, nanoparticles can exhibit therapeutic effects only at the site of disease. Additionally, theranostic nanoparticles are a promising application, being both diagnostic and therapeutic tools (Włodarczyk, 2022).

In therapeutic techniques based on magnetic hyperthermia, metal nanoparticles and metal oxides are commonly used, the most common being superparamagnetic iron oxide nanoparticles (SPION). These oxides are characterized by low toxicity, biocompatibility and surface modification capabilities. Due to their unique magnetic properties, iron oxide nanoparticles have become an object of increased interest. Their unique characteristics, such as superparamagnetism, surface-to-volume ratio, surface size and ease of separation, have contributed to the growing popularity of iron oxide in the MFH field. Superparamagnetic nanoparticles are susceptible to magnetic fields, however, they become demagnetized if an external magnetic field is lost. This property, combined with the maintenance of good colloidal stability, is crucial in the clinical context, minimizing the risk of aggregation of nanoparticles in the blood. In addition, SPIONs can be metabolized by hemoxygenase-1 with the production of hemoglobin in the blood, which contributes to maintaining iron homeostasis in the cell. In addition, MNPs can effectively cross the blood-brain barrier, which has proven to be an essential step in the treatment of brain cancer (Kong, 2012). MNPs can also be combined with biological molecules such as proteins, viruses or genes to facilitate targeted therapy (Pankhurst, 2003).

Within this group are iron oxides such as hematite (α-Fe_2O_3), maghemite (γ-Fe_2O_3), and magnetite (Fe_3O_4). The magnetite appears to be a particularly promising SPION from a medical perspective. Fe_3O_4

nanoparticles are characterized by an active surface, which allows them to effectively adsorb and immobilize molecules or drugs. In addition, their size and shape can be easily controlled through various synthesis methods, which makes them attractive due to tailoring their properties to specific medical applications (Surowiec, 2017).

An important aspect when obtaining nanoparticles is controlling their size. The optimal size of nanoparticles used in magnetic hyperthermia is still under discussion, mainly due to the lack of data summarizing the research to date. From a biological point of view, particles as small as 100 nm are already suitable for tissue penetration, but for hyperthermia, smaller nanoparticle sizes contained within 5-40 nm are preferred for better filling of tumor cells (Shingleton, 1962). Often such nanoparticles are additionally surface modified. Such particles are called core-shell. The core is usually an inorganic material with magnetic properties (e.g. Fe_3O_4), while the coating is usually an organic surfactant compound (e.g.: chitosan, polyethylene glycol or DMSA). The polymer coating (Pc) increases nanomaterials' stability and biocompatibility, providing hydrophilicity. It also makes it possible to attach various ligands (such as drugs) to Pc surface, which is used in targeted therapies. Pc also prevents agglomeration of nanoparticles, which due to large magnetic moments, tend to cluster into larger assemblies as the result of dipole interactions. Figure 4 illustrates transmission electron microscope (TEM) images showing magnetite nanoparticles coated with organic dimercaptosuccinic acid (DMSA). Well-separated nanoparticles with a regular spherical shape and of average size about 10 nm are presented in both images.

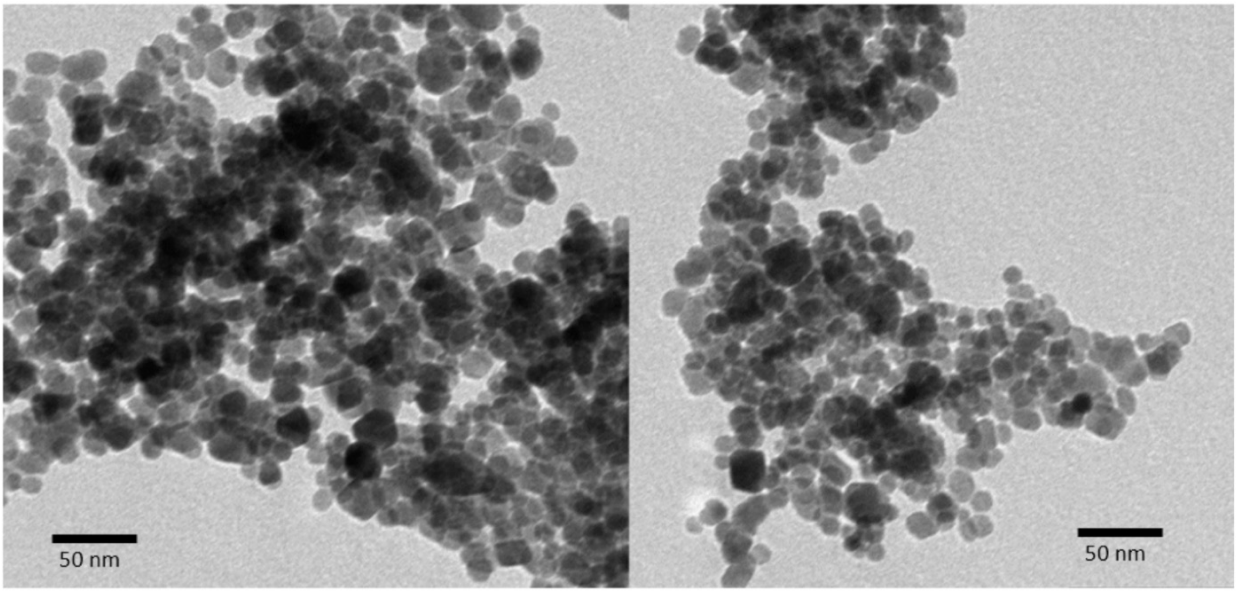

Figure 4. TEM image of magnetite nanoparticles coated with dimercaptosuccinic acid (DMSA).

Clinical aspects of magnetic hyperthermia

Magnetic hyperthermia experiments are progressing from in vitro studies in the laboratory to preclinical *in vivo* animal studies and clinical studies in humans. MFH laboratory studies confirm that nanoparticles are effective in generating heat under the influence of a safe and tolerable alternating magnetic field (Rajan and Sahu, 2020).

Kumar's team tested silica-coated ferrite nanoparticles in MFH therapy (Kumar et al., 2015). These nanoparticles were shown to have, high biocompatibility and colloidal stability, low toxicity and encapsulation efficiency. An *in vitro* study with HeLa cells showed that magnetic hyperthermia therapy at safe magnetic field parameters induced 80-85% apoptosis of cancer cells. The obtained results suggest the great potential of the developed magnetic nanosystems as innovative theranostic nanoprobes in the field of MHT (Kumar et al., 2015). The study carried out by Parekh and collaborators concerned the cytotoxicity of iron nanoparticles against HeLa cancer cells under the influence of a magnetic field. It was shown that after 24 hours of exposure to the magnetic field during MHT therapy, 75% of the cells died, confirming the significant effectiveness of heating iron nanoparticles (Parekh et al., 2019). Noteworthy, is that Albargi's research group evaluated the effectiveness of cobalt- and manganese-doped, hexagon-shaped iron oxide nanoparticles (CoMn-IONP) encapsulated in biocompatible PEG-PCL (poly(ethylene glycol)-b-poly(ε-caprolactone))-based nanocarriers in

hyperthermic magnetic therapy (Albarqi et al. 2019). In vitro results exhibited that MHT therapy with CoMn ions reduced tumor cell viability by 99%, in contrast to uncoated ions (efficacy lower by about 10%).

Preclinical studies carried out on animals (mainly rodents) indicate the significant and not yet fully recognized potential of magnetic hyperthermia as an effective therapeutic method for the treatment of breast, pancreatic, liver, prostate, colorectal, head and neck. and lung cancers, among others (Farzanegan, 2023).

A study on the efficacy of magnetic hyperthermia in the treatment of breast cancer (Kossatz et al., 2015) confirmed the effectiveness of iron oxide nanoparticles, delivered *in vivo* by injection into the tumor. The reduced activity of tumor cells, the highly effective heating potential of the nanoparticles in an alternating magnetic field and the increased cytotoxic effect of MNPs-based hyperthermia were demonstrated, resulting in a reduction in tumor cell colonization (up to 40% of the initial tumor volume) and, in many cases, complete tumor regression. Independently, at a breast cancer study (Pazouki et al., 2022) used Fe_3O_4 nanoparticles coated with carboxymethylchitosan (CMC) containing curcumin (CUR) to improve the drug delivery system. It was discovered that these nanoparticles combined with hyperthermia effectively inhibited cancer cell proliferation and significantly reduced their metabolic activity. It was found that the combination of MNP-CMC-CUR with hyperthermia can effectively inhibit the proliferation of MCF-7 cells. In turn, a study on the combination of hadron therapy with magnetic hyperthermia for the treatment of pancreatic cancer (Brero et al., 2020) used Fe_3O_4 nanoparticles delivered intratumorally in vivo by injection. An additive toxicity effect of about 50-60% was observed for cancer cells, which was due to a significant increase in DNA double helix breaks. Another pancreatic cancer study (Tansi et al., 2021) iron oxide was used, and the delivery of nanoparticles took place via hyaluronidase, which improved the penetration of MNPs into pancreatic cancer. This resulted in the destruction of tumor cells, which may confirm the effectiveness of this method in the treatment of pancreatic cancer. In a study on the efficacy of MFH in treating liver cancer (Arriortua et al., 2016), magnetite nanoparticles modified by adding 0.01 mg of tris(hydroxymethyl)aminomethane (TRIS) were used to block surface charges. When the alkyne-modified MNPs were combined with to the test molecule, a significant reduction in tumor viability was observed. Variable molecular weight polymer nanoparticles (VMWNPs) were used in a colorectal cancer study (Sarkar and Levi, 2021). VMWNPs were used to generate hyperthermia to enhance chemotherapy in colorectal cancer cells (CRC). The study showed that this treatment technique worked well even in resistant CRC cell lines. Magnetic hyperthermia, as a complementary method, increased the effectiveness of chemotherapy, leading to the destruction of drug-resistant tumor cells. A study on the efficacy of MFH therapy for head and neck cancer (Zhao et al., 2012) used an injection of iron oxide directly into the tumor. Effects included destruction of tumor cells, reduction in tumor size and increased survival of mice with intracranial glioma. A lung cancer study (Sadhukha et al., 2013) used inhalable iron oxide nanoparticles, resulting in significant inhibition of tumor cells. Targeted SPIONs were used, which were effectively retained in the tumor area by targeting epidermal growth factor receptor (EGFR), while limiting lung tumor growth in *in vivo* therapy. Recent scientific reports present a novel strategy combining magnetic hyperthermia with immunotherapy, demonstrating significantly effective potential in ablating the primary tumor and inhibiting tumor metastasis *in vivo*. The results confirmed that MFH can be an effective complementary therapy (Pan et al., 2020).

Following the promising results of MFH *in vivo* on animal models, clinical trials in humans were conducted. The first such study for the treatment of prostate cancer was performed by Johannsen in 2005. The results of this study indicate that applied hyperthermia with magnetic nanoparticles was well tolerated in a pilot study in previously irradiated patients with locally recurrent prostate cancer (Johannsen et al., 2005).

Summary

Magnetic hyperthermia is a promising method in the modern approach to cancer treatment. However, for MHT to become a widely used therapy, further research is needed to fully understand and optimize the efficacy of this innovative approach. Clinical and experimental studies are providing promising evidence of MHT's effectiveness in eliminating cancer cells, opening up new therapeutic possibilities. Despite the promising results, there are several issues that require further research and in-depth analysis. One major challenge is to determine the optimal conditions for hyperthermia to achieve maximum treatment efficacy with minimal side effects. In addition, it is necessary to understand the interaction between MHT and other forms of therapy in order to develop a comprehensive approach to cancer treatment. Prospects for the development of MHT in cancer treatment include the intensification of laboratory research, clinical trials and the exploration of inno-

vative technologies. The introduction of advanced magnetic nanoparticle delivery systems, precise techniques for imaging and monitoring the progress of therapy, and the development of new methods for evaluating the effectiveness of treatment are key to realizing the full potential of MHT. In perspective, the future of cancer therapy using MHT carries many potential applications that may result in revolutionary progress in the field of oncology.

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