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# Carbon Sorbents in Medicine and Proteomics

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## Abstract

Hemosorption (purifying the blood outside an organism) and enterosorption (detoxification of an organism through the gastrointestinal tract) are the most promising methods of the sorptional medicine. As far as the adsorption of toxic substances with different molecular mass and nature is concerned, carbon sorbents are of interest to meet the requirements of medicine. Sorbents of different nature and structure are described. Methods for controlling the adsorption activity of the sorbent are indicated. A particular attention is paid to the development of selective sorbents for using in sorptional medicine and proteomics.

**Key words:** carbon sorbents, sorptional medicine, proteomics

## INTRODUCTION

Ecologically unfavourable environmental conditions and different diseases accompanied by the accumulation of toxic substances in a human organism demanded for a new approach to solving the problems of preserving the internal environment and health of humans, because medical therapy was ineffective. This problem was solved *via* using in medical practice the methods of sorption detoxification of the organism. These include hemosorption (purifying the blood outside an organism), removing toxins from the plasma, lymph (plasmasorption, lymphosorption); enterosorption (detoxification of the organism through the gastrointestinal tract), ointment application of sorbents (vulnerosorption). The most promising method of sorptional detoxification of an organism is hemosorption, based on the ability of active sorbents to remove hazardous substances of different nature from the blood in the case of certain diseases (cancer, autoimmune, infectious, allergic ones, *etc.*).

Hemosorbents can be divided into two main classes depending on the predominant types of binding between the substance under extraction and the sorbent: 1) neutral adsorbents (activated carbons, silica gels, alumina gels, neutral copolymers, and non-ionic groups), 2) ion-exchange sorbents (organic and inorganic resins of synthetic and mineral origin).

For the purposes of sorptional medicine, carbon, carbon-mineral, specific immunosorbents are widely used.

Of particular interest for the sorption of toxic substances with different molecular mass and the nature are carbon sorbents meeting the requirements of medicine.

The porosity of carbon sorbents determines the direction of their use in the sorptional medicine. Thus, microporous carbon sorbents should be used to remove products with a small molecular mass from biological fluids, such as creatinine, aliphatic hydroxy acids, amino acids, uric acid, *etc*.

The developed mesoporous structure of sorbents satisfy the majority of hemosorption tasks. When removing toxic substances by carbon sorbents with hydrophobic surface, the main mechanism of sorption is presented by physical adsorption caused by dispersion forces. The efficiency of adsorption is determined by the proportionality between the molecules of adsorbed substances and the pores (mesopores) of the sorbent.

Adjusting the adsorption activity of sorbents, until recently, was performed mostly by changing the porosity of the surface, *i. e.*, *via* the geometric modifications of the structure.

However, this results in decreasing the strength of the sorbent granules.

The second way to control the adsorption properties of adsorbents consists in changing the surface chemistry of sorbents, the creation of chemically bound functional groups on the surface of the sorbent to be capable of sorbing the pathologic substances of different nature.

Currently an issue is topical concerning an increase in the efficiency of sorbing the pathological substances of certain nature aimed at developing selective sorbents for subsequent use in the sorptional medicine and proteomics (the science concerning the development of methods for the isolation and separation of proteins from biological media, and their identification).

## REQUIREMENTS FOR MEDICAL SORBENTS

Medical sorbents directly contacting with the biological fluid of an organism are made with special demands for quality: a high level of chemical purity, minimal content of impurities, non-toxicity, high mechanical strength and smooth surface relief of granules, the absence of dust formation (separation of ultrafine particles), high sorption capacity with respect to removing substances, compatibility with blood and inert properties with respect to blood corpuscles [1].

## TECHNOLOGY FOR OBTAINING ACTIVE COAL

The main properties of industrial activated carbons commonly used in medicine are determined both by the nature of source raw materials, and the production technology.

The technology for producing activated carbons involves three stages: the initial stage consists in the preparing raw materials; it is followed by the two stages of thermal processing such as carbonization (pyrolysis) and activation (gasification) those provide an increase in carbon content and the creation of a porous surface structure.

Activated carbon species produced via this technology from natural materials (wood, peat and fossil coal) have mainly microporous structure, which limits their adsorption activity with respect to substances with the molecular higher than 500 D. The granules of coal are of arbitrary shape with a rough surface, they are fragile to be destroyed in the course of chemisorption with releasing fine dust into the blood. As the result, the blood cells are injured, and the number of platelets and white blood cells after contact with the sorbent could be reduced by 80 %. The coals contain mineral impurities in great amounts (compounds of potassium, calcium, sodium, magnesium, iron, aluminum, silicon, etc.) those not only impair the adsorption and structural properties of coal, but also may pass into the blood [2].

Introducing the operations of reducing the content of mineral impurities (demineralization), of increasing the strength of granules and of improving the surface relief (encapsulation and additional processing of grains) to the technology allow improving some properties of coal, but this worsens the sorption characteristics.

This situation stimulated research work aimed at developing novel sorbents on the basis of high quality raw materials and special technologies. With regard to the medical practice, the main attention is focused on the development of carbon sorbents those have a number of special and unique properties: a high compatibility level with respect to blood and other organismal fluids, an ability to absorb hydrophobic toxic substances those almost cannot be removed by the sorbents of another nature, an inertness with respect to the tissues of internal organs; a wide range of pore structure and surface physicochemical properties [3].

In our country there are synthetic carbon adsorbents based on polymer resins developed and introduced into medical practice (SKN, SUGS, FAS, SKS, Simplex) as well as a carbon-mineral sorbent (SUMS-1) based on a mineral matrix such as γ-alumina, *etc.* (Fig. 1) [3–5]. The sorbents developed exhibit a different activity level with respect to substances caused by the chemical nature and porous structure of the surface of the sorbent granules, which narrows the range of their application. In addition, in recent years the production of these hemosorbents in Russia and Ukraine was for various reasons ceased or reduced.

In Japan synthetic sorbents BAC-MU and the BAC-LG from petroleum pitch were developed those consist of solid grains with a

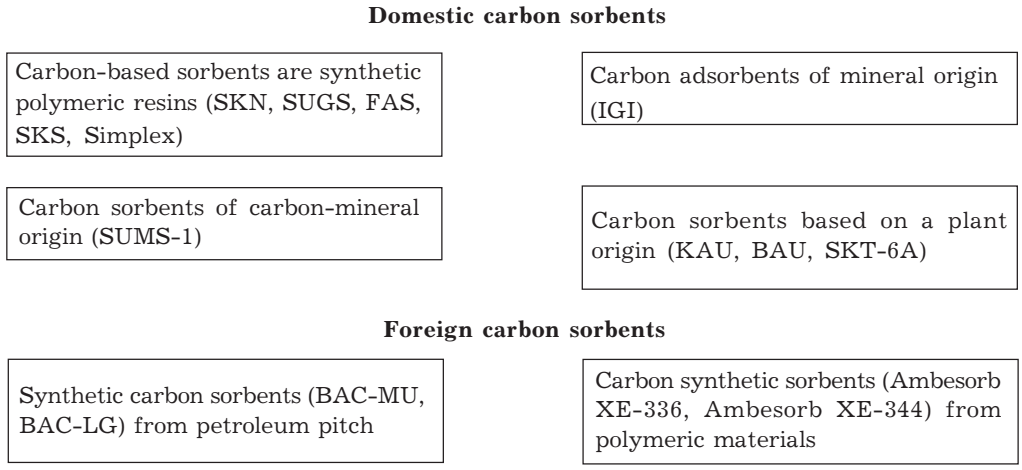


Fig. 1. Domestic and foreign sorbents of medical purpose.

smooth surface topography. In the USA, hemosorbents Ambersorb XE-336, XE-344 with heavy duty spherical granules those almost do not emit dust were obtained from polymeric materials (see Fig. 1).

Carbon synthetic sorbents became an excellent template for the creation of specific sorbents and immunosorbents via chemical modifying the surface. Basing on carbon adsorbents SKN, SUGS, KAU a number of biospecific adsorbents were developed: GSGD – a deligandization sorbent for the purification of proteins and blood cell membranes of blood GUDS – a biospecific DNA-containing sorbent, VUDS – DNA-containing plasma immunosorbent, and others (Fig. 2) [6].

The Belarusian State Medical University in cooperation with the Belarusians Center of Sorption Detoxification Methods, the Belarusian Research Institute of Hematology and Blood Transfusion, the Lomonosov Moscow State University developed a biospecific antiprotease hemosorbent "Ovosorb" based on the ovomucoid protein of duck eggs (naturally occurring protease inhibitor) [7].

## CARBON-CARBON COMPOSITE MATERIALS – A NEW GENERATION OF HEMOSORBENTS

At the IHPP, SB RAS (Omsk), technological approaches were developed to the targeted synthesis of a new class of porous carbon-carbon materials based on the globular nanodispersed carbon, and medical sorbents on this basis: a sterile carbon hemosorbent in physiological salt solution VNIITU-1 and a carbon enterosorbent VNIITU-2 [8, 9].

Basing on the studies concerning the mechanism and kinetics of the thermal decomposi-

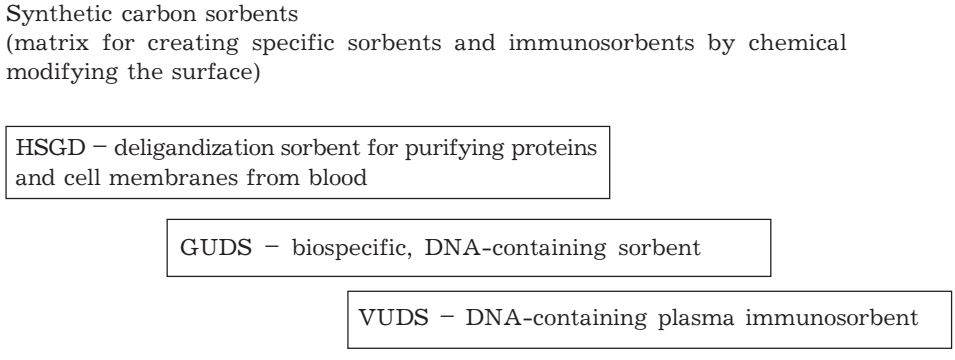


Fig. 2 Modified carbon sorbents based on synthetic carbon sorbents SKN, SUGS, KAU.

tion of hydrocarbons on the surface of dispersed carbon particles with the formation of pyrolytic carbon performed at the IHPP, a concept of the template synthesis of porous carbon materials was created. The synthesis is based on a two stage carbon transformation into nanodispersed carbon particles and pyrocarbon [8–11].

The feedstock is presented by natural gas and oil-refining gases, as well as petroleum and coal tar. At the first stage of the synthesis carried out in the gas phase at the temperature of 1250–1500 °C, nanodispersed pseudo-spherical carbon particles are formed with the size of 40–60 nm. The process is accompanied by the separation of mineral impurities and removing ash components *via* the use of special devices and desalinated quenching water. These nanoparticles are grouped into aggregates with carbon-carbon bonds, after the granulation with a binder form a carbon skeleton of a spherical shape (Fig. 3, position *1*, *2*).

At the second stage, a granular carbon-carbon composite consisting of nanosized carbon particles and pyrocarbon is formed resulting from the decomposition reaction of propane, butane and other gaseous hydrocarbons on the surface of carbon nanoparticles at the temperature of 750–900 °C. This composite (porous carbon material) at the stage of activation by steam at 700–950 °C converts into a mesoporous carbon material (see Fig. 3, positions *3*–*5*).

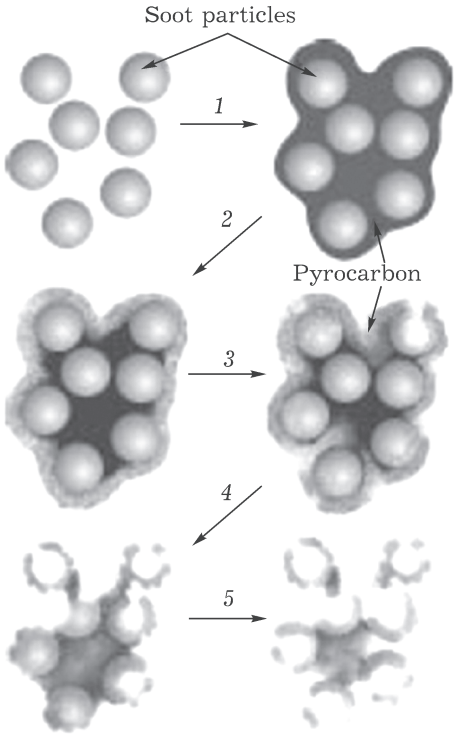


Fig. 3. Schematic diagram for the mechanism of porous carbon material formation. For design. see the text.

The technological process of obtaining medical sorbents from a matrix such as porous carbon material with certain porosity includes the operation aimed at providing its compatibility with blood, sterility and apyrogenicity.

The basic operation consists in pneumo hydromechanical treatment of the porous carbon material in a fluidized-bed mode. This operation allows one to remove dust carbon particles from the surface and pores of the sorbent, to bring the pH of the sorbent to physiological standard, to improve the overall strength of granules due to the destruction of the "weak" granules and to remove any surface irregularities ("polishing" the granules) [8]. The subsequent process steps consist in drying the sorbent, sterilization by air at 200 °C, packing in medical bottles under physiological solution layer, steam sterilization.

The aim of the new direction in the synthesis of carbon hemo- and enterosorbents was the creation of medical sorbents free from all the above-mentioned disadvantages those exhibit a good compatibility with blood.

## HEMOSORBENTS

The sterile carbon hemosorbent in physiological salt solution VNIITU-1 is comparable favourably in a number of parameters with many well-known sorbents. In particular, it is characterized by a high level of chemical purity, mesoporous structure, the minimum content of impurities, mechanical strength and smooth surface relief of granules, the absence of dust (separation of ultrafine particles), a high adsorbing capacity with respect to toxins with low and medium molecular mass got into an organism from the environment or produced in the course of life, non-toxicity, blood compatibility and inertness with respect to blood corpuscles (Table 1).

Tables 2 and 3 demonstrate physicochemical and biomedical characteristics of some hemosorbents.

TABLE 1

Physicochemical and biomedical characteristics of the sterile carbon hemosorbent in physiological salt solution VNIITU-1

| Parameters | Values |
|---|---|
| Ash content (%), less than | 0.15 |
| Mass fraction of total sulphur (%), less than | 0.30 |
| Specific surface area via nitrogen adsorption, $m^2/g$ | 300–400 |
| Specific surface area for CTAB adsorption*, $m^2/g$ | 65–125 |
| Iodine number, mg/g | 175–245 |
| Number of granules (0.5–1.0) mm in diameter (%), more than | 90 |
| Number of granules with the diameter less than 0.5 mm (%), less than | 10 |
| Strength of the granules under abrasion (%/min), less than | 0.30 |
| Concentration of NaCl solution, in equilibrium with hemosorbent, $mol/dm^3$ | 0.14–0.15 |
| pH of NaCl solution in equilibrium with hemosorbent | 6.0–7.8 |
| Impact on blood corpuscles under blood supply of 80–120 mm/min to 350 $cm^3$ of the sorbent: | |
| reduction in the number of leukocytes (%), less than | 10 |
| reduction in the number of platelets (%), less than | 15 |
| increase in free hemoglobin (%), less than | 6 |

*CTAB – cetyltrimethylammonium bromide.

The mesoporous structure of the surface of hemosorbent VNIITU-1 with a predominant pore size amounting to 50-60 nm caused its adsorption activity to increase with respect to medium molecular mass toxins. With the specific surface area ranging within 300–400 $m^2/g$ the hemosorbent extracts up to 95 % of substances having the average molecular mass within the range of 500–5000 D (see Table 3). Due to a small number of micro- and macropores inherent in the hemosorbent VNIITU-1 it is capable of absorbing substances with both low and high molecular mass.

The carbon hemosorbent VNIITU-1 is widely used in treating a wide range of diseases connected with the accumulation of toxins in an organism.

## ENTEROSORBENTS

Obtaining high-quality hemosorbents contributed to the development of other medical sorptional technologies such as: enterosorption, lymphosorption and vulnerosorption.

The enterosorption is based on the binding of endogenous and exogenous substances and their excretion from the gastrointestinal tract [12].

Modern enterosorbents should meet the following criteria: to be non-toxic with respect to an organism, with no decomposition and with no being absorbed in the course of passing through the gastrointestinal tract, to be rapidly and completely removed from an organism, with no injuring the mucous membranes of the mouth, esophagus, stomach and other organs;

TABLE 2

Porous structure of some carbon sorbents

| Carbon sorbents | Specific surface area *via* nitrogen adsorption, $m^2/g$ | Mass fraction of ash, % | Pore volume, $cm^3/g$ | | | |
|---|---|---|---|---|---|---|
| | | | Total | Micro- | Meso- | Macro- |
| VNIITU-1 | 350 | 0.12 | 0.34 | 0.01 | 0.33 | 0.02 |
| VNIITU-2 | 363 | 0.03 | 0.56 | 0.01 | 0.55 | – |
| SKN-1K | 1050 | 0.14 | 1.59 | 0.51 | 0.46 | 0.62 |
| SKN-4M | 1100 | 0.03 | 1.36 | 0.46 | 0.35 | 0.55 |

TABLE 3

Physicochemical and biological characteristics of hemosorbents

| Parameters | Hemosorbents | | | | | |
|---|---|---|---|---|---|---|
| | SUMS-1 | VNIITU-1 | FAS | SKN-1K | SKN-4M | ADSORBA 300C |
| Grain size, mm | 0.5–1.0 | 0.5–1.0 | 0.5–5.0 | 0.5–1.0 | 0.6–1.0 | 0.5–1.0 |
| Ash content (%), less than | – | 0.15 | 0.10 | 2.0 | 2.0 | 1.5–3.0 |
| pH of physiological salt solution in the equilibrium phase | 6–8 | 6.0–7.8 | 6.0–7.5 | 6.5–7.0 | 6–8 | 6.5–7.0 |
| Adsorption surface, $m^2/g$ | 200–300 | 300–400 | 1000–1100 | 1000–1200 | 1100 | 320 |
| Regression of total protein and blood cells after perfusion (mg/L), less than | 15–20 | 10–15 | 5–20 | 15–20 | – | 20 |
| Extraction coefficient for toxins with the average molecular mass, % | 33 | 77–95 | 60–70 | 55–70 | 50–60 | – |

to exhibit a high adsorption capacity with respect to toxins removed, to have a convenient dosage form, with no causing any adverse organoleptic responses.

In order to produce enterosorbents one uses carbonaceous materials of different nature: naturally occurring, synthetic ones, and others (Fig. 4).

Enterosorbents are available in the form of pastes, granules, powders, tablets, fibre. They are characterized by a high adsorption surface area (up to 1250 $m^2/g$ and higher), with the total pore volume of 0.4–1.2 $cm^3/g$, with the grain size ranging within 0.1–1.0 mm.

However, it should be noted that there are following disadvantages observed for the enterosorbents: swelling in organismal fluids, a small size of sorbent particles, or a high content of dust whereby they penetrate into the bloodstream through the walls of organs; an inconvenient dosage form that requires for preparing the sorbent to introduce into an organism, the presence of odor, a high content of impurities (ash).

The technology of matrix synthesis based on globular carbon allowed one to create enterosorbent VNIITU-2, the pharmaceutical preparation of high quality that completely meets the requirements of medicine (Table 4).

It represents a chemically pure sorbent (with carbon content of at least 99.5 %, mineral impurities not exceeding 0.5 %), solid granules, rounded, 0.5–1.0 mm in size, being not destroyed in the course of passing through digestive organs, those do not injure the mucous tunic. The

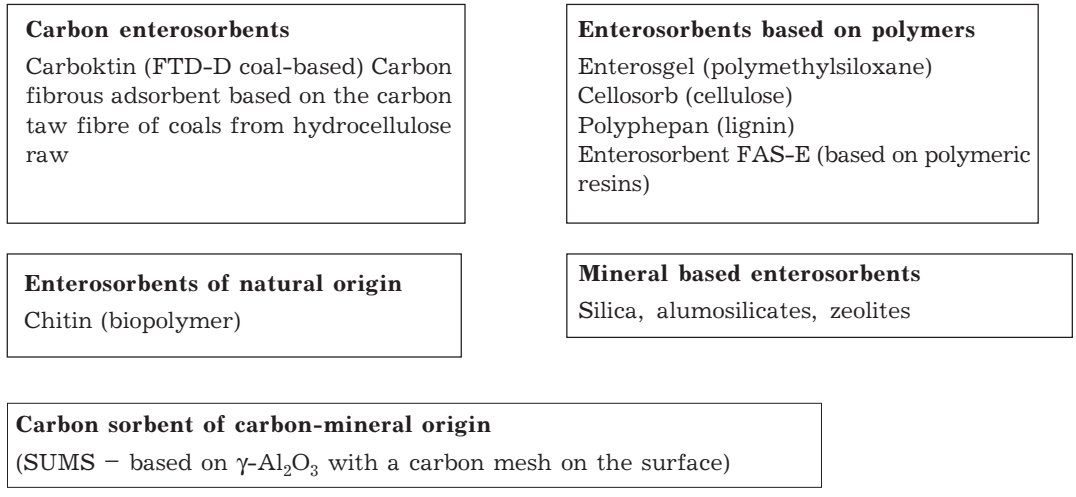


Fig. 4. Domestic medical sorbents.

TABLE 4

Physicochemical and biomedical properties of carbon enterosorbent VNIITU-2

| Parameters (according to standard FSP 42-0465-3814–03) | Quality requirements (according to standard FSP 42-0465-3814–03) |
|---|---|
| Description | Shiny black spherical granules, 0.5–1.0 mm in size, odourless and tasteless |
| Solubility | Almost insoluble in water, alcohol, ether |
| pH | 6.0–8.0 |
| Water-soluble substances (%), less than | 0.5 |
| Chlorides (%), less than | 0.01 |
| Sulphates (%), less than | 0.02 |
| Iron (%), less than | 0.12 |
| Substances soluble in dilute hydrochloric acid (%), less than | 0.5 |
| Metallic iron (%), less than | 0.01 |
| Moisture content (%), less than | 10 |
| Ash (%), less than | 0.5 |
| Adsorption capacity (g/g), not less | 0.03 |
| Fraction of grains larger than 1.0 mm and smaller than 0.5 mm (%), less than | 5 |
| Microbiological purity | 1 g of the preparation should contain no more than $10^3$ aerobic bacteria and less than than $10^2$ yeasts and mold fungi. There shall be no presence of fam. Entegobastegiaseae, Pseudomonas aeruginosa and Staphylococcus aureus in 1 g of preparation |

sorbent has neither smell nor taste. Mesoporous nature of the sorbent surface allows the removal of toxic substances with low and medium molecular mass from a human organism [8, 13].

### *Enterosorbents for animals*

A considerable part of foreign compounds penetrate in the human organism with food, especially with animal products.

Within the framework of the problem of protecting the internal environment of humans, increasing the quality and safety of animal products is considered to be of crucial importance. For this purpose, of wide application are enterosorbents (Polyisorb, Polyphepan, Enterosgel, activated carbon, *etc.*) those allow one to perform detoxifying an animal organism and remove hazardous substances those can be transferred into a human organism together with the production of livestock.

Requirements for quality enterosorbents for animals should not be worse than the demands concerning enterosorbents designed for a human organism.

According to the technology of matrix synthesis, enterosorbent Zookarb was developed that is not inferior in quality comparing to enterosorbent VNIITU-2 (Table 5) and is efficient for the detoxification of animals (cattle, horses, pigs, chickens, fur-bearing animals (mink), home animals) and poultry; it is widely used at livestock farms.

## DIRECTIONS OF DEVELOPING SELECTIVE SORBENTS

Creating materials with high adsorption activity with respect to toxic substances of protein nature by controlling the chemical nature *via* adjusting the chemical nature of their surface (chemical modification) is of considerable interest because it allows one to develop a wide

TABLE 5

Physicochemical and biomedical properties of carbon enterosorbent Zookarb

| Parameters | Characteristics and standard (engineering specifications TU 9318-003-71069834–2006) |
|---|---|
| Appearance, colour | Shiny spherical granules with from 0.1 to 1.0 mm in diameter, black or silver in colour, odourless |
| Mass fraction of carbon (%), not less | 99.5 |
| Mass loss after drying (%), less than | 10 |
| Residue after calcination (%), less than | 0.5 |
| Adsorption activity (μg/mg), at least | 30 |
| Granulometric composition | The residue on the sieve with 1.0 mm mesh and the fraction of grains passing through 0.1 mm mesh sieve should not exceed 0.5 % |
| Microbiological purity | 1 g of the preparation should contain no more than $10^3$ aerobic bacteria and less than $10^2$ yeasts and mouldy fungi. There shall be no presence of fam. Enterobacteriaceae, Pseudomonas aeruginosa and Staphylococcus aureus in 1 g of preparation |

range of efficient sorbents for using them the fields of medicine and proteomics. As a carrier for obtaining a selective sorbent, carbon hemosorbents with unique properties are considered promising.

There are several directions of creating selective sorbents:

– The creation of chemically bonded functional groups on the surface of the matrix (carboxyl, carbonyl, ester, *etc.*) capable of covalent interaction with a variety of biologically active substances (amino acids, enzymes, antibodies, antigens, *etc.*).

– The introduction of nitrogen, sulphur and other heteroatoms to the matrix.

– Coating the surface of the matrix with a polymer film which has functional groups suitable for covalent binding bioligands in its structure.

## CHOICE OF MODIFIER

The choice of a modifier (monomer) containing functional groups (nitrogen and oxygen), is vindicated by its chemical likeness to the functional groups of a protein. The modifier should exhibit a number of specific properties:

1) Non-toxicity,

2) Solubility in aqueous solutions,

3) The presence of nitrogen- and oxygen-containing groups,

4) The ability of organic compounds to enter into polycondensation reaction with the formation of polymer chains, which provides a low mobility of the modifier.

The main idea of the chemical modification consists in the fact that multifunctional interaction (involved in the formation of bonds of several reactive groups) plays an important role in the sorption of large organic molecules. Of greatest interest for modifying the carbon surface are organic substances those have nitrogen- and oxygen-containing groups in their structure. The interaction between the compounds of protein nature with the functional groups of the surface of the sorption material could result in the formation of covalent bonds according to the donor-acceptor mechanism. Thereby, –OH and $NH_2$– can serve as the donor groups, as well as –C=O and –COOH groups can serve as acceptor groups.

The IHPP of the SB RAS developed a set of methods for chemical functionalization of the surface of carbon adsorbents with a strong fixation of nitrogen- and oxygen-containing groups to give them selective adsorption properties concerning various toxic substances of protein nature. There were used a variety of modifiers [14, 15]. Of greatest interest are sorbents modified with the polymer of aminocaproic acid [15]. The choice of the modifier is caused by the presence of two chemically dif-

ferent functional groups of hydrophilic nature in the aminocaproic acid (−COOH and $NH_2$−) separated by a hydrophobic chain $(CH_2)_5$. The bifunctionality of the modifying compound creates the conditions for a homopolycondensation reaction with the formation of oligomeric and polymeric molecules with a low mobility and low solubility in water [16]. This provides the constancy of the chemical composition on the surface of the modified sorbent in the course of operation under contacting with blood plasma.

It should be noted that in the course of modifying the surface of the carbon sorbent one could observe "local" (insular) coating by a discontinuous polymer film (Fig. 5).

Bench testing the samples obtained was performed at the Central Scientific Research Laboratory of the Omsk State Medical Academy. The level of proinflammatory cytokines (tumor necrosis factor-α, interleukin-1β, interleukin-6 and interleukin-8) in the blood plasma toxic under the peritonitis was determined before and after contact with the initial and modified models of the carbon sorbent.

The studies have demonstrated that modified sorbents cause more than 1.5 times reducing the level of abnormal proteins.

The functionalization (modification) of the surface of the carbon sorbent with oxygen-containing and nitrogen-containing groups opens the prospects of new sorbents for the sorptional medicine.

In Russia there are biological technologies under development, aimed at comprehensive solutions concerning the modern problems of proteomics.

It is known that in the development of several diseases, including autoimmune, cancer and cardiovascular diseases, in human blood there is an increase in the level of extracellular protein-nucleic complexes. However, the structure of these complexes has not yet been established. One of the goals of proteomics consists in determining the structure of these complexes. In order to solve this problem it is necessary to develop biospecific (selective) sorbents those represent carriers (sorbents) with attached bioligands (enzymes, amino acids, functional groups, *etc*.). The choice of a particular bioligand and methods of binding are important for solving the posed by proteomics.

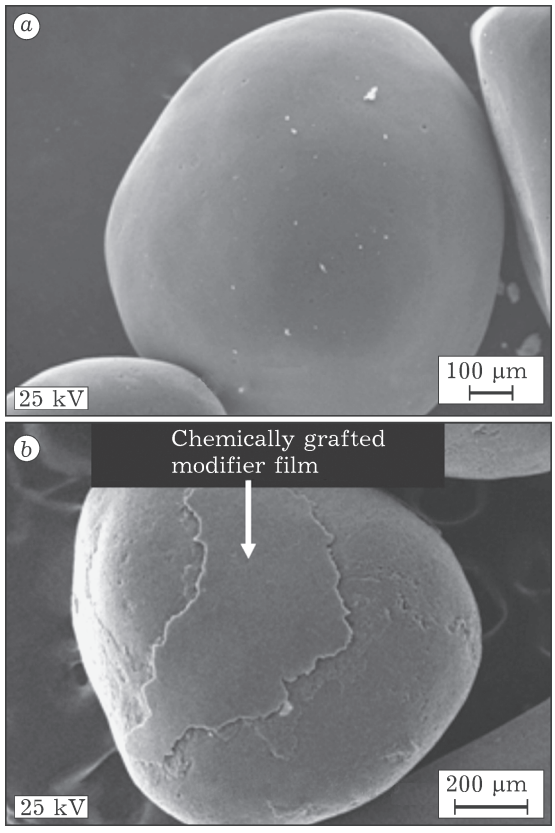


Fig. 5. Electron microscopic images of the sample granules of initial carbon hemosorbent VNIITU-1 (*a*) and of a modified carbon sample hemosorbent VNIITU-1 with "local" polymer film distribution on the surface (*b*).

Today there are no certified carbon sorbents for the selective action of proteomics in Russia. In this regard, the relevance of the development of these sorbents is incontestable.

Abroad, fullerenes and nanotubes are used as carbon carriers for solving the problems of proteomics [17−20]. The introduction of sorbents based on the mentioned carbon materials into medical practice in Russia is difficult in connection with requiring for additional biomedical research (toxicology, blood compatibility, *etc*.).

## CONCLUSION

The sorptional medicine (hemosorption and enterosorption) using carbon sorbents for the treatment and prevention purposes is one of the most efficient directions of the efferent therapy.

At the present time, sorbents with different nature and structure are widely used in medical practice. Of greatest interest are carbon-carbon composites based on matrix synthesis: carbon hemosorbent VNIITU-1, carbon enterosorbent VNIITU-2 and carbon enterosorbent Zoocarb.

Owing to their properties, carbon-carbon composites are promising materials for modifying in order to develop and obtain selective sorbents for medicine and proteomics.

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