https://doi.org/10.18321.ectj1647

Phytosomes – an Effective Drug-Delivery System. Development, Technology, Application.

I.A. Khabarov, S.D. Sergazy, A.S. Maikenova, A.N. Zhabayeva, O.V. Maslova*, S.M. Adekenov

JSC "Research and Production Center "Phytochemistry", 4, M. Gazaliyev Str., Karaganda, Kazakhstan

Article info

Received:
14 June 2024

Received in revised form:
21 July 2024

Accepted:
5 September 2024

Keywords:
Phytosome
Phosphatidylcholine
Phosphatidylethanolamine
Phosphatidylserine
Production methods
Bioavailability

Abstract

Herbal ingredients are widely used in practice due to their broad pharmacological effects and absence of side effects. However, despite their remarkable pharmacodynamic activity, most of the herbal ingredients have shown lower bioavailability *in vivo* conditions. New drug-delivery systems acquired vital importance because of higher bioavailability and overall therapeutic efficacy. A review of various studies on the production and application of phytosomal medical forms, which are in the form of hybrid molecules with high solubility in lipid and aqueous environments, is presented in this article. In an aquatic environment phytosomes group and form micelles. Phytosomes are used for increasing the bioavailability of the medical component, targeted delivery, and increasing the effect of the action of a medical drug while decreasing its therapeutic dose. Expanding the range of phytosomal medicinal forms, including sesquiterpene lactones, flavonoids, and other hydrophilic compounds is a perspective direction. In literary sources, methods for establishing quality control are practically absent and require development as well as unification.

1. Introduction

Most biologically active plant-based components are water soluble or polar, their application is limited by poor absorption, which reduces their bioavailability. To increase bioavailability (to get absorbed in gastrointestinal fluids and achieve an equilibrium with lipid biomembranes) plant-based drugs should have the right balance between hydrophilic and lipophilic molecules [1]. Plant-based drugs are widely used in modern medicine. Before, pharmacological research was conducted employing plant extracts and their components to estimate their potential in treating diseases. Recently, there has been significant progress in developing new drug-delivery systems based on plant extracts and active components. Applying modern methods of drug delivery, desired pharmacological effects can be achieved with a decreased dose of a drug. One method is the delivery of an active component directly to the site of action [2].

Plant-based drugs rivet more and more attention of scientists because of their effectiveness and increasing level of interest towards natural components. World Health Organization informs that 60% of the world's population prefers to rely on conventional medicine and approximately 80% of the population from developing countries has no other option but to use herbal medicines to sustain primary health care needs [3]. In the last years, plenty of scientific studies have focused on creating new plant-based drug delivery systems (Novel Drug Delivery System, NDDS). For plant-based drugs, NDDS methods such as plant compounds, liposomes, nanoparticles and polymeric nanoparticles, nanocapsules, transferosomes, phytosomes, and nanoemulsions present a list of benefits, including improvement of pharmacological activity, stability, distribution in macrophages tissues, solubility, and bioavailability, protection from toxicity, prolonged delivery and protection from physical inactivation. Thus, there is a promising potential for new delivery methods of plant-based drugs, which can improve activity and solve problems of conventional plant-based treatment. Liposomes

*Corresponding author.
E-mail address: m.olga.84@mail.ru

can carry both hydrophilic and lipophilic substances such as plant compounds due to their safety and biodegradation ability [4]. Delivery system NDDS can be used to increase the effectiveness of cosmetic products applied on the skin [5].

Transdermal application is not efficient for liposomal and niosomal delivery systems [6]. A new type of delivery system, so-called transferome allows the transferring of small and big molecules through the epidermis. These transferomes are chemically unstable and expensive. Problems with transferomes could be solved with Pharmacopoeia which possesses multiple different traits. These colloidal dispersions of pharmaceutical drugs are covalently bonded with lipids that can form ultrathin vesicular, micellar, or hexanol aggregates depending on the chemical composition of the drug-lipid complex [7]. During the Pharmacopoeia process any drug with an active hydrogen atom (-COOH, -OH or -NH2) can be esterified with a lipid with/without an intermediate bond, to create amphiphilic molecules that facilitate moving through the tissues [8]. To achieve better results of disease treatment, significant changes were implemented in the methods of plant-based drug delivery systems. In every country, natural ingredients are used as a way of self-treatment to get medical help that surpasses the abilities of modern medicine [9,10]. Expensive research is being carried out on new ways of drug delivery to improve the effectiveness of natural compounds that are employed in therapy. Because of toxicity and difficulties with absorption, various plant compounds derived from herbs cannot be fully investigated to detect their benefits for health. Furthermore, it is important to carry out broad research on plant-based drug delivery systems to increase the activity of active components. During the last century, plenty of plant extracts were chemically and pharmacologically tested to determine chemical compositions and benefits in the treatment of popular diseases. Most of the plant components of plant-based drugs are water-soluble compounds. Water-soluble plant components like flavonoids have poor solubility and are hard to absorb via simple diffusion due to their high molecular weight [11]. Since they are poorly soluble in fats and oils, transport through lipid-saturated outer membranes of small intestinal enterocytes is limited [12]. Several methods allowing for improved oral bioavailability were suggested, these methods include the addition of lipophilic carriers, structure modifications, and usage of absorption enhancers [13,14,15]. For each plant-based drug to be effective, active ingredients should be delivered in appropriate concentration. Phytosome technology of Indena company is solving all the above-mentioned problems, significantly increasing the bioavailability of drugs [16,17]. In comparison with simple plant extracts, these compounds complexed with phospholipids or so-called 'phytosomes' demonstrate higher bioavailability, stability, and rate of drug complexation compared to other types of drug carriers [18]. To support this, research written by Kanojiya et al. demonstrated that phytosomes can increase the absorption of some compounds by up to 20 times [19]. Examples of phytosome applications as drugs are shown in Table 1. As shown in Table 1, Indena company is actively using phytosomes to increase the solubility and bioavailability of plant-based drugs.

Phytosome technology is an example of a significant rise in bioavailability which leads to an increase in clinical effectiveness and ensures the delivery of active compounds to tissues without compromising nutrient safety [20]. Plant compounds, especially secondary metabolites like flavonoids are healthy for the human body. Most of the bioactive plant components are poorly soluble or insoluble in water. Toxicity and absorption issues limit the applications of the mentioned compounds. Bacterial intestinal enzymes and digestive enzymes can destroy plant extracts. Many research projects were performed aimed at developing methods to improve the effectiveness of plant-derived compounds [21]. The term "some" means structure and is like a cell, "phyto" stands for plant [22]. Some sources call this method "herbosomes". This new patented method combines standardized plant extracts or water-soluble phytocomponents with phospholipids to create lipid-compatible molecular complexes, which can notably increase absorption and bioavailability [23]. Phospholipids are the major membrane lipids that comprise lipid bilayers. This simple cellular structure serves as a shield and protects the cell against various external stress factors [24]. The group of phospholipids includes phosphatidylcholine, phosphatidylserine, phosphatidylethanolamine, and phosphatidylinositol. Among them, the most often used is phosphatidylcholine as it can also help in the treatment of liver diseases (e.g., hepatitis, alcoholic fatty liver disease) or liver damage caused by medical drugs. Besides that, phospholipids, taking part in the transport of nutrient substances, are soluble in water and oil [25]. Penetration of phytosomes through the stratum corneum is easier and more effective than with only phytochemicals is due to nano-vesicular form and lipid composition [11].

Table 1. Therapeutic application of phytosomal complexes

#	Trade/common name	Name of the company	Complex of phytocomponents	Biological activity
1	Siliphos®	Indena	Silibinin from Sílybum mariánum	Hepatoprotective and antioxidant action
2	Ginseng phytosome	Nature factors	Ginsenosides from Panax ginseng	Immunomodulator
3	Hawthorn phytosome	Indena	Flavonoids from Crataegus types	Antihypertensive and cardioprotective action
4	Ginkgoselect® phytosome	Herbal factors	Flavonoids from Ginkgo biloba	Protection against aging and cerebral vessels
5	Oleaselect™ phytosome	Indena	Polyphenols from Olea europaea	Anti-inflammatory and antihyperlipidemic action
6	Polinacea™ phytosome	Indena	Echinacoside from Echinacea angustifolia	Immunomodulating agents and nutraceuticals
7	Aescin β- sitosterol phytosome	-	Aescin β- sitosterol from fruits of Horse Chestnut	Antihyperalgesic
8	Ubiqsome® phytosome	Indena	CoQ10	Vital endogenous cofactor of the mitochondrial electron transport chain, antioxidant activity
9	Quercefit™ phytosome	Indena	Quercetin	Sport nutrition, seasonal allergy treatment, antioxidant activity
10	Vazguard™ phytosome	Indena	Citrus x bergamia Risso & Poit. – Fruit juice	Extremely effective for healthy blood level support by optimization of total cholesterol, LDL, HDL, triglycerides and glucose levels
11	Casperome® phytosome	Indena	Boswellia serrata Roxb. ex Colebr. – Resin	Healthy inflammatory response, joint health, gut health
12	Greenselect®/Green tea phytosome	Indena	Camellia sinensis (L.) O. Kuntze – Leaves	Body mass balance, antioxidant activity, anticancer and antioxidant activity
13	Leucoselect®/Grape seed phytosome	Indena	Vitis vinifera L. – Seeds	Cardiovascular and antioxidant activity
14	Curcumin phytosome	Indena	Curcuma longa L.- rhizome	Joint health, healthy inflammatory response, soothing
15	Virtiva®/Ginkgo biloba phytosome	Indena	Flavoglucosides Ginkgo, like ginkolids and bilobalids	Improving of cerebral insufficiency
16	18 ß-glycyrrhetinic acid phytosome	Indena	18 β- glycerotine acid from rhizome of Licorice	Soothing, anti-inflammatory action
17	Visnadex phytosome	Indena	Visnadin from Amni visnaga	Immune system improving
18	Polinacea phytosome	Indena	Root of Echinacea angustifolia	Immune system improving
19	Lymphaselect	Indena	Melilotus officinalis	Applied for treatment of chronic venous insufficiency of the lower limbs
20	Naringenin phytosome	-	Citrus aurantium	Antioxidant, anti-inflammatory action
21	Vazguard™/Naringenin phytosome	Indena	Extract of bergamot	Antioxidant, treatment of cardiometabolic disorders
22	Xanthones phytosome	-	Swertia alternifolia	Antioxidant
23	Mirtoselect®/Anthocyanin phytosome	Indena	Vaccinium myrtillus	Antioxidant, anti-inflammatory, diabetic retinopathy
24	Centevita®	Indena	Asiatic acid, madecassoside acid from Centella asiatica	For skin diseases, anti-ulcer diseases, wound healing, hair loss
25	Paridis rhizome phytosome	-	Rhizome paridis from Paris polyphylla, steroid saponin	Antitumor action, immune system correction, antiviral and anti-inflammatory action
26	Berberin phospholipid complex based phytosome	-	Berberin	Antidiabetic
27	Evodiamine phospholipid complex	-	Evodiamine	Antitumor
28	Ginseng phytosome	Indena	Panax ginseng	Nutraceutical, immunomodulatory
29	Soyselect®/Soy phytosome	Indena	Extract Glycine max	Antiangiogenic, anticancer, cardioprotective, immunostimulating and antihyperlipidemic actions
30	Cucurbita phytosome/Tocopherol, carotenoid phytosome	-	Cucurbita pepo	Anti-inflammatory, benign prostatic hyperplasia

For instance, Das M. and Kalita B. [26], discovered that Rutin phytosomes demonstrated a significantly greater ability to penetrate through the skin than Rutin in its original form. The absorption rate of Rutin phytosomes was higher approximately by 154.1% [26].

The Phytosome process is a patented method for creating lipid-compatible molecular complexes. Phytosomes can be obtained by adding water-soluble plant extracts or compounds to phospholipids. The Phytosome process creates a protective layer around valuable plant extracts preventing them from destruction by gastric fluids and microorganisms.

Research conducted by Goyal et al. [28] provides information that the pharmacological and pharmacokinetic properties of phytosomes can be improved. Due to the better ability of phytosomes to penetrate through lipid membranes and get into the bloodstream, they have higher bioavailability in comparison with plant extracts [2]. In modern methods of drug-delivery, there are different pharmaceutical carriers like particulate systems, macro- and micromolecular systems, polymeric micelles, and microparticulate systems. Vesicular systems are easier to control when one or several concentrated lipid bilayers are combined. In contact with water, these mechanisms help to prolong the effect of drugs by decreasing their toxicity and slowing down the speed of release from the body [29]. Italian pharmaceutical and nutraceutical company was the first to combine phospholipids with plant extracts that contain water-soluble components to increase the bioavailability of these extracts. This combination was patented as “Phytosome” [30]. Because of the creation of hydrogen bond between phospholipids and polar hydrophilic groups of phytocomponents and phytosomes, medical drugs are easier to be absorbed in the body. This promotes the increase of bioavailability and enhances the therapeutical effect.

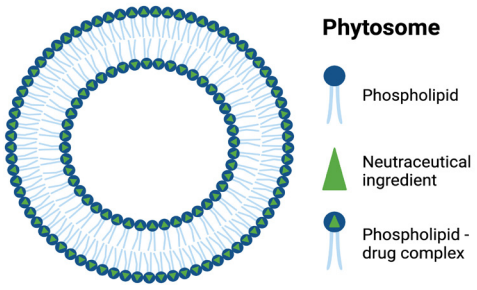


Fig. 1. Structure of phytosome complex. Adapted from [27].

2. Methods of obtaining phospholipid complexes

Different methods are used to obtain phytosomes, they allow the production of stable structures that provide encapsulation of active substances. The technology of obtaining phytosomes means implementing phospholipids (such as phosphatidylcholine, phosphatidylethanolamine, and phosphatidylserine) into standardized plant extracts.

Phosphatidylcholine (PH) (conventional name – lecithin) is a biologically active compound that plays an important role in the human body. PH is a solid, wax-like compound that can be dissolved in chloroform and mixtures with methanol, has a poor solubility in acetone, and is not soluble in petroleum ether; has a high ability to form micelles in aquatic and non-polar environments.

Phosphatidylethanolamine (PEA) makes up to 30% of total membrane lipids and is present in all tissues and cells of the human body and blood lipoproteins. PEA is metabolically connected to PH and in some animal tissues can serve as a predecessor of PH synthesis. The polar part of PEA contains ethanolamine.

Phosphatidylserine (PS) is a naturally occurring phospholipid synthesized from phosphatidylcholine or phosphatidylethanolamine by a base-exchange reaction where the head group is replaced with serine, the reaction is by catalyzed by specific enzymes such as phosphatidylserine synthase.

Comprehensive computational research was carried out to investigate the type of behavior that takes place when phytosomes created between phosphatidylcholine (PH) and a list of various polyphenols (PP), including epigallocatechin-3-gallate, luteolin, quercetin, and resveratrol. Obtained quantum-mechanical calculations have shown that intermolecular hydrogen bonds (HB) of phosphate and glycerol parts of phosphatidylcholine with polyphenolic compounds are the main force in creating phytosomes. The most powerful hydrogen bond (with HB energy – 108.718 kJ/mol) is formed between the epigallocatechin-3-gallate molecule and phosphatidylcholine. This hydrogen bond is formed because of the flexible structure of the medical drug that with several van der Waals (vdW) interactions creates the most stable complex (adsorption energy – 164.93 kJ/mol). Modeling results of controlled molecular dynamics are in good agreement with the results of experimental data and confirm that the phytosomal platform eases penetration of polyphenols to membrane cells [31].

Phytosomes are obtained by combining polyphenolic plant components and a mix of phospholipids. Depending on the substance, a mass ratio of 1:1.5-1:4 can be observed. Different methods of phytosomes preparation and resulting complex can differ depending on the employed medical compound [32–34]. There are three main different methods to get phospholipid complexes, including antisolvent precipitation, solvent evaporation, and freeze-drying.

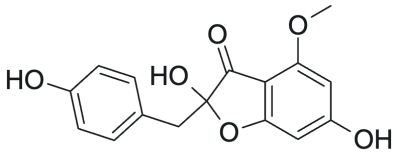
2.1 Antisolvent precipitation method

New methods of obtaining phytosomes were developed, including antisolvent precipitation that allows controlling the size of particles and degree of encapsulation of active ingredients [26]. This method is important to obtain phytosomes of high quality with optimal physicochemical characteristics which are very important in medical applications.

The method has been patented for preparing phytophospholipid complexes of andrographolides using dichloromethane as a reaction medium and *n*-hexane as an antisolvent for the final precipitation of the product. Many researchers use the traditional antisolvent precipitation technique by using *n*-hexane as an antisolvent to precipitate the drug phospholipid complex from an organic solvent. During research work, another similar method was patented, this method of producing phospholipid complex of andrographolides using dichloromethane as a reaction medium and *n*-hexane as a final antisolvent for product precipitation. After the mixture is evaporated the residue is commonly dried out in a vacuum [32,35].

2.2 Solvent evaporation method

In the most popular solvent evaporation method, the medical drug and phospholipids are placed in the same flask that contains an appropriate system of solvents like tetrahydrofuran or ethanol. The reaction is carried out at an appropriate fixed temperature during a fixed period to get the maximum possible yield and trapping of the medical compound. The marsupsin-phospholipid (1) complex was developed by mechanical disperse-oriented precipitation by a liquid antisolvent. Soy lecithin is dissolved in diethyl ether by ultrasound and marsupsin (1) in two times distilled water. Later mixture of medical drug is added dropwise to the phospholipid solution during ultrasound processing. The obtained reaction mixture is later cooled down. Complex analysis has shown that 44% of marsupsin (1) were trapped with 20% overall drug release [36].



(1)

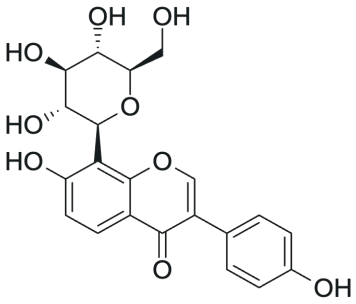
2.3 Freeze-drying method

The solvent evaporation method is a popular and traditional way to obtain phospholipid complexes. However, this process contains multiple stages and takes a lot of time and the quality of the final product in terms of size particles, morphology, and hygroscopicity often depends on the way how residue drying is performed. This step was not optimized in any research methods. To overcome the drawbacks of conventional methods, the method of supercritical fluid (SCF) can be applied because the size and spread of particles can be easier to control in very mild temperature conditions.

Supercritical fluids (SCF) are an effective instrument to obtain particles of sizes from 5 to 2000 nm. To improve the solubility profiles of poorly soluble medical compounds different methods of supercritical fluids were applied. Some of those are precipitation with compressed antisolvent (PCA), supercritical antisolvent (SAS), the rapid expansion of supercritical solutions (RESS), gas antisolvent (GAS), and solution enhanced dispersion by supercritical fluids (SEDS) [32]. For instance, Le et al., have implemented and described a method of supercritical fluid to get a puerarin-phospholipid (2) complex [37]. The complex was created by employing three different traditional methods. Solvent evaporation, lyophilization, and micronized puerarin (2) are qualitatively comparable to the complex that was obtained by supercritical precipitation with the antisolvent method.

GAS and SEDS methods are used to prepare different complexes. In the GAS technique, supercritical antisolvent is added to the solvents of medical drugs and phospholipids separately to achieve final pressure. After that, the reaction vessel is incubated at a fixed temperature of 38 °C and pressure of 10 MPa for 3 h without any stirring. In the SEDS method, liquid solution and supercritical antisolvent are constantly added to the precipitation system. Gaseous hydrogen dioxide allows penetration through the nozzle with a 0.1 mm diameter to the mixture of phospholipids and puerarin (2) in the solvent. Experimental conditions are optimized with the tem-

perature 35 °C, pressure 10 MPa, the mass ratio of medical drug and phospholipid 1%, and puerarin (2) concentration 100 mg/ml. This method allows the production of complex with 93% yield. Stated that the morphology of the product acquired through the SEDS method has the form of aggregated ordered particles about 1 μm in size while products obtained by conventional methods have the form of nodular granules with fused or viscous plates. The surface area of SEDS particles has increased from 0.50 to 1.08. The supercritical complex of phospholipids has demonstrated quick dissolution with an increase of puerarin (2) by 1.91 times from 2.87 mg/ml to 5.49 mg/ml of its phospholipid complex. It was proved that the product of the supercritical method GAS has more controllable morphological characteristics while SEDS particles present a complete loss of crystallinity [32].



(2)

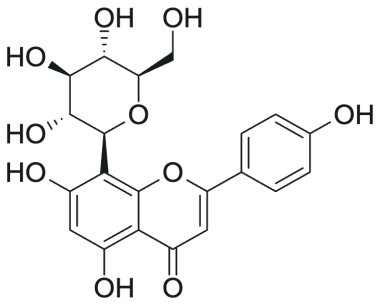
One of the other main methods is thin film hydration. In this method phospholipids and phytochemical components are dissolved in organic solvent (for instance, acetone or dichloromethane) and later evaporated, forming a thin film layer. The obtained film is hydrated with a water solution to produce vesicles [38].

In literature sources, modified phytosome-obtaining methods were found, like lyophilization or microwave irradiation that were developed to increase the encapsulation of phytochemical compounds and improve the stability of vesicles. Particularly, the lyophilization method that was applied to create phytosome from green tea extract allowed for increased encapsulation of active ingredients up to 80% and additionally increased stability during a prolonged time [39].

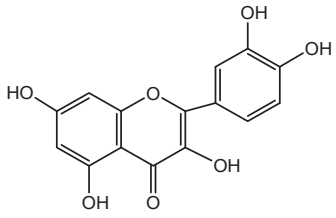
The main factors influencing on formation of phospholipid complexes are solvent, stoichiometric ratio of biologically active ingredients, and reaction time [32,40].

Research has shown the solubility and bioavailability increase of vitexin (3), this was achieved with phytosome technology utilizing soy and egg yolk phosphatidylcholine as carrier agents. The influence of carrier types and the ratio of vitexin (3) to carrier based on the physicochemical properties, solubility, and thermal stability of vitexin-loaded phytosomes (3) was studied. Phytosome obtained with egg yolk demonstrated a high yield of encapsulation at 97.60% and the efficiency of encapsulation was equal to 98.27%, solubility of 89.15% [41].

Quercetin-loaded (4) phytosomes were produced by thin-layer hydration using several molar ratios of quercetin, phosphatidylcholine, and cholesterol. The process involved dissolving quercetin and phosphatidylcholine in methanol, while cholesterol was dissolved in dichloromethane. The resulting mixtures were moved to a round-bottom flask, and the organic solvents were removed by rotary evaporation at 45 °C until the formation of a dry lipid film on the bottom of the flask. To ensure complete solvent removal, the film was vacuum dryed and then sprayed with nitrogen gas. On the next day, the lipid film was then hydrated with distilled water using a rotary evaporator at 45 °C. To achieve the small size of phytosome particles, three methods were employed: bath sonication at 45 °C, homogenization with 20.000 rpm, and probe sonication [42].



(3)



(4)

Soybeans that are used for the production of healthy food products are also used to get phytosomes of *Centella asiatica*. Particularly, the extract of *Centella Asiatica* was dissolved by shaking at room temperature with 70% ethanol and after non-dissolved compounds were removed with filter paper. Powder of phosphatidylcholine obtained from soy is dissolved in 95% ethanol. After mixing of first and second solutions, the reaction mixture is stirred 10

times 30 sec each with a high-speed stirrer, and after ethanol is removed by distillation at room temperature by vacuum distillation to get half of the initial volume. The obtained reaction mixture is moved to plate with 5 mm thickness and liquid components are removed with a vacuum freeze dryer at a temperature -20 °C for 3 h, and as a next step, it was vacuumed for 12 hours. The solid compound is collected by spatula and ground in mortar for 3 minutes until the final production of *Centella Asiatica* phytosome [43].

In order to prepare phytosomes containing extracts of mulberry and ginger, these plant extracts were mixed together according to the ratio of 1:1 (w/w). Resulted mixture was added to 100 ml of 50% ethanol to dissolve, while phosphatidylcholine was dissolving in 50 ml of dichloromethane. Once compounds were completely dissolved, solutions were placed on a magnetic stirrer for 8 h at 25 °C. Later solvents were removed by rotary evaporator at 45 °C. The obtained solution was placed for a night in a frezeer at -80 °C. Later lyophilization was used for complete drying (-86 °C, 0.008 mbar). Finally, phytosomes were packed and stored desiccator with a silica gel [44].

A new method of improving bioavailability of orally consumed genistein was developed, it included the preparation of genistein-loaded phytosomes using 3 different forms of phospholipids. The molar ratio of genistein to phospholipid inside of phytosome, including liquid phospholipid dissolved in long-chain triglycerides, is 1:3 [45].

A conducted analysis of literature data says that phytosome are acquired by complexation of polyphenolic phytocomponent or a mixture of phospholipids with a mass ratio 1:1.5-1:4, depending on the medical drug. There are three main methods to produce phyto phospholipid complexes, including antisolvent precipitation, solvent evaporation (Fig. 2), and freeze-drying. These methods of phytosome production and obtained complexes can differ from each other depending on the medical drug used.

3. Biological effects of phytosomes

Phytosomes possess several key advantages over other forms of drug-delivery systems due to their unique ability to encapsulate phytochemical components in lipid shells. This allows for significantly increased bioavailability and effectiveness of phytochemical compounds, which under normal conditions have low solubility in aquatic environments and limited absorption in the gastrointestinal tract.

One of the important examples of phytosomes is curcumin (5), an active component of turmeric that has been famous for its anti-inflammatory, antioxidant, and antitumor effects for a long time. However, curcumin (5) has low bioavailability because of weak solubility in water and rapid metabolic degradation. Application of curcumin (5) in the form of phytosomes allowed to significantly increase its therapeutic effectiveness. This is because of lipid shell of phytosomes protects curcumin (5) from premature degradation and improves its penetration through membrane cells. A study performed by Baradaran et al. compared the effects of curcumin (5) and its phytosomal form, results have shown that nano-phytosomes loaded with curcumin helped to improve antioxidant and behavioral responses in the mice with inflammation caused by carrageenan [46].

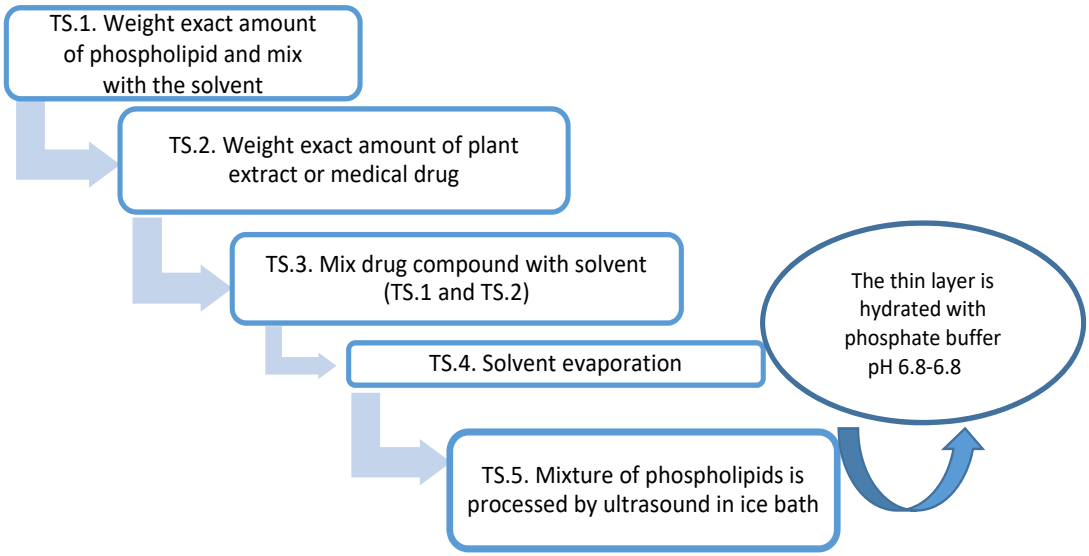
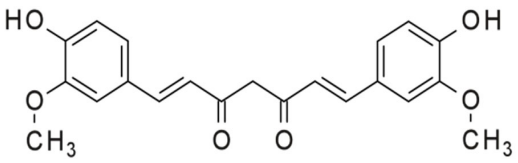
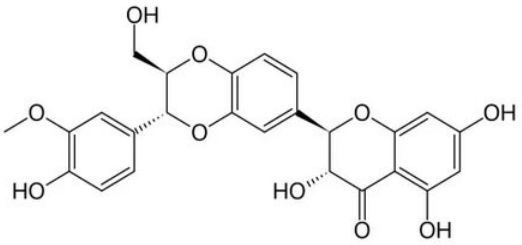


Fig. 2. Technical scheme of phytosome production by solvent evaporation method.

Also, an important role is played by silymarin phytosomes (6) that are used to treat liver diseases. Sylimarin (6) is a mix of flavonoids derived from *Sylibum* plant that has strong antioxidant and anti-inflammatory properties. Silymarin (6) is actively used to protect the liver from toxic effects like alcohol or medical drugs. As phytosomes, silymarin showed a much higher liver protection that was proved in animal testing. In particular, a decrease in enzyme levels that show liver damage such as ALT and AST as well as an improvement in the overall health of liver cells [47].



(5)



(6)

Researchers discovered that extracts from leaves of the plant *Ginkgo biloba* contain flavone glucosides, terpenelactones (ginkgolides and bilobalides), and other extractive compounds that have strong properties, influencing central nerve system (CNS), hepatoprotective, antidiabetic, antiasthmatic, and antioxidant effects. Research has shown that 200 mg/kg of phytosome G. Biloba significantly reduced damage to cardiac muscle caused by isoproterenol. Histopathological analysis of the myocardium admitted evidence that phytosomes can protect the heart. This happens by decreasing the amount of damage caused by cardiac muscle necrosis (as shown by a decrease in the level of ferments AST, LDH, and CPK and also by changes in histoarchitecture) and increased levels of the body's antioxidants [48].

Besides that, according to studies, 1.1% of people taking a rifampicin antibiotic have developed clinical hepatitis. The effect of Ginkgo Select Phytosome® was tested on rifampicin (RMP)-induced liver injury in rats. According to current research, the positive effects of Ginkgo Select Phytosome® on antioxidant protection and the ability to protect the liver from oxidative stress induced by RMP can be explained by phytosome's ability to eliminate free radicals [49].

Pharmaceutical composition for the prevention and treatment of skin inflammation was developed which is a phytosome of *Centella Asiatica* and extract of *Mori Radicis Cortex* [50].

An interesting direction of research is the application of phytosomes to treat neurodegenerative diseases such as Alzheimer's disease. An example is the application of phytosomes with green tea extracts which can protect neurons from free radicals and slow down the development of cognitive impairment because of their antioxidant properties. Mechanisms of action of phytosomes include the penetration of active compounds through the blood-brain barrier that allows them to directly affect brain cells, improving their functional health and protecting them from inflammatory processes (Fig. 3) [18].

Over the last decades, several new drug-delivery systems have been developed to increase effectiveness, safety, and patient compliance with taking biologically effective compounds, mainly by increasing solubility in water and improving characteristics of solubility, preventing undesirable metabolism, optimizing routes of administration, targeting delivery, and release control. Therefore, incorporating sesquiterpene lactones and flavonoids into new delivery systems is widely viewed as a promising approach to increase their bioavailability and biological activity.

To deliver sesquiterpene lactones, alkaloids, and flavonoids, several new delivery systems were developed, including solid dispersions, emulsions, crystal-technique drugs, complexes, and various nanocarriers [23].

In this way, the conducted review proves that applied methods for improving bioavailability of medical drugs are mostly focused on particular types of technologies and diseases. For instance, improvement of the bioavailability of flavonoids administrated orally, studies on flavonoids-based nanocarriers for cancer chemotherapy, for topical applications in the treatment of skin diseases. However, methods for clinical applications of pharmacologically active compounds such (as sesquiterpene lactones, and flavonoids) from a new delivery system point of view are absent.

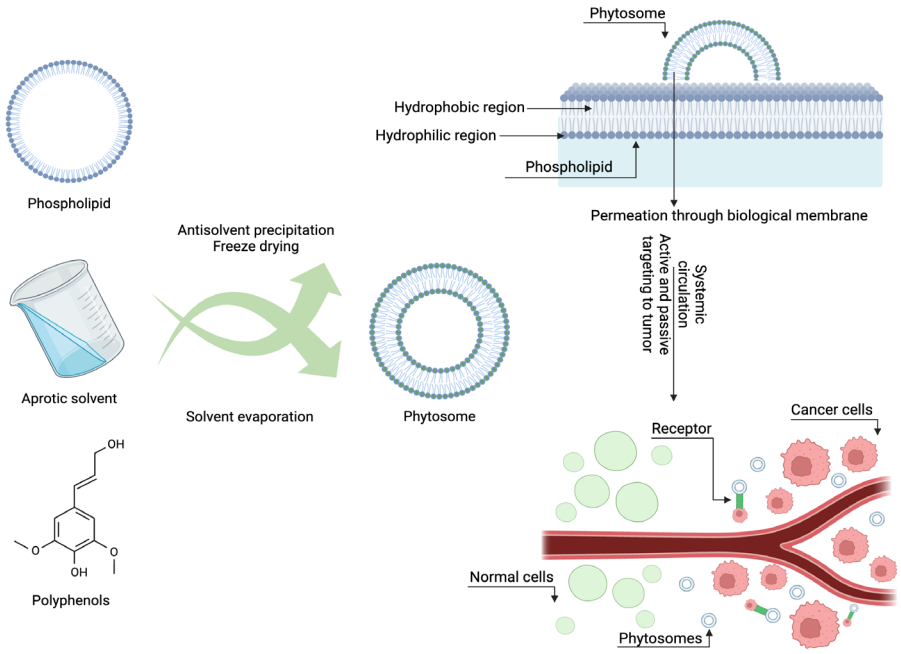


Fig. 3. Synthesis and mechanism of drug release from phytosome. Adapted from [18].

4. Conclusions

In the literature, there is data about phytosomes that contain predominantly plant extracts or individual flavonoids. However, data about the possibility of including other plant hydrophilic, poorly water-soluble compounds in lipid complexes are practically absent. This opens wide perspectives for researchers in developing new methods of phytosome complex production.

Methods of forming phytophospholipid complexes provide opportunities to increase the bioavailability of plant-based drugs *in vivo*, which, despite demonstrating positive results *in vitro*, cannot induce a similar reaction *in vivo*. Introducing phospholipids like phytosome can effectively solve the problem and allow obtaining medical drugs of plant origin with comparatively high lipid permeability, higher concentration, and stable therapeutical levels in plasma with a slower release rate.

Phytosomes and intracellular vesicles are powerful tools for the delivery of medical drugs and biologically active compounds. Their unique physiochemical properties, high bioavailability, and biocompatibility make them promising for usage in different spheres of medicine, including oncology, cardiology, dermatology, and gene therapy.

One of the key directions of research is to improve encapsulation methods and modifications of phytosomes for more precise delivery of therapeutical agents. It is also important to continue studying the biocompatibility and safety of systems described above and also the development of new methods for their large-scale production for clinical applications.

Besides that, a perspective direction is the creation of combined delivery systems, that include both phytosomes and exosomes. These systems can be used for the complex delivery of several therapeutical agents which will improve results of treating complex diseases like cancer or genetic disorders.

Future studies on standardization of production methods and optimization of drug-delivery by phytosomes and intracellular vesicles will allow them to expand their applications in clinical practice. It is also important to continue research on the safety of these technologies and their long-term influence on the human body for successful implementation into widespread clinical practice.

The potential of phospholipid complexes has a bright future for practical medicine thanks to the efforts of researchers in experimental and clinical pharmacology and pharmaceutical production technologists.

Funding

The work is funded by the Science Committee of the Ministry of Science and Higher Education of the Republic of Kazakhstan within the framework of the IRN project AP23489904 “Phytosome development – an effective form of targeted transport of original medical compounds in the human body”.

References

[1]. R. Pandey, M. Bhairam, S.S. Shukla, *B Gidwani, DARU J. Pharm. Sci.* 29 (2021) 415–438. DOI:10.1007/s40199-021-00403-x

[2]. A. Gandhi, A. Dutta, A. Pal, P. Bakshi, *J. Pharmacogn. Phytochem.* 1 (4) (2012) 6–14. https://www.phytojournal.com/archives/2012/vol1issue4/PartA/2.1.pdf

[3]. M.S.A. Khan, I. Ahmad. New look to Phytomedicine, Chapter 1 - Herbal Medicine: Current Trends and Future Prospects. Academic Press, Cambridge, USA (2019) p. 3–13. DOI:10.1016/B978-0-12-814619-4.00001-X

[4]. O.P. Medina, Y. Zhu, K. Kairemo, *Curr. Pharm. Des.* 10 (2004) 2981–2989. DOI:10.2174/1381612043383467

[5]. D. Chanchal, S. Swarnalata, *J. Cosmet. Dermatol.* 7 (2008) 89–95. DOI:10.1111/j.1473-2165.2008.00369.x

[6]. R. Rajan, S. Jose, V.P. Mukund, D.T. Vasudevan, *J. Adv. Pharm. Technol. Res*. 2 (2011) 138–143. DOI:10.4103/2231-4040.85524

[7]. N.G. Shinde, N.H. Aloorkar, A.S. Kulkarni, *Res. J. Pharm. Dosage Form. and Tech.* 6 (2) (2014) 110–120. https://rjpdft.com/AbstractView.aspx?PID=2014-6-2-8

[8]. S.S. Biju, S. Talegaonkar, P.R. Mishra, R.K. Khar, *Indian J. Pharm. Sci.* 68 (2006) 141–153. https://www.ijpsonline.com/articles/vesicular-systems-an-overview.html

[9]. H. Yuan, Q. Ma, L. Ye, G. Piao, Molecules 21 (5) (2016) 559. DOI: 10.3390/molecules21050559

[10]. P.K. Mukherjee, *Ther. Innov. Regul. Sci.* 35 (2001) 623–632 (2001). DOI:10.1177/009286150103500235W

[11]. W.S. Alharbi, F.A. Almughem, A.M. Almehmady, et al., *Pharmaceutics* 13 (2021) 1475. DOI:10.3390/pharmaceutics13091475

[12]. A.M. Singh, A.P. Singh, N. Verma, *Asian Journal of Chemistry* 23 (2011), 5189. https://asianpubs.org/index.php/ajchem/article/view/11082/11064

[13]. V. Piazzini, B. Lemmi, M. D'Ambrosio, et al., *Appl. Sci.* 8 (2018) 1163. DOI: 10.3390/app8071163

[14]. C. Li, T. Dai, J. Chen, et al., *Crit. Rev. Food Sci Nutr.* 63 (2023) 10637–10658. DOI:10.1080/10408398.2022.2083572

[15]. J. Zhao, J. Yang, Y. Xie, *Int, J, Pharm.* 570 (2019) 118642. DOI:10.1016/j.ijpharm.2019.118642

[16]. www.indena.com; Accessed on May 20 (2010).

[17]. K. Gnananath, S.K. Nataraj, G.B. Rao, *Adv. Pharm. Bull.* 7 (2017) 35–42. DOI:10.15171/apb.2017.005

[18]. S.S. Gaikwad, Y.Y. Morade, A.M. Kothule, et al., *Heliyon* 9 (2023) e16561. DOI:10.1016/j.heliyon.2023.e16561

[19]. D. Kanojiya, G. Parmar, B. Chauhan, et al., *J. Nat. Remedies* 24 (2024) 239–253. DOI:10.18311/jnr/2024/34470

[20]. Gupta Amit, M. S. Ashawat, Saraf Shailendra, Saraf Swarnlata, *J. Plant Sci.* 2 (2007) 644–649. DOI:10.3923/jps.2007.644.649

[21]. E. Middleton, C. Kandaswami. The Flavonoids Advances in Research Since 1986, chapter 15 - The impact of plant flavonoids on mammalian biology: implications for immunity, inflammation and cancer. Editor(s): J.B. Harborne. Routledge. Milton Park, UK. (1994). DOI:10.1201/9780203736692

[22]. K. Mane, S. Baokar, A. Bhujbal, et al., *Journal of Advanced Scientific Research* 11 (2020) 68-78. https://sciensage.info/index.php/JASR/article/view/508

[23]. Y. Dwivedi, Pranjal Sachan, Pranay Wal, et al., *J. Res. Pharm.* 7 (2023) 1687–1733. DOI:10.29228/jrp.457

[24]. Y. Dai, H. Tang, S. Pang, *Front Physiol.* 12 (2021) 775648. DOI:10.3389/fphys.2021.775648

[25]. P. Shivanand, P. Kinjal, *International Journal of PharmTech Research* 2(1) (2010) 627–631. https://sphinxsai.com/sphinxsaiVol_2No.1/PharmTech_Vol_2No.1/PharmTech_Vol_2No.1PDF/PT=99%20(627-631).pdf

[26]. M.K. Das, B. Kalita, *J. App. Pharm. Sci.* 4 (2014) 051-057. DOI: 10.7324/JAPS.2014.401010

[27]. D. Dwivedi, A.K. Shukla, S.P. Singh, *Int. J. Res. Pharm. Sci.* 13 (2022) 8–14. DOI:10.26452/ijrps.v13i1.11

[28]. A. Goyal, S. Kumar, M. Nagpal, *Journal of Pharmaceutical Education and Research* 45 (2011) 225-235. https://www.researchgate.net/publication/272495358_Potential_of_Novel_Drug_Delivery_Systems_for_Herbal_Drugs

[29]. S. Saha, A. Sarma, P. Saikia, T. Chakrabarty, *Sch. Acad. J. Pharm.* 2 (2013) 12–20. https://www.researchgate.net/publication283076774_Phytosome_A_Brief_Overview

[30]. E. Bombardelli. Phytosome: new cosmetic delivery system. *Boll. Chim. Farm*. 130 (1991) 431–438. https://typeset.io/papers/phytosome-new-cosmetic-delivery-system-3m1etfv3rh

[31]. H. Hashemzadeh, M. Yahya Hanafi-Bojd, M. Iranshahy, et al., *Sci. Rep.* 13 (2023) 2501. DOI:10.1038/s41598-023-29237-0

[32]. A.R. Gaikwad, K.D. Ahire, A.A. Gosavi, et al., *J. Drug Deliv. Ther.* 11 (2021) 138–152. DOI:10.22270/jddt.v11i3.4847

[33]. C. Chi, C. Zhang, Y. Liu, et al., *Eur. J. Pharm. Sci.* 144 (2020) 105212. DOI:10.1016/j.ejps.2020.105212

[34]. P.M. Patel, C.M. Modi, H.B. Patel, et al., *J Phytopharmacol.* 12 (2023)51-58. DOI:10.31254/phyto.2023.12108

[35]. V. Murugan, K. Mukherjee, K. Maiti, P.K. Mukherjee, *J. Agric. Food Chem.* 57 (2009) 4559–4565. DOI:10.1021/jf8037105

[36]. M.S. Sikarwar, S. Sharma, A.K. Jain, S. Parial, *AAPS PharmSciTech*. 9 (2008) 129–137. DOI:10.1208/s12249-007-9020-x

[37]. Y. Li, D.-J. Yang, S.L. Chen, et. al., *Int. J. Pharm*. 359 (2008) 35–45. DOI:10.1016/j.ijpharm.2008.03.022

[38]. R. Mohsenian Kouchaksaraee, D. Kazemi, S.N. Ebrahimi, *J. Med. Plants* 21 (2022) 50–61. DOI:10.52547/jmp.21.83.60

[39]. N. Karimi, B. Ghanbarzadeh, H. Hamishehkar, et al., *Applied Food Biotechnology* 2 (2015) 17–27. DOI:10.22037/afb.v2i3.8832

[40]. S.D. Saoji, N.A. Raut, P.W. Dhore, et al., *AAPS J*. 18 (2016) 102–114. DOI:10.1208/s12248-015-9837-2

[41]. M. Peanparkdee, R. Yooying, *NFS J.* 31 (2023) 28–38. DOI:10.1016/j.nfs.2023.03.001

[42]. S. Rasaee, S. Ghanbarzadeh, M. Mohammadi, H. Hamishehkar. Nano phytosomes of quercetin: A promising formulation for fortification of food products with antioxidants. *Pharm. Sci.* 20 (2014) 96–101. https://ps.tbzmed.ac.ir/Article/PHARM_2238_20140916092941

[43]. Patent KR20190081126 Phytosome comprising *Centella asiatica* extracts and the method preparing thereof / Chungbuk N.U., Found A.C. Published. 2019/07/09.

[44]. N. Palachai, J. Wattanathorn, S. Muchimapura, W. Thukham-Mee, *Oxid. Med. Cell. Longev*. 1 (2019) 5972575. DOI:10.1155/2019/5972575

[45]. I.A. Komeil, W.M. El-Refaie, M. Gowayed, et al., *Int. J. Pharm*. 601 (2021) 120564. DOI:10.1016/j.ijpharm.2021.120564

[46]. S. Baradaran, A.H. Moghaddam, S.K. Jelodar, N. Moradi-Kor, *J. Inflamm. Res.* 13 (2020) 45–51. DOI:10.2147/JIR.S232462

[47]. A.G. Mahmoudabad, F. Gheybi, M. Mehrabi, et al., *Bioimpacts.* 13 (2023) 301–311. DOI:10.34172/bi.2023.24128

[48]. V.S. Panda, S.R. Naik, *Exp. Toxicol. Pathol*. 60 (2008) 397–404. DOI:10.1016/j.etp.2008.03.010

[49]. S.R. Naik, V.S. Panda, *Fitoterapia* 79 (2008) 439–45. DOI:10.1016/j.fitote.2008.02.013

[50]. Patent KR102073009 (B1) Composition for prevention or treatment of skin inflammation comprising *Centella asiatica* phytosome and *Mori Radicis Cortex* extract / Soon P.M., Keun M.P., Ho P.J., Sung J.J., Sung K.H. Published 04/ 02/2020.