UDC 615.014:615.456.3 https://doi.org/10.15407/biotech15.05.024

INFLUENCE OF THE LIPID COMPOSITION ON THE PROPERTIES, TECHNOLOGY AND QUALITY INDICATORS OF LIPOSOMAL DRUGS

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Received 10.08.2022
Revised 23.09.2022
Accepted 31.10.2022

Liposomal drug delivery system is an example of the use of nanodrugs in medical practice. Encapsulation of active pharmaceutical ingredients in liposomal nanoparticles allows increasing their bioavailability and efficacy.

Aim. The article is devoted to the analysis of the lipid composition of liposomal drugs developed in Ukraine, its influence on the choice of technology and control parameters.

Results. The lipid compositions of liposomal drugs developed in Ukraine in recent years were reviewed. The advantages and disadvantages of natural phosphatidylcholine as the main membrane-forming lipid were analyzed. Data on the influence of anionic phospholipids and cholesterol in the liposomal membrane composition on the stability of liposomal nanoparticles and the level of active pharmaceutical ingredient encapsulation were given. The main technological stages of obtaining liposomes with hydrophilic and hydrophobic active pharmaceutical ingredients were considered. The main groups of quality indicators of liposomal dosage forms have been determined.

Conclusions. The lipid composition determines the structure and physicochemical properties of the lipid membrane, the mechanism and level of active pharmaceutical ingredient encapsulation, which significantly influences the pharmacological efficacy of liposomal drug delivery systems.

Key words: nanobiotechnology; drug delivery system; liposomal drug; phospholipids; anionic phospholipids; phosphatidylcholine; cholesterol.

Using drug delivery systems, the pharmacokinetics of active pharmaceutical ingredients (APIs) can be changed, and its bioavailability and effectiveness can be increased [1]. The development of liposomal drugs (LS-drugs) is one of the promising areas of modern nanopharmacology due to a number of advantages of LSs [2–5]: they prolong the action of encapsulated APIs in the body; change the pharmacokinetics of drugs, that significantly increases their pharmacological efficacy; protect APIs from degradation; protect healthy cells and pathological organs from the toxic effects of drugs; increase the bioavailability of lipophilic APIs.

LS-drugs are the only real example of the use of nanopreparations in medicine, for example, in Ukraine LS-drugs are licensed for use in cardiology, ophthalmology, oncology, etc. [2, 6–9]. In addition, LSs show high efficiency as adjuvants in vaccines.

LSs are colloidal spherical nanorange particles formed by a phospholipid bilayer [10]. There are single-layer (unilamellar) vesicles (ULVs), multilayer vesicles, which are divided into oligolamellar (OLVs) and multilamellar

(MLVs) vesicles, and multivesicular LSs (MVLs). OLV and MLV contain 2–5 or more than 5 concentric lipid bilayers. Unlike MLVs, MVLs consist of hundreds of concentric water compartments bounded by a single lipid bilayer membrane. Depending on the particle size, ULVs are divided into small unilamellar vesicles (SUVs) with a size of 30–100 nm, large unilamellar vesicles (LUVs) with a size of more than 100 nm, and giant unilamellar vesicles (GUVs) with a size of more than 1000 nm (Fig. 1).

The structure and efficacy of LSs depend heavily on the lipid composition of the LS membrane. The lipid composition determines the particle size and stability, the level of API encapsulation, and the methods of LS preparation [11].

The aim of the work was to analyze the lipid composition of LS-drugs developed in Ukraine, to characterize the main functions of lipids in the composition of LS-drugs, to highlight the main control points in the preparation of LSs.

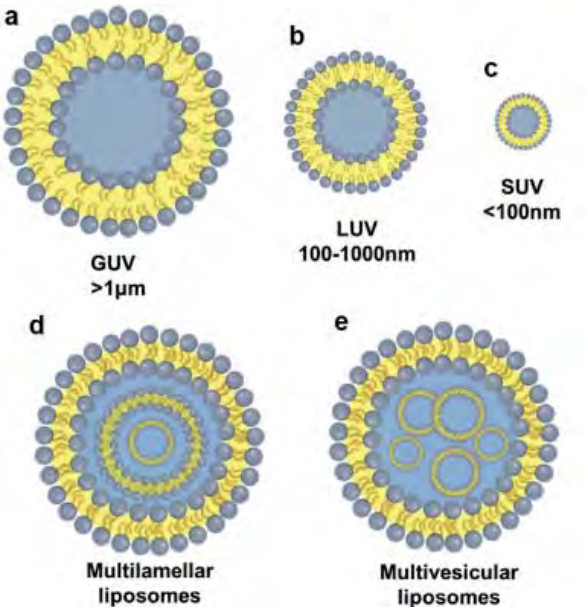

Fig. 1. **Classification of liposomal nanoparticles by size and number of lipid bilayer [10]**

Lipids in LS-drug

Most of commercial LS-drugs, which are available on the market, are ULVs capable of passive targeting and long-term circulation in the body. In this article we focused on LS-drugs, which were developed by us in Ukraine in 1989–2021 (Table 1).

Analyzing the lipid composition of this LS-drugs, the following components can be identified: EPC, DPhG, DPPG, PhG, PhI, and Chol (Fig. 2).

Table 1. **LS-drugs, developed in Ukraine**

Product name	Application area	API composition	LS size, nm	Lipid composition	Development stage	Ref.
Lipin®	Pulmonology, nephrology, cardiology	EPC	80–140	EPC	Licensed in 1991	2, 32
Lipodox®	Oncology	Doxorubicin hydrochloride	80–120	EPC, Chol	Licensed in 1998	2, 9, 22
Lioliv®	Hepatoprotector	Antral	90–130	EPC	Licensed in 2003	2, 27
Lipoflavon®	Cardiology, ophthalmology	Quercetin	130–160	EPC	Licensed in 2006/2007	2, 26
LS irinotecan	Oncology	Irinotecan hydrochloride	80–120	EPC, Chol	Preclinical trials	24, 25
LS cytochrome C	Cardiology	Cytochrome C	120–170	EPC, DPPG	Preclinical trials	12
Lipotax	Oncology	Docetaxel	120–150	DPhG, EPC	Laboratory studies	2, 19, 25
Lipoplat	Oncology	Cisplatin	140–180	EPC, Chol, PhG, PhI	Clinical trials	2, 6, 21
LS curcumin	Antioxidant, cardioprotector	Curcumin	150–200	DPPG, EPC	Laboratory studies	13, 14
LS coenzyme Q10	Antioxidant, cardioprotector	Coenzyme Q10	140–180	DPPG, EPC	Laboratory studies	2

Legend. EPC — egg phosphatidylcholine, DPhG — diphosphatidylglycerol, DPPG — dipalmitoylphosphatidylglycerol, Chol — cholesterol, PhG — phosphatidylglycerol, PhI — phosphatidylinositol.

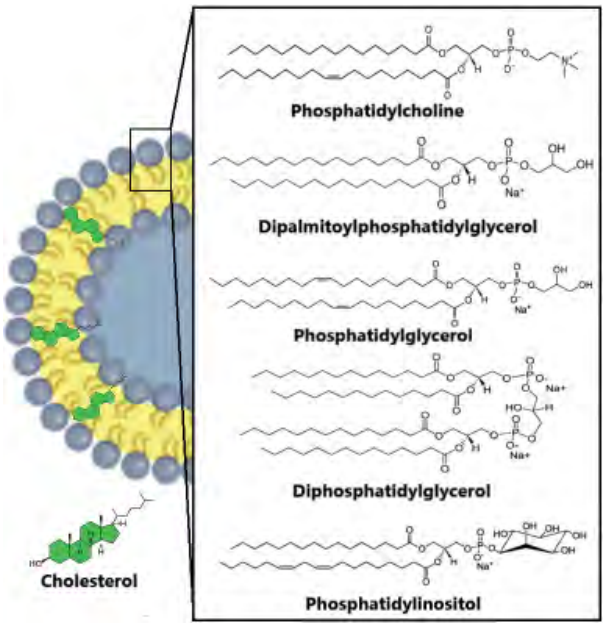

Fig. 2. **Structure of phospholipids**

We used EPC as the main membrane-forming lipid in LS-drug developing. The advantage of natural EPC is the low cost of production compared with semi-synthetic and synthetic PCs, such as DSPC, DPPC, DOPC, etc. EPC is composed of a family of fatty acids, and a wide range of fatty acid composition causes a low standardization of the EPC. LysoPC (1.0%) and sphingomyelin (3.0%) are detected in the natural EPC, obtained according to the previously developed technology [12], and the purification of them leads to reducing the cost of the product due to a significant decrease of the product yield. Presumably, sphingomyelin of the EPC can influence the stability of the LS structure [13], especially in acidic medium with pH 2.0–3.0 used in the preparation of LSs by transmembrane pH gradient method of hydrophilic APIs encapsulation, such as doxorubicin hydrochloride or irinotecan hydrochloride.

We used semi-synthetic DPPG in the preparation of a number of LS-drugs, for example, in the preparation of a complex with cytochrome C. DPPG can interact with a positively charged API, such as cytochrome C, to form a stable complex. In addition, DPPG has a negative charge and can prevent the aggregation of LSs [14]. DPPG was also used in the preparation of LS-drug with bilayer-encapsulated lipophilic APIs, curcumin and coenzyme Q10 (Table 1). The introduction of anionic DPPG allowed not only to increase the API incorporation (by 10–15 %) into the bilayer of the nanoparticle, but also to stabilize LSs [15–17]. Using curcumin-containing LSs, the pharmacological activity of the LS-drug was confirmed, namely, cardioprotective and antioxidant properties were shown. Based on the high pharmacological activity of curcumin [18–20], the development of its hydrophilic form in LS gives hope for using the product in various pharmacological models. The use of natural DPhG stabilized the structure of a docetaxel-containing LSs [21, 22].

We used Chol as a component of a lipid bilayer in preparation of LSs with hydrophilic APIs, doxorubicin [23–25] and irinotecan [26, 27]. The encapsulation of Chol into the LS bilayer facilitates the packing of fatty acid chains and thereby forms and stabilizes the lipid bilayer. Furthermore, Chol in nanoparticles largely determines the rigidity of the LS membrane, which can influence the API encapsulation into the inner water space of LSs and the subsequent release in the organism. The Chol encapsulation into LS-drugs containing irinotecan or doxorubicin can stabilize APIs in acidic medium. In addition, Chol was not used in LS-drugs with lipophilic APIs, which are incorporated in the lipid bilayer, for example, quercetin in Lipoflavon® [2, 28] (used in cardiology, ophthalmology, oncology), and antral in Lioliv® (hepatoprotector) [2, 29, 30]. In our opinion, lipophilic substances incorporated in the LS bilayer can independently stabilize the LS membrane and influence the membrane

rigidity. A number of authors have also reported the high pharmacological activity of quercetin-containing LS-drugs [2, 31–33]. The influence of the lipid composition on the LS structure and the pharmacokinetics of anthracycline antibiotics and 5-fluorouracil encapsulated LS-drugs was studied [6]. The Chol increase in LS composition leads to an increase in the size of LSs and consequently to decrease in the API encapsulation and complicate the sterilizing filtration. The cumulative and prolonging effect of aforementioned LS-drugs have been established, and the distribution of anticancer APIs in organs was shown.

Technological methods for LS-drugs preparation

The lipid and API composition of LS-drugs largely determines the technology for producing products. The production of developed LS-drugs has been discussed in detail in our previous studies [2, 7, 27]. To prepare LS-drugs with lipophilic APIs, we used the lipid film method followed by high-pressure homogenization, sterilizing filtration, and lyophilization. According to this scheme, Lipin® [34, 35], Lipoflavon® [28], Lyoliv® [29], Lipotax [22], and Latanoprost [36] were prepared. LS-drugs with hydrophilic APIs were prepared by lipid film method, emulsion rehydration, high pressure homogenization or sonication, transmembrane pH gradient method, sterilizing filtration and lyophilization. LS forms of doxorubicin hydrochloride (Lipodox®) [24] and irinotecan hydrochloride [26] were prepared in this way. Non-encapsulated APIs were removed using sterilizing filtration through a cascade of membrane filters, centrifugation, ultrafiltration or gel filtration. Sterilizing filtration was applied in following stages: preparation of sterile solutions of lipid components in organic solvents, cryoprotectant solutions and buffer solutions. In addition, a number of stages were carried out under aseptic conditions [2]. The lyophilization was carried out using cryoprotectant solutions, lactose or trehalose.

It has been established that physicochemical characteristics of LS-drugs depend on a number of factors in their obtaining: pressure of homogenization, intensity of sonication, process temperature, lipid concentration, number of cycles, etc. Even minor deviations from the established regulatory standards result in changes in properties of LS samples. At the same time, it is well known that the size of LSs, their charge, and fatty acids oxidation determine pharmacological properties of LS-drugs, which is primarily associated with altered pharmacokinetics in the organism. The influence of lyophilization modes on the stability of the physicochemical parameters of LS-drug was shown. The properties of the product are also affected by the structure and properties of the API [2, 27].

Control of LS-drugs

The standardization and control of LS-drugs containing different compositions of lipids and APIs need to be considered. LS-drugs were controlled in accordance with international [38] and national [39, 40] requirements. We proceeded from the definition of three groups of indicators [37]: I — indicators characterizing the identification and quantity of individual biologically active components of the drug: API, lipids (EPC, Chol, anionic phospholipids), cryoprotectant; II — quality indicators characterizing the dosage form of the drug (sterility, pH value, abnormal toxicity, pyrogenicity (endotoxins)); III — indicators characterizing the properties of LSs (encapsulation of API in LSs, size and charge of LSs, etc.). Tests should control those properties of the product, which are subject to changes during the storage and may affect the quality of the finished product, and the methods of quantitative determination should characterize the stability. The profile of new products of degradation of the drug components also need to be taken into account. In this case, new products of degradation must be identified. Thus, the limit concentrations of impurities should be identified and indicated, such as limit concentrations of lysoproducts or free fatty acids for EPC, and limit concentrations of impurities and degradation products for API. When developing LS-drugs, the identity of the qualitative and quantitative compositions of the APIs and lipid composition after freeze-drying and subsequent rehydration were proved.

Conclusions

The main task of the LS drug delivery system is to increase the bioavailability and effectiveness of the API. The lipid composition determines the structure and physicochemical properties of the lipid membrane, the mechanism and level of API encapsulation into the LS nanoparticle, that fundamentally impacts the pharmacological

efficiency of this drug delivery system. The LS-drug composition (both lipids and APIs) has the greatest influence on the choice of technological methods for obtaining LSs and the main control indicators of the finished product.

Funding source. The work was performed within the research program "Comprehensive research and optimization of industrial and pharmaceutical biotechnologies" (State Registration No.0118U002336, 2018–2021). There is no conflict of interest.

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ВПЛИВ ЛІПІДНОЇ КОМПОЗИЦІЇ НА ВЛАСТИВОСТІ, ТЕХНОЛОГІЮ ТА ПОКАЗНИКИ ЯКОСТІ ЛІПОСОМАЛЬНИХ ПРЕПАРАТІВ

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Ліпосомальні системи доставки ліків є прикладом застосування нанопрепаратів у медичній практиці. Інкапсуляція активних фармацевтичних інгредієнтів у ліпосомальні наночастинки дозволяє збільшити їх біодоступність та ефективність.

Мета. Стаття присвячена аналізу ліпідного складу розроблених в Україні ліпосомальних препаратів, його впливу на вибір технології одержання та контрольних параметрів.

Результати. Розглянуто ліпідний склад ліпосомальних препаратів, розроблених в Україна за останні роки. Проаналізовано переваги та недоліки природного фосфатидилхоліну як основного мембраноутворюючого ліпіду. Наведені дані щодо впливу аніонних фосфоліпідів та холестерину у складі ліпосомальної мембрани на стабільність ліпосомальних наночастинок та ступінь інкапсуляції активного фармацевтичного інгредієнту. Розглянуто основні технологічні етапи одержання ліпосом з гідрофільними та гідрофобними активними фармацевтичними інгредієнтами. Визначено основні групи показників якості ліпосомальних лікарських форм.

Висновки. Ліпідна композиція визначає структуру та фізико-хімічні властивості ліпідної мембрани, механізм та ступінь інкапсуляції активного фармацевтичного інгредієнту, що суттєво впливає на фармакологічну ефективність ліпосомальних систем доставки ліків.

Ключові слова: нанобіотехнологія, система доставки ліків, ліпосомальний препарат, фосфоліпіди, аніонні фосфоліпіди, фосфатидилхолін, холестерин.