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Prospective Clinical Applications of Nanosized Drugs

Yu. M. Krasnopol'skii[a], V. Yu. Balaban'yan[b], D. L. Shobolov[b], and V. I. Shvets[c]

[a] *Kharkiv Polytechnic Institute National Technical University, ul. Frunze 21, Kharkiv, 61002 Ukraine*

[b] *ChemRar High-Tech Center, ul. Rabochaya 2a-1, Khimki, Moscow oblast',141400 Russia*
e-mail: bal.pharm@mail.ru

[c] *Lomonosov Moscow State University of Fine Chemical Technologies, Moscow, Russia*

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Abstract—Liposomes reduce toxicity of their encapsulated APIs. They allow drugs to penetrate cell membranes, serve as containers for drug delivery, protect drugs from enzymatic degradation, provide prolonged action due to slow drug release, and protect drugs from the reticuloendothelial system. Liposome-encapsulated drugs break through the blood brain barrier. Liposomes can solubilize water-insoluble drugs [54, 55, 58, 76, 77, 82].

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The development of novel drugs and their novel dosage forms are only possible on the basis of the most modern findings in pharmacology, biotechnology, biochemistry, pharmacy, and other sciences. Many active pharmaceutical ingredients (APIs) are still applied based on nothing more than a belief that they will eventually reach a target tissue, organ, or cell. However, this is not always the case. Therefore, particular attention of researchers is presently focuses on the search for carriers capable of drug targeting [3, 10, 14, 24, 28, 29, 56, 67, 92, 99, 128].

The discovery of nanoparticles of various structures and development of their fabrication technologies made it possible to develop novel unique drugs. Every discovery in nanobiotechnology is a further step on the way to more efficient, less toxic, and better targeted drugs. It is quite important that drugs can be targeted not only to pathologically changed cells, but also to their separate elements, for instance, biologic membranes. Some real examples of the use of nanoparticles, specifically polymer nanoparticles, cyclodextrines, metal nanoparticles, nanodispersions, and artificial membranes (liposomes), as drug carriers have already been reported. Of the mentioned nanoparticles, liposomes are the most popular object for research in terms of application in novel dosage forms [24, 29, 56, 87–89, 97, 99].

Liposomal dosage forms have found successful application in oncology, ophthalmology, cardiology, and treatment and prevention of infectious diseases. Extremely important is the fact that some of these dosage forms have demostrated much higher efficiency in the therapy of resistant forms of diseases compared to free drugs, for example, cytostatics and antibiotics [6, 7, 37, 80, 93, 104, 116].

Nnaotechnologies allow extension of the range of drugs and enhance efficiency of APIs. The medical application of nanoparticles has now developed in a new field of medicine–nanomedicine. According to the leading expert in this field R. Freitas: "Nanomedicine is the monitoring, repair, construction, and control of human biological systems at the molecular level, using engineered nanodevices and nanostructures."

Let us dwell on the principal properties of liposomes as drug carriers.

Liposomes are nanosized colloid spheres comprising a lipid shell encapsulating an API [15, 28, 29, 35, 99, 109, 133]. Development of lyposomes, artificial spherical membrane constructions on the basis of lipids, is one of the most promising fields of modern bionanotechnology.

Liposomes were first prepared by Bangham in his research on the role of phospholipids in blood clotting [68]. Liposomes can be "loaded" with various drugs, such as vitamins, hormones, enzymes, cytostatics, etc. Having entered the body, drug-loaded liposomes react with cellular membranes, bind with them, and transfer the drug to the cell. Over the past 30 years liposomal

Table 1. Developed liposomal drug formulations

Name, administration route	Producer	Drug substance	Principal pharmacological action	Research phase
AmBisone, intravenously (i/v)	NeXstar Pharmaceuticals, USA	Amphotericin B	Antifungal	Commercial formulation
Daune-Home, i/v	NeXstar Pharmaceuticals, USA	Doxorubicin	Antitumor	The same
Vinca-Home, i/v	NeXstar Pharmaceuticals, USA	Vincristine	Antitumor	1–2 phase
MiKasome, i/v	NeXstar Pharmaceuticals, USA	Amikacin	Antibacterial	2–3 phase
Doxil, i/v	Alza Pharmaceuticals, USA	Doxorubicin	Antitumor	Commercial formulation
Amphocil Amphotec, i/v	Alza Pharmaceuticals, USA	Amphotericin B	Antifungal	The same
Cuelyx, i/v	Schering-Plough, Belgium	Doxorubicin	Antitumor	″
Myocet, i/v	Elan Pharma, USA	Doxorubicin	Antitumor	″
Ampholip, i/v	Elan Pharma, USA	Amphotericin B	Antifungal	″
Lipin, i/v	Biolek, Kharkov, Ukraine	Phosphatidyl choline	Antihypoxic, antioxidant, membrane-protective	″
Lipidoks, i/v	Biolek	Doxorubicin	Antitumor	″
Lioliv, i/v	Biolek	Antral	Hepatoprotective	″
Lipoflavon, i/v	Biolek	Quercetin	Cardioprotective, antioxidant	″
Lipoflavon, eye drops	Biolek	Quercetin	Wound-healthing, vasoprotective, anti-inflammatory	″
Lipoplat, i/v	Biolek	Cisplatin	Antitumor	Clinical trials completed
Lipotax i/v	Biolek	Docetaxel	Antitumor	Preclinical trials
Visudyn, i/v	Novartis Pharma, France	Verteporphyrin	For photodynamic therapy	Commercial formulation
Abelcet, i/v	Liposome Company, USA	Amphotericin B	Antifungal	The same
Evacet, i/v	Liposome Company, USA	Quercetin	Antitumor	3 phase
Epaxol-Berna Vaccine, intramuscularly (i/m)	Swiss Serum Vaccine Institute, Switzerland	Hepatitis A antigene	Antiviral	Commercial formulation
Inflexal virosomal Influenza Vaccine, i/m	Swiss Serum Vaccine Institute	Hemagglutinin and neuraminidase	Antiviral	The same
HepaXen Combintd vaccine, i/m	Swiss Serum Vaccine Institute	Hepatitis B antigene	Antiviral	″
Diphtheria /Tetanus/ Hepatitis – A vaccine, i/m	Swiss Serum Vaccine Institute	Diphtheria and tetanus toxoids, hepatitis A antigene	Antiviral, antibacterial	1–2 phase

Table 1. (Contd.)

Name, administration route	Producer	Drug substance	Principal pharmacological action	Research phase
Hepatit A / B Tetanus Diphtheria vaccine, i/m	Swiss Serum Vaccine Institute	Diphtheria and tetanus toxoids, hepatitis A and B antigenes	Antiviral Antibacterial	1–2 phase
Lipovaca Influenzal Vaccine, i/m	Bolgaria	Hemagglutinin and neuraminidase	Antiviral	Commercial formulation
Nyotron, i/v	Aronex Pharmaceuticals, USA	Nystatin	Antifungal	2–3 phase
Atragen, i/v	Aronex Pharmaceuticals	Retinoic acid	Antitumor	2–3 phase
E.coli 0157: H7 vaccine, per os	Novovax , USA	E.Coli 0157: H7, antigene	Antibacterial	1 phase
Sh. Flexneri 2A vaccine, per os	Novovax	Sh.Flexneri 2A, antigene	Antibacterial	1 phase
Tears again, aerosol	Novovax	Natural phospholipids	Treats dry eye syndrome	Commercial formulation
LE-M, i/v	NeoPharm, USA	Mitoxantrone	Antitumor	1–2 phase
LE-P, i/v	NeoPharm	Paclitaxel	Antitumor	1–2 phase
LE-SN38, i/v	NeoPharm	Irinotecan metabolite	Antitumor	1–2 phase
SPI-077, i/v	Alga Pharmaceuticals, USA	Cisplatin	Antitumor	1–2 phase
SPI-077-B-103, i/v	Alza Pharmaceuticals	Cisplatin	Antitumor	1 phase
SPI-119, i/v	Alza Pharmaceuticals	SD-4	Antitumor	Preclinical trials
VSLI onco TCS, i/v	Nana Biosciences,	Vincristine	Antitumor	2 phase
Invivac virosomal Influenza vaccine, i/m	Solvay	Influenza surface antigen	Antiviral	Commercial formulation
Lipoferon, per os	Jadran	Interferon alpha	Antiviral	The same
EndoTAG-1	MediGene, Germany	Paclitaxel	Antitumor	3 phase
Docetaxel	MediGene	Docetaxel	Antitumor	Preclinical trials
Irinotecan	MediGene	Irinotecan	Antitumor	The same

Table 1. (Contd.)

Name, administration route	Producer	Drug substance	Principal pharmacological action	Research phase
Camptothecin	MediGene	Camptothecin	Antitumor	″
Methotrexate	MediGene	Methotrexate	Antitumor	″
Cisplatin	MediGene	Cisplatin	Antitumor	″
Aroplatin	Antigenics, USA	Cisplatin	Antitumor	2–3 phase
ThermaDox	Gelsion, USA	Doxorubicin	Antitumor	1–2 phase
Lipoplatin	Regulon , USA	Cisplatin	Antitumor	3 phase
Lipoxal		Oxaliplatin	Antitumor	2 phase
Mepact	IDM Pharma, USA	Muramyl tripeptide	Immunoadjuvant in chemotherapy	Commercial formulation
DepoCyt	Enzon Pharmaceuticals, USA	Cytarabine	Antitumor	The same
Nanocort	Galapagos, Belgium	Prednisolone	Treats rheumatoid arthritis, disseminated sclerosis	3 phase 2 phase
Liposome Forte Tricortin 1000	Fidia Farmaceutical SPA, Italy	Nervous tissue phospholipids	Neurotropic	Commercial formulation
LipoHep Viatromb	Poland Fabril Farma, Germany	Heparin	Anticoagulant, antiedemal	The same
Fluidosomes	Axentis Pharma, Switzerland	Tobramycin	Antibacterial	″

formulations have found application in medicine, both in therapy and in diagnostics [1, 8, 16, 60, 69, 86, 93].

We and our colleagues have accumulated certain experience in the development and commercial production of liposomal formulations. The unique compositions and technologies, high pharmacological efficiency, and low toxicity of our developed formulations gives us grounds to expect that, provided production conditions meeting the GMP standards will be created, this group of formulations may be launched to the world pharmaceutical market. To meet the GMP standards is a necessary condition for Russian products to be let enter the world pharmaceutical markets [21].

In previous papers [19, 22–24, 51, 52] have discussed the main methods of production, control, and standardization of liposomal formulations. The present review focuses on the characteristics of formulations approved for clinical applications or advanced into the final stages of clinical trials. The paper is accompanied by an extended bibliography including relevant publications which are discussed in the text and recommended to readers. At present the world pharmaceutical industry has developed and commercialized more than 30 targeted liposomal drugs (see Table 1). Now tens millions patients undergo treatment with such commercial liposomal drugs as Doxil, DepoCyt, AmBisone, Lipin, Visudyn, Lioliv, and Lipoflavon [9, 10, 24, 42, 43, 60, 63, 74, 85, 93, 99] .

The usefulness of liposomes in principle is first of all based on the functions of biological membranes. In certain cases pathological changes are primarily occur in lipid components of a membrane, and this makes it possible to repair the damaged membrane by introducing phospholipid liposomes into the body. An illustrative example is provided by the successful use of the world's first commercial formulation Lipin for repairing damaged membranes in patients with various diseases (pulmonological, nephrological, gynecological, cardiological) [1, 2, 4, 5, 16, 26, 40, 44, 48, 49].

Phosphatidylcholine liposomes were found to efficiently repair brain tissue in patients with Alzheimer's disease. Evidence for the efficiency of liposomal formulations in the case of pathologies leading to reduced levels of phosphatildylcholine, for example, in membranes was obtained. Thus, the damage of cellular membranes caused by hemorrhagic shock not infrequently entails a progressive decrease of membrane phosphatildylcholine levels. In was found that in animals subjected to hemorrhagic shock and treated with phosphatildylcholine liposomes, already 30-min after bleeding initiation the phosphatildylcholine level in spinal bulb mitochondria was 2.5 times higher compared with that in untreated animals. Simultaneously, recovery of the phosphatildylcholine levels in the frontal lobe mitochondria and hepatocytes, as well as long-term stabilization and maintaining of the blood pressure at the subnormal level were observed. The authors of [27, 48, 69] found that yolk phosphatildylcholine liposomes are much more efficient in the therapy of hemorrhagic shock compared with known drugs (superoxide dismutase, buprenorphine, butorphanol, etc.

Evidence for the use of liposomes for detoxification and, therefore, their transfort function was obtained. Thus, yolk phosphatildylcholine liposomes were applied as a toxicotropic agent in the treatment of $CC1_4$ poisoning. After intravenous injection of loaded liposomes, a lower inhibition degree of enzymes, specifically succinate dehydrogenase and adenosine triphosphatase, was observed. Liposomes loaded with clodronate (a drug for bone damage therapy) injected intra-articularly in patients with rheumatoid arthritis decreased the levels of macrophages and adhesive molecules in the synovial membrane [41]. It should be noted that liposome-encapsulated drugs can break through the blood–brain barrier, as was demonstrated with the drug DOFA encapsulated in phoshatidylcholine liposomes, which is applied in Parkinson's disease treatment. Therewith, one of the symptoms of Parkinson's disease could be reduced at doses lower by an order of magnitude than with a free DOFA drug, which was related to the fact that the liposomal shell protected the active substance from enzymes [15].

The promise associated with liposomal formulations is evidenced by the progressively increasing number of publications on the design of novel drugs on the basis of liposomes, including those describing preclinical and clinical trials.

A liposomal form of prednisolone (Nanocort), intended for use in the therapy of rheumatoid arthritis and multiple sclerosis, is presently under clinical trials. Thus, Y. Barenholz, a researcher and developer of a highly efficient anticancer drug Doxil, proposed to use this liposomal formulation in osteoarthritis therapy. This disease involves inflammation of the synovial fluid, which leads to enhanced friction in joints. The inflammation causes cartilage damage, which, in its turn, entails a direct bone-to-bone contact. The latter brings up a heavy pain and makes joints less mobile. To releive inflammation, the author of Doxil proposed intra-articular injections of phosphatildylcholine and hyaluronic acid liposomes.

The use of liposomes in cancer therapy is based on their ability to enhance the effect of known drugs by changing their pharmacokinetics, which favors a higher antitumor activity and lower toxicity. Noteworthy is a slow release of drugs from liposomes, which ensures prolonged action and transport of unstable drugs. Because of different physiologies of normal and tumor tissues the latter characteristically better uptake liposomes containing cytostatics. This is just the reason that nanocarriers allow internal transport into the tumor tissue of encapsulated antitumor drugs in high concentrations. The active interest of oncologists in liposomes is explained by their tendency for enhanced accumulation in the tumor tissue. Tumor cells proliferate very fast, and this prevents normal development of the blood vessel wall endothelium. As a result, tumor blood vessels have pores 0.3–0.4 μm in diameter. Moreover, the extracellular space in the tumor tissue, too, is larger than in healthy tissues. For the above reasons, liposomes less than 200–300 nm in diameter can penetrate into and accumulate in the tumor tissue [118]; this process is known as the EPR effect (Enhanced Permeability and Retention). The available evidence gives grounds to expect that liposomal forms of cytostatics will be really used for the treatment of malignant tumors of different localization. The effort of specialists all over the globe is presently focused on the development dosage forms of cytostatics encapsulated in liposomes, which extends considerably the capabilities of tumor chemotherapy and enhances its efficiency.

The reduced toxicity of liposomal dosage forms of, in particular, such drugs as hemotoxic and cardiotoxic anthracycline antibiotics, substantially attenuates the adverse effects of chemotherapy. The cardiotoxicity of anthracycline antibiotics is a factor which prevents

their wide clinical application. As the rate of cardiotoxic effects is dose-dependent and increases at high cumulative doses, the antitumor potential of anthracycline antibiotics cannot be realized on a full scale. The encapsulation of antibiotics in liposomes allows one not only to take a maximum advantage of their useful properties, but also to increase the dose of the drug. The latter becomes possible in view of the changed pharmacokinetics of the drug and its lower accumulation in the cardiac muscle. Moreover, phosphatidylcholine liposomes are probably capable of decelerating peroxide oxidation of lipids and attenuating their direct effect on cardiomyocyte mitochondria and nucleus [57, 59].

The clinical practice shows that with liposomal forms of cytostatics less side effects, specifically, lower nephro- and cardiotoxicity and lower rates of vomiting, nausea, alopecia, peripheral neuropathies, and immunity depression, are observed [49, 64, 70, 75, 85, 99, 103, 114, 119, 129, 142].

The pharmacokinetics of liposome-encapsulated drugs, in particular, cytostatics, depends on two factors: the rate of liposome clearance from plasma and the stability of the liposomal formulation in the blood stream. The latter factor is dependent on the properties of the active substance and liposomal carrier, specifically, the size of nanoparticles and their physicochemical properties, permeability of tissues, and nature of liposome–drug binding. Polyethylene glycol (PEG-2000 PE or PEG-5000 PE) used since recently as a coating for liposomes makes them more protected from the reticuloendothelial system [105, 118, 139, 144], which, in its turn, prolongs the circulation time of the drug due to its slow release into the tumor rissue. The PEG coating also inhibits protein-assisted binding with cells. Apparently, small liposomes as carriers for cytostatics offer advantages of reduced drug entrapment by the reticuloendothelial system and prolonged circulation time [60, 105, 120, 140, 143].

An important property responsible for the high efficieny of liposomal drug formulations is their selective accumulation, and, as a consequence, targeted action in the pathologically changed tissue. The targeted delivery of liposome-encapsulated drugs is made possible first of all by the defect nature of pathologically changed blood vessels, for example, in malignant tumors or in inflamed tissues in the case of rheumatoid arthritis. The blood vessel walls fast growing under the action of neoangiogenesis growth factors get more proliferable. It was shown that the extracellular space in the endothelial lining of such pathological blood vessels in most peripheral tumors varies from 200 to 600 nm, which in itself would favor, due to the large spaces, fissures, and other defects in the damaged tissue, liposome permeation. Drug-loaded liposomal nanoparticles can accumulate in certain body sites, for example, in solid tumors and myocardial infarction–affected areas. Drugs, such as the anthracycline antibiotic doxoru-bicin (the liposomal forms are Doxil, Myocet, and Lipidoks), are accumulated in tumors due to the defectness of their blood vessel walls and exert a targeted cytostatic effect.

Cytostatics are the most efficient medicines for different tumors and oncohaetomologic diseases. However, their use is limited by toxicity. Liposomal cytostatics are less toxic and can accumulate in the tumor tissue, thus enhancing the efficiency of therapy. Moreover, which is of no little importance, the liposome shell protects the cytostatic from being destroyed by blood serum enzymes. Finally, the liposomal form of cytostatics may help to overcome drug resistance due to a longer circulation time and selective accumulation in tumor tissues.

Table 2. Liposomal hemoglobin formulations

Producer	Composition	Phase of clinical trials
Baxter, IL, USA	Recombinant hemoglobin	1 phase
Biopure, MA, USA	Hemopure, cross-linked bovine polyhemoglobin	Approved for clinical use
Northfield, IL, USA	Polyheme, cross-linked human polyhemoglobin	3 phase
Sangart, CA, USA	Hemospan, poly(ethylene glycol)−hemoglobin	1/2 phase
Hemosol, Ontario, Canada	Hemolink, D-raffinose cross-linked hemoglobin (by Awasthi, V., 2007)	3 phase

There are a lot of liposomal forms of the doxorubicin (Dox) anthracycline antibiotic, differing from each other in the content of encapsulated antibiotic, as well as size and composition of liposomes, available at the world pharmaceutical market. They include Daune-Home (NeXstar Pharmaceuticals, USA), Doxil (Alza Pharmaceuticals, USA); Cuelyx (Schering-Plough, Belgium); Lipidoks (Biolek, Ukraine); Myocet (Elan Pharma, USA) (Table 2).

Doxil is the first of the developed liposomal formulations (composition: phosphatidylcholine, cholesterol, and steric stabilizer dipalmitoyl phosphatidylethanolamine with PEG-2000 PE) containing the Dox antibiotic (STEALTH liposomes). Doxorubicin is also contained in such formulations as Cuelyx (pegylated liposomes) and Lipidoks (yolk phosphatidylcholine liposomes), and Myocet (Dox–citrate complex, phosphatidylcholine liposomes). The size of liposomes in these formulations varies from 80 to 150 nm.

The listed liposomal formulations exhibit high antitumor and antileukemic activities, they ensure free release of Dox and its transport from blood to tissues and organs, thereby decreasing toxicity of the antibiotic. The formulations feature prolonged action, much lower cardiotoxicity, and weaker myelo- and immunosuppressive effects compared to free Dox. According to trial results, with limosomal forms of Dox, nausea and vomiting are not so long and do not require pharmacological correction.

In our animal study in 1998 on the distribution of Dox incorporated in the Lipidoks formulation and of free Dox we revealed no brain accumulation of the antibiotic in the latter case and detected Dox in the brain tissue when Lipidoks was used [18]. It was suggested that liposomes ~160 nm in size and smaller worse break through the blood–brain barrier, whereas most chemotherapeutics not. Our findings were later confirmed by other authors [6, 7].

Without doubt, the closest candidate for clinical application is Lipoplatin, a liposomal form of cisplatin, fabricated from dipalmitoyl phosphatidylglycerol, soya phosphatidylcholine, and cholesterol, and stabilized with PEG-2000 PE. The size of this form is ~100 nm. A high degree of cisplatin encapsulation in the liposomal formulation (95–97%) was observed [65, 71, 72, 105, 121, 132].

Preclinical trials of Lipoplatin on laboratory animals established its high antitumor activity. Comparison of Lipoplatin and cisolatin in vitro on the cell lines obtained from non-small cell lung cancer, kidney cancer, as well as from normal precursors of haemopoetic cells showed that Lipoplatin is highly toxic for all tumor cell models and much less toxic for normal cells compared to the free form of cisplatin. A higher antitumor activity of the liposomal form was established. The intraperitoneal injection of Lipoplatin induces less toxic effects than intravenous injection. The pharmacokinetics of isotope-labeled Lipoplatin and free cisplatin were studied in model experiments on mice with Ehrlich's ascites carcinoma. The liposomal form was found to longer present in the blood and tumor of animals. Accumulation of liposomal cisplatin in spleen and liver and reduced accumulation in kidney were found. In view of the high degree of nephrotoxicity of cisplatin formulations, the latter data are of particular interest.

Clinical tests on Lipoplatin in patients with stomach, colon, and glandular cancers revealed minor manifestations of nephrotoxicity and ototoxicity. Direct measurements showed that the Pt concentration on the tumor tissue is higer 10–50 times (up to 200 times in the colon tumor) compared to the normal tissue. Aerosolized Lipoplatin was tested in patients with lung cancer (17 people). The patients inhaled the aerosol twice a day. The resulting data gave evidence for a low toxicity, fair therapeutic effect, and tolerability of the liposomal formulation. Stabilization of the process after treatment courses was observed in 12 patients.

Phase 1, 2, and 3 clinical trials of Lipoplatin in patients with different types of cancer led researchers to a common opinion: Lipoplatin is much less toxic than cisplatin. With this in mind, the concentrations of the drug injected in patients can be increased. Lipoplatin fairly slowly releases cisplatin, and the residence time of platinum in the body is much longer than that of the free form of cisplatin. Lipoplatin is preferentially accumulated in the tumor tissue, and, therefore, normal tissues are damaged to a lower extent.

At present multicenter clinical trials of the liposomal form of paclitaxel (antitumor agent), sold by MediGene (Germany) under the trademark EndoTAG-1, are in progress in a number of countries. The formulation comprises lyophilized liposomes (average size ~200 nm) consisting of *N*-{1-(2,3-dioleyloxy) propyl}-*N,N,N*-trimethylammonium chloride and 1,2-

dioleyl-*sn*-glycero-3-phosphocholine with encapculated paclitaxel (ratio 50 : 47 : 3 mole percent) [70, 113, 120, 124, 130]. Cationic liposomes selectively act on negatively charged enrothelial cells and prevent formation of new blood vessels stimulating tumor growth, thereby preventing further tumor development.

One-year-long clinical trials of EndoTAG-1 in combination with Gemzar (gemcitabine) were performed in 200 patients with pancreatic adenocarcinoma. In the case of monotherapy with Gemzar, the 1-year survival rate was 17%. The survival rates among patients treated with the two formulations were found to depend on the dose of EndoTAG-1: At a low dose, the 1-year survival rates at low, medium, and high doses were 22%, 36%, and 33%, respectively. When the treatment was prolonged, the 1-year survival rates at low, medium, and high doses were 25%, 52%, and 40%, respectively. It was established that liposomal paclitaxel and gemcitabine formulations nearly doubled the survival rate of patients compared with that characteristic of traditional chemotherapy (13.6 and 7.2 months). Taking into account that pancreatic carcinoma is one of the most deadly forms of cancer, these results can be considered encouraging. In 2007, phase II clinical trials of EndoTAG-1 for treatment of breast cancer were initiated. The first results were obtained by the end of 2009 and the final results, in 2010.

The liposomal form of paclitaxel was tested on experimental models of prostate cancer in animals. The liposome-encapsulated paclitaxel was injected in tumor-bearing animals on days 12, 14, 16, and 19 after tumor induction; the control group was treated by traditional methods using free paclitaxel, cationic liposomal formulations, and glucose. After the treatment had been complete, the tumor volume in animals treated with liposomal paclitaxel was (2.49±0.84) cm^3, which was much smaller than the tumor volumes in animals treated with free paclitaxel, glucose, and cationic liposomal formulations: (5.59±0.45), (5.17±1.7), and (3.87±1.25) cm^3, respectively. These results gave evidence showing that the liposomal form of paclitaxel offers obvious advantages over traditional anticancer drugs in the treatment of prostate cancer.

Verschraegen et al. tested EndoTAG-2 containing the anticancer drug camptothecin instead of paclitaxel (ingredient ratio 50 : 47 : 3 mol %) [142]. The tests were performed using C57/Bl6 mice with implanted metastatic human pancreatic carcinoma. Compared to control, EndoTAG-2 showed a high antitumor activity. A significant reduction of vessel density (up to 50%) in model tumors, including Lewis lung carcinoma, was observed. The liposomal form of camptothecin was found to exhibit a much stronger antitumor effect than the free form of this drug.

In 2007, a new commercial liposomal formulation DepoCyt was launched to the world pharmaceutical market. The active substance in this formulation is cytarabine at a concentration of 10 mg/mL. The liposomes are obtained from cholesterol (4.1 mg/mL), triolein (1.2 mg/mL), dioleyl phosphatidylcholine (5.7 mg/mL), and dipalmitoyl phosphatidylglycerol (1.0 mg/mL). The formulation has successfully passed all phases of preclinical and clinical trials and was recommended for treatment of lymphomatous meningitis and cerebral tumors in adults and children. Occasional side effects were reported: arachnoidite, headache, or nausea [85, 119]. The formulation is injected intrathecally. It offers advantages of slow release of cytarabine and prolonged maintaining of its therapeutic level in the spinal fluid. This allows the dose of injected drug and the number of injections to be decreased. The half-life of liposomal cytarabine is 56.7 h, whereas that of free cytarabine is 32.7 h. The median time to progression with the liposomal form is 77 days, and the respective time with free cytarabine is as short as 48 days. The clinical trials of DepoCyt in patients with different forms of tumors led researchers to the following conclusion: DepoCyt is much less cytotoxic than the free form of cytarabine. The low toxicity makes it possible to increase the dose of injected cytarabine. The active substance is fairly slowly released from DepoCyt and, due to the fact that the cytostatic is accumulated predominantly in the tumor tissue, it resides in patient's body much longer than free cytarabine. With the liposomal drug, much less damage of the normal body tissues is observed.

At present liposomal formulations containing cytostatics (cisplatin, oxaliplatin, irinotecan, camptothecin, vincristine, etc.) are undergoing phase 2 or 3 clinical trials in a number of countries [24, 25, 30, 38, 39, 79, 83, 85, 98, 101, 107, 108, 115, 119, 129, 132, 135, 136, 142, 143]. It should be noted that the commercial liposomal formulation Mepact containing muramyl tripeptide is used in the immunoadjuvant chemotherapy of oncologic diseases.

The liposomal forms of broncholitic drugs are being presently under active development.

Aerosolized β-2-adrenoreceptor agonists still remain among principal medications to treat bronchial asthma. However, such medications frequently cause side effects, which calls for their further improvement. The liposomal form of berotec (fenoterol hydrobromide) opens up new possibilities for correction of bronchial hyperreactivity. The liposomes were fabricated from soya phospholipids and cholesterol at a molar ratio of 6 : 1.5, the liposome size was ~250 nm. The liposomal formulation was tested on a rabbit model of bronchial asthma; the rabbits were presensitized with ovalbuminum. The formulation was administered in animals directly into the respiratory tract by means of an unltrasound inhalator. The inhaled liposomal berotec produced a promter and longer lasting broncholytic effect in virtually all rabbits. It is important that the broncholytic effect was reached with the berotec dose about 2–3 times lower than with the free form of berotec.

Comparative assessment of the efficiency of the liposomal form and aqueous solution of intal in patients with infection-dependent bronchial asthma was performed. The drugs were introduced during fibrobronchoscopy by pulse lavage of the tracheobronchial tree after a session of artificial high-frequency jet lung ventilation. The best results were observed in patients treated with the liposomal form of Intal: Clinical symptoms of asthma attack were arrested within 10–12 day. Active regression of endobronchial symptoms up to the development of a normal mucous membrane in the tracheobronchial tree was observed in 95% of patients. The course dose of liposomal Intal was 3–4 times lower than with the free form of the drug. The enhanced efficiency of the liposomal form is associated with a high anti-inflammatory activity of intal, its intracellular transport into the target organ, and ability to repair and stabilze cell membranes.

There is some evidence showing that hemoglobin liposomes can transport oxygen. Testing liposome-encapsulated hemoglobin as a substitute in blood transfusion in the treatment of massive hemorrhage revealed the ability of liposomes to transport oxygen to peripheral tissues and to maintain normal oxygen metabolism. The liposomal form of hemoglobin was proposed as a candidate for blood substitute applications in the treatnment of acute massive hemorrhages. It was found that liposome-encapsulated hemoglobin can entrap oxygen in lungs and transport it to tissues [66, 112, 117, 123, 137, 138].

Much effort in the research on liposome-encapsulated hemoglobin is focused on the development of lipid compositions of liposomes, effect of particle size on the biological activity of formulations, enginnering aspects of fabrication, etc. A series of liposomal formulations capable of oxygen transport and used in transfusion medicine are presently at different phases of clinical trials (Table 1).

Massive bleeding associated with hemorrhagic shock is a reason of deaths in various diseases (ulcers, stomach cancer, postpartum hemorrhages, aneurism rupture, etc.). A method of treatment of hemorrhagic shock by intravenous injection of multilayer liposomes fabricated from soya phosphatidylcholine was proposed. The formulation containing 0.5 mg/mL of phosphatidylcholine is injected at a dose of 1 mL/kg body weight. Trials in animals exposed to hemorrhagic shock showed that liposomes much relieved the late period of hemorrhagic shock and substantially prolonged animal lifespan. The incorporation of liposomes into the cell membranes of target organs makes it possible to protect the latter against hemorrhagic shock. Multilayer coarse lipo-somes (unlike those fabricated by ultrasonication) exhibit a higher efficiency due to their more rapid clearance from bloodstream and incorporation into cell membranes. Note that the liposomal forms of peptides and proteins, hemoglobin and its derivatives, broncholytics, hormones, and other substances (budesonide, Albuterol, etc.) help to restore the respiratory function [102].

In 1991 the world's first liposomal formulation Lipin (lyophilized egg phosphatidylcholine liposomes) was patented in Ukraine. Over the past two decades a great body of information has been published on experimental and clinical studies on this formulation [1, 2, 48, 49]. Summarizing the published evidence we can draw the following conclusions. Lipin exhibits an antihypoxic activity by driving oxygen diffusion from lungs into blood and from blood into tissues; it normalizes tissue breathing; restores the functional activity of endothelial cells and synthesis and release of the endothelial relaxation factor; improves microcirculation and rheologic properties of blood; inhibits peroxide lipid oxidation in blood and tissues; maintains activity of antioxidant defence systems; exhibits the membrane protective activity; improves nonspecific immunity; when inhaled, it assists in the retention of lung surfactant (lipoproteid complex), which, in its turn, improves pulmonary and alveolar

ventilation, accelerates transmembrane oxygen transport; does not disturb the functional activity of body organs and systems; and is nontoxic.

The results of ling-standing clinical trials allowed Lipin to be recommended for the following indications: acute and chronic respiratory distress syndrome of any genesis in adults and children, including disporders of respiratory control in the newborns, associated with perinatal hypoxia and birth asphyxia. The drug is recommended to prevent diseases caused by long-term exposure to dust (silicosis, anthracosis).

Of undeniable interest are data on the use of Lipin for correction of lung ventilation in the newborn subjected to long-term artificial lung ventilation. The efficiency of Lipin was assessed from the dynamics of the normalization of blood gas composition, oxygen saturation, and change of clinical inidicators. It was shown that the use of Lipin for the treatment of acute lower respiratory tract diseases in children with acute obstructive bronchitis and pneumonia normalizes the phagocytic activity and raises the phagocytic index and the number of alveolar macrophages.

Ultrasound inhalations with a suspension of Lipin liposomes were found to efficiently mitigate airways obstruction and corrects lipid and protein metabolism in patients with chronic bronchitis in the exacerbation phase (primarily, mine workers). Moreover, Lipin shortens the course of treatment of patients with obstructive chronic bronchitis in an average of 2–4 times. Lipin is recommended in the case of late gestosis and intrauterine hypoxia. This formulation was found to be efficient against kidney diseases (acute and chronic pielonephritis, glomerulonephritis, diabetic nephropathia, cystic diseases, and kidney failure).

Thus, the high clinical efficiency, virtually complete absence of counterindications, except for individual intolerance, and extremely low toxicity allow the use of the liposomal drug Lipin in pulmonology, cardiology, gastroenterology, obstetrics, and gynecology. Lipin was also shown to hold promise in the auxiliary therapy of cancer patients.

In our opinion, the role of Lipin in clinical practice has not yet still been appreciated to a sufficient extent. The liposomal formulation which mimics a biologic membrane and possesses a unique pharmacotherapy range can serve as a protector for the most part of body membranes. Evidence for this suggestion is provided by numerous diverse research works fulfilled over the past two decades.

In 2006 Lipoflavon, a liposomal form of the quercetin bioflavonoid, was launched to the Ukrainian market. The phospholipid in this formulation is phosphatidylcholine. As known, quercetin-containing drugs both treat hemodynamic disorders and significantly reduce the degree of necrosis caused by acute myocardial ischemia and reperfusion. This effect is due to the membrane-stabilizing effect of quercetin, as evidenced by the sharp retardation of the degradation of membrane fragments in the stunned myocardium, as well as by the inhibition of lipoxygenases and nonenzymatic pro-oxidant reactions. It is suggested that an important factor responsible for the cardioprotector activity of quercetin is its ability to increase the level of nitrogen oxide in tissues and myocardial endothelium. The clinical application of quercetin is first of all prevented by its hydrophobilicity. The development of Lipoflavon as a liposomal form of quercetin allowed solution of this problem. The efficiency of Lipoflavon was demonstrated by the treatment of acute myocardial infarction, unstable angina, and reperfusion disorders after thrombolythic therapy [32–34, 43, 61, 90, 91].

Research into the efficiency of the liposomal formulation Lipoflavon against various pathologies is continuously in progress. Over the past 3 years successful use of Lipoflavon in cardiology has been reported [46]. A possibility to correct the cytokine homeostasis and left ventricular diastolic dysfunction in patients with arterial hypertension was demonstrated [17]. Lipoflavon was shown to be quite efficient in the treatment of diabetic retinopathy, which is accompanied by a decrease in the levels of the anti-inflammatory cytokines 1L-1β and TNF-α by 17.0% and 14.5%, respectively (according to [11, 12], the levels of 1L-1β and TNF-α in the therapy without Lipoflavon decrease by 9.5% and 4.9%, respectively). Furthermore, a decrease in the gastric motor dysfunction on the background of type 1 or 2 diabetes [31] and in the respiratory function was observed [13]. The possibility of regeneration of the nervous tissue deserves special mentioning. It was established that the use of Lipoflavon to treat traumas of peripheral nerves increased the number of nerve fibers and activates regeneration, which drives invasion and myelination of nerve fibers [47, 50].

In 2011 Harel-Adar et al. [95] proposed using liposomes in the therapy of myocardial infarction.

Liposomes comprising phosphatidylcholine, phosphatidyl serine, and cholesterol in a 1 : 1 : 1.33 ratio and the particle size 1.2±0.3 μm were prepared. The active substance was phosphatidylserine residing on the liposome surface and mimicking myocardial cell apoptosis. In its turn, this induces macrophages to repair myocardial tissues. The therapeutic efficiency of the "deceit strategy" was demonstrated both *in vitro* and *in vivo* in rats with induced myocardial infarction administered intravenously phosphatidyl serine liposomes 2 days after induction of infarction. Myocardial tissue regeneration was found to be initiated within 96 h. Control animals treated with phosphatidylcholine and cholesterol liposomes died.

Evidence was obtained for the efficiency of liposomes in ophthalmology [32, 33, 93]. At present four commercial liposomal drugs: Visudyn, Lipoferon Lipoflavon, and Tears Again are applied in ophthalmological practice.

Lipoflavon is a liposomal form of quercetin. Lipoflavon eye drops are applied in the following cases: keratopathy (infiltrative and non-infiltrative); surgical corneal wounds (after corneal extraction); keratitis of different genesis; eye inflammations. The action of the formulation is underlain by the inflammatory, wound-healthing, and angioprotector activity of liposomal quercetin. Quercetin exhibits antioxidant and antiviral effects, inhibits synthesis of leucotrienes that cause bronchoconstriction, reduces pathologically elevated vascular tissue permeability, and normalizes tissue trophism (cell nutrition processes). Lipoflavon is well tolerable by patients and induces no side effects and allergic reactions. This drug efficiently treats traumatic keratitis: It accelerates epithelization and favors shorter attacks of pain compared with the control group.

An important feature of Lipoflavon eye drops is that they contain no preservatives. In our opinion, the formulation containing liposome-encapsulated quercetin can be used to treat other diseases. This opinion is based on the broad-spectrum activity of quercetin (antibacterial, antiviral, antioxidant, anti-inflammatory, and antitumor) [90, 91].

Tears Again is a liposomal aerosol containing natural phospholipids. This aerosol is applied in the case of a moderate dry eye syndrome with a lipid layer deficiency by spraying on closed patient's eyelids. It functions as a sealing agent which induces tear production. A decrease of the eyelid temperature in patients with dry eye syndrome (hypersecretion filamentary keratoconjuctivitis) was observed.

Along with the mentioned liposomal formulations which have already been introduced in clinical practice, a lot of liposomal drugs for ophthalmology, such as Gentamicin, Norfloxacin, Tobramycin, Aciclovir, Amphotericin B, Dexamethasone, Ciclosporin, 5-Fluorouracil, 5-Fluoroorotate, Clodronate, Disulfiram, Adenosine Phosphate, etc., are presently under experimental study. These studies provided evidence for lower clearance and toxicity of the liposomal formulations compared to the free form of these drugs. It was found that the liposomal formulations of antifungal or antibacterial drugs are as or more efficient than the free form of such drugs [93].

One of most difficult problems associated with the application of eye drops is that these drugs poorly penetrate the eye tissue, and, therewith, their residence time is extremely short. At the same time, it was shown that positively charged liposomes prolong the residence time of a drug on the cornea. There is an opinion that liposomes can function as efficient carriers exclusively for lipophilic eye drugs. It was found that the lipophilic antiinflammatory drug Indoxol encap-sulated in liposomes is 2.5 times more absorbable than "ordinary" eye drops. At the same time, liposomes adversely affect absorbability of such hydrophilic drugs as epinephrine and dihydrostreptomycin, but enhance absorbability of insulin and triamcinolone 10 and 4 times, respectively.

At present a limited number of liposomal formulations are used in ophthalmological practice. Apparently, such formulations will receive wide recognition in terms of the diagnostic and treatment and research aspects of ophthalmology.

Liposomal formulations hold undeniable promise for photodynamic therapy applications. Liposomal derivatives of benzoporphyrin (verteporphyrin) are light-sensitive stains, but they exhibit cytotoxicity by forming oxygen radicals on activation (λ 689 nm). The liposome-encapsulated verteporphyrin acts on tumor vessel and neovascular endothelial cells. Verte-porphyrin induces formation of cytotoxins only under light irradiation in the presence of oxygen. As a result, an unstable, short-living, and highly reactive singlet oxygen is generated. Singlet oxygen destroys biological structures, which, in its turn, favors local cell

damage and death. The selectivity of photo-dynamic therapy using liposomal verteporphyrin is based not only on the localized light exposure, but also on the selective and rapid capture and retention of verteporphyrin by rapidly proliferating cells, including endothelial cells of the choroidal neovascularization area. Naturally, treatment in all such cases is associated not only with the formation and action of singlet oxygen. Obviously, a complex of other changes takes place in the composition and activity of numerous participants of reactive oxygen transformations in tissues, incliding pro- and antioxidantt enzymes (oxigenases, dysmutases, etc.). The final result of such reactions is quite difficult to generalize, but the very fact of their cytostatic or cytolythic effect can be considered established (Visudyn formulation).

Over the past years much effort has been focused on the development of thermally sensitive liposomes, specifically cytostatics encapsulated in liposomes which are destroyed when heated to a certain temperature. Liposomes containing a drug freely circulate in the patient's body and start to release the cytostatic only in the tumor region due to its local heating. The most promising approach involves a concurrent use of thermally sensitive liposomes and hyperthermia. The optimal melting point of lipids in drug-encapsulating liposomes is 40–43°C. It is just these temperatures that tumor heating leads to destruction of the liposomes and release of the cytostatic directly into the tumor, which, in its turn, enhances selectivity of exposure. Thermally sensitive liposomes with prolonged citculation times having as phospholipid components dipalmitoyl phosphatidylcholine, distearoyl phosphatidylcholine, and dipalmitoyl phosphatidyl glycerol in a 5 : 2 : 3 ratio were developed [24].

Ample evidence has been accumulated for the hepatoprotector activity of liposomal formulations containing metal complexes. Experiments on animal primary hepatocyte cultures were performed, as well as experiments *in vivo* in rats with induced toxic hepatocyte damage (single intraperitoneal injevtion of carbon tetrachloride). Exposure of hepatocyte cell culture to metal phosphatidylcholine liposomes did not lead to evident changes in the structural and functional state of intact cells. It was shown that metal liposomes did not cause changes in the shape and area of contacting cell nuclei, which gave evidence for the lack of a mutagenic effect of the metal liposomes on the cells. A higher efficiency of liposomes containing aluminum compared to copper-containing formulations was noted.

Similar results were obtained with studying the effect of metalloliposom *in vivo*. The integral normalizing dose-dependent effect of aluminum-containing phosphatidylcholine liposomes on damaged hepatocytes relates to a combination of regenerative and adaptive compensatory factors: regeneration of liver architectonics on the background of a sharp decrease of necrotic core and activiation of metabolic processes. The encapsulation in distearoyl phosphatidylcholine and cholesterol liposomes of amorophous complexes of metals (chromium, aluminum, vanadium, manganese, etc.) allowed creation of therapeutics for diverse diseases [24, 131].

The model of acute toxic hepatitis in rats, induced by subcutaneous injection of an oil solution of CCl_4, was used to study the effect on certain parameters of liver function. The hepatoprotectors used in this research were Essentiale, Siliborum, Antral, Superoxide Dismutase, as well as the liposomal formulation Lioliv fabricated from phosphatidylcholine and an aluminum complex of 2,3-dimethylphenylanthranilic acid. It was found that Lioliv exhibits the strongest antioxidant and anticytolytic effects. Thus, for example, the levels of malonaldehyde and marker aminotrasferases increased to a lesser extent than with the other hepatoprotectors. Lioliv was recommended as an efficient hepatoprotector whose action is based on a high antioxidant effect [8, 24, 131].

Preclinical testing established that parenteral (injections and inhalation) and entheral (oral) administration of Lioliv in the therapy of liver injuries caused by various hepatotoxins and their combinations increased the survival rate of experimental animals, normalized activity of microsomal enzymes and transaminases of blood serum, mitigates the effect of hepatotoxins, activates reparative processes in hepatocytes and cellular metabolism, which leads to normalization of the liver's protein synthesis and lyotropic functions. Evidence for the positive effect of Lioliv in the case of acute liver injuries comes from the liver pathomorphology which reveals sharply reduced dystrophic changes and enhanced hepatocyte regeneration processes.

The hepatoprotector activity of Lioliv is associated with the inhibition of peroxide lipid oxidation, support to endogenous antioxidant body systems, stabilization of liver structure and hepatocyte membranes, as well as with the nonspecific detoxification function. Evidence for the hepatospecificity of Lioliv is

provided by pharmacokonetic data which show that this liposomal formulation preserves structural integrity in the blood stream and tissues and is preferentially accumulated in liver and spleen. Along with the hepatoprotector effect, Lioliv exhibits an expressed prolonged anti-inflammatory effect.

Clinical trials of Lioliv in patients with acute viral hepatitis C gave evidence for its high hepatoprotector efficiency. Lioliv favored more rapid regression of clinical symptoms of the disease, including the intoxication and dyspeptic syndromes and earlier development of bile attack, and much improved the patient's quality of life. The drug exhibited expressed detoxification properties, positively affected the dymanic of principal biochemical parameters of liver function, and reduced manifestations of the principal cytolytic, mesenchymal inflammatory, and cholestatic syndromes. Clinical signs, liver function parameters, serum amino acid composition, free-radical oxidation and antioxidant protection, and cellular and humoral immunity were studied in patients with acute and chronic alcoholic hepatitis. In the patients who obtained Lioliv, normalization of alkaline phosphatase, ALT, and AST levels was observed. The dynamics of normalization of enzyme activity in the control groups was much less expressed. After diversified clinical trials the liposomal formulation Lioliv was registered in Ukraine in 2003.

The research on liposomal forms of hypothalamus and cerebral cortex neural tissue phospholipids of newborn animals, initiated as far back as 1990s, resulted in the development of two liposomal injection formulations Liposome Forte and Tricortin 1000 (producer Fidia Farmaceutical SPA, Italy). Phopholipids were found to activate metabolism, normalize neuronal function, activate membrane enzymes and neurotransmitters, and enhance glucose metabolism. Safety testing in various animal species revealed no toxicity and mutagenicity, as well as a good tolerability of the formulations.

Liposome Forte is a liposomal form of the hypothalamic basal ganglion phospholipids of newborn pigs. It is injected intravevously and intramuscularly. The indication for use is therapy of metabolic anomaly associated with cerebral neouroendocrine disoder. Furthermore, Liposome Forte was found to be an efficient auxiliary in the treatment of Parkinson's disease. The formulation activates hypothalamus by driving dopamine, tyrosine hydrolase, and adenylate cyclase metabolism. Liposome Forte was also applied to treat anxiety and depression during menopause. Efficiency and safety of the formulation in the therapy of depressive psychosis in women was established. The efficiency of anxiety and depression mitigation in the control group was lower.

Tricortin 1000 is a liposomal form of cerebral cortex phospholipids of newborn pigs. It is given as intravenous and intramuscular injections. The indications fou use are as follows: Therapy of the metabolic anomaly of nervous system after traumatic brain injury, neurosis syndrome (headache caused by endogenous and exogenous intoxication), and alcoholic polyneuropathy.

Particular interest of researchers is focused on the search for liposomal formulations providing targeted delivery of a required drug to pathologically changed cells or separate cell elements (the target therapy). Liposomes with encapsulated elements of genetic information can be used as drug carriers. The action of formulations is based on the interaction of the drug containing a nucleic acid with the genetic material of definite cells in the body.

Quite an important issue is the use of liposomes in genetic therapy. The key goal is to deliver a DNA molecule. The DNA molecule should be packed in such a way as to make it possible DNA binding with target cells but to prevent, wherever possible, it from binding with other cells. Special methods are required to ensure successful delivery of the long unstable polyanionic DNA molecule in a target cell through three lipid bilayer, i.e. through the cell membrane and the double nuclear membrane. First, special conditions should be created to protect DNA from mechanical and enzymatic degradation. Second, DNA should "survive" until it has reached the cell nucleus. Therefore, having entered the cell, DNA should keep away from endosomes and lysosomes (cellular organelles) and find way to cell nucleus. Targeting DNA can be delivered though formation of cationic complexes of phospholipids with liposome-encapsulated DNA. There complexes bear a positive charge. Liposomes can merge with cellular membranes and thus let DNA to penetrate into cells. Gene vaccines act in the same way. When DNA vaccines are introduced into patient's body, the DNA molecules which contain genes code immunegenic proteins of the pathogenic microorganism [24].

We cannot sidestep the issue of the role of liposomal nanoparticles in the transport and introduction into the

body of hydrophobic compounds. The ability of liposomal membranes to "dissolve" hydrophobic drugs makes the latter much more bioaccessible and extends the range of drugs which could never be used in injections before the advent of liposomal formulations (AmBisone, Lipoflavon, Lioliv, etc.).

Liposomes as vaccine adjuvants play a special role. With lipids as adjuvants, one can get a high immune response using a smaller quantity of drugs (antigenes). Liposomal adjuvants and liposomal vaccines offer the following advantages. Low-immunogenicity antigenes can be converted into highly efficient antigenes. Liposomes can used to encapsulate hydrophobic antigenes. Adjuvants and antigenes can together be encapsulated in liposomes. Liposomal vaccines allow one to obtain high-titer specific antibodies and ensure their prolonged specific action. Liposomes reduce toxicity and pyrogenicity of antigenes and adjuvants. Such properties of lipids as safety and biodegradability make them highly promising adjuvants.

At present liposomal anti-influenza (Invivac virosomal, Lipovaca Influenzal, Inflexal virosomal) and antihepatitis A (Epaxol-Berna) drugs are used for antiviral prophylaxis in tens millions children. Prophylactic drugs for diphtheria, lockjaw, lyssa, and other infections are in different phases of clinical trials [20, 63, 96].

Recent research showed that liposomes can fairly easily penetrate into the body by absorption through the enteral wall or pulmoaortic tissue. Preserving specific chemical and biological activity, they later exhibit it being incorporated into one or another intra- or extracellular tussie structure. Thus, several liposomal drugs for use as aerosols have been proposed, specifically, those containing the Amikacin antibiotic and the insulin hormone. Commercial liposomal formulations loaded with anticoagulants, in particular, a low-molecular heparin (Viatromb, LipoHep), produced as a gel for topical application, showed good results.

Liposomes are presently widely used in cosmetology in the form of creams and gels including vitamins, enzymes, microelements, amino acids, and other biologically active substances.

The liposomal forms of antibiotics deserve special mentioning. The encapsulation of antibiotics in liposomes allowed development of novel high-efficiency formulations of known pharmacologically active substances. Thus, Axentis Pharma (Switzerland) developed a liposomal form of the antibiotic Tobramycin for therapy of chronic pulmonary diseases. The formulation was proposed to be produced as an aerosol [36, 37, 45, 62, 73, 74, 78, 84, 86, 94, 104, 106, 116, 122, 125, 127, 134]. A therapeutic abtibacterial effect with respect to *Burkholderia cenocepacia* in patients with mucoviscidosis was observed. Over the past years liposomal commercial formulations containing such antibiotics as doxorubicin, daunorubicin, amphotericin B, tobramycin, amikacin, vincomycin, and others have been developed. In our opinion, liposomal rifabutin and rifampicin may hold promise as antituberculosis drugs. Liposome-encapsulated antibiotics as antibacterial means offer the advantage of being protected from exogenous hydrolases, which is one of the ways to fight against antibiotic resistance. The liposomal forms of antibiotics demonstrate a markedly longer action that the free forms of the latter. Liposomes loaded with antibiotics merge with the external membrane of the bacterial cell wall and penetrate inside the bacterial cell, leading to its death. Liposome-encapsulated antibiotics exbibit a higher antimicrobial activity and cause less side effects than free antibiotics.

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