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Perspectives of the Development of Pharmaceutical Nanotechnology

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Abstract—The paper describes the principal lines of development of nanocarriers for medical substances, morphological groups of nanocarriers, and influence of the physical and chemical properties of matrix substances on the key stages of the technological process. Technology aspects of manufacturing nanocarriers, differences in the conditions and techniques for polymer and lipid drug delivery systems are presented in detail.

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The key problem of modern chemotherapy is to enhance selectivity of drug action. In this connection, search for new approaches to targeted drugs has assumed particular importance. However, the main obstacle to achieving a maximum efficiency of drugs is their nonspecific distribution in the body. This is explained by the fact that drugs are distributed according to their physicochemical properties which commonly prevent drug penetration through physiological barriers.

The progress of nanotechnologies has opened up the possibility for controlling drug distribution and release at the tissue, cellular, and subcellular levels. One of the most promising approaches to the problem of enhancing drug efficiency is development of colloidal drug delivery systems on the basis of nanocarriers [1].

Development of Drug Nanocarriers

First Generation of Nanocarriers

On intravenous injection nanocarriers of the first generation, irrespective of their composition and morphology, are rapidly removed from the blood stream, being captured by the reticuloendothelial system. According to tissue distribution data, nanocarriers are predominantly accumulated in liver, spleen, and bone marrow cells. The key role is the accumulation and metabolism of nanocarriers belongs to the Kupffer cells of the liver reticuloendothelial system. Such selectivity gave reasons to suggest that drug dosage forms on the basis of nanosystems would prove efficient for therapy of liver neoplasms. Further research showed that the therapy with poly(butyl cyanoacrylate) nanoparticles loaded with the antitumor drug Doxorubicin reduced considerably the rate of metastasis of M5076 histiocytic sarcoma, an experimental cancer model. On the other hand, with a nanosomal drug form, the concentration of Doxorubicinin in the heart muscle, and, as a result, its toxic effect on the myocard is much reduced.

Nanosomal systems were found efficient for treatment of intracellular infections resistant to most standard antibiotics. It was found that poly(isohexyl cyanoacrylate) nanospheres encapsulating the half-synthetic antibiotic Ampicillin are 120 times more efficient for treatment of the infection caused by a *Salmonella typhimurium* infection in mice. The success of such treatment can be explained by the development of several directions of attack on the pathogen: First, Ampicillin associated with nanospheres is primarily accumulated in liver and spleen and, second, due to its enhanced penetration into phagocites, Ampicillin exhibits enhanced antibacterial effect on persistent forms of *Salmonella typhimurium* [2].

Second Generation of Nanocarriers

Regardless of quite promising results with first-generation nanocarriers, the applicability of such carriers is limited by their rapid elimination from the blood stream due to recognition of the mononuclear phagocyte system. Further research in this field was focused on the development of so-called invisible nanocarriers not captured by the reticulo–endothelial system [3].

A great breakthrough was the development of nanosomal systems coated with polyethylene glycol. The polymer coating allows extension of drug elimination half-time to several hours. There are two principal approaches to such sterically stabilized nanosystems: (1) adsorption of a propylene oxide−ethylene oxide copolymer on the surface of ready nanocarriers, (2) synthesis of a copolymer containing, in equal ratios, a hydrophilic polyethylene glycol and a hydrophobic biodegradable material (cyanoacrylate, polyester, etc.), which are introduced at the initial stage of production of nanocarriers.

Coating nanocarriers with a nonionogenic surfactant Poloxamine 908 allows the capture degree to be decreased to 8% (against 90% without coating) and, as a result, the fraction of nanocarriers in the blood stream to be increased to 65%. Physicochemical analysis of the nanocarrier−copolymer system revealed a much decreased opsonization degree (affinity of phagocytes to bacteria).

Two principal approaches allowing to avoid capture of nanocarriers with the reticuloendothelial system and to ensure their prolonged circulation in the blood stream. (1) Using polyethylene-glycolated nanosystems as carriers for substances with a short elimination half-time, as well as for unstable, rapidly metabolized or inactivated substances (for example, cytokines, growth factor, nucleic acids). (2) Therapy of various pathophysiological disorders associated with structural changes in the blood stream, which allows selective transport of a long-circulating nanocarrier directly to an affected tissue site. This is especially important in view of the physiological features of the endothelial whose permeability is much increased by inflammatory reactions, autoimmune diseases, malignant neoplasms, etc.

Since most drugs are either unable or scarcely able to overcome the blood−brain barrier (BBB), of particular interest are investigations into targeted drug transport to the central nervous system (CNS) [4]. When one needs to deliver a drug to specific targets in the CNS, the effect of a poor BBB permeability is compensated for by increasing drug dose, which, naturally, results in increased rates of adverse side effects. Drug transport could be induced by coating nanocarriers (to enhance their penetration power) with Polysorbate 80. This technological approach made it possible to transport through the BBB such drugs as Dalargin, Loperamide, Tubocurarine, and Doxorubicin. It is suggested that Polysorbate 80 induces adsorption of apolipoproteins E (the protein component of lipoproteids, which is independently involved in lipid metabolism in blood and in cholesterol metabolism in brain and some other organs) on nanoparticles, which ensures binding with specific receptors on the endothelial BBB surface and subsequent penetration of nanocarriers to the CNS.

Third Generation of Nanocarriers

The principal approach to the development of efficient nanocarriers for targeted drug delivery involves purposeful surface modification of nanocarriers to endow them with affinity to biological receptors by means of target molecules. Such molecules can be quite diverse in nature: antibodies, peptides, poly- and oligosaccharides, hormones, vitamins, etc.

Experimental tests of the efficiency of surface-modified nanocarriers, they were associated with folic acid. As known, receptors sensitive to folic acid are synthesized in large amounts on the surface of cancer cells, whereas the number of such receptors in healthy sites is quite limited [6]. Moreover, receptors exhibit expressed affinity to the ligand (folic acid), which allows especially efficient intracellular transport of a chemotherapeutic drug directly to the target. Note that folates associated with polyethylene-glycolated cyanoacrylate nanoparticles exhibit a higher affinity to receptoes that free folic acid, which is probably explained by the multivalence of the representative site [6].

The choice of the most suitable particle size for drug carriers depends on a number of factors: passability of arteriovenous capillaries (the particle size should be less than 1 μm), but this does not relate to “bypassing” particles which, sticking in capillaries, gradually release drug and then degrade; stability of nanocarrier suspensions in blood plasma, since particle aggregation causes strong toxic effects up to middle- and small-vessel thromboses [6]; ability of nanocarriers to penetrate into cells, which is characteristic of particles 50−300 nm in size; and viscosity of nanocarrier suspensions in blood plasma.

Morphological Groups of Drug Nanocarriers

In their structural characteristics nanocarriers for medical use destination are divided into two morphological groups: nanoparticles and nanocapsules.

Nanoparticles

This group of nanocarriers holds the greatest promise in terms of achievement of controlled drug release parameters, since the mobility of drug is restricted by a solid matrix [7].

Drug nanosystems of this type are monolithic, most commonly spherical formations containing drug either in the whole bulk of the nnaoparticle or on its surface. Drug release occurs gradually at a controlled rate from the surface or from the bulk of the nanoparticle as a result of its degradation or swelling.

There are several most common groups of carriers, differentiated by the material of the nanoparticles:

– thermally or chemically modified albumine;

– chemically modified polysaccharides (for example, dialdehyde starch);

– nanocrystals consisting exclusively of drugs ground to corresponding sizes which ensure their dissolution at rates higher than the dissolution rates of larger particles;

– biodegradable polymers and copolymers which gradually degrade in the body (polyalkyl cyanoacrylates, polylactide glycolides).

Drug nanocrystals compared with other nanosystems offe the following advatages: high content of the active substance (~100%); simple and predictable drug delivery (the release rate depends on the dissolution rate of nanocrystals); drug distribution in the body is controlled by the kinetic laws of drug dissolution; and simple and efficient production technology. Nanocrystals are not infrequently incorporated into macrocapsules, matrix tablets, etc. Addition of biospecific mucoadhesives allows the action of nanocrystals to be localized in a specific site of the gastrointestinal tract.

In the case of poorly soluble drugs, nanocrystal suspensions behave similarly solutions and can be used to prepare aerosols, say for beclomethasone dipropionate, a glucocorticosteroid used in asthma therapy. Injection of nanocrystals ensures longer retention of drug in the injection site and makes it possible to control drug distribution in the body and to avoid drug absorption with phagocytes.

Nanocrystals are used in diagnostic investigations of the lymphatic and circulatory systems, liver, and other organs by X-ray analysis, computed tomography, and magnetic resonance.

At present nanosystems on the basis of polymer carriers have attracted increasing interest in pharmacology, since they represent a type of therapeutic systems and are able to deliver drugs into cells. Such carriers protect the drug they contain from inactivation and prolong their action [5, 8]. Moreover, drug delivery nanosystems on the basis of polymer carriers offer such advantages as the possibility of fast and reproducible large-scale production, encapsulation of substances poorly soluble in water, and controlled drug accumulation in different body tissues and organs depending on particle size.

Nanocapsules

These nanocarriers are hollow spherical containers (wall thickness 10−30 nm) charged with a liquid drug solution. Drug release occurs via diffusion or via rupture of the nanocapsule. The release rate depends on the design of nanocapsules and their production technology.

Nanocapsules which possess a large specific surface area are especially suitable for encapsulation of poorly soluble drugs. After oral administration the absolute bioavailability of drug is enhanced, while the individual variability and influence of food consumption are attenuated. The maximum concentration of drug in plasma is reached faster.

Depending on the morphology of the material of nanocapsules and their production technology, several the most widespread types of such nanocarriers can be recognized: liposomes, polymer liposomes, and polymer micelles.

The membrane of liposomes consists of natural phospholipids, which predetermines many their attractive qualities. They are nontoxic, biodegradable, can be absorbed by cells under certain conditions, and liposomal membrane can merge with cellular membrane, which ensures intracellular delivery of the liposome content [9]. Moreover, the substance encapsulated in liposomes is protected from contact with enzymes, and this enhances the efficiency of drugs susceptible to biodegradation in biological fluids.

Liposomes (like other nanoparticles) form the basis for constructing efficient anticancer drugs. Since liposomes are larger than blood vessels, then, for instance, after intravenous injection nanoparticles do not leave the blood stream, i.e. their ability to penetrate into organs and tissues is limited. Consequently, the toxic effects of substances encapsulated in sharply decreased. On the other hand, this property can be employed for targeted delivery of chemotherapeutic drugs into solid tumors and inflammatory lesions, since capillaries supplying blood to these sites are, as a rule, strongly perforated, and liposomes will be accumulated in the tumor. This phenomenon was given the name "passive targeting."

At present a number of liposomal anticancer drugs (Anthracycline, Daunomycin, Doxorubicin, Vincristine, Annamycin, and Tretinoin) were launched on the global pharmaceutical market; many drugs are being at the stage of final clinical trials.

Liposomes, like other nanoparticles, are fairly rapidly captured by the reticuloendothelial system. This occurs due to interaction of liposomes with plasma proteins, viz. opsonins. Opsonins "label" drugs making them targets for reticuloendothelial cells. It is clear that prolongation of the circulation time of liposomes will further enhance the efficiency of liposomal drugs. Several years ago the surface of liposomes was suggested to modify with polymers with a flexible hydrophilic chain, for example, phosphatidyl ethanolamine conjugated with polyethylene glycol.

Liposomes are quite efficient for encapsulation of drugs targeted at reticuloendothelial cells, since it is just these cells that actively absorb nanoparticles. For example, liposomal drugs are used for treatment of intracellular microbial infection and for vaccination. Delivery of Amphotericin B directly to infected cells gives excellent results of treatment of systemic fungal infections. Such drugs (AmBiosome, ABLC, or Amphocil) are already available in many European countries; the latter drug has been licensed for the Russian market.

Polymer liposomes are lyotropic liquid crystals comprising amphiphilic bilayers with introduced polymerizing groups. Polymer liposomes are formed on dispersion in the aqueous medium of animal cell and lipid membranes. Depending on the size and number of bilayers, liposomes are divided into three classes: multilamellar vesicles, small monolamellar vesicles (diameter < 100 nm), and large monolamellar vesicles (diameter > 100 nm).

Like in simple liposomes, in polymer liposomes, too, the membrane consists of phospholipids of the plant or animal origin (sunflower oil, soya, or egg yolk), as well as ceramides (lipid components of the membrane, consisting of sphingosine and a fatty acid), cholesterol, fatty acids, and synthetic ionic and nonionic surfactants.

To prepare polymer analogs of biological membranes and polymer liposomes, the hydrophilic or hydrophobic part of phospholipids (or structurally similar synthetic analogs) are modified with groups capable of polymerizing in oriented ordered systems. The most common groups used for this purpose are methacrylic acid residues with terminal aliphatic radicals [10].

The principal disadvantage of liposomes as drug carriers is their fairly low stability in storage. This disadvantage is not characteristic of polymer nanoparticles which have the same application fields. However, unlike liposomes, polymer nanoparticles are made of a less safe material.

Polymer micelles are classed with lyophilic colloid systems which are associates of surfactant molecules. The morphology of micellar forms which can be obtained from amphiphilic polymers is quite diverse. It is commonly suggested that copolymers form micelles close to spherical in shape. However, as known, a large number of nonspherical micelles exist. These are various rod-shaped forms, rings, lamellar structures, band-like forms, tubular structures, and hexagonal packings.

The advantages of nanocapsules as drug carriers include their low toxicity (natural lipid components can be applied), as well as the possibility to obtain products with a high degree of separation due to special techniques (homogenization under pressure) [11]. However, controlled drug release from nanocapsules is hindered because of primarily small sizes and liquid components of carriers. It was found that extended release It was found that for extended release very lipophilic drugs should be included: Their octanol : water partition index should be more than 1000000 : 1.

Aspects of the Production Technology of Drug Nanosystems

The production technologies of nanosystems can be divided into two big groups, depending on what starting materials are used in their synthesis: lipid nanocarriers and polymer nanocarriers.

Drugs on the Basis of Lipid Nanocarriers

The principal ingredients of such preparations are an active substance, a lipid, an emulsifier, and water, as well as osmotic agents, matrix systems for freeze-drying, buffer solutions, etc. To decrease the risk of development of acute or chronic toxicity of drugs, they are produced using primarily physiologic lipids (here for the term "lipid" we mean triglycerides, monostearates, fatty acids, waxes, etc.) [12].

The choice of emulsifier depends on the administration route of the drug, which is largely limited to oral administration. The most common emulsifiers used in this case are various polysorbates, lecithin, bile acids, etc.

The majority of production technologies of drugs on lipid carriers are based on two processes: (1) homogenization of ingredients under various conditions and using different homogenization machines and (2) emulsification or microemulsification.

Homogenization is performed by rotary grinding or ultrasonic dispersion. Both technologies are fairly simple in operation. However, in the case of ultrasonic dispersion the dosage form may be contaminated with microparticles of the housing material of the dispersion machine.

Ahlin et al. [13] made use of a rotary homogenizer to produce lipid nanocarriers by the melt-emulsification process. Influence of various parameters of the process (emulsification time, stirring speed, cooling conditions, etc.) on the size of nanoparticles and zeta potential on their surfaces. In most cases the average particle size ranging from 100 to 200 nm results at the stirring rate of 20000−25000 rpm within 8−10 min.

Rotary homogenization consumes a lot of energy at a fairly low efficiency: The resulting average particle size is 0.5−2.5 μm, but this parameter may vary depending on the properties of the material to be ground. Furthermore, mechanical grinding endows particles with a surface electrostatic, which entails enhanced particle association. To avoid electrostatic charging of particles, a grinding technology with addition of surface stabilizers (glass, zinc oxide, ceramics, plastics) is applied. Thermal degradation of substances is prevented by performing the process at ~40°C. When drug crystals are ground in aqueous solution in the presence of a hydrophilic stabilizer, the pressure that develops may prove so high that the resulting drug nanoparticles are suspended in the stabilizer solution to form a stable system.

The high-pressure homogenization technology (10−200 MPa) makes it possible to obtain minimum-size particles and avoid their aggregation. This technology is based on the principle of grinding of particles in a high-speed fluid flow. The content of lipids in the substrate to be homogenized (normally 5−10%) has no effect on the grinding process, but successful homogenization is possible even if the lipid fraction is about 40%.

Thermal homogenization is performed at temperatures above the melting point of the lipid used. The same temperatures are used for mixing the primary emulsion (drug-charged lipid phase) with the aqueous emulsifying phase. The structure of the primary emulsion strongly affects the morphology of the final product, and, therefore, this phase is desirable that the phase is dispersed into droplets about a few micrometers in size. Further homogenization is performed already at an elevated temperature. Higher temperatures favor smaller particles, probably due to decreasing density of the inner medium [9], but, however, too high temperatures may be harmful both for the drug and for the carrier.

The homogenization process can be repeated many times, up to 3–5 cycles at a pressure of 50–150 MPa. Further increase of pressure may entail formation of coarser particles due to coalescence.

The primary product of melt homogenization is an emulsion formed by fluid-structured lipids [6, 14]. Lipid nanoparticles in themselves are formed when the emulsion is cooled to room or slightly lower temperature. Crystallization of lipids can be much delayed because of a small particle size, and the emulsion can preserve the state of a "supercooled melt" for a few months.

Cold homogenization allows solution of the three main problems of the above-described technology: (1) drugs are not destroyed under the action of high temperatures, (2) drugs are not redistributed into the aqueous phase when the components are mixed, and (3) the structure of lipids is not modified and the "supercooled melt" is not formed.

The production of lipid-encapsulated drugs by the cold homogenization technology requires temperature control to preserve lipids from melting.

The first stage here, like in thermal homogenization, involves drug incorporation into a hot lipid layer, after which the system is quenched (by means of dry ice or liquid nitrogen). The solidified lipid layers is ground to a particle size of 50–100 μm, which is favored by its enhanced shortness. Further on solid microparticles are dispersed in a cold emulsifier solution. The primary suspension is loaded into the homogenization machine at room or slightly lower temperature [5, 15].

This technology allows one to minimize exposure to heat (but not to avoid it completely). In general, coarse particles are formed, with a wide size distribution.

The emulsion homogenization process involves dissolution of the lipophilic materials in a water-immiscible solvent (for example, cyclohexane), followed by emulsification in water to obtain an oil/water emulsion. The solvent is evaporated under reduced pressure to obtain a dispersion of lipid nanocarriers.

The diameter of the resulting particles depends on the lipid content of the organic phase. Small particles are obtained at the lipid content of about 5% with respect to the organic solvent. At higher concentrations the dispersion efficiency decreases due to increasing density of the dispersion medium.

The advantage of this technology is that it excludes any exposure to heat; its principal disadvantage is the use of organic solvents.

The microemulsification production technology of nanosystems consists in dilution of a microemulsion formed by agitation of a mixture including a low-melting fatty acid (for example, steric), emulsifier (Polysorbate 20, 60, etc.), co-emulsifier (butanol, sodium monooctyl phosphate), and water. A hot microemulsion is dispersed in a cold water (2–3°C) at ratios ranging from 1:25 to 1:50. The degree of dilution depends on the composition of the microemulsion. According to published data, nanosized particles are already present in the microemulsion, and, as a result, no additional energy consumption for forming submicron particles is required. The latter circumstance is one of the principal advantages of microemulsification. However, due to dilution the content of lipids in the secondary emulsion, where nanoparticles are formed, is much lower than in other technologies [15].

In general, evaluating lipid-based nanosomal drug delivery systems, we would like to note that they are physiologically friendly and accessible, but, at the same time, their disadvantage is the lipid nanocarriers are unstable and drug release from them is hard to control. Moreover, the lipid component of the nanosystem is thermally unstable, which complicates certain technological stages. These technological and functional disadvantages of lipid-based dosage forms restrict their applicability, and such nanosystems should be improved [16].

Drugs on the Basis of Polymer Nanocarriers

Polymer nanocarriers are more stable than above-considered ones. However, the indubitably lower physiological friendliness of polymers necessitates correction to fit certain requirements.

Polymers for medical applications should be quite pure, and, in particular, should contain as little monomer admixtures as possible.

The key requirement is that the polymer carrier of biologically active substances should be biocompatible. Note that biocompatible polymers, even being nonpathogenic, are still able to cause undesirable reactions. Therefore, a short excretion time is the main requirement to biocompatible polymers.

Of importance is also biodegradability of carrier polymers. Since the principal route of degradation of substances in human body is enzymatic cleavage, the key task is to introduce groups structurally similar to natural substrates of the corresponding enzyme into the main and/or side chains of the carrier polymer. Therewith, polymer degradation reactions should not involve formation of toxic, pathogenic, or antigenic products or intermediate products. Naturally, the polymers in themselves, too, should not exert such effects. When it comes to polymer carriers for medical applications, it should be borne in mind that polymer forms of biologically active substances, introduced in human body, not infrequently caused sarcoma, which was observed in animal experiments. This fact is not probably associated with the nature of the polymer, since this effect was not observed in the case of implanted polymer particles loaded with noble metals.

The principal components of polymer drugs delivery systems are the drug itself, polymer, emulsifier, and water or organic solvent. Depending on the drug application, the formulation can also include such components as osmotic agents, matrix systems for freeze-drying, buffer solutions, etc. [17].

Polymer nanocarriers can be obtained by different technologies, the most common of which are direct dissolution (dispersion), dialysis, and emulsification (nanoprecipitation) [18].

The first technology involves direct dissolution of polymers in the aqueous phase at room or elevated temperature to obtain a solution, where the concentration of the polymer is much higher than the critical micelle concentration. The nanocolloid particles obtained by this technology include nanospheres and micellar systems. It is important to take into account that this technology is suitable for generating nanoparticles from readily water-soluble copolymers, such as Pluronics or structurally similar copolymers.

In this technology, nanocarriers are formed spontaneously, as a result of dispersion of the macro phase into colloid particles. To form nanoparticles, quite a strong decrease of the surface tension is required, up to 10^2–10^3 mJ m^{-2}. The reasons causing formation of self-organized structures are largely dependent on the nature of the liquid phase and the nature of the polymer [10]. The self-organization processes in aqueous solutions are associated with a total entropy increase of the system $dS > 0$, which is contributed by changes of the entropies of the disperse phase dS_d and dispersion medium dS_m. In this case, the local entropy decrease of copolymer molecules in micellization and aggregation processes is overcompensated by an increase of the entropy of water molecules and a total charge of the entropy of the system $dS > 0$.

Nanocarriers from scarcely water-soluble copolymers are commonly prepared by the dialysis technology. To this end, polymers are dissolved in a mixture of water and water-miscible organic solvents (DMSO, DMF, acetonitrile, THF), and this mixture is dialyzed against water.

The polymer nanosystems obtained by the direct dissolution and dialysis technologies generally have a spherical shape, but other shapes are also not excluded.

To obtain nanocarriers, primarily nanospheres, nanocapsules, and nanocrystals, by the emulsification technology (or double emulsification for nanocapsules), an amphiphilic polymer is dissolved in an organic solvent and the resulting solution is diluted with water to form an emulsion stabilized with the amphiphilic polymer. A nanoemulsion is formed by unltrasonicaltion of the emulsion. The organic solvent is then removed, after which both amorphous and crystalline ultradisperse nanocarriers may form in the aqueous phase [19].

The emulsification technology, like dialysis, are suitable for polymers with strongly expressed hydrophobic properties.

Nanocarriers are also produced by the supercritical fluid technology. The most common supercritical fluid used in this technology is carbon dioxide, which is due to its low toxicity, nonflammability, low cost, and high solubilizing ability. The latter characteristic of carbon dioxide can be controlled by varying pressure or temperature. The formation of a new nano- or microdisperse phase is based on the principle, according to which phase separation occurs when the solvent dissolving the substance to be precipitated is replaced by another solvent. Mixing of supercritical gas or fluid with a solution of a substance to be precipitated (the antisolvent process) was used for production of ultrafine particles [20].

The above-described technological approaches to production of nanosized drug carriers allow a lot of variations. The multifactor and polyfunctional parameters of nanoparticle production technologies and physicochemical features of individual substances make possible essential optimization of the process of production of therapeutic delivery systems.

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