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Phytosomes: A promising approach for enhancing herbal medicinal efficacy

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Abstract
Phytosomes are innovative vesicular drug delivery systems that improve the bioavailability and absorption of phytoconstituents. These complexes are formed by reacting phospholipids with standardized plant extracts, resulting in a lipid-compatible molecular complex. Phytosomes have been shown to enhance the oral absorption of polar phytoactive compounds, leading to improved bioavailability and therapeutic effects. They also demonstrate promise in improving phytoconstituents' percutaneous absorption, making them suitable for topical treatments of skin disorders. Phytosomes have a unique structural feature, with phospholipids surrounding and binding the bioactive phytoconstituents of herb extracts. Various methods of preparation, including solvent evaporation, mechanical dispersion, and salting out techniques, have been employed to produce phytosomes. Characterization and evaluation of phytosomes involve determination of percentage yield, particle size and size distribution, degree of swelling, visualization, and drug excipient compatibility.

Keywords: Phytosome, phosphatidylcholine, phospholipids, phytoconstituents, lipid-compatible molecular complex

1. Introduction
Phyto" refers to a plant, and "some" denotes a structure that resembles a cell [1]. Phytosomes are a kind of herbosome that are mostly made up of phytoconstituents, which are 500 nm-100 µm-long phytoconstituents (neutraceuticals like flavonoids and terpenoids). The drug's bioavailability, solubility, and absorption of water-soluble phytoconstituents are all improved by this complex of lipid molecules [2]. The shortcomings of traditional plant-based drug delivery systems (DDSs) are addressed by phytosomes, which are innovative vesicular DDSs [3]. Early in the 1990s, the Italian pharmaceutical and nutraceutical company Indena initially proposed the idea of phytosomes. Since then, a great deal of study has been done to investigate how phytosomes might improve the delivery of different phytochemicals, such as piperine and curcumin [4]. Lipid surrounds and binds the bioactive phytoconstituents of herb extracts in this sophisticated type of herbal preparation. Many chemicals found in biologically active plants are polar or soluble in water. phytoconstituents that dissolve in water, such as tannins, flavonoids, glycoside aglycones, etc. Flavonoid molecules that are soluble in water are transformed into lipid-compatible molecular complexes known as "Phytosomes" [5]. Phytosomes provide a new way to increase the efficacy and bioavailability of natural substances, especially those made from plant extracts. This sophisticated method combines phospholipids with a material obtained from plants, usually a herbal extract. Phospholipids, which are essential parts of cell membranes, provide the resulting phytosome complex a unique structural feature [6].

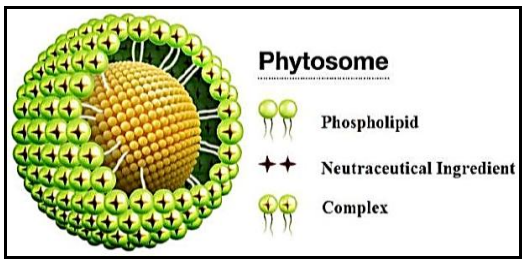

Fig 1: Structure of phytosome [7]

A phytosome is a botanical formulation that contains the active compounds of a plant extract that have formed a bond with phospholipids, generally phosphatidylcholine, to improve the bioavailability and absorption of the formulation. In order to make these substances, phospholipids, frequently phosphatidylcholine, are linked to the active components present in herb extracts. Active ingredient compounds are more easily absorbed and transported through biological membranes as a result of this complexation method [8]. Drugs produced in lipid complexes may become more soluble and have less gastrointestinal toxicity. A phytosome is a drug-phospholipid combination with hydrogen atoms that can bind to phospholipids and amphiphilic characteristics [9]. "Phyto" indicates that the phytosomal complex's bioactive component came from a plant, and "some" indicates that the complex's structure resembles that of a cell. Phospholipids, primarily phosphatidylcholine (PC), are joined to phytoconstituents via hydrogen bonding to form the vesicular complexes known as phytosomes. Phospholipid molecules are combined with hydrophilic phytoconstituents or standardized plant extracts to create a lipid-compatible vesicular complex known as a phytosomal complex [10]. The technology of herbosomes enhances the bioactivity of plant extracts and serves as a link between the conventional and NDDS systems. It is a mixture of lipids and phytoconstituents that improve plant extract penetration. Lipophilicity and multiring molecular architectures are the two fundamental obstacles that molecules must overcome to pass through the cell [11].

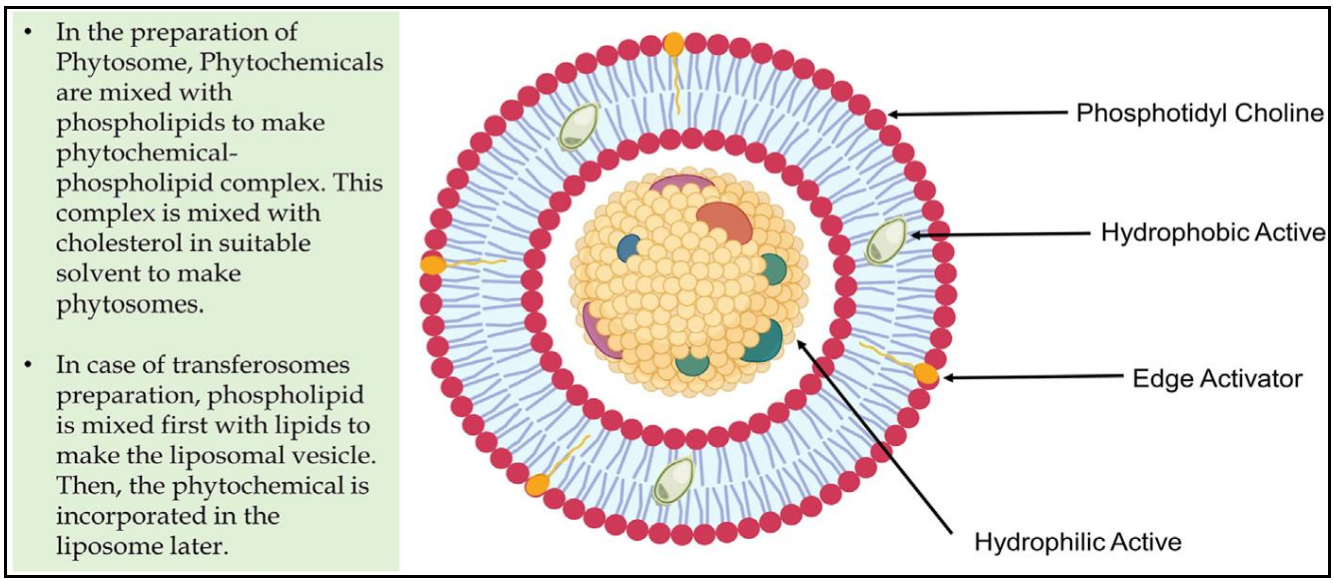

Fig 2: Structural feature of Phytosome [12]

2. Mechanism of phytosomes

Phytosomes are created when a standardized extract comprising typically polyphenolic chemicals reacts in a solvent with a standard quantity of phosphatidylcholine. With a hydrophilic choline structure joined by a lipophilic structure, phosphatidylcholine (PC) is an amphiphilic material [13]. A lipid-soluble chemical compound called the Phyto phospholipid complex is created when phospholipids and phytomolecules combine. The chemical relationship between phytomolecules and the polar choline head of phospholipids can be confirmed by precise spectroscopic methods. The unit phytosome is frequently a flavonoid molecule connected to at least one phosphatidylcholine molecule, per in-depth chemical investigation. As a result, a small cell or microsphere forms. In the blue phytosome spectrum, the red spectrum of the polyphenol is masking by the orange spectrum of phosphatidylcholine. This is consistent with the phosphatidylcholine molecule physically trapping the polyphenol [14].

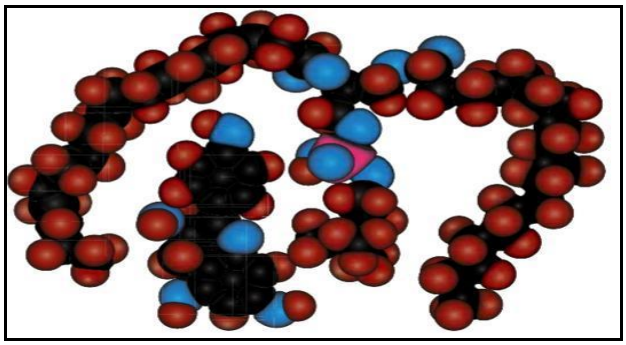

Fig 3: Schematic of The Phytosome Molecular Complex [15]

3. History of phytosome

First, in 1991, Bombardelli created phytosome in Milan. It was referred to in several articles as a "herbosome," "phyto-vesicle," and "phytophospholipid complex." To address issues with absorption, phospholipids (phosphotidylcholine, phosphotidylserine, etc.) were utilized, primarily for flavonoids, tannins, terpinoids, and triterpens. The chemical and pharmaceutical sciences have advanced the compositions, biological activities, and health advantages of several plant extracts throughout the past century [16].

Table 1: The preparation method of phytosome prepared recently, the method use, the solvent used for the production and their characterization of the phytosome [17].

Marketed phytosomes	Method of preparation	Solvent employed	Drug; phospholipid ratio	Temp.	Chemical analysis
Thymoquinoneloaded soy-phospholipid	Anti-solvent precipitation method	Dichloromethane	1:1, 1:3, 1:5	-	FT-IR vesicle size measurement, TEM, *in vitro* release
Terminalia arjuna phytosome	Solvent evaporative process	Dichloromethane and n-hexane at 40 °C for 1.5 hrs.	-	40 °C	Entrapment Efficiency, DSC, SEM and FTIR
Curcumin phytosome	Rotary Evaporation method	Dichloromethane, n-hexan, phosphate buffer 6.8	1:1, 1:2, 1:3, 1:4 and 1:5	40 °C	SEM, Entrapment efficiency *in vitro* released study
Cocoa pod phytosome	Solvent evaporative	Ethanol	1:3 for 24 hrs	40 °C	Particle size distribution
Ursolic acid-phospholipid complex	Solvent-assisted grinding method	Methanol, ethanol, acetone, ethyl acetate	0.5:1, 1:1, 1.5:1 and 1:2	40 °C	DSC, XRD, TEM, *in vitro* pharmacokinetic study
Myricetin nanophytosome	Thin layer film hydration sonication technique	Dichloromethane, acetone, ethanol	Myricetin: phosphati-dylcholine: Cholesterol (1:1:0.4, 1:2:0.4, 1:3:0.)	35 °C	Particle size and entrapment efficiency
Novel protamine-decorated tripterine phyosomes	Solvent evaporative process	Anhydrous ethanol	1.3	40 °C	Particle size, SEM and TEM

4. Structure of phytosome

Phospholipids are molecules that have hydrophilic (they attract water) and hydrophobic (they reject water) "tails". They are found naturally in the body and are essential parts of cell membranes. Sources such as soy lecithin are used to create phospholipids in advance of phytosome nanotechnology [18].

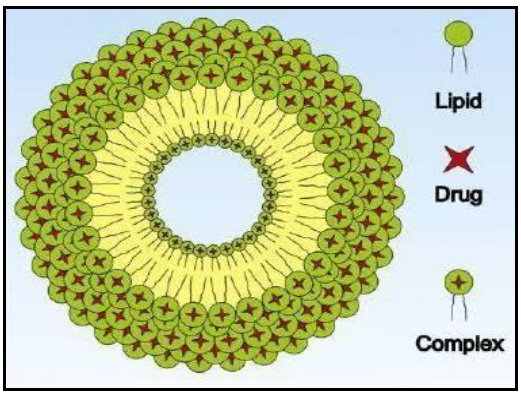

Fig 4: Structure of Phytosome [19]

The polar component of complexes may be encircled by the two long fatty acid chains, creating a lipophilic surface. Dilution of phyto-phospholipid complexes in water results in agglomerates that resemble tiny cells and share certain characteristics with liposomes [20].

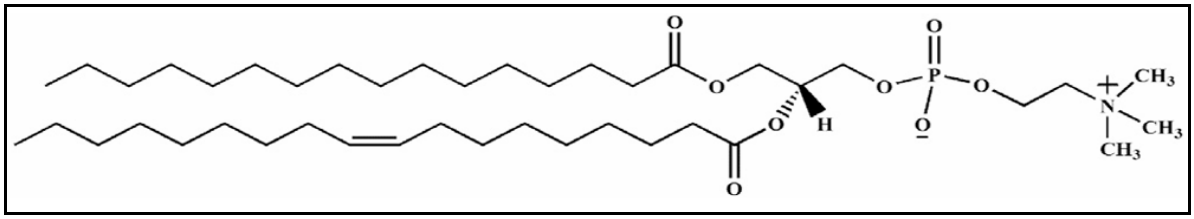

Fig 5: Structure of Phosphatidylcholine [21]

Phytosomes are new complexes made by reacting three to two moles, but ideally one mole of a natural or synthetic phospholipid, like phosphatidylcholine, phosphatidylethanolamine, or phosphatidyiserine, with one mole of a component, like flavolignanans, either by itself or in a natural mixture in an aprotic solvent like dioxane or acetone [22]. Between 0.5 and 2.0 moles of these two moieties are involved in the complicated construction of phytosomes. The optimal ratio of phospholipid to flavonoids is 1:1, per Bombardelli (1987) [23]. The ratio of these two moieties in the complex development of phytosomes varies between 0.5 and 2.0 moles. Phospholipid to flavonoid ratios of 1:1 is ideal [24].

5. General method of preparation of Phytosome

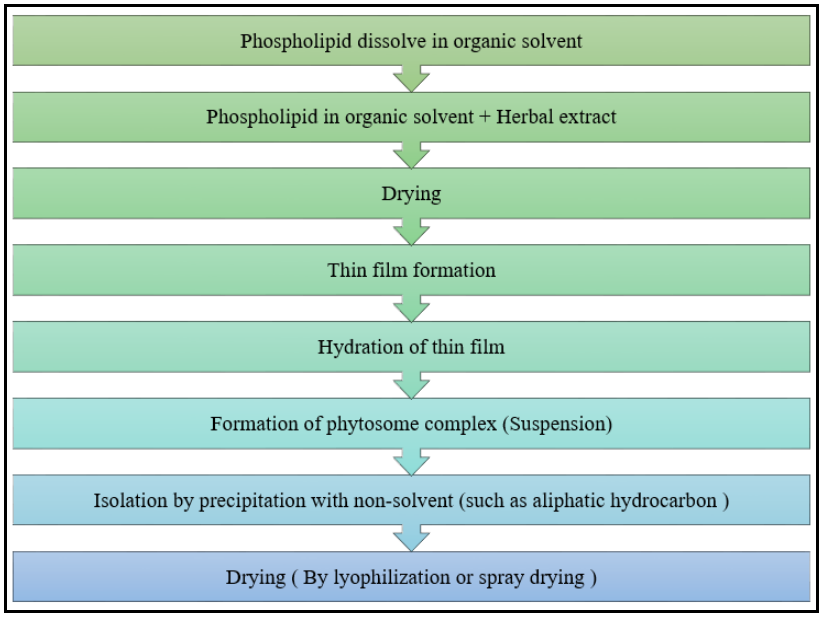

Fig 6: General method of preparation [24]

5.1 Different method of preparation of Phytosomes

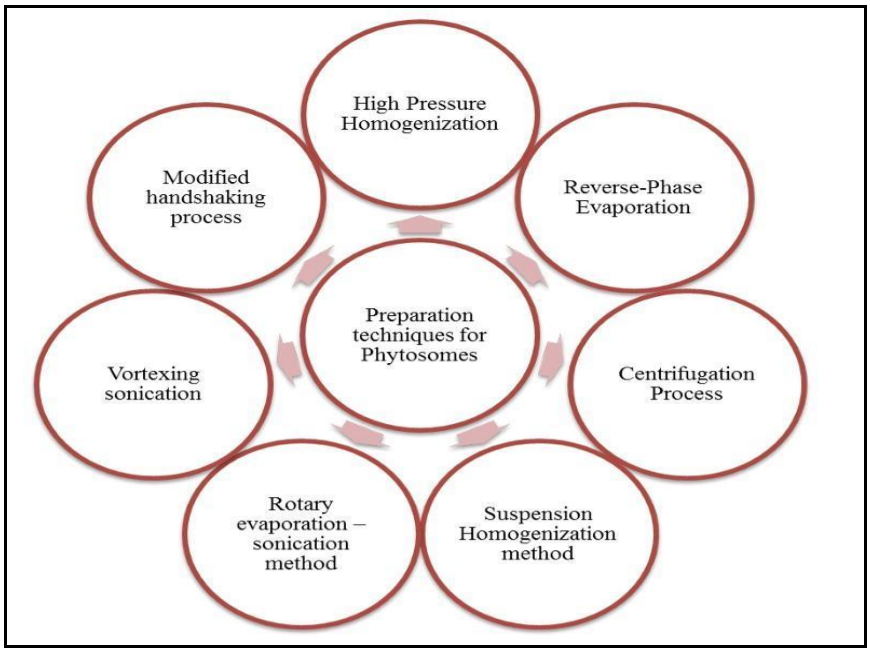

Fig 7: Various preparation techniques for Phytosomes [25]

A. Solvent evaporation method

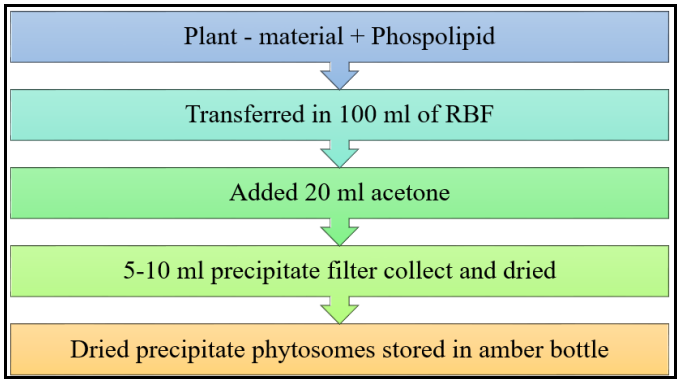

Fig 8: Solvent evaporation method [26]

B. Mechanical dispersion method [27]

The mechanical dispersion approach involves mixing an aqueous phase containing the medication with lipids that have been dissolved in an organic solvent. Phytosomes is produced when the organic solvent is subsequently removed under lower pressure.

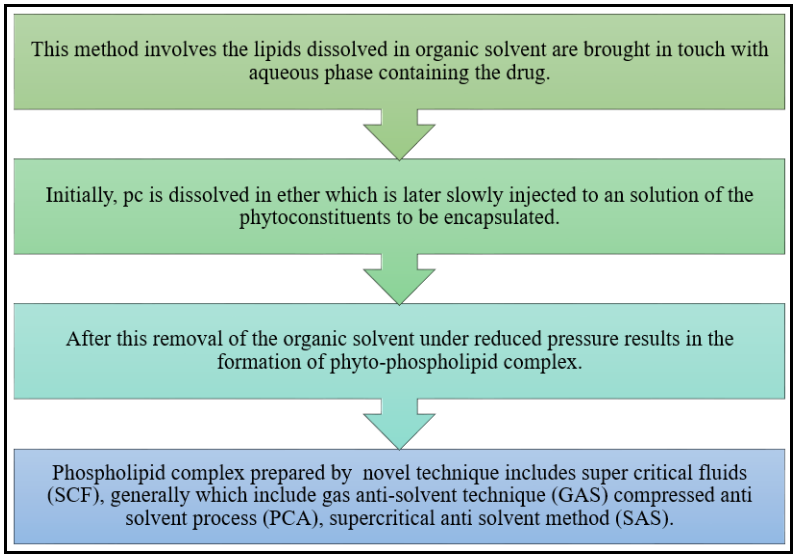

Fig 9: Mechanical dispersion method [28]

C. Salting out technique [27]

Phospholipids and plant extracts are dissolved in an appropriate organic solvent as part of the salting-out process. An extract-phospholipid complex is formed when n-hexane is added because it causes precipitation.

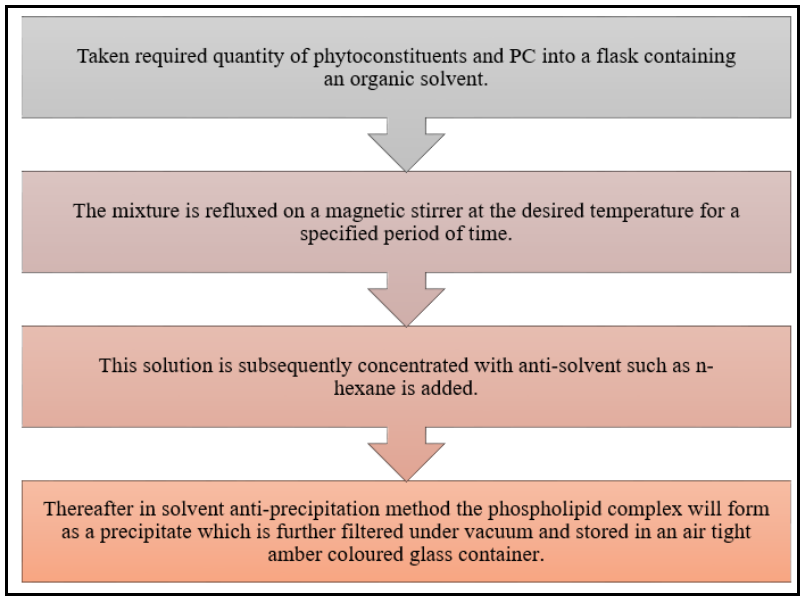

Fig 10: Salting out method [28]

D. Ether-injection technique [29]

This process dissolves the drug's lipid complex using an organic solvent. The mixture is then slowly infused into a heated aqueous agent to initiate the production of vesicles. The state of amphiphiles is determined by their focus. Amphiphiles function as monomers at low concentrations, but as concentration increases, various forms, including spherical, cylinder, disc, cubic, and hexagonal structures, can form.

E. Dehydration-rehydration technique [30]

The bioactive component and phospholipid are dissolved in an organic solvent. At a reduced temperature and pressure, the organic solvent and aqueous content are then completely removed using a rotating vacuum evaporator. A thin layer of a conjugated phospholipid and bioactive molecule would form in the round-bottom flask. Water is utilized to counter the monolayer in order to completely remove the solvents. The monolayer is then rehydrated with water to form micelles. The micelles produced by the thin layer of phospholipids after being exposed to water are then probe-sonicated to achieve the proper micelle size.

F. Reverse phase evaporation technique [31]

This method involves dispersing the "He" in distilled water after the lipids have been dissolved in an organic solvent while being mixed. The 'He' is then added to the solvent and mixed thoroughly. The suspension is then separated by centrifugation after being heated in a water bath to evaporate the organic solvents. Thus, niosomes filled with Hypericum perforatum extract were produced.

6. Advantages of phytosome [32, 33, 34, 35]

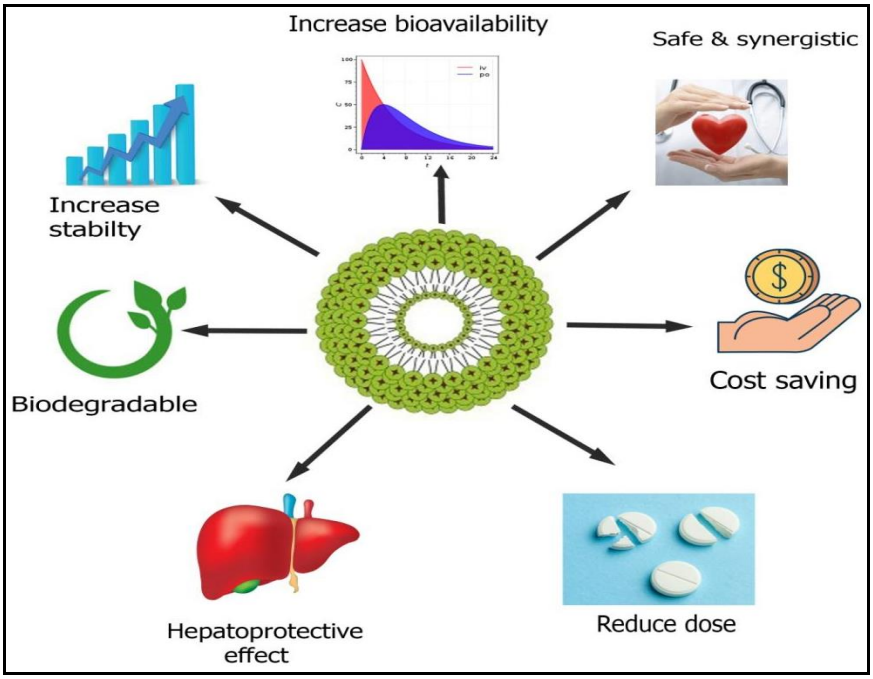

Fig 11: Advantages of phytosomal drug delivery [32]

1. Because of the lipid layer around the phytoconstituent, phytosomes can penetrate the skin and increase their efficacy.
2. Phytosomes improve liver targeting by making bile more soluble in phytoconstituents of herbal origin.
3. The capacity of phytosomes to enhance the oral absorption of polar phytoactive chemicals, resulting in improved bioavailability and increased therapeutic effects, is another significant benefit.
4. Phytosomal formulations have also demonstrated promise in improving phytoconstituents' percutaneous absorption, which makes them a good choice for topical treatments of skin disorders.
5. In addition to serving as a carrier, phosphatidylcholine, which is utilized to form phytosomes, has hepatoprotective properties, which results in a synergistic effect when hepatoprotective drugs are used.
6. Because of their high lipid profile and greater skin penetration, phytosomes are frequently employed in cosmetics.
7. To improve intestinal lumen absorption, phytosomes penetrate the non-lipophillic botanical extract.

7. Disadvantages of phytosome [36, 37, 38]

1. Despite all the benefits, phytosomes have the potential to quickly eliminate the phytoconstituent.
2. The MCF-7 breast cancer cell line can proliferate when exposed to phospholipid.
3. The main drawback of phytosomes is said to be the phytoconstituent's leaching off of some, which decreased the expected medication concentration.
4. Its production costs are substantial, and allergic reactions to its phytosomal components can occasionally be seen.
5. It has a brief half-life.
6. Phospholipid molecules undergo oxidation, fusion, hydrolysis, and leakage.
7. Burst drug release is caused by drug leakage.
8. Hydrophilic medicines have poor loading efficiency.
9. A costly method.
10. The biological half-life of liposomes is brief.
11. Chemical characteristics that are unstable.
12. Issues with the phospholipids' purity.

Table 2: Difference between phytosome and lyposome [39, 40, 41, 22, 5, 10]

Phytosome	Liposome
Phytosomes interact with solvents with lower dielectric constants, including acetone, dioxane, metyhlenechloride, hexane, and ethylacetate. Liposomal drug complexes form in the presence of water or a buffer solution.	When water or a buffer solution are present, a liposomal drug complex occurs.
Phytosomes metabolize phosphatidylcholine and form a 1:1 or 2:1 molecular complex with plant components through molecular bonds, depending on the complexed molecule.This resulted in enhanced bioavailability and absorption.	Liposomes don't form chemical bonds. The water-soluble substance is surrounded by phosphorylcholine molecules. The water-soluble material could be surrounded by hundreds or even thousands of phosphtidylcholine molecules.
Compared to liposomes, phytosomes have a significantly higher bioavailability	Compared to liposomes, phytosomes are more bioavailable.
Chemical bonds are involved in phytosomes.	Phosphatidylcholine molecules wrap water-soluble components without forming a chemical connection.
However, in phytosomes, it is an important component of the membrane, with molecules connected to the polar head of the phospholipids via chemical bonds.	In this situation, the phosphatidylcholine molecules wrap the water-soluble substance without causing any chemical reaction.
In skin care products, phytosomes beat liposomes.	In skin care products, phytosomes outperform liposomes.

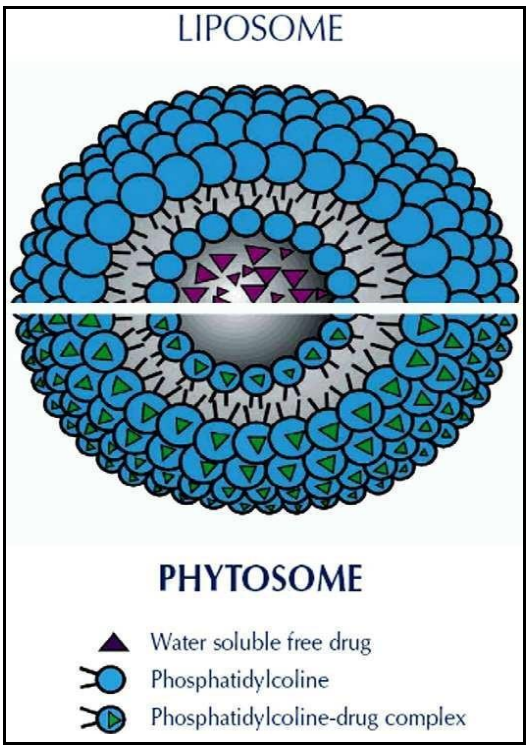

Fig 12: Major Difference between Phytosome and Liposome [41]

8. Characterization and evaluation of phytosome

8.1 Determination of Percentage Yield [42]

The percentage yield of the phytosome complex is calculated using the following formula:

$$\% \text{ Yield} = \frac{\text{Practical Yield}}{\text{Theoretical Yield}} \text{ x } 100$$

8.2 Particle Size and Size Distribution [43]

The particle size and size distribution of the phytosomes are determined using a Malvern Zetasizer, which employs the laser light scattering technique. The instrument is fitted with an Argon laser to facilitate accurate measurements.

8.3 Degree of swelling of microspheres [44]

The percentage degree of swelling of the microspheres is calculated using the following equation:

$$\text{Percentage of swelling} = \frac{Wt - W0}{W0} \text{ x } 100\ \%$$

Where

Wt is the weight of the swollen microsphere and W0 is the initial weight of the microsphere.

8.4 Visualization Techniques [45]

Transmission electron microscopy (TEM) and scanning electron microscopy (SEM) are employed to visualize the phytosomes. These techniques provide valuable information on the morphology and structure of the phytosomes.

8.5 Drug-Excipient Compatibility Studies [46]

The Fourier Transform Infrared Spectrophotometer (FTIR) is used to investigate the infrared spectrum of the phytosome complex. The KBr dispersion method is employed to determine the physicochemical compatibility between the extract and polymer mixture. The final spectrum is compared to the initial spectrum to detect any changes or shifts in the peaks, which would indicate incompatibility between the components.

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