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Review Article

Phytosomes: A Novel Approach for Phytomedicine

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Abstract

Phytosomes, phosphatidylcholine is bound to the various elements of a herbal extract. As drug delivery technology advances, phytopharmaceuticals are being used to enhance the bioavailability of vegetative extracts for therapeutic purposes. Hydrophilic bioactive phytoconstituents of herbs are housed in phytosomes, a novel drug delivery system, and are bound by phospholipids around them. It has enormous potential in the medical, pharmaceutical, and cosmetic industries. It has been proven to be effective and safe, making it advantageous for the treatment of a variety of illnesses in both humans and animals. Numerous active components of herbal plants have in vitro pharmacological effects that have been well-established. However, they show fewer or no in vivo activities because of a number of inherent issues, which severely restricts their clinical applications. By combining phospholipids and polyphenolic phytoconstituents, mainly phosphatidylcholine, which molecularly binds elements to one another. For the delivery of polyphenolic phytoconstituents, phytosomes were developed. Through a range of drug routes, phytosomes are able to deliver standardized plant extracts and phytoconstituents. Only a few natural medications have been developed and are marketed as phytosomes. Several studies have been conducted on phytosomes, numerous applications, as well as many others are anticipated in the upcoming years. These formulations are made with clear and highly profitable techniques. One such cutting-edge method that helps make polyphenolic phytoconstituents more skin permeable and absorbable from the gastrointestinal tract is phytosome technology. This article discusses the properties, characteristics, and manufacturing process of the phytosomes. There are numerous commercial applications for automation. Pharmaceutical companies can now offer new pharmaceutical products made with water-soluble drugs thanks to phytosomes, which also brings about advancements in the medical field.

Keywords: Phytosomes; phospholipid complex; polyphenolic phytoconstituents; novel drug delivery

Introduction

Phytosomes, a mixture of phospholipids and active ingredients that occur naturally, when applied topically or orally, increase the absorption of isolated active ingredients or herbal extracts [1,2]. Phospholipids, a fundamental part of cellular membranes, are necessary for life. They are typically regarded as both natural carriers and digestive aids for active substances that are both polar and non-polar. The majority of phospholipids are nutrient-rich, including phosphatidylserine, which is essential for the nutrition of brain cells, and phosphatidylcholine, which is crucial for the regeneration of liver cells. Because of their amphiphilic nature, hydrogenated phospholipids and soy phospholipids have a lipid-reducing effect and are the foundation for the creation of stable liposomes, respectively [3]. The recently developed microsphere or cell form of herbal products known as phytosomes is more readily absorbed and produces a preferred pharmacodynamic and pharmacokinetic profile of herbal extracts that are common. Herbosomes is another name for them [4]. The active ingredients of the standardized extracts or components of plants can be found in phytosome structures when phospholipids are attached, mainly phosphatidylcholine, forming a molecular complex that is compatible with lipids.

All known life forms use complex molecules called phospholipids to create their cell membranes. These proteins, which include a wide range of transport proteins, enzymes, and other biological energy converters, including receptors, fit into the matrix that makes up the cell membrane, which is composed of these building blocks. In addition, phospholipids are used for humans and other higher animals, natural nutrient carriers and digestive aids that are both fat-soluble and water-soluble. Phosphatidylcholine is a bioactive nutrient to treat liver disease. Additionally, serving as a non-active "carrier" for bioactive flavonoids in phytosomes. It keeps beneficial parts of herbs from being destroyed by bacteria in the digestive fluids and gut. India developed the patented Phytosome method to significantly enhance the absorption and utilization of standardized extracts by adding phospholipids.

The production of phytosomes, a type of advanced herbal product, involves converting each unchangeable substance that transforms phosphatidylcholine from a herbal extract that is both more palatable and more useful than traditional herbal extracts. Numerous well-known herbal extracts have undergone the phytosome process, including those from curcumin, milk thistle, Kushenin, marsupsin and olive fruits, leaves and others. Pharmacokinetic and activity studies carried out on both animals and humans have shown that phytosomes have a higher bioavailability than the more straightforward, non-complex plant extract. Based on their physiochemical and spectroscopic properties, these compounds can be regarded as novel substances. Currently, phytosomes are primarily utilized water-soluble components to the skin when used in cosmetics. Because phospholipids allow for greater product adhesion to the surfaces it comes into contact with, this technology is also advantageous in pharmaceutical preparations used to manage the oral cavity, where there is little contact time [5-7] (Table 1).

Table 1: Difference Between Phytosomes & Liposomes.

Phytosomes	Liposomes
Phytosome is formed by mixing a water-soluble substance with phosphatidylcholine and here chemical bond is formed between individual plant components and phosphatidylcholine.	A liposome is formed by mixing a water- soluble substance with phosphatidylcholine. No chemicalbond is formed; molecules of phosphatidylcholine mutually surround the water-soluble substance. Hundreds or even thousands of phosphatidylcholines molecules surround the water-soluble compound.
NOTE: Stoichiometric 1:1 or 2:1 complex form which depends on the extract or phytocon- stituent and the phospholipid used. This difference results in increased absorption of active constituents from phytosome than from liposomes.	
Phytosome it is an integral part of the membrane, being the molecules anchored through chemical bonds to thepolar head of the phospholipid **(Figure 1).**	Liposomes the active principle isdissolved in the medium contained in the cavity or in the row of the membrane.
Phytosome process phosphatidylcholine and the individual plant components actually from a 1:1 or a 2:1 complexconfides in on the substance. This difference results in Phytosomes being much better absorbed those liposomes. Phytosomes are superior to liposomes inskin care products.	Liposomes are used primarily incosmetics to deliver water soluble substances to the skin. A liposome is formed by blending a water-soluble substance with phosphatidylcholine.No chemical bond is formed; the phosphatidylcholine molecules surround the water-soluble substance There may be hundreds or even thousands of phosphatidylcholine molecules surrounding the water-soluble compound.

Advantages of phytosomes:

The advantages of phytosomes over traditional herbal formulations are as follows:

a) They demonstrate better bioavailability, enhancing the therapeutic benefit of lipid-insoluble polar botanical extract when administered orally and topically.

b) By making herbal ingredients more soluble in bile, phytosomes make it easier for the liver to find them.

c) They are frequently used in cosmetics because they have a high lipid profile and can penetrate the skin more deeply.

d) Phytosomes increase the bioavailability of active ingredients in herbs by increasing their absorption [8-10].

e) Phytosomes display a high stability profile due to the phosphatidylcholine molecule's chemical bonds with the botanical extract.

f) Since the active component(s) are more readily absorbed, even a small dose of them can produce the desired effects.

g) Because phytosomes can more easily transition from a lipid-friendly environment, (like an enterocyte) into a water-friendly environment, such as the cell membrane, they can be targeted systemically. Phosphatidylcholine, a carrier as well as a hepatoprotective, is a component used in the production of phytosomes, which when combined with other hepatoprotective agents has a synergistic effect [11-13].

Disadvantages of phytosomes

a. One of the biggest drawbacks of phytosome is that when the phytoconstituents are separated from the "some," they are unstable, as evidenced by the decrease in the desired drug concentration. The growth of the breast cancer cell line MCF-7 can be induced by phospholipids (lecithin), despite the fact that phytosomes have many beneficial properties [14].

b. The removal of phytoconstituent from phytosomes is quick [15].

c. They decrease their bioavailability when applied topically or orally. [16].

Phytosomes preparation

Phospholipids like phosphatidylcholine, phosphatidylethanolamine, or phosphatidylserine, whether they are organic or synthetic, are used to create phytosomes (Table 2). The most popular method for creating phytosomes is the solvent evaporation method. The aprotic solvent is frequently required to avoid the disruptive interactions between the active ingredients and the phosphatidylcholine. The typical candidate solvents include ethyl acetate, dichloride methylene, acetone, and tetrahydrofuran [17]. After forming phytosomes, the complexes are much more soluble in these solvents than the active component is by itself. The development of real stable complexes is what causes the change in solubility. Hydroethanolic solvents have recently been used to develop a newer method for making phytosomes because the results are in compliance with the rules governing food and health products.

Table 2: Commercial Phytosome Preparations.

S.NO.	Phytosomes	Phytoconstituentscomplexed	Indication
1.	Centella Phytosome	Terpenes	Vein and Skin disorders
2.	Echinacea Phytosome	Echinacosides from Echinacea angustifolia.	Nutraceutical, immunomodulator
3.	Ginkgo PhytosomeTM	24% Ginkgo flavonoid from Ginkgo biloba	Protects brain and vascularlinings, anti-skin ageing
4.	Ginseng	37.5 % ginsenoside fromPanax ginseng.	Immunomodulator ,Nutraceutical
5.	Green Tea PhytosomeTM	Epigallocatechin 3-O-gallate from Camelia sinensis	Food Product, Systemic antioxidant, Cancer protectant.
6.	Grape Seed PhytosomeTM	Procyanidins from Vitisvinifera	Nutraceutical, cardio-protective, systemic antioxidant.
7.	Hawthorn	Flavonoids fromCrataegus sp	Nutraceutical, cardio-protectiveand antihypertensive
8.	Olive oil Phytosome	Polyphenols from Oleaeuropaea oil	Antioxidant, anti-inflammatory, anti-hyperlipidemic
9.	Panax GinsengPhytosomeTM	37.5 % ginsenosides fromroots of Panax ginseng	Food Product
10.	Super Milk thistle Extract	Silybin from Silymarin	Food Product; antioxidant forliver and skin
11.	Silybin PhytosomeTM	Silybin from Silybummarianum	Hepatoprotective, antioxidantfor liver and skin.
12.	Silybin PhytosomeTM	Silybin from Silymarin	Antioxidant for Liver and skin

Methods to Prepare Phytosomes by Dıfferent Technıques

Creating preliminary test batches to choose a method

The 1:1 molar ratio phytosome complex of lawsone was created using a variety of techniques, including antisolvent precipitation, rotary evaporation, and solvent evaporation.

Solvent evaporation method

A 100 ml round bottom flask was filled with lawsone and soy lecithin, and it was refluxed for two hours at 50 to 60 oC with 20 ml of acetone. The admixture is boiled, and the precipitate is obtained and reduced to 5 to 10 ml, which is then filtered with the help of funnel and filter paper and the final precipitate is collected. This precipitate is then stored in a glass bottle (amber colored) and kept at an ambient temperature [18].

Method of rotary evaporation

In a rotary round-bottom mounted flask, Lawson & soy lecithin were mixed with 30 milliliters of tetrahydrofuran. The admixture was stirred for 3 hours at a temperature no higher than 40 oC. Before adding the n-hexane, the sample was made into a thin film and stirred constantly using a stirrer the precipitate is made and then collected. This precipitate is then stored in a glass bottle (amber colored) and kept at an ambient temperature [19].

Antisolvent precipitate preparation

In a round-bottom mounted (100 ml) flask, soy lecithin & lawsone were added, which was then heated at no more than 60 oC for two hours with dichloromethane (20 ml). The admixture has been reduced to a volume of 5–10 ml upon boiling and by adding concentrations [20,21]. To make the precipitate, Hexane (20 ml) was added carefully while the admixture was being stirred all the time. The precipitate was gathered, filtered, and overnight stored in vacuum sealed desiccators to avoid drying out [22]. In a mortar, the precipitate is squeezed and then put through a sieve no. 100 mesh. At room temperature, the complex was ground up and placed in a glass bottle with an amber colour [23,24].

Lawson's phytosome complex preparation

Table 3 shows the molar ratios of lawsone and soy lecithin in a variety of lawsone phytosome complexes (Figure 1) that were made using the antisolvent precipitation technique.

Table 3: Preparation of Phytosome Complexes of Lawsone.

Phytosomes	Phytosome (Molar ratio)	Drug	Phospholipid	Solvents
F1	1:1	lawsone	Soya lecithin	Dichloromethane + n-hexane
F2	1:2	lawsone	Soya lecithin	Dichloromethane + n-hexane
F3	1:3	lawsone	Soya lecithin	Dichloromethane + n-hexane
F4	1:4	lawsone	Soya lecithin	Dichloromethane + n-hexane

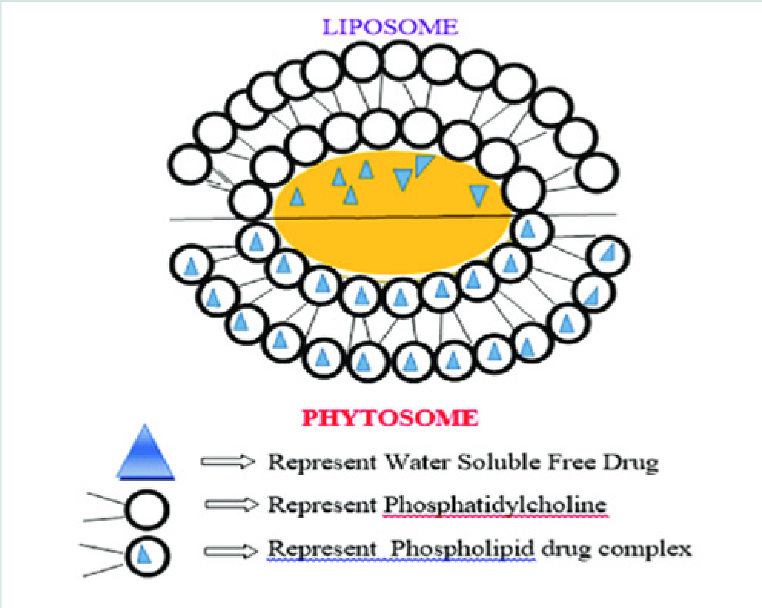

Figure1: Difference Between Phytosomes & Liposomes.

Mechanism of phytosomes

Two factors are primarily responsible for the low retention and solubility of polyphenolic constituents. These main components consist mainly of ringed molecules and are not too small to be taken in by diffusion. The second factor is that the main components of polyphenols, flavonoid molecules, are very poorly soluble in lipids. These constraints prevent their absorption through biological membranes. In a 1:1 or 1:2 ratio, polyphenols and phospholipid form a complex that primarily contributes to the evolution of phytosomes. The formation of phytosomal complexes with lipid coatings surrounding their components is primarily due to a composite of polyphenols and phospholipid in a 1:1 or 1:2 ratio, according to research published in 2016.

Characterization of phytosomes

Scanning electron microscopy and Transmission electron microscopy

They are useful for analyzing the surface morphology of the complex. The polar portion of phospholipids is combined with active components to form the complex. Many complexes spontaneously create a vesicle structure when stirred in distilled water. As a result, there are numerous particles suspended in water that resemble liposomes but are not really liposomes [25].

Differential scanning calorimetry

The temperature transition, the disappearance of endothermic peaks, changes in the relative peak area, the appearance of new peaks, and other phenomena can all be seen. A variety of sample properties can be measured using the thermoanalytical method known as differential scanning calorimetry (DSC).

UV spectra

According to some findings, the UV absorption properties of the active ingredients before and after complexation typically do not differ, which is a strong indication that the drug's bonding with phospholipids has no impact on the drug's conjugation system and that the chromophores are unaffected. The UV spectra are obtained using appropriate amounts of the test samples (the complex's active components, phospholipids, and their physical mixture).

Solubility studies

In order to conduct solubility studies, it is necessary to ascertain the active ingredient's solubility, as well as that of its phytosomes and the physical combination of the active ingredient and phospholipids in n-octanol or water, also referred to as water or n-octanol "partition coefficient (P)". Lipophilicity & hydrophilicity of active constituent phytosomes can be significantly increased if they are highly dispersible or have an amorphous form. Phytosomes may be much more soluble than their active constituents [26].

PCS and DLS

Photon correlation spectroscopy can also be used to measure the size of phytosomes' particles. Dynamic light scattering (DLS) is a method that measures the size and zeta potential of particles with the help of a computerized inspection system.

X ray diffractometry

On the basis of their crystal structure, XRD is used to identify crystalline compounds. The findings of related studies demonstrate how active constituents' powder X-ray diffraction patterns typically feature: A sign that an organic molecule is crystalline is that it has sharp, partially crystalline peaks. Contrarily, phospholipids frequently exhibit an amorphous structure devoid of crystalline peaks. The crystalline peaks typically disappear when comparing the phytosomes to the physical mixture [27].

In a flask with a round bottom, the proper amounts of active ingredients and phospholipid are added and then dissolved in the reaction medium. The complex can then be separated by vacuum drying, spray drying, or lyophilization drying. It is crucial to confirm that the reaction medium has been taken out as entirely as possible. In order to obtain pure active constituent phytosomes, the dried residues are filtered. Figure 2 depicts the common steps for preparing phytosomes. A central composite design path and a spherical symmetric design response surface methodology are used for process optimization because the yield (percent) is greatly influenced by the reaction temperature, phospholipid to active constituent ratio, reaction time, and drug concentration. A crucial indicator for the preparation is the yield (in percent) of the active component in complex with phospholipid. Precipitation and separation take place with the free active components. Using the following formula equation, the yield (percent) of the active constituent in complex with the phospholipids is determined: The yield (percent) is equal to [(a - b)/a] 100%. Where "a" represents the amount of active ingredients in phospholipid complexes, "b" represents the amount of free active ingredients in the complex.

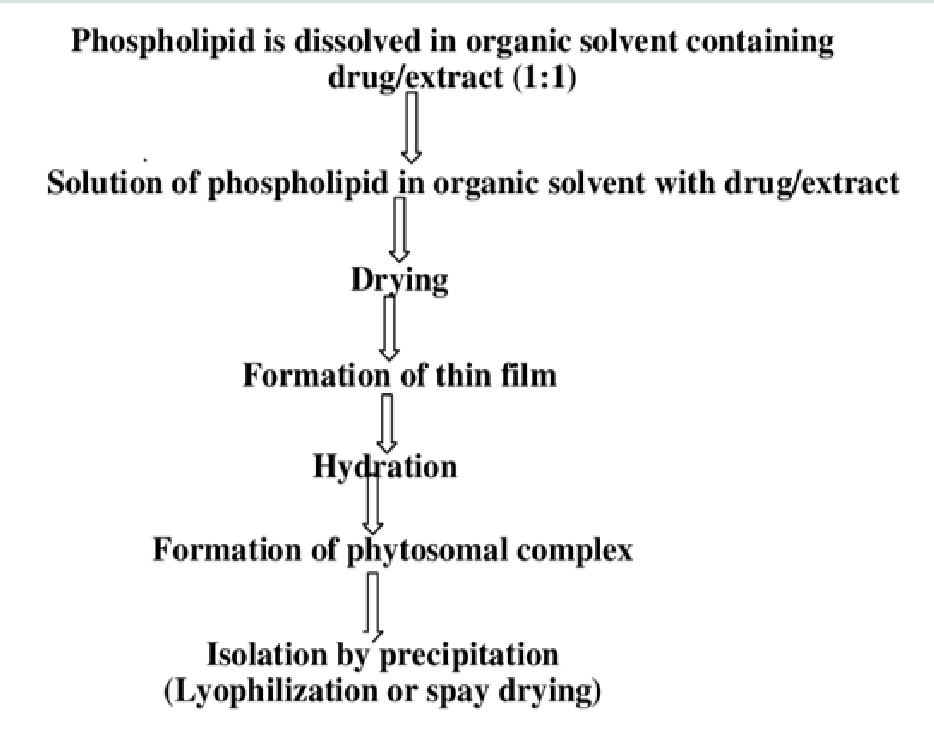

Figure 2: Common stages for preparation of phytosomes.

Application of phytosomes

Silymarin Phytosome

Acute and chronic liver diseases with toxic metabolic, infectious, or degenerative causes are treated with phytosomes. The majority of the phytosomes are concentrated on Silybum marianum, which has highly effective flavonoids that protect the liver. Milk thistle (S. marianum, Family Asteraceae) fruit contains flavonoids with hepatoprotective properties. Silymarin has been demonstrated to be effective in treating a variety of liver conditions, including hepatitis, cirrhosis, fatty liver caused by chemicals and alcohol, and bile duct inflammation [28-30].

Phytosomes of curcumin

Curcumin and naringenin phytosomes were created by Maiti et al (flavonoid from grape, Vitis vinifera). In comparison to the free compound, the phytosome of naringenin produced better antioxidant activity. (Curcumin, a flavonoid derived from Curcuma longa linn) [31].

Phytosomes of grape seed

The main benefits of grape seed procyanidin flavonoids include an increase in overall antioxidant capacity and stimulation of the plasma's physiological defenses. Oligomeric polyphenols of various molecular sizes complexed with phospholipids make up the grape seed phytosome.

Phytosome of green tea

Epigallocatechin 3-O-gallate, a polyphenolic compound, is the primary constituent of green tea leaves (Thea sinensis). These substances have the power to modulate a number of biochemical processes that are connected to the breakdown of homeostasis in serious chronic degenerative diseases like atherosclerosis and cancer.

Discussion

Although phytosomal products continue to be primarily researched in the cosmetics industry due to their high potential, growing evidence of their potential for the delivery of herbal drugs has emerged in recent years. There are two main reasons why some constituents, in particular poly phenolics, are poorly absorbed. Because they are multiplexing molecules, they cannot quite pass through the intestine and enter the blood. Second, they frequently exhibit lipophilicity with lipids such as oils. The lipophilicity of active ingredients can be significantly increased by phytosomes, which may be helpful for getting through cell membranes and into the bloodstream or the interior of tissue cells to have pharmacological effects. Pharmacokinetics studies or pharmacodynamic tests on animals have shown that phytosomes have a higher bioavailability than free herbal active ingredients. Many new drug delivery methods have recently been developed, and those based on phospholipids have great potential. It has also been investigated how active constituent phytosomes evolve. The formation of phytosomes involves a variety of interactions, including ionic interactions, hydrogen bonds, and Vander Waals forces. It cannot, however, explain why some active components are unable to combine with phospholipids to form phytosomes. More apt explanations will surface as phytosome research develops. To further increase solubility, the active component phytosomes can also be used to create solid dispersions, microemulsion nanoparticle, mixed micelles, self-emulsifying drug delivery systems (SEDDS) polymer gel, and other formulations. In order to increase the therapeutic potency of the active ingredients, it is essential to carry out further research on phytosomes.

Conclusion

This article discusses the properties, characteristics, and manufacturing process of the phytosomes. There are numerous commercial applications for automation. Pharmaceutical companies can now offer new pharmaceutical products made with water-soluble drugs thanks to phytosomes, which also brings about advancements in the medical field. These days, phytosomes are mainly used in cosmetics to apply water-soluble ingredients to skin. The automation can successfully deliver the product orally and topically. Future research on phytosomes will uncover a variety of potential pharmaceutical applications. The therapeutic or health-promoting properties of various phytosome products have been significantly greater than those of traditional plant extracts. Phytosomes can be developed as nutraceuticals for preventative and health benefits, such as hepatoprotection, cardiovascular health, liver disease, anti-inflammatory, immunomodulator, anticancer, and antidiabetic effects.

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Author contributions

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Conflict of Interest

The authors declared no conflict of interest.

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