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# BIOCOMPOSITE CONTAINING FUCOIDAN FOR DRUG DELIVERY

**Suprunchuk V. E.*, E.V. Denisova, S.F. Andrusenko and E.A. Melchenko**

*North-Caucasus federal university, Stavropol, Russia*
* E-mail:vikasuprunchuk@gmail.com

## ABSTRACT

Therapeutic agents target delivery may enhance the effectiveness of drug action and at the same time reduce a number of side effects. Therefore, the development of drug delivery systems using natural polymers is a burning problem. A high-molecular-weight polymer, fucoidan in particular, along with magnetic particles was used for the research. The hydrodynamic radius of the obtained biocomposites was studied using the dynamic light scattering. The results show that with the increase in magnetic nanoparticles in specimens, electrokinetic potential grows. High proportion of polysaccharide in the obtained systems may provoke a high biological activity and matrix biocompatibility.

**Key Words:** Fucoidan, magnetite, biocomposite, target delivery, functionalization

## INTRODUCTION

Biocomposites can be practically applied in a variety of fields, for instance, medical and pharmaceutical material formation. Biodegradable nanocomposites capable of magnetic guidance represent a new class of functional materials with controlled parameters which enhance the scope of application. In this regard, the usage of polysaccharides in such systems as an alternative to synthetic polymers allows for the exclusion of toxic solvents (Talgatov, 2016), and a number of reactive groups in each unit of their structure allow for the formation of stable complexes with a variety of compounds. Such hybrid polysaccharide inorganic systems along with the magnetic field control can be used as bioactive substances in the target therapy, including a thrombolytic agent, and they fall within the domain of magnetic pharmacology. What is more, it is preferable to use the magnetic field for the target delivery due to the limited depth of ultrasonic wave penetration into tissues (Elbialy *et al.*, 2015; Oberti *et al*., 2010), and strong electric fields contribute to damage of nerve and muscle tissue cells (Elbialy *et al.*, 2015; Schaefer *et al.*, 2000).

Active targeting of drugs to a target site under the action of a magnetic field allows for its local action by decreasing the system toxicity of the drug as well as for the improvement of enzyme effectiveness. Different approaches are used in order to design such systems.

Using such polysaccharide as fucoidan as nanobiocomposite matrix will allow for the creation of a unique bioactive, biocompatible and biodegradable material. Fucoidan is a highly sulfated heteropolysaccharide with L-fucose being the main monosaccharide residue. It boasts a wide range of bioactivities and is used as a component in the development of drug delivery system (Elbialy *et al.*, 2015; Talgatov, 2016), including the combination with magnetite nanoparticles, where the polysaccharide appears only as a hydrophilic coating which changes physical and chemical characteristics of the surface (Oberti *et al*., 2010; Schaefer *et al.*, 2000). According to the literature data, the biopolymer has a variety of bioactivities, namely antimicrobial and anti-inflammatory effect, it allows for the neogenesis owing to the interaction with growth factors (the main growth factor of fibroblasts (bFGF) and the transforming growth factor -β (TGF-β)) (O'Leary and Rerek, 2004; Sezer and Cevher, 2011; Khotimchenco, 2014; Yanagibayashi *et al*., 2012), increases the regeneration and re-epithelization rate (Sezer *et al*., 2008), which provides significant advantages over the other polysaccharides in use. Thus the fucoidan appears to be a promising polymer for the creation of new medical materials with targeted properties, including the formation of active targeting delivery systems.

Concurrently, magnetic particles, namely magnetite nanoparticles, are a promising component when developing delivery systems due to the biocompatibility, low cost and simplicity of the synthesis, functioning as a targeting agent (Goswami, 2016). However, in spite of physiological inactivity of the particles in question, they can hardly be applied as drug carriers since they can easily be absorbed by the reticuloendothelial system in the blood stream as a result of opsonization (O'Leary and Rerek, 2004) and their small size. On the other hand, fucoidan functionalization by such particles will allow for the increase in time of magnetite nanoparticles circulation in the blood stream by the inhibition of this process (Sezer and Cevher, 2011). It is important to note that in the literature there is no information about inorganic nanoparticle functionalization of macromolecules of fucoidans, used as drug delivery systems.

## MATERIALS AND METHODS

One mL of a 2% $Fe_2O_3$ suspension was added dropwise to a 10 mg / mL solution of fucoidan of a given volume, at room temperature and stirring. The resulting volume was brought to 10 mL and stirred on a shaker for 2 hours. The volume of the polysaccharide solution was calculated from the change in the ratio magnetite: fucoidan 1: 2.5 (FM1); 1: 5 (FM2); 1: 100 (FM3); 1: 150 (FM4). A solution of fucoidan was prepared by dissolving the polysaccharide in 0.1 M phosphate-buffered saline (PBS) (pH 7.4). Two percent $Fe_2O_3$ suspension was prepared in accordance with the method of chemical coprecipitation of $Fe^{2+}$ and $Fe^{3+}$ ions in the presence of $NH_3$ at room temperature (Khotimchenco, 2014).

The study of the hydrodynamic radius of the particles was estimated by the method of dynamic light scattering (DLS). Zeta-potential and hydrodynamic diameter were measured using Photocor Compact Z (Fotokor LLC, Russia) at 23°C using «Dynals» software. The measurement was carried out at 23°C at an angle of 20° and a radiation power of 10 mV; in determining the zeta potential, a carbon electrode and a voltage of 10 V/cm were used.

## RESULTS AND DISCUSSION

Nanobiocomposites, as nanocomposites containing natural polymers as well as inorganic fragments, represent a separate class of compounds that have improved functional features, and appear as a new group of nanostructured hybrid materials (Khan *et al*., 2017; Li *et al*., 2014). The usage of polysaccharides for the creation of such structures will allow for the compliance with the green chemistry principles during their formation as an alternative to synthetic polymers, which eliminates the usage of toxic solvents (Talgatov, 2016). The literature data provide evidence of a variety of polysaccharide bioactivities, and the presence of several reactive groups for each unit in their structure allows for the formation of stable complexes with many compounds. The creation of composites using metal nanoparticles and their oxides also arouses heightened interest due to the appearance of unique physical and chemical properties. The presence of inorganic component allows for the regulation of targeting system by ultrasound, magnetic or any other effect (Talgatov, 2016; Antipina, 2016).

Therefore, the creation of Nanobiocomposites containing polysaccharide as a matrix along with inorganic magnetite nanoparticles is of special interest in the field of drug delivery system development.

In the research it was planned to form a delivery system as a matrix-carrier of an enzyme agent by combining macromolecules of low-molecular-weight fucoidan, obtained upon the high-intensity ultrasound treatment, with magnetite nanoparticles. As a result of self-assembly it was expected to obtain particles with a sphere-like shape.

The size measurements of the obtained particles using dynamic light scattering showed that the hydrodynamic diameter of the obtained sol particles changes from 150 to 230 when varying fucoidan and magnetic nanoparticles ratio in the system (Table 1). The increase in fucoidan concentration in the system leads to the increased hydrodynamic diameter of the formed particles due to the fact that alongside the interaction of magnetic nanoparticles $Fe_2O_3$ with fucoidan polysaccharide chains, there occur fucoidan-fucoidan and fucoidan-composite multiple intermolecular association accompanied by the formation of aggregates. The observed electrochemical potential decay also contributes to the latter process. Fucoidan functionalization by magnetite leads to the increased zeta-potential from -7 mV to 11 mV, which will facilitate further immobilization of some enzyme agents.

Table 1. Fucoidan/magnetite carrier properties.

| | **FM1** | **FM2** | **FM3** | **FM4** |
|---|---|---|---|---|
| Hydrodynamic diameter, nm | 149 | 155 | 190 | 230 |
| Zeta-potential, mV | 10,7 | 8,5 | 7,7 | 7,1 |
| Nanobiocomposite yield (%) | 30 | 15 | 14,5 | 9 |

The amount of applied magnetite was determined by gravimetric analysis following the thermal decomposition of synthesized particles, with the polysaccharide degradation carried out at 200 °C. Fucoidan addition into the composite was estimated by the amount of polysaccharide in the supernatant. A greater quantity of applied magnetite is observed for *FM1* specimens. With the increase in proportion of magnetic nanoparticles in specimens the electrokinetic potential growth is observed. Moreover, the results showed that *FM1* specimens also have the best polysaccharide: magnetite mass ratio suitable for the creation of magnetic nanocomposite carriers with a high grade of magnetite concentration and the smallest size (Table 1).

In conclusion, the research proposes the first developed method of synthesis of magnetically operated biocompatible nanocomposite systems applicable for the drug delivery based on a natural polymer – fucoidan. Particles with the minimum mean hydrodynamic radius 150 nm were obtained during the research. This method of drug delivery system formation is quick and simple. It is realized in the aqueous solution without toxic solvents. The obtained results can be applied for the theranostics drug development, target delivery of antitumor agents in particular, MRT diagnostics as a contrast agent. Further research will aim at studying the possibility of immobilization of enzyme drugs applied in thrombolytic therapy. The application of active targeting of some antiblast drugs, in particular such an antitumor antibiotic as doxorubicine, will also be studied.

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