

SECTION 10.

CHEMISTRY, CHEMICAL ENGINEERING AND BIOENGINEERING

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LIPOSOMES IN HUMAN THERAPY: A REVOLUTION IN DRUG DELIVERY

Abstract. *Current developments in pharmaceutical science are focused on improving drug delivery systems to enhance the efficacy and safety of pharmacotherapy. One of the most promising areas is the use of liposomes nanostructured vesicles consisting of phospholipid bilayers capable of encapsulating both hydrophilic and lipophilic drug substances. Liposomes possess high biocompatibility, low immunogenicity and the potential for surface modification to enable targeted drug delivery. This paper provides an overview of current understanding of the structure of liposomes, the mechanisms of their interaction with cells, the advantages and limitations of liposomal drug formulations, as well as the main areas of their application in clinical practice. Particular attention is paid to the use of liposomes in oncology, antimicrobial therapy and vaccine development. It is demonstrated that liposomal delivery systems enable an increase in the bioavailability of medicinal substances, a reduction in their systemic toxicity and the provision of controlled release of active compounds.*

Introduction. One of the key challenges facing modern pharmaceutical science is the development of effective drug delivery systems that ensure the targeted action of active pharmaceutical ingredients and minimise side effects. Traditional dosage forms are often characterised by low bioavailability, rapid degradation of active substances and insufficient selectivity of distribution within the body [1,2].

In recent decades, considerable attention has been paid to the use of nanotechnologies in pharmacy, with liposomes occupying a special place among them. Liposomes are spherical vesicles consisting of one or more phospholipid bilayers surrounding an aqueous phase. Such structures are capable of encapsulating a wide range of medicinal substances and ensuring their controlled release. [3].

Thanks to their structure, liposomes can transport both hydrophilic compounds and lipophilic substances embedded in the lipid bilayer of the membrane. This makes them versatile drug delivery vehicles. [4].

The high biocompatibility of phospholipids, which are similar in composition to cell membranes, accounts for the low toxicity and good tolerability of liposomal drug delivery systems [5].

The aim of this study is to analyse current scientific data on liposomes as a drug delivery system and to assess the prospects for their use in human therapy.

History of application and technological development. The history of the development of liposomal drug delivery systems began in the second half of the 20th century and is closely linked to advances in research into membrane biophysics and pharmaceutical nanotechnology. Liposomes were first described in 1965 by the British scientist Alec D. Bangham and his colleagues whilst studying phospholipids using electron microscopy. The scientists discovered that phospholipids in an aqueous medium are capable of spontaneously forming closed bilayer structures, similar in structure to cell membranes [6]. This discovery marked the beginning of a new field of research focused on the study of lipid vesicles and their potential applications in biomedicine.

In the 1970s, the first studies were conducted aimed at using liposomes as drug delivery vehicles. During this period, it was established that liposomes are capable of encapsulating various pharmacologically active compounds and protecting them from enzymatic degradation in the body [7]. At the same time, methods for producing liposomes were actively studied, including hydration of a thin lipid film, ultrasonic dispersion and extrusion, which made it possible to control the size and structure of the resulting vesicles [8].

In the 1980s, research into liposomal drug delivery systems advanced significantly thanks to improvements in stabilisation techniques. One of the most important achievements was the development of so-called ‘long-lived’ or ‘stealth liposomes’, whose surface is modified with polyethylene glycol (PEG). This modification made it possible to reduce the uptake of liposomes by cells of the reticuloendothelial system and increase their circulation time in the bloodstream [9].

The next stage in the development of the technology was the introduction of liposomal drugs into clinical practice. In 1995, the first liposomal anticancer drug was registered a liposomal form of doxorubicin (Doxil®), intended for the treatment of certain oncological diseases [10]. The use of the liposomal formulation made it possible to significantly reduce the cardiotoxicity of doxorubicin and improve its pharmacokinetic characteristics.

In the years that followed, other liposomal preparations were developed and introduced into medical practice, including a liposomal formulation of amphotericin B for the treatment of systemic fungal infections and liposomal formulations of cytostatic drugs for anticancer therapy [11]. The clinical success of these

preparations confirmed the high efficacy of liposomes as a drug delivery system.

In the 21st century, the development of liposomal technologies is closely linked to advances in nanomedicine. Current research is focused on creating targeted liposomes, the surface of which is modified with antibodies, peptides or receptor ligands for selective interaction with specific cells or tissues [12].

In addition, stimulus-responsive liposomes are being actively developed, capable of releasing drugs in response to specific factors, such as changes in pH, temperature or enzymatic activity [13].

Lipid nanoparticles, structurally similar to liposomes, have gained particular significance in recent years due to the development of nucleic acid delivery technologies. They are used to transport mRNA and other genetic constructs, opening up new prospects in the fields of vaccinology and gene therapy [14].

Thus, over the course of several decades, liposomes have evolved from an experimental model of membrane structures into one of the most promising drug delivery platforms. The development of liposomal technologies continues to be one of the key areas of modern pharmaceutical science and nanomedicine [15].

Structure and classification of liposomes. Liposomes are spherical vesicles formed by one or more phospholipid bilayers that surround an aqueous internal phase. Liposomes form in an aqueous medium as a result of the spontaneous self-assembly of amphiphilic phospholipid molecules. The hydrophilic polar heads of the phospholipids are oriented towards the aqueous phase, whilst the hydrophobic hydrocarbon chains are located within the lipid bilayer. This structure ensures that liposomes resemble biological cell membranes, which accounts for their high biocompatibility and low toxicity [6].

The phospholipid bilayer is the main structural element of liposomes. Natural or synthetic phospholipids, such as phosphatidylcholine, phosphatidylethanolamine, phosphatidylserine and sphingomyelin, are most commonly used to produce liposomes. To increase the stability of liposomal membranes, cholesterol is often incorporated into the lipid phase, as it regulates the fluidity and permeability of the lipid bilayer [16].

One of the most important characteristics of liposomes is their ability to encapsulate various drug substances. Hydrophilic compounds are localised within the aqueous interior of the liposome, whereas lipophilic molecules can become embedded in the lipid bilayer of the membrane. Amphiphilic substances, in turn, are capable of distributing themselves in both the lipid and aqueous phases of the liposome [8]. As a result, liposomes are regarded as a universal drug delivery system.

Liposomes can be classified according to several parameters, including size,

the number of lipid bilayers and structural features. The most common classification is based on the number of lipid bilayers and the size of the vesicles [1].

Based on the number of lipid layers, liposomes are classified as unilamellar vesicles, which consist of a single lipid bilayer, and multilamellar vesicles, which have several concentrically arranged lipid membranes.

Key parameters of liposomes. The efficacy of liposomes as a delivery system is determined by a number of key characteristics:

1. Particle size - ranges from 50 to 300 nm (sometimes up to 1 μm). The size determines circulation in the blood, penetration through the endothelium and the pharmacokinetic profile [11, 15].

2. Lamellarity - single-layer (SUV, Small Unilamellar Vesicles), multilamellar (MLV, Multilamellar Vesicles) and large single-layer (LUV, Large Unilamellar Vesicles). Multilamellar liposomes provide greater capacity, whilst unilamellar liposomes offer more controlled release [8,17].

3. Membrane composition - includes phosphatidylcholine, phosphatidylethanolamine, cholesterol and functionalised lipids. The composition determines the membrane's rigidity, its resistance to oxidation and its biocompatibility [9,12].

Unilamellar liposomes, in turn, are classified into several types based on size:

- single-layer, with a diameter of 20–100 nm, provide rapid release and are easily modified.
- LUV (Large Unilamellar Vesicles) — single-layer, 100–1000 nm, high capacity, suitable for encapsulating large molecules.
- MLV (Multilamellar Vesicles) — multilamellar, 500–5000 nm, high capacity for drug substances, slow release [11].

Multilamellar vesicles (MLVs) are characterised by the presence of several phospholipid bilayers separated by aqueous layers. Their diameter typically ranges from 0.5 to several micrometres. Such structures have a high capacity for encapsulating lipophilic compounds, but are characterised by less controllable kinetics of drug release [9].

Furthermore, modern pharmaceutical technology distinguishes specialised types of liposomes with modified properties. These include:

- pegylated liposomes (stealth liposomes) the surface is modified with polyethylene glycol to increase circulation time in the bloodstream;
- targeted liposomes — on the surface of which antibodies, peptides or receptor ligands are attached for selective interaction with specific cells;
- stimulus-responsive liposomes, capable of releasing drugs in response to specific factors, such as changes in pH, temperature or enzymatic activity [13].

Thus, the variety of liposome structural types and the possibility of modifying their composition make it possible to create drug delivery systems with specified pharmacokinetic and pharmacodynamic characteristics. This makes liposomes one of the most promising platforms for the development of modern medicinal products [15].

Advantages of liposomal drug delivery systems. Liposomes are one of the most extensively studied and widely used nanostructured drug delivery systems. Their use in pharmaceutical technology is due to a number of advantages associated with the structural features and physicochemical properties of phospholipid vesicles. Due to their structure, liposomes are capable of significantly altering the pharmacokinetics and pharmacodynamics of drug substances, thereby enhancing the efficacy and safety of pharmacotherapy [15].

One of the key advantages of liposomal systems is the enhancement of the bioavailability of medicinal substances. Encapsulating active compounds within liposomes helps to protect them from chemical and enzymatic degradation in biological fluids, thereby preserving the therapeutic activity of the drug and prolonging its duration of action [18].

Another important advantage is the reduction in drug toxicity. Many pharmacologically active substances, particularly anticancer drugs and antifungal agents, have pronounced side effects. Encapsulating such compounds in liposomes helps limit their interaction with healthy tissues and reduce systemic toxicity [11]. For example, liposomal forms of doxorubicin are characterised by significantly lower cardiotoxicity compared to traditional forms of the drug [10].

Liposomes also provide sustained release of medicinal substances. The lipid bilayer acts as a barrier that regulates the rate of diffusion of the medicinal compound from the interior of the liposome into the external environment. This allows the therapeutic concentration of the drug to be maintained in the body for a longer period [13].

A key advantage of liposomal systems is their ability to deliver drugs in a targeted manner. Modern technologies allow the surface of liposomes to be modified with various ligands, antibodies, peptides or carbohydrate residues capable of interacting with specific receptors on target cells. This approach ensures selective accumulation of the drug in pathologically altered tissues and enhances the efficacy of therapy [17].

Of particular importance is the use of pegylated liposomes (stealth liposomes), the surface of which is coated with polyethylene glycol. This modification reduces the recognition of liposomes by cells of the mononuclear phagocytic system and increases their circulation time in the bloodstream. Consequently, the likelihood of

drug delivery to target tissues is increased [9].

Furthermore, liposomes possess high biocompatibility and biodegradability. The main components of liposomal membranes phospholipids and cholesterol are natural components of human cell membranes. This reduces the risk of toxic and immune reactions when using liposomal drug formulations [8].

Another advantage of liposomes is their versatility in encapsulating various types of drug substances. Liposomes are capable of carrying hydrophilic, lipophilic and amphiphilic compounds, as well as biomolecules, including proteins, peptides and nucleic acids [14]. As a result, liposomal systems are actively used not only for the delivery of traditional drugs, but also in modern fields of biomedicine, including gene therapy and vaccinology.

Thus, the combination of high biocompatibility, the ability to control drug release, and the potential for targeted delivery makes liposomes one of the most promising platforms for the development of modern pharmaceuticals. Their use allows for a significant increase in the efficacy of pharmacotherapy and a reduction in the risk of adverse drug reactions [19].

Prospects for the development of liposomal drug delivery systems. The development of liposomal drug delivery systems remains one of the most dynamic areas of modern pharmaceutical science and nanomedicine. Thanks to the ability to modify the composition of the lipid membrane, particle size and surface properties, liposomes can be adapted to address a wide range of therapeutic challenges. Current research is focused on creating more effective, selective and safe liposomal formulations capable of ensuring the controlled delivery of drugs to target tissues [15].

One of the most promising areas is the development of targeted liposomal delivery systems. Such systems are created by modifying the surface of liposomes with specific ligands, antibodies, peptides or protein fragments capable of interacting with target cell receptors. This enables the selective accumulation of the drug in pathological tissues, such as tumour cells, thereby increasing the efficacy of therapy and reducing the risk of side effects [12].

An important area of research involves the development of stimulus-responsive liposomes capable of releasing a drug in response to specific physicochemical or biological stimuli. Such factors include changes in pH, temperature and enzymatic activity, as well as exposure to external physical factors, such as ultrasound or a magnetic field. Such systems enable the controlled and localised release of drugs directly at the site of the pathological process [13].

The development of multifunctional liposomes combining several mechanisms of action is of considerable interest. Such systems can simultaneously provide

targeted drug delivery, controlled drug release and diagnostic functions. Such nanostructures are regarded as promising platforms for so-called theranostics, which combines diagnostics and therapy within a single system [17].

A separate area of research involves the use of liposomes for the delivery of biomacromolecules, including proteins, peptides, nucleic acids and gene constructs. In recent years, lipid nanoparticles, which are structurally similar to liposomes, have been actively used for the delivery of mRNA and other genetic materials. This field opens up new prospects in the development of vaccines, gene therapy and personalised medicine [14].

Another promising area is the development of biomimetic liposomes, whose structure mimics natural cell membranes. Such systems may incorporate membrane proteins, glycolipids and other biologically active components, thereby improving the interaction of liposomes with the body's cells and enhancing the efficiency of drug delivery [20].

Furthermore, considerable attention is being paid to improving technologies for the industrial production of liposomal drug formulations. Current research is focused on developing methods for the scalable production of liposomes with a narrow size distribution, high encapsulation efficiency and storage stability. The use of microfluidics, high-efficiency extrusion and controlled self-assembly technologies allows for a significant improvement in the reproducibility and quality of liposomal preparations [21].

Thus, the further development of liposomal drug delivery systems is linked to the integration of advances in nanotechnology, molecular biology and pharmaceutical technology. The creation of intelligent liposomal platforms with high selectivity and controlled drug release characteristics opens up broad prospects for improving the efficacy of pharmacotherapy and the development of innovative medicinal products [11].

Conclusion. Liposomes represent one of the most promising and extensively studied drug delivery platforms in modern pharmaceutical science.

Over the past six decades, liposome technology has progressed from fundamental research into membrane structures to the implementation of clinically significant drug formulations, including anticancer drugs, antifungal agents and vaccines [6,10,19].

The main advantages of liposomal systems lie in their ability to encapsulate a wide range of drug substances, protect them from enzymatic degradation, ensure controlled release and reduce the systemic toxicity of drugs [11,15,18]. The ability to modify the surface of liposomes using polyethylene glycol, antibodies, peptides and other biologically active molecules allows the creation of targeted delivery

systems capable of selectively accumulating in pathological tissues, which significantly increases the efficacy of therapy [7,17].

Recent studies confirm that liposomes are capable of effectively encapsulating both small molecules and biological macromolecules, ensuring targeted delivery to diseased tissues and minimising systemic toxicity [14,17]. Various modifications of liposomes have been developed PEGylated, targeted and ‘smart’ systems that respond to internal stimuli within the body, thereby expanding their therapeutic potential [14,15].

Key achievements include the clinical efficacy of liposomal preparations in oncology, infectious and rare diseases, as well as the introduction of nanotechnologies to improve the pharmacokinetics and safety of therapy [18,19]. The main limitations are related to technological and manufacturing challenges: ensuring formulation stability, reproducibility of particle parameters, scaling up production, and compliance with strict regulatory requirements [6,15].

Potential for expanding clinical applications. Liposomes offer great potential for broadening the therapeutic spectrum: they can be used to deliver gene therapies, vaccines, combination therapies and drugs for the treatment of central nervous system disorders [11,15]. The combination of targeted modifications and intelligent release control systems opens up new possibilities in personalised medicine.

A look to the future: personalised and targeted medicine. The future of liposomal systems lies in the integration of nanotechnology and molecular targeting, which will enable the creation of personalised and highly effective therapies with minimal side effects. The development of ‘smart’ liposomes, combined and multifunctional delivery platforms promises to revolutionise approaches to the treatment of complex diseases and expand the horizons of targeted medicine [12,14,17].

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