The Pharmaceutical and Chemical Journal, 2021, 8(2):1-5

Available online www.tpcj.org

Research Article

ISSN: 2349-7092
CODEN(USA): PCJHBA

Ferrite Magnetic Nanoparticles in the Design of Novel Drug Delivery Systems

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Abstract The expediency of using the method of chemical condensation as a method of synthesis of ferrite nanoparticles for their use in drag delivery systems with magnetic properties has been proved. Partial replacement of iron (II) cations of magnetite $Me_x^{2+}Fe_{1-x}^{2+}Fe_2^{3+}O_4$ allows carry out synthesis in one stage without additional high-temperature ferritization. The particles synthesized according to this scheme have a size of up to 20-30 nm and the high magnetic parameters. When studying the functional parameters of the synthesized ferrites, the extreme nature of the dependence of the content of the substituent cation in the structure of ferrites on its properties with a maximum at x = 0.4.

Keywords ferrite nanoparticles, magnetic drug delivery system

Introduction

The creation of fundamentally new drugs for the prevention and treatment of various diseases is one of the most pressing problems of nanomedicine and nanopharmacy today [1-6]. New terms have appeared that today indicate the directions of development of pharmacy - nanopharmacy, targeted drug delivery.

Targeted drug delivery systems are being developed to optimize medical practice. The system is based on a method that ensures the delivery of a therapeutic agent to a damaged area of the body for a prolonged therapeutic effect, avoiding any damage to healthy tissues by the action of drugs. Targeted drug delivery systems are a highly integrated field of science that brings together various disciplines such as chemistry, biology, physics, medicine, and pharmacy. In the case of using nanoparticles with magnetic properties for such purposes (magnetic targeted drug delivery), the possibility of creating "smart" magnetically controlled drugs opens up.

The main requirements for highly dispersed ferrite materials for medical and biological purposes are: biological compatibility, given by the chemical composition; the dispersion of the powder, depending on the production technology; high magnetic susceptibility, given by high saturation magnetization at a low value of the magnetic anisotropy field; superparamagnetic state, determined by the volume of particles, the constant of magnetic anisotropy, temperature, and external magnetic field. The use of various ferrites (ferritic acid salts $Fe_2O_4^{2-}$), particularly synthetic particles of magnetite ($FeFe_2O_4$), makes it possible to successfully solve this rather complex multifactorial problem.

Given the rapid rate of development of magnetic nanotechnology in pharmacy, the establishment of the conditions for the synthesis of magnetic nanoparticles of various compositions for pharmaceutical preparations is of actual practical importance. For this purpose, comprehensive studies of the possibilities of the chemical condensation

method as a method for the synthesis of ferrite nanoparticles of various compositions and structural types were carried out.

The aim of this work is to analyze the development of nanotechnology in pharmacy, to develop conditions for the synthesis of ferrite nanoparticles - components of drugs with magnetic properties and to investigate chemical coprecipitation method for synthesis ferrite particles in design novel magnetic drug delivery systems.

Materials and Methods

In the experimental work, particles of ferrite various structural types and composition shave been synthesized by chemical condensation method. Based on the results of previous studies, the methodology of the synthesis has been established [7-12]. The reaction has been conducted by using solutions of the corresponding metal cations (99.99% purity, Aldrich) in an alkaline medium. The X-ray diffraction patterns of the samples were recorded on a Siemens D500 X-ray powder diffractometer using copper radiation. Slow scans of the selected diffraction peaks were carried out in the step mode (step size 0.03°, measurement time 75 s). The crystallite size of the nanocrystalline samples was measured from the X-ray line broadening using the Debye-Scherrer formula. Magnetization measurements were performed in a vibrating sample magnetometer at 300 K using a superconducting magnet to produce fields up 2 kOe. The samples were analyzed in a PEM-125k transmission electron microscope.

Results and Discussions

Figure 1 shows an illustration of the prospects for the development of the world market for goods and services of the three main directions of nanotechnology in medicine - the result of the work of scientists from the United States and Germany, presented in the scientific work "Nanotechnology in medicine" [4, p. 26], where the results are analyzed and the prospects for the development of this issue throughout the world are presented.

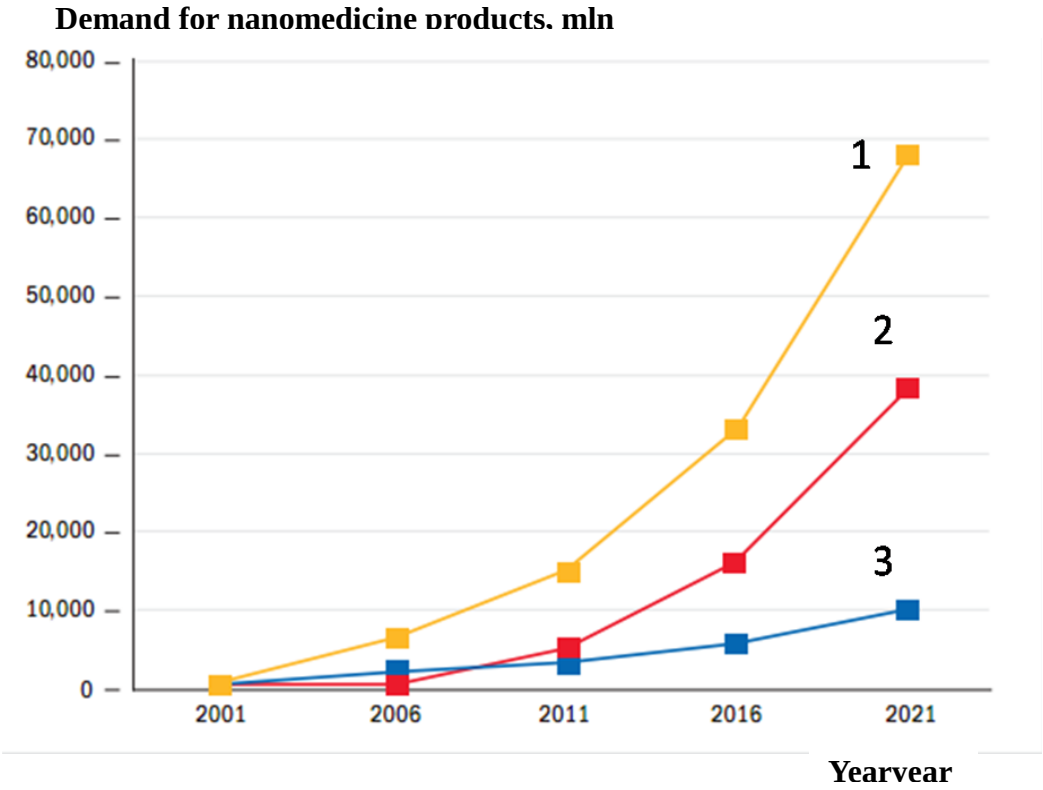

Figure 1: Prospects for the development of nanotechnology in medicine: targeted drug delivery (1), medical materials and implants (2), diagnostics, including analysis tools and instruments (3)

Targeted drug delivery is at the forefront of nanomedicine today, which is projected to increase by 80% by 2021 (Figure 1). Combining the two concepts (nanopharmacy and targeted drug delivery), a scientific direction for the development of nanotechnology in pharmacy appears - magnetic nanopharmacy. The use of nanoscale magnetic materials in pharmaceuticals is one of the common topics of nanopharmacy today [1-3, 5, 6].

A drug with magnetic properties solves the targeted delivery of an active substance, its fixation in the pathological zone, opens up new prospects for the development of medical and pharmaceutical science. Today, magnetic nanoparticles are the focus of the attention of many researchers, along with other objects of nanopharmacy, such as fullerenes and carbon nanotubes. This is confirmed by the extremely high number of publications related to the study of magnetic nanoparticles, which has grown 8 times over the past fifteen years (analysis of data from the search engine SciFinder Scholar, using keywords "magnetic nanoparticles").

Already nowday, the development and production of magnetic micro-and nanoparticles in the composition of drugs are most actively engaged in by American and some European companies: Bangs Laboratories, Polysciences Inc. Magforce Nanotechnologies AG [13].

The method of chemical condensation, in which ferrites are obtained from aqueous solutions of metal cation salts in an alkaline medium, has a number of advantages. When mixing and settling the components in the liquid phase, a high dispersion and close contact is achieved, and a uniform distribution of the constituent components of the ferrite particles is ensured. As a consequence, the synthesis products are characterized by the reproducibility of the chemical composition and properties. The method allows one to obtain particles of the nanoscale range, which corresponds to their superparamagnetic state.

The synthesis method involves the process of magnetic separation of synthesis products in solution. Under these conditions, by-products of the reaction (taking into account their paramagnetic properties) are completely evacuated from the reaction mixture. The synthesized ferrite particles have a minimum of impurities, which is important for their use in pharmacy and medicine. Moreover, this method is quite affordable, simple and cheap, does not require complex and expensive chemical equipment. Based on this, the method can be successfully applied to the synthesis of magnetic components of drugs.

In this work, magnetite particles were obtained by coprecipitation of iron (II) and (III) salts in an ammonium hydroxide medium according to the reaction equation:

$$Fe^{2+} + 2Fe^{3+} + 8OH^- = Fe_3O_4 + 4H_2O$$

Using the structure of magnetite $Fe^{3+}Fe^{2+}{}_3O_4$ as the base structure, the substitution of the iron (II) cation with another divalent metal cation (Me) leads to the production of completely $Me^{2+}Fe_2O_4$or partially substituted $Me_x{}^{2+}Fe_{1-x}{}^{2+}Fe_2{}^{3+}O_4$magnetite. Doping of magnetite with cations of other metals will make it possible to simultaneously solve several problems. A multicomponent ferrite particle in this case is a depot of not only iron, but also other microelements, which ensures the synergism of their action. The use of ferrites of various compositions, as well as their mixtures, opens up prospects for the creation of magnetic materials that will have predictable properties in advance.

The complete replacement of Fe^{2+} ions of the magnetite structure with other divalent ions in the synthesis of ferrites by chemical condensation leads to a slowdown in the aging of the precipitate and the need for its calcination to complete the ferritization process (formation of a certain crystal lattice and magnetic properties). It has been established that the preparation of completely substituted spinel magnetite particles with Cu^{2+}, Mn^{2+}, Ni^{2+}, Co^{2+} cations, as well as Ba^{2+}hexaferrite particles can be carried out in two stages: coprecipitation of the starting materials in an alkaline medium and high-temperature feritization of coprecipitation products:

$$Cu^{2+} + 2\ Fe^{3+} + 8\ OH^- = CuO\times\ 2Fe(OH)_3 + H_2O$$

$$CuO\times 2Fe(OH)_3 \xrightarrow{t^\circ} CuFe_2O_4 + 3H_2O$$

The synthesis of highly dispersed ferrite particles of partially substituted spinel magnetite was carried out using zinc cations and bivalent cations of the ferum triad:

$$2Fe^{3+} + yFe^{2+} + xMe^{2+} + (6+x+2y)\ OH^- \rightarrow Me_xFe_yFe_2O_4 + (6+x+y)\ H_2O$$

Partial replacement of iron (II) cations allows the synthesis of magnetic particles to be carried out in one stage without additional high-temperature ferritization. The particles synthesized according to this scheme have a size of up to 20-30 nm and higher value of magnetic properties (Figure 2, Table 1). When studying the functional parameters of the synthesized ferrites, the extreme nature of the dependence of the content of the substituent cation in the structure of ferrites on its properties with a maximum atx = 0.4.

Table 1: The parameters derived from X-ray diffraction pattern and saturation magnetization of the ZnMNPs

Chemical composition	**Mol. mass, (g/mol)**	**Lattice parameter a (Å)**	**X-ray density (g/cm^3)**	**Crystallitesize and microstrain, nm/ %**	**Saturation magnetization (emu/g)**
$FeFe_2O_4$	232.0	8.3560(3)	5.2854	10.8/0.14	67.4
$Zn_{0.2}Fe_{0.8}Fe_2O_4$	233.8	8.3773(4)	5.2931	7.8/0.60	65.8
$Zn_{0.3}Fe_{0.7}Fe_2O_4$	234.7	8.3841(13)	5.2935	7.0/0.90	54.9
$Zn_{0.4}Fe_{0.6}Fe_2O_4$	235.6	8.3906(3)	5.3054	9.2/0.17	75.2
$Zn_{0.5}Fe_{0.5}Fe_2O_4$	236.5	8.3850(10)	5.3352	5.8/0.50	63.2

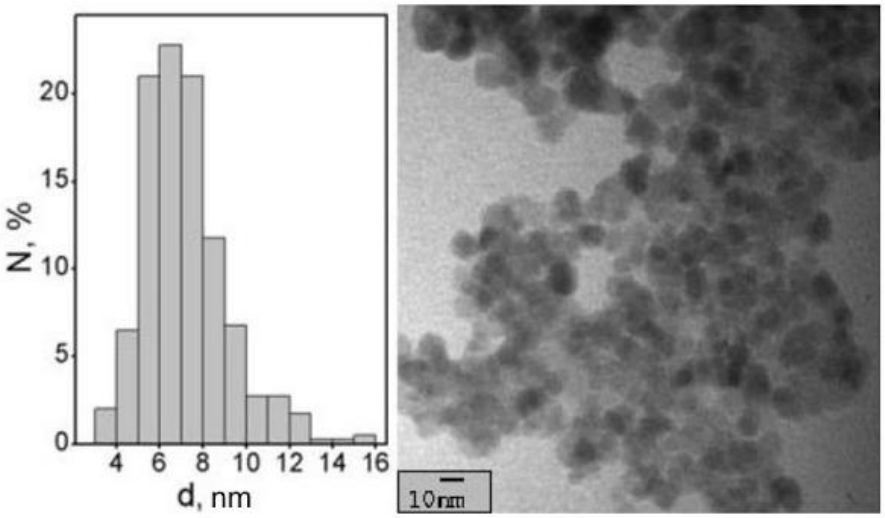

Figure 2: Electron microscopy image of the powder zinc ferrite particles and their size distribution for the composition x= 0.4

As a result of the studies carried out, a universal methodology for the synthesis of partially substituted spinel magnetite particles of the type $Me_xFe_{3-x}O_4$, substantiated the expediency of introducing a substituent cation with a concentration of 40% to obtain effective changes in the functional properties of the synthesized structures.

The established combination of high functional characteristics of synthesized ferrite particles - high magnetization with a particle size of several nanometers, allows the obtained particles to be recommended for use in drugs with magnetic properties.

Conclusions

The scientific direction of the development of modern nanopharmacy - the creation of magnetic drugs, certainly has the prospect of its development all over the world. This is confirmed by numerous publications and international conferences on this issue. As world practice shows, the long, thorny path "from idea to development and subsequent implementation into production" can be significantly reduced by cooperation within the framework of scientific programs and projects. With such cooperation, the contribution of biomedical and pharmaceutical nanotechnologies, which originated at the turn of the 20th and 21st centuries, according to forecasts, will reach its highest level in 2025–2035.

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