**Dissertation title**

Processes of obtaining organic aerogels based on sodium alginate and compositions on their basis

**A detailed abstract**

The Ph.D. thesis is devoted to experimental and theoretical studies of the processes of obtaining organic aerogels based on sodium alginate and compositions on their basis using supercritical fluid technologies. The urgency of the work is due to the need to create new highly porous materials with a developed internal structure for use in various fields of science and industry. Examples of such materials are aerogels that possess such unique properties as high specific surface area (200-1500 $m^2/g$), high porosity (up to 99%), low density (0.003 - 0.5 $g/cm^3$). Due to the above-mentioned unique properties, it is possible to impregnate various substances into aerogels: active pharmaceutical ingredients, aromatic oils, additives for the food industry, vitamins and many others, which makes it possible to use aerogels and compositions based on them in such industries as food, pharmaceutical, and also in medicine. Of particular interest are organic aerogels in the form of particles that can be used to solve a number of problems in the pharmaceutical industry, namely, they can be used as modern drug delivery systems. To date, there is no industrial production of organic aerogel particles. Thus, studies that would make it possible to transfer the processes of obtaining organic aerogels particles from the laboratory to the industrial level are extremely relevant.

In the course of the Ph.D. thesis, the following scientific and technical problems were solved:

1. Experimental studies of the processes of obtaining organic aerogels particles based on sodium alginate by laboratory (emulsion-gelation and dripping methods) and semi-industrial methods (high-pressure homogenization and spraying) are carried out. Analytical studies of the aerogel particles obtained were carried out and the factors influencing the characteristics of the obtained samples were evaluated. Based on the data obtained, the possibility of a large-scale transition from laboratory to semi-industrial level for the production of aerogel particles based on sodium alginate is shown.

2. A method has been developed for combining the processes of solvent exchange under pressure (using carbon dioxide) and supercritical drying in one apparatus. To solve this problem, a study was carried out of the solvent exchange process in alginate gel particles under normal conditions, a theoretical study was carried out of a three-component system «carbon dioxide-water-isopropyl alcohol» at different pressures and the parameters for conducting the solvent exchange process under pressure in a carbon dioxide medium. Based on the results of the conducted studies, it is shown that the proposed method allows to reduce the solvent exchange time by more than 5 times in comparison with the traditional solvent exchange. The combination of solvent exchange processes under pressure in carbon dioxide medium and supercritical drying in one apparatus was realized,

which made it possible to shorten the time of the process of obtaining aerogel particles as a whole.

3. Mathematical modeling of supercritical drying of aerogel particles based on sodium alginate was carried out. Using the mathematical model, the effect of the carbon dioxide consumption and the size of the dried particles on the course of the supercritical drying process using a mathematical model was studied.

4. A complex study of the process of supercritical adsorption of active pharmaceutical ingredients into aerogel particles based on sodium alginate was carried out. Ketoprofen, loratadine and nimesulide were chosen as model active substances. The compositions «aerogel-active substance» were obtained and the analysis of the factors influencing the value of the mass loading of active substances into aerogels was carried out. For each composition obtained, the number of adsorption layers was calculated. The experimental isotherms of adsorption of ketoprofen into aerogel particles based on sodium alginate were obtained for the first time. Using the obtained isotherms and data presented in the world scientific literature, the most suitable equations for describing the supercritical adsorption process are chosen.

5. The possibility of using the obtained compositions «aerogel-active substance» as drug delivery systems has been investigated. Within the framework of this part of the work, an investigation of compositions «aerogel-active substance» was carried out by X-ray analysis for the evaluation of the state of adsorbed substances. Eighteen X-ray diffraction patterns were obtained for the compositions obtained with different mass loading values. The results of this study showed that the corresponding active substances in the aerogel compositions are in an amorphous state, the stability of which was confirmed after 6 months of storage. The analysis of factors influencing the state of adsorbed active substances in various compositions «aerogel-active substance» was carried out. In order to confirm the possibility of using the obtained compositions as drug delivery systems, an In Vitro study of the kinetics of the release of active substances was carried out. Comparison of the aerogel active substance release profiles with the release profiles of the initial pharmaceutical substances showed a reduction in the release time of 50% of the active substance to 6.6 times. It has been shown that supercritical adsorption of active substances into aerogel particles makes it possible to obtain compositions with improved pharmacokinetic properties in which the active substances are in a stable amorphous state.

**Highlights of the Ph.D. work**

A study of the processes of obtaining organic aerogels particles based on sodium alginate by oil-emulsion and dripping methods was made. The factors influencing the characteristics of the obtained samples are estimated. These methods for obtaining gel particles based on sodium alginate are implemented at the semi-industrial level using high-pressure homogenization and spraying through pneumatic nozzles. The obtained results can be used for large-scale transition from laboratory to semi-industrial level for the production of aerogel particles based on sodium alginate

The properties of the three-component system «carbon dioxide-water-isopropyl alcohol» at different pressures are theoretically investigated. Steps have been chosen for carrying out the process of the solvent exchange under pressure in a carbon dioxide medium to shorten the time of this process. It is shown that the proposed method allows to reduce the solvent exchange time by more than 5 times in comparison with the traditional solvent exchange. Theoretically and experimentally proved the possibility of carrying out processes of solvent exchange and supercritical drying in one apparatus, which allows to ensure resource and energy saving and to shorten the time of the process of obtaining aerogel particles based on sodium alginate.

A mathematical model of the supercritical drying process is developed to describe the drying process of gel particles based on sodium alginate; the model makes it possible to investigate the local heat and mass transfer within the apparatus of arbitrary geometry, the model can be used to develop new designs for high-pressure apparatuses.

The process of supercritical adsorption of active pharmaceutical ingredients into aerogel particles based on sodium alginate has been studied: various compositions have been experimentally obtained: «aerogel - ketoprofen», «aerogel - nimesulide», «aerogel - loratadine». Factors affecting the mass loading of active substances into aerogel particles based on sodium alginate were investigated. The the number of adsorption layers for the resulting compositions of «aerogel - ketoprofen», «aerogel - nimesulide», and «aerogel - loratadine» has been calculated to estimate the possible adsorption mechanism.

X-ray analysis was conducted for the compositions «aerogel-ketoprofen», «aerogel-nimesulide», «aerogel-loratadine», according to which the adsorbed active substances are in a stable amorphous state, including after 6 months of storage.

On the example of the test «Dissolution», which was conducted in accordance with the relevant pharmacopoeia articles, an improvement in the release kinetics for these compositions is shown, namely, a reduction in the release time of 50% of the active substance to 6.6 times as compared with the corresponding active substances in the crystalline state. These compositions can be used in the pharmaceutical field as drug delivery systems.

**The list of the most relevant publications linked to the Ph.D. work, already published or in press**

**1.** Menshutina N.V., Lovskaya D.D., Lebedev A.E., Lebedev E.A. Production of Sodium Alginate-Based Aerogel Particles Using Supercritical Drying in Units of Different Volume // Supercritical fluids: Theory and Practice. 2017. V. 12, I. 2, 35-48 pp.

**2.** Lovskaya D.D., Lebedev A.E., Menshutina N.V. Aerogels as drug delivery systems: In vitro and in vivo evaluations // The Journal of Supercritical Fluids. 2015. V.106, 115-121 pp.

**3.** Menshutina N., Lebedev A., Khudeev I., D. Lovskaya. Supercritical drying process modeling and equipment design // 17th International Multidisciplinary Scientific GeoConference SGEM. 2017.
**4.** Solovieva A. B., Kopylov A. S., Savko M.A., Zarkhina T. S., Lovskaya D. D., Lebedev A.E., Menshutina N.V., Krivandin A. V., Shershnev I.V., Timashev S. L. Photocatalytic properties of tetraphenylporphyrins immobilized on calcium alginate aerogels // Scientific reports. Nature Publishing Group (United Kingdom), 2017. V.12, № 7, 1-10 pp.
**5.** N.Menshutina, S. Ivanov, D. Lovskaya, V. Saprina, A.Lebedev. Process of production of aerogels based on polysaccharides for medical applications // 16th International Multidisciplinary Scientific GeoConference SGEM. 2016. B.6. V.1.
**6.** Larchenko E.Yu., Khonina T.G., Shadrina E.V., Pestov A.V., Chupakhin O.N., Menshutina N.V., Lebedev A.E., Lovskaya D.D., Larionov L.P., Chigvintsev S.A. Pharmacologically active hydrogels derived from silicon glycerolates and chitosan // Russian Chemical Bulletin. 2014. V. 63, I. 5, 1225-1231 pp.

**Laboratory and supervisor names and address**
Dmitry Mendeleev University of Chemical Technology of Russia. Faculty of Information Technologies and Management (ITM Faculty). Department of cybernetics of chemical engineering processes.
**Supervisor name:** Professor Dr. Menshutina Natalia V.

**Environment description: number of students and supervisors dealing with supercritical fluids in the team where the work was done**
Number of students: 3
Number of supervisors: 1

**Duration of the work (number of months) and date of defense**
Duration of the work is 3,5 years. Date of the defense: December 28, 2017.

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