UDC 578.81: 615.33 https://doi.org/10.15407/biotech16.05.022

PROSPECTS FOR THE CREATION OF LIPOSOMAL ANTIMICROBIALS BASED ON PHAGES

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Received 2023/09/15
Revised 2023/10/17
Accepted 2023/10/31

The emergence of many pathogenic microorganisms, which are resistant to known antibiotics, indicates the need to find new strategies to fight them.

Aim. The article is devoted to the analysis of modern research on liposomal forms of phages as a promising strategy for fighting microbial infections.

Methods. Analysis of modern national and foreign research devoted to the bacteriophage encapsulation into liposomes and the evaluation of the efficacy of this drug delivery system in antimicrobial therapy.

Results. Bacteriophage encapsulation into liposomal nanoparticles protects phages from the negative effects of external factors, increases the period of circulation in the organism, ensures increased bioavailability of phage particles and, as a result, increases the efficacy of antimicrobial treatment. Liposomal forms of phages have demonstrated their effectiveness in fighting many common pathogenic bacteria, including *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Mycobacterium tuberculosis*, *Salmonella*, etc.

Conclusions. Liposomal phages have prospects as antimicrobial drugs, however, for their widespread use in clinical practice, preclinical and clinical studies are required to confirm their effecace and safety.

Key words: nanobiotechnology; drug delivery system; liposome; bacteriophage; phage therapy; antimicrobial drug.

Increasing resistance of pathogenic microorganisms to antibiotics has led to the emergence of new generation of drugs, such as liposomal (LS) forms of antimicrobials. LS is a promising strategy for treatment options for currently untreatable infections [1–3]. There are FDA-approved LS forms of antibiotics on the pharmaceutical market, such as amphotericin B, amikacin, nystatin, etc. LS forms of polymyxin B, vancomycin, gentamicin, tobramycin, norfloxacin, azithromycin, and carbapenem are at various stages of research. In addition, antitumor antibiotics in the LS form, daunorubicin and doxorubicin hydrochloride, are widely used in the clinic, that make it possible to fight resistant forms of tumors [1–3].

The use of LSs as components of drug delivery system allows to change the pharmacokinetics of the encapsulated active pharmaceutical ingredient (API), increase its bioavailability and efficiency [4–7]. LS forms of APIs have undeniable advantages in the development of antimicrobial drugs. In terms of practical use, LS drug delivery systems are the most successful in nanomedicine. The creation of LS drugs is one of the promising areas of modern medicine and nanopharmacology due to the following advantages of LSs [1, 2, 8–10]:

– to prolong the circulation of the API in the body;

– to change the pharmacokinetics of drugs, significantly increasing their pharmacological effect;

– to protect the API from the degradation by external factors in the body (enzymes, pH, oxidation, etc.);

–- to suppress API-resistant forms of bacteria and tumor cells;

– to protect the cells and tissues of the body from the toxic effects of drugs;

– to increase the bioavailability of lipophilic APIs;

– to provide direct interaction or fusion of LS lipid bilayers and membranes of bacterial or tumor cells, increasing the concentration of antibiotic in bacteria or tumor cells and thus improving the therapeutic effect of the antibiotic;

– to penetrate through the blood-brain barrier and deliver the LS encapsulated API to the cells of microorganisms or tumor cells;

– to be administrated intravenously, orally, inhalation and other ways, as sterile dosage forms that do not contain endotoxins and toxic substances.

The emergence of resistant forms of microorganisms has led to a resurgence of interest in bacteriophage, or phage therapy. The relevance of phage therapy is also explained by the fact that every year there are very few new antibiotics or new dosage forms of known antibiotic APIs, while humanity is facing an increase in resistant forms of infectious agents. Phages are recognized as safe for use in the clinic and do not lead to significant specific side effects [11–17]. The action of a lytic bacteriophage is as follows: the lytic phage binds to a specific surface receptor and introduce the phage DNA into bacterium, where early gene expression, particle assembly and release of phage from the host cell is carried out. A full lytic cycle typically creates 100–200 new phage particles and is completed in about the same time as the doubling time of the bacterial host cell.

Bacteriophages as antibacterial agents

The development of modern science has revived interest in drugs based on phages. Biotechnology allows to introduce phages into our daily lives in new ways. Approved preparations based on bacteriophages prevent contamination of a number of products, such as meat, fish, fruits, vegetables, dairy products [18, 19], with pathogenic bacteria, such as *Listeria monocytogenes*, *Salmonella enterica*, *Chigella*, *Escherichia coli*. Sprayable phage solutions are approved for protecting growing plants and animals from bacterial diseases, phage-based biocides can penetrate biofilms to treat and protect surfaces from contamination or bacterial corrosion. Biotechnological methods are constantly being developed and allows to use bacteriophages for gene delivery and carriers of vaccine antigens. In addition, lytic phages can act as selective and specific probes for the detection of pathogenic bacteria, such as *Staphylococcus aureus* [20–21].

The possibility of using bacteriophages in the treatment of infectious diseases is limited by a number of factors, we are going to focus only on the main problems [22–25]:

1. The instability of phages is associated with their physical and chemical properties as well as external environmental factors. Despite the fact that phage preparations are stable in buffer-salt solutions for at least 1–2 years at a temperature of 2–8 °C, when taken orally, intravenously or intramuscularly, phage suspensions enter the environment with high temperature, non-optimal pH value, different osmotic conditions, enzymes in the stomach and intestines, that leads to instability of phage particles. In addition, the phage stability can be affected by the shape and size of phages, namely the size of the head, and the length and thickness of the tail. The loss of stability of phage naturally leads to a loss of titer, and consequently to a loss of infectivity of it. It should also be noted that it is proposed to use a mixture of phage particles (a phage cocktail) for phage therapy to prevent bacterial infections in clinic. The administration of phage cocktails may effectively prevent bacterial resistance and improve clinical outcomes. According to a number of authors, a mixture of phage cocktails is less stable.

2. The loss of specificity of phages is associated with bacterial resistance and emergence of resistance to phages.

3. The emergence of phage-neutralizing antibodies is one of factors that reduce the activity of phage therapy. Furthermore, the phage therapy requires repeated administration of phages, that in turn leads to an increase in the level of phage-neutralizing antibodies.

4. The phage therapy is low effective for patients infected with intracellular pathogens (*Mycobacterium tuberculosis*, *Salmonella*, *Staphylococcus*) located, for example, in phagocytic cells.

Perspectives of liposomal forms of phages

The encapsulation of phages into LS nanoparticles is one of the strategies for increasing the efficacy of phage therapy, as it has been demonstrated for antibiotic therapy.

Having the experience in LS drugs creation, we believe that LS drugs are the most promising direction of drug delivery systems today.

By analyzing the problems related to the use of phages, advantages of LS forms and our knowledge in the liposomology, we believe that there is a real opportunity to use LSs as drug delivery system in phage therapy in the field of oncology and infectious diseases. In this case, the LS system of phage therapy will significantly overcome these problems. Taking into account that a number of viruses were successfully encapsulated in LSs while maintaining their high cell transfection efficiency, the creation of LS forms of bacteriophage preparations is quite realistic [26–29]. Oncolytic viruses, polioviruses, retroviruses, and others were encapsulated in LSs of various compositions, and LSs containing the virus were able to infect cells by merging with the cell membrane. The transfection efficiency of LS form of adenovirus was 4 times higher compared to non-encapsulated one. Unlike the viruses, the encapsulation of phages into LSs will require another lipid compositions of LS nanoparticles and another technological schemes, because of different size and properties of phages and other viruses. However, it could be used the same technological principles for obtaining of LS forms of phages, lyophilization or spray drying, and cryoprotectant selection as for obtaining LS forms of other preparations.

In recent years, research efforts have been focused on the possibility of using LSs for phage therapy, for example, against *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, *Enterococcus faecium*, *Mycobacterium tuberculosis*, *Salmonella*, *Listeria monocytogenes*, etc. Various methods have been proposed for obtaining bacteriophages-containing LS nanoparticles [30, 31]. The following paragraphs are devoted to research describing the production and properties of LS phages.

Bacteriophages against *Salmonella*

Salmonellosis is one the main intestinal infections in humans and animals, caused by bacteria of the family *Enterobacteriaceaee* — *Salmonella*, which colonizes the intestinal cells, resulting in intoxication and damage of the gastrointestinal tract. Salmonella phages were among the first to be used for phage therapy and encapsulated in LSs. Bacteriophages UAB_Phi20, UAB_Phi78, UAB_Phi87 against *Salmonella* strains were encapsulated in positively charged LSs (31.6 mV) with a diameter of 309 to 326 nm. LSs were prepared by the lipid film method followed by hydration and extrusion. LSs consisted of 1,2-dilauroyl-sn-glycero-3-phosphocholine (DLPC), cholesteryl-PEG600, cholesterol, and cholesteryl-3β-N(dimethylaminoethyl) carbamate hydrochloride in a molar ratio of 1 : 0.1 : 0.2 : 0.7. In order to study the stability of phages, LSs were subjected to the action of stomach acid (pH 2.8), and the phage titer decreased from 3.7 to 5.4 log units, whereas the titer of non-encapsulated phages decreased from 5.7 to 7.8 log units in stomach acid, that confirms the protection of the phage activity in LS form in low pH conditions. Both LS phages and free phage suspension protected salmonella-infected chickens *in vivo* when administered daily for 6 days. However, LS phages protection was maintained up to 1 week after treatment was stopped, and free phage activity was completely lost by this time [32].

Using salmonella phage, two different methodologies for bacteriophage encapsulating using two biocompatible materials were offered, a cationic lipid mixture and a combination of alginate with anthracite $CaCO_3$ [33]. The purified phage lysate with concentration of 10^{10}–10^{11} PFU/ml was used for phage encapsulation. Both techniques have been successfully applied to encapsulate salmonella phages with different morphologies, and what is important the used material does not change the antibacterial action of phages. The authors believe that both technologies can also be adapted to encapsulation and stabilization of any bacteriophage for, that will allow to protect phages from critical environmental conditions. Orally administered LS form of salmonella phages was stable in the stomach in mice.

Bacteriophages against *Mycobacterium tuberculosis*

The discovery of phages specific to *Mycobacterium* gives hope that phage therapy will be safe and effective against extracellular bacteria [34]. The phage penetration into intracellular and granulomatous media, as well as synergistic effects with antibiotics, are important issues in the treatment of tuberculosis. The use of LSs can provide an effective intracellular penetration of bacteriophages [35]. Mycobacteriophage TM4 encapsulated LSs were prepared from 1,2-dipalmitoyl-sn-glycero-3-phosphocholine

(DPPC), 1,2-dioleoyl-sn-glycero-3-phosphocholine (DOPC), and the fluorescent lipid Texas Red™ 1,2-dihexadecanoyl-*sn*-glycero-3-phosphoethanolamine (DHPE). The resulting LS size was less than 5 μm, and the possibility of inhalation delivery of mycobacteriophage containing LSs to lungs was shown. In addition, phages encapsulated in LSs penetrated monocyte cells more efficiently than free phages. According to the authors, LS phages can make it possible to fight off intracellular pathogens due to their penetration into eukaryotic cells [36].

LS form of lytic mycobacteriophage D29 for the treatment of tuberculosis infection was prepared from phosphatidylcholine (PC) and cholesterol in a ratio of 3:1 by two methods: extrusion and chromatography on Sephadex G-75 using sodium deoxycholate in 20% ethanol [37]. The first method gives LSs with a size of 0.8 μm and a phage encapsulation of about 40%, and the second method gives LSs with a size of 0.25 μm and a phage encapsulation of about 25%. The lytic effect of the LS form of mycobacteriophage D29 was established both on the model of tuberculous granuloma formed in the presence of *M. tuberculosis* in human mononuclear blood cells *in vitro*, and on the model of tuberculous infection in C57Bl/6 mice. The use of the LS form of lytic mycobacteriophages D29 with a size of 0.8 μm showed the most pronounced significant antimycobacterial effect.

The macrophage cell culture RAW264-7 was infected for 24 hours with *M. tuberculosis* H37RV at a concentration of 10^7 CFU/ml, and macrophages were isolated by centrifugation in a Ficoll density gradient [38]. Phage D29 in a concentration at least 10^8 PFU/ml was purified on an ion exchange column packed with Q-sepharose, and then shaken with a phospholipid film containing PC and cholesterol, the obtained lipid particles containing mycobacteriophage were homogenized by 20-fold extrusion and filtered through filters with pore size of 0.4 μm. The phage encapsulation into LSs was controlled by PCR analysis of phage DNA. There were 82 colonies of *M. tuberculosis* H37RV in control sample, 17 colonies in the sample treated with free mycobacteriophage, and 7 colonies in the sample treated with LS form of phage, that proves a higher antibacterial effect of mycobacteriophages encapsulated in LSs with a size of about 400 nm. In the following research the antimycobacterial action of lytic bacteriophage D29 both in free and LS forms was shown to varying degrees in cell models of intracellularly infected macrophages RAW264-7 and tuberculous granuloma formed by human blood mononuclear cells [39].

Bacteriophages against *Klebsiella pneumoniae*

Nosocomial infections caused by *K. pneumoniae* are the main cause of morbidity and mortality among burn patients [40]. The phage therapy is a safe and effective strategy for fighting against antibiotic resistant pathogens. Despite the fact that the promise of the phage therapy has been confirmed in a number of studies [41–43], to date, none of the phage-based treatments has been comprehensively studied in patients and has not reached commercialization. One of the reasons is the rapid clearance of phages from our body by reticuloendothelial system and a poor pharmacokinetic profile, that negatively affects the treatment efficacy. In this regard, attempts are being made to create LS forms of bacteriophages, in particular, for the treatment of diseases caused by *K. pneumoniae*. For example, a decrease in pro-inflammatory and a significant increase in anti-inflammatory cytokines in the lung homogenates of mice treated with the LS form of lytic bacteriophage T7 was shown, which indicates an increased effectiveness of the LS phages in the treatment of pneumonia in a model of *K. pneumoniae* B5055 mediated croupous pneumonia in mice [44]. The phage suspension was rapidly absorbed by the reticuloendothelial system and phages could not be determined, whereas encapsulated in LSs or bound to nanoparticles phages were detected in the body for a longer time [45]. LSs consisted of PC, cholesterol, Tween-80, and stearylamine in a ratio of 8 : 2 : 1 : 0.5. The average size of LS nanoparticles was 229.83 nm, and the phage encapsulation was 79.2 ± 5.6%. The use of LS encapsulated phage cocktail led to an increased therapeutic effect in the treatment of *K. pneumoniae* mediated burn wounds [46]. The pharmacokinetics of a phage cocktail containing five bacteriophages against *K. pneumoniae* encapsulated in cationic LSs was studied in intraperitoneal administration in BALB/c mice [46]. When studying the circulation time of phages in the blood and the residence time in various organs, LS encapsulated phages were detected in the spleen, liver and blood for almost 48 hours, while free phages were eliminated after 24 hours. An efficacy of LS phage was performed in a model of *K. pneumonia*

mediated burn wound infection in mice. Due to the long circulation time, a number of bacteria in the blood of mice treated with cationic LS phages was reduced more effective in comparison with mice treated with free phage. Furthermore, the use of phages encapsulated in cationic LSs provided a faster infection. LS particles containing phages against *K. pneumoniae* remained in the blood for a longer period than free phage particles, and chitosan-coated small LSs containing phages was detected in the gastrointestinal tract longer than large multilamellar LSs.

Bacteriophages against *Staphylococcus aureus*

S. aureus is a common and virulent human pathogen, which causes a number of serious diseases, including skin abscesses, wound infections, endocarditis, osteomyelitis, pneumonia, and toxic shock syndrome. Like many other infectious agents, *S. aureus* is resistant to a wide range of antibiotics, that increase the interest in the phage therapy. The study of phages is carried out both on various animal models and in a number of human diseases, and the use of phage cocktails allows more targeted treatment [47]. But as mentioned before, there remain many obstacles to phage therapy, especially in terms of their impact on the body *in vivo*, as well as the influence of the external environment of the body on bacteriophages. Naturally, as for other pathogenic agents, scientists turned to the encapsulation of phages in nanoparticles. Thus, LS encapsulated bacteriophages against *S. aureus* (namely, MR-5 and MR-10) were more stable and showed a higher therapeutic effect compared to the free forms in diabetic wound infection in mice [48]. This cationic LSs were prepared from PC, cholesterol, Tween-80, and stearylamine in a ratio of 8 : 2 : 1 : 0.5 by a lipid film method followed by mixing with a phage suspension and sonication the mixture. The average size of LSs was 212 nm, and the phage encapsulation was about 87%. The use of phage loaded LSs led to a reduction in wound healing time by 33%, owing to the more effective capture of phage cocktail in LS form then free phage, that provided twofold increase in the phage titer in damaged tissue, increased rate of the infection resolution and effective treatment of diabetic wound surface.

Two LS preparations of bacteriophages against *E. coli T3* (the size is about 65 nm) and *S. aureus K* (the size of capsid head is 80 nm and tail length — 200 nm) were obtained by microfluidic method [49]. LSs were prepared from 1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC) and cholesterol by the thin film method, followed by dissolution in isopropanol to the concentration of 10 mg/mL. Then, an isopropanol solution of lipids and an aqueous buffer solution were fed through special devices using microfluidic pumps, and the resulting solution was filtered through 0.1 μm syringe filters. Using a co-current microfluidic glass device, the sterile solution was mixed with a concentrated phage suspension to encapsulate two model bacteriophages against *E. coli T3* and *S. aureus K* in submicron-sized LSs. The resulting preparation was dialyzed to remove residual isopropanol, and free phages were separated by ultrafiltration. The average size of LSs varied from 100 to 300 nm. The titer of encapsulated *E. coli T3* phage was 10^9 PFU/ml, but for *S. aureus K* phage it was significantly lower than 10^5 PFU/ml. The effectiveness of the *E. coli T3* phage encapsulation depended on the phage aggregation, while *S. aureus K* phage interacted with the lipid bilayer of LSs, and a large amount of it bound outside the LS nanoparticles rather than encapsulated into them. The authors inactivated LS bound *S. aureus K* phages, while maintaining the activity of the encapsulated phages.

A change in the cholesterol concentration in the LS composition of led to an increase in the average size of LSs and in the particle size distribution. The size of LSs based on only DSPC was 134±13 nm, on the mixture of DSPC and cholesterol in a molar ratio of 5 : 1 — 206±28 nm, and on the mixture of DSPC and cholesterol in a molar ratio of 1 : 1 — 301±32 nm. It should be considered that in the treatment of gastrointestinal infections, nonencapsulated in LS phages can be inactivated by the low acidity of stomach acid (pH 2.5).

Bacteriophages against *Cutibacterium acnes*

C. acnes is a cause of the acne disease, which is a multifactorial disease associated with the colonization of the skin follicles by *C. acnes* of *Propionibacteriaceae* family. The treatment of the acne disease is based on the combination of various products derived from retinoids, antibiotics, and hormonal antiandrogens, which takes a long time, can have side effects, be expensive, and not always effective. in this context, the evaluation of cytotoxicity of free and encapsulated in LSs

Pa.7 bacteriophage from *C. acnes* in HaCaT cells is of interest [50]. LS encapsulated Pa.7 bacteriophage (*Pseudomonas* phage PA7, equivalent to Pa.7 bacteriophage) did not exhibited cytotoxicity to HaCaT cells, which are a spontaneously transformed aneuploid immortal keratinocyte cell line from the adult human skin. It was proposed to use LS encapsulated bacteriophages for skin treatment.

Thus, lipid-based nanovesicles is a universal approach to phage delivery, as well as many other drugs. LSs protect phages from external stress factors such as low gastric pH, reticuloendothelial system, and neutralizing antibodies, increase the circulation time *in vivo*, and also the encapsulation of phages in LSs allows to gain access to intracellular pathogens (Fig. 1). LS phage delivery is safe, the used products are not toxic, and phages in LS form are less immunogenic [32, 44–46, 51, 52]. LSs can provide easier unhindered diffusion of phages through the epithelium [53]. The possibility of modifying the LS surface using conjugation with polymers, sucg as chitosan, alginate, PEG, is also important to note. For example, PEGylated LSs are shielded and less visible [15].

Research on pharmacokinetics and pharmacodynamics of LS forms of phages both for oral and intravenous administration is of particular importance for the creation of drugs for phage therapy. The biodistribution and transcytosis through the intestinal cell layer of orally administered LS encapsulated bacteriophages were analyzed on Caco-2 and HT29 cells (human colorectal adenocarcinoma) [54]. Phage lysate was obtained from *Salmonella enterica* serovar Typhimurium LB5000. The culture was infected with the bacteriophage UAB_Phi20 of the *Podoviridae* family), having an icosahedral head with a size of 60±2.7 nm and a non-contracting tail with a size of 13±0.7 nm. LSs were prepared from DLPC, cholesteryl-PEG600, cholesterol, and cholesteryl-3β-N(dimethylaminoethyl) carbamate hydrochloride in a ratio of 1 : 0.1 : 0.2 : 0.7. The size of the obtained LSs was 341.6±8.6 nm, the zeta potential was between 29 and 34 mV, the final product contained 46% of encapsulated and 54% on non-encapsulated phages. Fluorochrome labeled phages were visualized in the stomach and intestines of mice, and besides, the presence of phages encapsulated in LSs were detected in stomach and other internal organs, including the spleen and liver, and muscles by conventional culture methods. The study of phage adhesion showed that orally administered LS encapsulated phages remained in the stomach, confirming that LS encapsulated phages are protected until their release. Moreover, when the encapsulated phages reach the intestine, the attachment to the intestinal wall temporarily protects them from the action of bile acids and excretion. On the model of *Pseudomonas aeruginosa* phage (PEV20 has s 91 kb genome and a capsid size

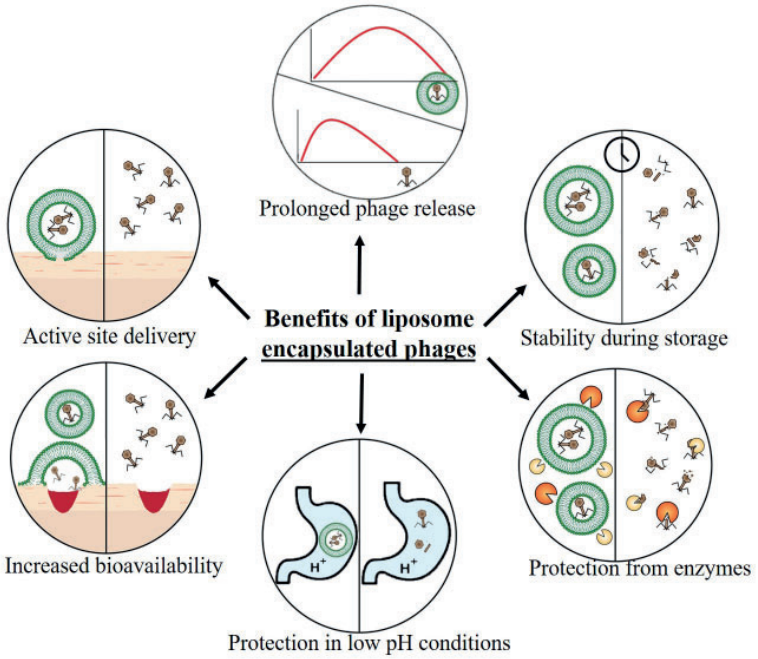

Fig. 1. **The main benefits of the LS encapsulated phages [31]**

of 60 nm), when intravenously administrated to rats, the phages accumulated in the liver, spleen and lymph nodes (where they were absorbed by the mononuclear phagocyte system), and also in lungs and muscles [55]. Renal clearance was limited. The authors found another source of phage inactivation, phage-neutralizing antibodies. When treated with repeated doses of phages, the level of specific phage-neutralizing antibodies increased.

Bacteriophages in the combination antimicrobial therapy

The combination therapy of phages and antibiotics takes a special place in phage therapy. Synergistic effects of a combination of phages and antibiotics have been identified [56, 57], for example, in fighting against *Citrobacter amalonaticus* which causes infections of respiratory and urinary tracts. Eight different antibiotics with different mechanisms of action (cefotaxime, gentamicin, meropenem, tigecyclin, etc.) were used in combination with phage MRM57 to study the effect of the combined treatment on the minimal inhibitory concentration. The authors found that synergism depends on the concentration of antibiotics, notably to varying degrees for a very low amount of phage. And only cefotaxime did not show any synergies.

Considering that the use of phages for compassionate treatment is often used in desperate situations, the absence of side effects in debilitated patients is reassuring [58]. When the introduction of high doses of phages over a long period of time, some phage proteins can apparently elicit an immune response. However, neutralizing anti-phage antibodies have been found in humans who have not been treated with phages, that may limit the success of phage therapy [69]. LS forms of phages can also be used in individual phage therapy for various infections [59]. The antibacterial action of LS nanoparticles themselves should be also taken into account [60].

A significant number of works are devoted to obtaining LSs and studying the stability of the LS forms of phages [51, 61–64].

Conclusions

In conclusion, LS phage drugs makes it possible to create drugs for oral, intravenous, external, and inhalation administration. When administered orally, LS nanoparticles can significantly protect bacteriophages from acid degradation and inactivation by enzymes during transit through the gastrointestinal tract, as well as prolong the residence time of phages in the intestine. At the same time, oral administration leads to low bioavailability of phages. In this regard, the intravenous administration of LS encapsulated phages can provide higher efficacy, because these drugs are safe, and LS forms allows to increase the residence time of the encapsulated product and its antibacterial activity, which is especially important in case of multidrug-resistant infections.

Increasing resistance of pathogenic bacteria to antibiotics has led to a revival of interest in bacteriophage therapy, which was actively used in a number of countries before the era of antibiotics [65]. The search for new forms of phage preparations has begun today in many countries of the world, preclinical and clinical stages of research are underway [66–69]. Current research suggests mechanisms for interaction of phages with nanoparticles, for example, metal nanoparticles, which is based on the value of the zeta potential [70]. The authors believe that particles with a zeta potential below minus 35 mV effectively bind to positively charged phage tails, and particles with a zeta potential above 35 mV effectively bind to negatively charged phages. If particles that do not meet these requirements, the physical interaction of phages with nanoparticle becomes nonspecific.

Using the knowledge of practical use of nanosystems in pharmacy and medicine, it is possible to develop drug delivery system based on nanoparticles, including LSs for phage therapy to overcome the difficulties associated today with the use of phages. Thus, we can talk about the prospects of using LS forms of phages for the treatment of infectious diseases. Perhaps the liposomal form of phages and the liposomal form of antibiotics are especially attractive due to a synergistic effect of these two dosage forms. However, for the licensing and clinical use of phage drugs, a large number of studies, both *in vitro* and *in vivo*, must be conducted to confirm the effectiveness and safety of the treatment.

Funding source. The work was performed within the research program of "Use of biotechnological methods in rational nature management, veterinary medicine and innovative production" (State Registration No. 0121U113717, 2022–2026).

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ПЕРСПЕКТИВИ СТВОРЕННЯ ЛІПОСОМАЛЬНИХ АНТИМІКРОБНИХ ПРЕПАРАТІВ НА ОСНОВІ ФАГІВ

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Поява великої кількості патогенних мікроорганізмів, резистентних до відомих антибіотиків, вказує на необхідність пошуку нових стратегій боротьби з ними.

Мета. Стаття присвячена аналізу сучасних досліджень ліпосомальних форм фагів як перспективної стратегії боротьби з мікробними інфекціями.

Методи. Аналіз сучасної вітчизняних та іноземних досліджень, присвячених інкапсуляції бактеріофагів у ліпосоми та оцінці ефективності цієї системи доставлення ліків у протимікробній терапії.

Результати. Інкапсуляція бактеріофагів у ліпосомальні наночастинки захищає фаги від негативного впливу зовнішніх факторів, збільшує період циркуляції в організмі, забезпечує підвищену біодоступність фагових частинок і, як наслідок, підвищує ефективність протимікробного лікування. Ліпосомальні форми фагів продемонстрували свою ефективність у боротьбі з багатьма поширеними патогенними бактеріями, зокрема *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Mycobacterium tuberculosis*, *Salmonella* та ін.

Висновки. Ліпосомальні фаги мають перспективи як протимікробні препарати, проте для широкого застосування у клінічній практиці потребують проведення доклінічних та клінічних досліджень для підтвердження їхньої ефективності та безпечності.

Ключові слова: нанобіотехнологія; система доставлення ліків; ліпосома; бактеріофаг; фагова терапія; антимікробний препарат.