STATE BUDGETARY EDUCATIONAL INSTITUTION OF HIGHER EDUCATION
"VOLGOGRAD STATE MEDICAL UNIVERSITY" OF THE MINISTRY
HEALTHCARE RUSSIAN FEDERATIONS

DEPARTMENT PHARMACOLOGY AND BIOINFORMATICS

A.A. Spasov, D.S. Yakovlev, V.A. Kosolapov, P.M. Vasiliev, M.P. Voronkova, L.V. Naumenko, O.Yu. Grechko, L.I. Bugaeva, D.V. Maltsev, D.A. Babkov, R.A. Litvinov, N.M. Shcherbakova

BASICS OF CREATING MEDICINES (SELECTED LECTURES, PART I)

edition second corrected and supplemented

EDUCATIONAL MANUAL

VOLGOGRAD 2023

UDC 615. 012. 8 (075)

Authors:
Alexander Alekseevich Spasov, Dmitry Sergeevich Yakovlev,
Vadim Anatolyevich Kosolapov, Paul Mikhailovich Vasiliev,
Maria Pavlovna Voronkova, Ludmila Vladimirovna Naumenko, Olesya Yuryevna Grechko, Love Ivanovna Bugaeva, Dmitry Vasilievich Maltsev,
Denis Alexandrovich Babkov, Novel Alexandrovich Litvinov, Nadezhda Mandzhievna Shcherbakova

Reviewers:
Ivan Nikolaevich Tyurenkov, deserved worker the highest schools Russian Federation, Honored Scientist of the Russian Federation, Corresponding Member of the Russian Academy of Sciences, Doctor of Medical Sciences, Professor
Galina Petrovna Dudchenko, doctor biological sciences, professor

In print by solution RICE VolGMU

(protocol No. __from _____(2023)

Fundamentals of drug creation drugs (selected lectures): Textbook / A.A. Spasov, D.S. Yakovlev, V.A. Kosolapov, P.M. Vasiliev et al. / Ed. A.A. Spasova. - Volgograd: VolgSMU Publishing House, 2022. – 181 p.

In the educational benefits information is provided about modern approaches to development new medicinal drugs. Provided main stages drug development, fundamentals of evidence-based medicine, pharmacoepidemiology and pharmacoeconomics, modern trends in gene therapy and pharmacogenetics.

Intended for For students medical universities By specialties: medicinal case, pediatrics, pharmacy, medical biochemistry, dentistry, medical and preventive case.

Chapter 6. PROSPECTIVE MECHANISMS OF CONTROLLED DELIVERY NEW MEDICINAL FORM, MODERN OF MEDICINAL DRUGS TO TARGET ORGANS

Voronkova M.P.

As a rule, traditional dosage forms (DF) contain one or more individual medicinal substances (DS) in forms suitable for enteral or parenteral administration. The approaches used to administer drugs into the human body, based on the use of traditional DF, have a number of significant disadvantages, such as:

1. Increased consumption of medicinal substance caused by the fact that the medicinal substance does not reach all the necessary biological targets or reaches them, but in a concentration significantly lower than the necessary therapeutic one. Therefore, it is necessary to use doses that are 1-2 orders of magnitude higher than the theoretically necessary ones.
2. The non-targeted action of a drug, i.e. interaction with non-target bio-objects, often leads to side effects caused by its metabolites and to non-targeted, irrational consumption of drugs.
3. The inability to maintain the optimal therapeutic concentration of the drug for the required time and, as a consequence, the need for frequent administration of the drug.
4. Insufficient biocompatibility and undesirable physiological effects in the area of drug administration. The need to use special methods of drug administration.
5. Significant difficulties in using drugs with suboptimal transport properties (e.g. high lipophilicity).

The listed disadvantages are most clearly manifested when using drugs with pronounced side effects (most antitumor drugs) and drugs that act on the central nervous system (CNS): narcotic analgesics, drugs for the treatment of Alzheimer's disease, etc., i.e. medicinal agents whose action requires overcoming the blood-

brain barrier (BBB). Unfortunately, significant limitations in the use of a significant proportion of traditional drugs are associated with the presence of these undesirable consequences. Moreover, the use of traditional drugs is impractical when creating high-tech and expensive drugs with high affinity, high activity and selectivity in relation to target biological targets.

Modern development of research methods and technologies has prepared the basis to create new, innovative LF, not not only devoid of the above-mentioned disadvantages, but also capable of targeted transport of drugs to the site of the pathological process. In addition, they help reduce the extremely undesirable side effects of drugs, as well as their toxic metabolites. Some advanced LF allow visualization of the diagnostic and treatment process.

At present, methods and technologies developing at the intersection of organic chemistry and the chemistry of high-molecular compounds (polymers), medical and physical chemistry, instrumental research methods and analytical chemistry, molecular biology and molecular genetics make it possible to effectively solve most scientific and technological problems associated with the creation of effective LF. The rapid development of micro-, nano- and biotechnology allows create particles With given properties, such as: particle size, properties of the particle "body" and its surface, dependent "response" to local and remote impact, and also the possibility of visualizing the action of the drug and diagnostic results. The listed properties allow the effective use of micro- and nanoparticles in the creation of new effective forms delivery of drugs specifically to the site of an inflammatory or pathological process. The main significant characteristics of such particles, as applied to the creation of drug transport systems, are listed below:

1. encapsulation "complex" LV;
2. visualization, sensors;
3. cellular/tissue specificity;
4. local activation (pH, temperature And etc.);
5. remote activation;
6. magnetic properties;
7. controlled selection;
8. protection from external environment;
9. mechanical properties/support fabrics.

IN complex application similar methods And technologies allows:

- prolong action LS, And How consequence, reduce frequency taking the drug;
- provide necessary biocompatibility;
- protect LS from premature biodegradation;
- increase bioavailability substances With suboptimal transport properties;
- overcome biological barriers, including BBB And walls Gastrointestinal tract;
- to carry out targeted transport of drugs (tissue- and/or target- specific delivery);
- provide controlled release LS (back answer, local or remote activation);
- support optimal therapeutic concentration LV;
- minimize side effects effects LV And their metabolites;
- provide the ability to visualize the focus of the pathological process, control the interaction of drugs with target biological targets and the results of treatment at the cellular level.

New LFs with a reverse response have already been developed, for example, those that secrete insulin depending on the concentration of glucose in the blood. Relatively recently, nanomolecular modifications of camptothecin, a topoisomerase inhibitor, have been developed, which significantly increase its effectiveness And selectivity. Modern methods of drug delivery with controlled release of the active substance at a set rate in advance, after a specified time, in a certain place, in accordance with the needs of the body are called therapeutic systems (TS). The main elements of the TS are: drug; an element that controls the release of the drug; a platform on which the system is placed; a therapeutic program. TS are obtained by technological (physical, chemical) and technical (engineering) methods. Depending on the design and release mechanism, TS are distinguished: physical (diffusion, osmotic, hydrostatic), chemical (immobilized, chemically modified), bioengineered. Depending on the place of application, TS are divided into: gastrointestinal (oral), ocular, intrauterine, transdermal, dental.

1. Oral mechanism delivery: formulas prolonged action; use of excipients, liposomes and microspheres.

Systems that attach to the mucous membrane are bioadhesive systems, the principle of retention of which is based on the ability to “stick” and remain on the

surface of the gastric mucosa. The disadvantage of these systems is the attachment to particles of the stomach contents, as well as the pH dependence of bioadhesive materials. Reduced acidity of gastric juice can cause a significant decrease in the adhesive properties of the system and its efficiency. Local absorption systems are designed for proteins and peptides. The essence of the technology lies in the use of specific ligands that allow absorption on a specific area of the surface of gastrointestinal epithelial cells. Ligands are associated with coated microparticles of protein and peptide drugs, which protects their contents from destruction in the gastrointestinal tract before they are delivered to a specific area. Examples of local absorption systems: – **spherical absorption form – microencapsulation of drugs** in time-disintegrating beads for controlled release; – programmed absorption form – a combination of multiparticles of a hydrophilic matrix of tablets, which allows for different release; – intestinal-protective absorption form – high-density beads that minimize intestinal irritation; – insoluble absorption systems – improve bioavailability and controlled release of drugs with low solubility. Vaccines have been developed for per os, which are micronanoparticles of a certain size containing antigens dispersed in a biodegradable polymer or **polymerized liposomes in** which the antigens are covered with a stable membrane.

For example, wide spreading received oral TS "OROS", in which the release of drugs is regulated by the action of osmotic pressure. System developed For insoluble LV With opti-ical characteristics – pulsating release, delayed effect. The ORO S system is a perforated film-coated tablet, which consists of a core and a semipermeable membrane with an opening. Water penetrates through the membrane into the tablet and dissolves the medicinal substance located in the core. The solution inside the membrane is saturated and, under the influence of osmotic pressure, comes out through the opening of the membrane. An important criterion is the choice of polymer used to manufacture the membrane, which not only regulates the rate of release of the medicinal substance, but also provides a constant volume of solvent during the dissolution of the core. The membrane must have sufficient mechanical strength, be free of cracks, and be resistant to the action of

gastric juice. Cellulose acetate is used to manufacture such membranes, and permeability is regulated With with help plasticizers. Size holes membranes is 250-300 μm, and laser technology is used to obtain it. For example, the drug of the OROS system contains 85 mg of indomethacin, the release rate of which from the drug is 10 mg / h. TTS is a convenient form for application to the skin containing drugs and active substances. Thus, an example of prolongation of drugs can be enteric-coated tablets containing this drug. They are obtained by coating them with a gastro-resistant shell or by pressing granules or microcapsules pre-coated with such shells. If necessary, the shells can provide a longer dissolution delay than 1 hour, which the tablet spends in the stomach. The shell can be quite thick, for example, sugar, which sometimes has a greater mass than the core of the tablet containing the drug. Thin film coatings (less than 10% of the tablet weight) can be made of cellulose, polyethylene glycols, gelatin, gum arabic, etc. By selecting the coating and introducing additional substances, it is possible to slow down the increase in the concentration of the active substance in the blood, which is important for reducing the risk of developing an adverse reaction, and (or) shift the time to reach the maximum by several hours, if it is necessary to prolong the effect of the drug and thereby reduce the frequency of administration in order to improve compliance. Extended-release tablets (retard), for example, are usually obtained by pressing microgranules of the drug in a biopolymer shell or by distribution in a biopolymer matrix. With gradual (layer-by-layer) dissolution of the base or shell, the next portions of the drug are released. Modern high-tech delivery methods make it possible to achieve gradual uniform release of the drug, for example, by creating osmotic pressure inside the capsule with the active substance. New dosage forms of well-known drugs such as nifedipine (Corinfar Uno), indapamide (Indapamide retard-Teva), piribedil (Pronoran®), tamsulosin (Omnic Okas), glipizide (Glibenez retard), trazodone (Trittico) have been created on this principle. Controlled release can be achieved by using microcapsules with a medicinal substance coated with a special polymer in tablets. After the outer layer dissolves, liquid begins to flow into the capsule and as the core dissolves, the medicinal substance is gradually released

and diffuses through the capsule membrane. The main factor limiting the production and use of such dosage forms remains the requirement to release the entire active ingredient during the time the tablet passes the main sites of drug absorption in the gastrointestinal tract –

2. Pulmonary delivery.

Drug delivery systems for the treatment of diseases that introduce active ingredients into the circulatory system are numerous and include systems for oral, transdermal, inhalation, subcutaneous and intravenous administration. Inhalation-delivered drugs are typically delivered using positive pressure relative to atmospheric pressure, in air with propellant gases. These delivery systems medicines deliver medicines V form sprayed or evaporated-aerosols . Recently, the delivery drugs into the pulmonary textile began to be provided with dry powder inhalers. Dry powder inhalers can be actuated by inspiration or breath energy and can deliver drugs by converting drug particles in a carrier into a respirable dry powder that is entrained in the airstream and inhaled by the patient. Drugs delivered using a dry powder inhaler are no longer limited to the treatment of lung disease alone, But can Also be sucked in big circle blood circulation and, therefore, they can be used to treat many diseases, including, but not limited to, diabetes and obesity.

Dry powder inhalers used to deliver drugs to the lungs contain a system of doses of powdered drug, usually either as bulk drug or as divided quantities of individual doses contained in unit dose units such as hard gelatin capsules or blister packs. The bulk drug containers are fitted with a patient-activated metering system to release a single dose from the powder immediately prior to inhalation.

Dosage reproducibility requires that the drug be homogeneous and that the dose can be delivered to the patient in a consistent and reproducible manner. results. That's why, theoretically, system The dosage system should produce complete release of all the drug, in fact, during the inhalation manipulation when the patient takes his dose. However, complete release is not usually required if reproducible dosing can be ensured. The rheological properties of the powder drug and the long-

term physical and mechanical stability are therefore more critical for bulk drug containers than for single unit-dose cells. Reliable moisture protection can be more easily achieved for unit-dose cells, e.g. blisters. However, materials, applied For manufacturing blisters, allow air into the drug compartment and, therefore, the drugs may lose viability during long-term storage. In addition, dry powder inhalers that use blisters for inhalation drug delivery may deliver inconsistent doses to the lungs due to variability in the air passage architecture resulting from puncture of the films or tearing of the blister films.

All known dry powder inhalers can form drug particles or suitable inhalation jets during inhalation manipulation by deagglomeration of the powder preparation inside the cartridge or capsule. The amount of respirable powder emitted from the mouthpiece of the inhaler during inhalation depends to a large extent, for example, on the interaction forces between the macroparticles in the powder preparation and the efficiency of the inhaler in separating the said particles to a state in which they are suitable for inhalation. Delivery of drugs through the pulmonary circulation provides numerous advantages, which may include rapid entry into the arterial circulation, elimination of drug breakdown due to metabolic processes in the liver, ease of use, i.e. the absence of discomfort when administered by other routes of administration .

3. Transdermal delivery

The principle of creating transdermal transport systems (TTS) is to regulate the rate of drug delivery through the skin. From the point of view of the physical and chemical laws of diffusion, the skin is considered a simple membrane. The rate of drug release depends on the surface area of the skin where the drug is located and on its concentration. The main condition for the constant delivery of drugs into the body is the membrane-regulated rate of their release. TTS consist of 4 layers. The outer impermeable layer prevents the action of environmental factors on the stability of the drug. And speed release LV. Second layer represents tank, containing the drug. Then follows a membrane that regulates the rate of drug release. The last sticky layer contains a small amount of the drug necessary for

immediate adsorption and creation of therapeutic concentrations in the blood plasma.

Thus, the TTS intended for application behind the ear has a round shape, where the skin area is located that has favorable conditions for the adsorption of the drug. For example: TTS "Transderm-Nitro" and «NitroDur» are a multilayer laminated membrane system with a thickness of 0.2 mm. The outer layer consists of aluminized polyester, which protects the TTS from moisture and prevents evaporation of nitroglycerin. The reservoir contains a viscous silicone liquid where nitroglycerin and lactose are placed. The membrane is made of ethylene vinyl acetate copolymer and is permeable to nitroglycerin. The adhesive layer is represented by silicone rubber.

For transdermal applications use Also such TTS How:

– D-TRANS is a patch that releases drugs through the skin into the bloodstream; the polymer membrane controls the release of drugs;

– E-TRANS – uses iontophoresis to improve transdermal release. The system consists of an adhesive layer that holds the drug, an energy source, and a controller to create an electrical impulse.

When administered orally, many protein-peptide hormones and drugs are inactivated by gastrointestinal enzymes. The use of mucoadhesive polymers has led to *progress technologies buccal LF* . Mucoadhesion - the ability of an object to remain on mucous membranes, which leads to an increase in the concentration of the drug at the site of application and allows for a reduction in the total administered dose of the drug. To impart mucoadhesive properties to the dosage form, the following are added to the dosage form: carbomers, natural resins, gums, OPMC, carbopol, polycarbophil, and sodium CMC.

The intranasal route of drug administration is currently becoming more and more widespread. IN difference from injection introductions, intra-nasal administration of drugs is non-invasive and does not require special participation of medical personnel. At the same time, due to the rapid absorption of drugs in the nasal cavity, the rate of development of the therapeutic effect with intranasal

administration is comparable to the injection route of administration. Usually, the systemic effect with intranasal administration of drugs develops within 5-10 minutes after their use. This is a convenient way to deliver such drugs into the body as: vaccines; drugs for the treatment of osteoporosis, migraine, diabetes (insulin), diabetes insipidus (Desmopressin); immunopreparations (Derinat); glucocorticosteroids (Budesonide), cromoglycic acid (Intal). Currently, special sprayers-dispensers are used for intranasal administration of drugs, while simultaneously resolving the issue of dosages of drugs, because at each When pressed, a strictly defined amount is released. The drugs in sprayers are in the form of solutions or suspensions with the addition of special explosives that increase the viscosity of the drug in order to slow down the evacuation of the drug from the nasal cavity. In metered-dose aerosols, the drugs are under pressure, which prevents bacterial contamination. Low bioavailability of drugs when administered intranasally is associated with the functioning of 25 proteins that are part of the mucous membrane of the nasal cavity and control the transport of all molecular and cellular objects penetrating through the mucous membrane. To increase the intranasal absorption of drugs, non-toxic substances have been developed that bind to the proteins of the mucous membrane according to the principle of receptor interaction and open transport channels. To increase the bioavailability of intranasal drugs, new formulations of drugs and technical means for intranasal administration are being developed.

4. Delivery with help polymers.

Increasing the selectivity of drug action is the most important task of modern pharmacology. In this regard, the search for new approaches to the creation of targeted drugs is of particular importance. One of the most promising ways increases efficiency LV iscreation of delivery systems based on nanocarriers. In-depth study of nanotechnology began in the 1980s, during the development of polymer chemistry, which made it possible to synthesize biodegradable and biocompatible materials. Pharmaceutical nanocarriers are colloidal systems of submicron sizes (less than 1 ml), consisting of polymers. There are three

generations of nanocarriers:

The first generation of nanocarriers. When administered intravenously, nanocarriers were quickly removed from the bloodstream by their capture by the RES, regardless of their composition and morphological features. Accumulation of nanocarriers was carried out in the liver, spleen, and bone marrow cells. The main role in the process their savings. And metabolizing belonged to the liver, which is why LF based on these nanosystems were used for the treatment of liver tumors. The possibility of treating intracellular infections resistant to a number of antibiotics using nanosomal systems was demonstrated.

The second generation of nanocarriers. The use of the "first generation" of nanocarriers was limited by rapid elimination from the bloodstream due to recognition by the mononuclear phagocytic system. Further research in this area was aimed at creating so-called "invisible" nanocarriers capable of avoiding capture by the RES. Thus, the developed nanosomal systems coated with polyethyleneglycol increased the half-life to several hours. The following methods for obtaining nanosomal systems were used:

– adsorption of polyoxypropylene, polyoxyethylene copolymer on the surface of ready-made nanocarriers;

– chemical synthesis of a nanocarrier by copolymerization of hydrophilic polyethylene glycol and a hydrophobic biodegradable polymer (polycyanoacrylate, polyester).

Most drugs are characterized by low permeability through the BBB, therefore special interest represent research, directed on carried out transport of compounds in the central nervous system. The process of transfer of compounds was successfully induced by coating nanocarriers with polysorbate. This technological method allows transporting such drugs as dalargin, loperamide, tubocurarine, and doxorubicin through the BBB.

Third generation of nanocarriers. The main direction of development is the targeted change of the surface structure of the nanocarrier in order to impart a number of properties and parameters using target molecules to biological receptors.

The following molecules began to be used: antibodies, peptides, oligosaccharides, hormones, vitamins. Nanocarriers are used for oral, injection (intravenous and intramuscular), inhalation, intraocular and transdermal administration.

Nanocarriers are also widely used in cosmetics. Nanocapsules are hollow spherical containers with a wall thickness of 10-30 nm, containing a liquid medium in which the drug is dissolved. The drug is released from the nanocapsule by diffusion through the wall or by rupture of the capsule. The release rate is regulated by the design of the nanocapsules and the method their receipt. Nanocapsules use for poorly soluble LV, They are characterized by high bioavailability and low toxicity.

5. Usage liposomes V quality vectors delivery.

Liposomes are spherical vesicles containing one or more lipid molecules. bilayers. Membrane liposomes consists of from natural phospholipids. They are non-toxic, biodegradable, and under certain conditions can be absorbed by cells. Thus, the membrane of liposomes can fuse with the cell membrane, which leads to intracellular delivery of their contents. The drug enclosed in liposomes is protected from the effects of enzymes, which increases the effectiveness of drugs subject to biodegradation in biological fluids. Liposomes are widely used in chemotherapy of metastatic tumors and breast cancer. For example, antitumor antibiotic ***doxorubicin*** was open V 1960s years. However, its use has been limited due to side effects on the heart. Address delivery of this substance To tumors can decide this one problem by reducing systemic toxicity and cardiac effects. The first liposome-based doxorubicin drug introduced into therapy, “Myocet”, is a doxorubicin salt (10,000–15,000 molecules) enclosed in a bilayer lipid vesicle.

The bilayer is formed *phosphatidylcholine* and *cholesterol*, which are contained in cell membranes. The advantages of "Myocet" over free doxorubicin are slower elimination from the body and a different distribution of the drug in the body. At the same time, the dangerous accumulation of the antibiotic is significantly reduced. V cardiac muscle. Liposomes other preparation doxorubicin — "Doxila" — contain positively charged lipid

distearoylphosphatidylethanolamine, covalently stitched With polymer- rum *methoxypolyethylene glycol* (*MPEG*). Additional layer shells from a polyethyleneglycol derivative allows one to “trick” immune cells (phagocytes), preventing the absorption of liposomes and increasing the circulation time of such “stealth liposomes” in the body. Liposomes can also act as nanocarriers for genetic material in gene therapy. One of the varieties of such liposomes is *lipoplex* - used for delivery to cancer cells *short interfering RNA* (*siRNA*) The discovery of RNA interference and its introduction into tumor therapy required the development of new carriers and modification of existing ones due to the presence of a negative charge on RNA molecules. RNA interference is based on the interaction of siRNA 20–25 nucleotides long and its complementary target mRNA, leading to the destruction of the latter. With its help, it is possible to suppress abnormally high transcription or transcription of a gene with a mutation, characteristic of cancer cells. Such “healing” siRNAs are often called *antisenses* . This type of therapy is impossible without targeted delivery, since the lifetime of free RNA in the blood is measured in minutes, A recognition free nucleic acids immune system gives allergic reactions. Lipoplexes can be used to deliver RNA. A lipoplex is a liposome containing lipids with positively charged amino groups: the phosphate groups of RNA interact with them. Polymeric liposomes are lyotropic liquid crystals consisting of amphiphilic bilayers. They are formed by dispersing animal cell membranes and lipids in an aqueous medium. Depending on the size and number of bilayers, liposomes are divided into three classes: multilamellar vesicles; small unilamellar vesicles, less than 100 nm in diameter; large unilamellar vesicles, more than 100 nm in diameter. The membrane of polymeric liposomes consists of phospholipids of plant and animal origin (sunflower oil, soybean, egg yolk), as well as ceramides, cholesterol, fatty acids, and synthetic surfactants. In order to obtain polymer analogs of biological membranes and polymeric liposomes, groups capable of polymerization are introduced into the hydrophilic or hydrophobic part of phospholipids. Polymeric liposomes can be obtained by polycondensation of esters of long-chain amino acids. The disadvantage of nanocapsules is the

impossibility of controlled release of drugs.

6. Controlled delivery and controlled target organ specificity.

Nanoparticles are a promising DF for achieving controlled release parameters due to the reduced mobility of the drug due to the solid structure of the matrix. These are monolithic, spherical formations containing the drug either throughout the entire mass of the nanoparticle or on its surface. The release of the drug from the nanoparticle occurs gradually at a controlled rate from the surface or from the entire mass of the nanoparticle as a result of its disintegration or swelling. Depending on the morphological features of the material used for the synthesis of nanoparticles, carriers are distinguished: nanocrystals, consisting 44 from LV, subjected crushing; thermally or chemically modified serum albumin; chemically modified polysaccharides, polymers and copolymers (polyalkyl cyanoacrylates). One of the modern methods for obtaining nano- and microparticles is the precipitation method using supercritical solvents, the use of which allows to significantly simplify the technological process. The use of nanocrystals for analgesics is relevant, when rapid pain suppression is important. For example, the dispersion of naproxen nanocrystals after 20 minutes gives a 3-5 times higher concentration of the drug in the plasma compared to with regular suspension or tablets and less dependence on contents stomach. Injection introduction nanocrystals gives longer retention of drugs at the injection site, allows to control their biodistribution in the body and avoid absorption of drugs by phagocytic cells. The use of nanocrystals in diagnostics includes lymphography, angiography, diagnostics of the liver and other organs by means of X-ray analysis, computed tomography and magnetic resonance imaging. Nanocrystals are often included in macrocapsules, matrix tablets and other dosage forms. Polymer nanocarriers are stable, form stable forms during synthesis and storage. The following requirements are imposed on polymer carriers: – polymers must have certain physicochemical properties - high purity, i.e. contain a minimum amount of various impurities and monomer impurities. It is necessary to use copolymers based on non-toxic

monomers; – the molecular weight of the polymer determines the rate of elimination of the corresponding drug from the bloodstream and its entry into certain organs. Even a biologically inert synthetic polymer can cause undesirable effects in the body if its molecular weight exceeds a critical value; – molecular weight distribution. In natural polymers, all molecules in a sample are the same size. In synthetic polymers, depending on the method of their production, there are macromolecules different size, possessing different speed You- removal from the body; – the structure of the side chain affects the interaction of the reactants and the efficiency of the resulting TS. When high-molecular ligands are attached to the carriers, the distance between the side functional groups of the carrier polymer and its main chain has a significant effect on bioavailability; – biocompatibility of the drug. The main requirements for biocompatible polymers include: complete elimination from the body in a short period of time, chemical, pharmacological indifference, absence of toxicity; – biodegradability. Since the main route of decomposition of substances in the body is their enzymatic cleavage, it is necessary to introduce groups similar to the natural substrates of the corresponding enzymes into the main or side chains of the carrier polymer. In this case, the polymer destruction reactions should not be accompanied by the release of toxic, pathogenic and antigenic products. Pharmaceutical polymer nanocarriers are obtained by the following methods: direct dissolution technology (dispersion), dialysis and emulsion method (nanoprecipitation). The main ingredients in the production of polymer nanoparticles are the drug, polymer, emulsifier, water or organic solvent. Depending on the specifics of further application, such EVs as osmotic agents, matrix systems for lyophilization, buffer solutions may be present. When obtaining polymer nanocarriers by the direct dissolution method, the polymers are directly dissolved V water phase at 46 room temperature or at heating the solution. This method produces nanoparticles, nanospheres, micellar systems on polymers that are highly soluble in water. Pharmaceutical nanocarriers from copolymers that are poorly soluble in water are obtained by dialysis. To do this, polymers are dissolved in a mixture of water and water-miscible organic compounds. solvents (DMSO,

DMF, acetonitrile, tetrahydrofuran, then dialyze this mixture against water. To obtain pharmaceutical nanocarriers such How nanospheres, nanocapsules And nano-crystals, the emulsion method is used. The method consists of dissolving the polymer in an organic solvent, adding an aqueous phase to obtain an emulsion stabilized by an amphiphilic polymer. When obtaining a nanoemulsion, the size of the emulsion droplets is reduced using ultrasound, then removing the organic solvent from the solution. As a result, both amorphous and crystalline ultrafine nanocarriers are formed in the aqueous phase.