Prospects for the use of hexagonal ferrite particles for targeted drug delivery and local heating of organic nanocontainers

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Abstract. Currently, it seems more promising to combine controlled drug delivery using liposomes or other agents in combination with ferrite nanoparticles for the treatment of oncological diseases. The release of drugs can be carried out by heating the particles with an alternating magnetic field. In this case, the local temperature can be set more precisely by selecting the chemical composition and structure of the ferrite in such a way as to obtain the necessary Curie temperature. Moreover, it is possible to concentrate nanoparticles in the desired area with extremely small dimensions using an oriented constant magnetic field. The article analyzes the existing methods of delivering antitumor antibiotics using magnetic nanoparticles, presents its own solutions in the field of magnetic transportation and tracking of nanocontainers, considers the problems of the depth of penetration of the magnetic field into the tissues of the body and minimizing their hyperthermia. The authors proposed to use magnetic particles of hexagonal strontium ferrite synthesized by cryochemical technology for controlled delivery and release by heating.

1. Introduction

Currently, the direction of targeted drug delivery is actively developing in medicine. In pharmacology, the concepts of vector and nanocontainer are often used. A vector is a device or molecule for targeted drug delivery. The main task of the vector is to ensure the flow of biologically active compounds (drugs, toxins, proteins, oligonucleotides, genes, etc.) into the target cells of the body, including the required intracellular compartment (nucleus, cytoplasm, organelles), into the focus of pathological damage, while simultaneously preventing the inactivation and manifestation of biological activity of these substances before accumulation in a given area [1].

In general, the vector includes a nanocontainer, in which therapeutic substances are packed, and a targeted delivery system located on the outer surface of the nanocontainer. In some cases (nanoconjugates, "two-faced" particles, nanosomes, multifunctional nanoparticles in medicine), this targeted delivery system (especially in molecular design in biopharmacology) is also called a vector. Nanoparticles made of biocompatible linear polymers (polyethylene glycol, polyactic acid, etc.) and branching polymers (dendrimers), liposomes, as well as viral particles devoid of the ability to reproduce...
are used as nanomaterials for creating vectors. The prospects of using fullerenes, nanotubes and other non-biological nanoobjects modified to make them biocompatible for these purposes are being studied. One of the variants of such modification is PEGylation, i.e. coating of nanoparticles with a polyethylene glycol (PEG) shell. To address nanocontainers, they are modified with molecules that recognize the surface receptors of target cells, for example, antibodies to these receptors, folic acid molecules, etc. [1-3].

Since the 1980s, the delivery of antitumor antibiotics using nanoparticles has been actively developed. Nanoparticles penetrate into the tumor due to the so-called "enhanced permeability and retention" effect (Enhanced Permeability and Retention, EPR). The EPR effect occurs due to excessive vascular proliferation (angiogenesis) caused by the tumor's need for oxygen and nutrition [1-3]. During pathological angiogenesis, pores up to 200 nm in diameter appear in the vessel walls. Also, the growth of the tumor causes compression of the lymphatic vessels and prevents the normal outflow of intercellular fluid. Nanoparticles penetrate the tumor through the pores and cannot leave it due to impaired drainage. The path of entry into the cancer cells themselves is determined by the material of the nanoparticle.

A number of authors [4] evaluated biocompatible superparamagnetic nanoparticles with a diameter of 6-12 nm and their preparation at a Curie temperature in the range of 44-47 °C, which allows for self-regulating temperature control in an alternating magnetic field. Thus, the problem of temperature control can be partially solved. Currently, all magnetic particles used in medicine are biocompatible stabilized magnetic liquids based on Fe₃O₄ nanoparticles with a Curie temperature of Tₐ = 585°C [5-10]. Currently, there is no suitable magnetic material for the preparation of ferrofluids with an ideal Curie temperature (Tₐ = 44-47°C). But different systems of ferrite-spinels with different properties depending on the composition and the simplicity of synthesis using the method of chemical co-deposition seem to be suitable for research. Recently, a ferrofluid prepared for technical applications and based on Mn-Zn ferrite nanoparticles substituted with Gd was synthesized by the method of co-deposition [9, 10] with a relatively low TC (about 100°C). Therefore, there are good chances for the further development of such "advanced" ferrite nanoparticles with the desired magnetic properties.

We propose to use ferrite particles for controlled delivery and release by heating. During the last experiments [4], we obtained submicron (350-500 nm) ferrite particles with the necessary characteristics and a suitable composition. Now we are working on reducing the particle size. The cryochemical synthesis technology we used earlier seems to be effective for the transition to nanoscale particles. The synthesis of samples of W-type hexagonal ferrites was carried out using the cryochemical technology described in detail in [5].

There are at least 3 mechanisms by which magnetic materials generate heat in an external alternating magnetic field [6]. Superparamagnetic nanoparticles with a size of about 10-25 nm are characterized by heat generation through relaxation losses. Such losses occur according to two models: the Neel model and the Brown model. As a result of the Neel relaxation, the magnetic moments initially fixed along the crystal axis rotate from this axis to the applied field. Due to the movement of the magnetic moment inside the particle, "internal friction" occurs, which leads to the release of heat. Heat is released by the Brownian mechanism as a result of the physical rotation of the particle in an external magnetic field with a moment fixed along the axis of the crystal, under the action of a thermal force against a viscous resistance in a liquid medium. This mechanism is a component of the mechanical thorn in this environment [6].

The energy P dissipated by nanoparticles in an external alternating magnetic field is described by the formula:

\[
P = \pi\mu_0\chi_0 H^2 f \frac{2\pi f \tau}{1 + (2\pi f \tau)}
\]

where \( H \) and \( f \) are the amplitude and frequency of the applied magnetic field, respectively, \( \chi_0 \) is the equilibrium magnetic susceptibility, \( \tau \) is the effective relaxation time, consisting of 2 values of the non-Yell relaxation time \( \tau H \) and the Brownian relaxation time \( \tau B \):
\[ \tau^{-1} = \tau_N^{-1} + \tau_B^{-1} \]  \hspace{1cm} (2)

which are described by the following expressions:

\[ \tau_N = \frac{\sqrt{\pi}}{2} \frac{\tau_0 \exp(\Gamma)}{\sqrt{\Gamma}} , \]

\[ \tau_B = \frac{3\eta V_H}{kT} \]

где \( V_H \) – гидродинамический объем магнитных наночастиц, \( k \) – постоянная Болцмана, \( \Gamma \) – магнитная анизотропия.

Hysteresis losses leading to the release of heat are characteristic of large nanoparticles (about 100-200 nm), usually ferromagnetic, and multi-domain nanoparticles. Heat generation in this case occurs as a result of the heterogeneity of the magnetization processes, which is associated with the lag of the change in the magnetization vector when the applied magnetic field strength vector changes [6].

Hysteresis losses can be determined by integrating the area of the hysteresis loop, which is a measure of the scattered energy per magnetization cycle. Such losses depend on several factors, including the amplitude of the applied field, the size of the magnetic nanoparticles, the magnetic background of the sample, etc. But this is not the only way to evaluate them. In [6], the following formula is proposed for calculating the heat capacity generated by magnetite:

\[ Q = k_m f D_w B^2 \frac{Bm}{M_d} \]  \hspace{1cm} (3)

where \( D_w \) is the mass density of nanoparticles, \( f \) and \( B \) are the frequency and induction of the applied magnetic field, respectively, \( k_m \) is the magnetic coefficient.

Induction heating of particles, which occurs when eddy currents flow in their volume, is characteristic of particles of a fairly large size (about 1 microns) made of electrically conductive materials, such as gold, silver, etc. In the case of the dominance of such a heating mechanism, the dissipated power is calculated by the formula:

\[ P = \frac{\pi B_p^2 f^2 d^2}{6k \rho D} \]  \hspace{1cm} (4)

where \( B_p \) is the magnetic induction in Tl, \( d \) is the size of the nanoparticle, \( f \) is the frequency of the magnetic field, \( \rho \) is the resistance of the nanoparticle material, \( D \) is the density of the material.

2. Results and discussion

We have obtained particles of hexagonal ferrite powder, the appearance and magnetic characteristics of which are presented below. Figure 1 shows the morphology of strontium hexaferrite particles.
Figure 1. Micrographs of samples of the composition $\text{SrNi}_{0.6}\text{Co}_{1.4}\text{Fe}_{16}\text{O}_{27}$ (1200 °C, 10 hours).

The particle size distribution was calculated from micrographs. The histogram of the particle distribution is shown in Figure 2.

Figure 2. Histogram of particle size distribution for a sample of the composition $\text{SrNi}_{0.6}\text{Zn}_{1.4}\text{Fe}_{16}\text{O}_{27}$ (1300°C, 10 hours).

High-temperature annealing of the powder leads to an increase in the coercive force, which is due to the formation of a submicrocrystalline structure. The powders obtained by such processing are not prone to texturing in a magnetic field, due to the formation of randomly oriented crystallites of strontium hexaferrite in the powder particles. This leads to an increase in the coercive force ($\mu_0H_{\text{si}}$) to 0.42 - 0.45
T (with a crystallite size of 130-150 nm), which is approximately 3 times higher than that of powders obtained by traditional technology.

The coercive force was measured by induction method in a field with a strength of up to 9000 oersted. The hysteresis loops were removed using a Permagraph C hysteresis scanner.

Figure 3. The limit hysteresis loop measured for a sample of the composition SrNi_{0.4}Co_{1.6}Fe_{16}O_{27}, 1200°C 4 hours.

Figure 4. The limit hysteresis loop measured for a sample of the composition SrNi_{0.4}Co_{1.6}Fe_{16}O_{27}, 1200°C 10 hours.
Figure 5. The limit hysteresis loop measured for a sample of the composition \( \text{SrNi}_{0.4}\text{Co}_{1.6}\text{Fe}_{16}\text{O}_{27} \), 1300 °C 4 hours.

Figure 6. The limit hysteresis loop measured for a sample of the composition \( \text{SrNi}_{0.4}\text{Co}_{1.6}\text{Fe}_{16}\text{O}_{27} \), 1300 °C 4 hours.
Dependence of the coercive force on the temperature and duration of annealing for a sample of the composition $\text{SrNi}_{0.4}\text{Co}_{1.6}\text{Fe}_{16}\text{O}_{27}$ is shown in Figure 7.

**Figure 7.** Dependence of the coercive force on the temperature and duration of annealing.

### 3. Conclusion

The paper analyzes the possibility of using submicron and nanoscale particles of W-type hexagonal strontium ferrite to solve problems of targeted drug delivery with subsequent heating using an alternating magnetic field. The results of experiments on the synthesis of magnetic powders and the determination of the coercive force allow us to speak about the possibility of controlling the magnetic characteristics of powder particles by changing the temperature and duration of annealing. This approach will allow us to obtain the magnetic particles necessary for the formation of controlled nanocontainers with a narrow size distribution and the necessary magnetic characteristics that provide the possibility of heating to a strictly set temperature.

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