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PHYTOSOMES IN HERBAL FORMULATION: AN UPDATED REVIEW

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Abstract

Phytosomes, a phospholipid-based self-assembled delivery system, can improve oral bioavailability of polyphenolic compounds. These systems, prepared by reacting polyphenolic phytoconstituents with phospholipid, can enhance the passage of lipophilic herbal constituents across the lipid membrane. Phytosomes are used in various herbal drugs like Ginkgo biloba, Camelliasinensis. Recent advancements in phytosomes technology have led to the development of transdermal routes for delivering phytoconstituents. These products are increasingly used in dietary supplements for homeostatic management of inflammation, toxicities, cancers, and weight loss. This technique increases the hydrophilicity of highly lipophilic drugs, making them suitable for drug delivery and allowing hydrophilic phytoconstituents to cross biological membranes. Researchers are exploring the transdermal route as a potential way to deliver phytoconstituents, which are increasingly being used in dietary supplements for homeostatic management of various diseases. We will explore an updated review of Phytosomes in herbal formulation.

Keywords: *Phytosomes, Phytoconstituents, Phospholipid, Bioavailability, Polyphenolic compounds.*

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Introduction

Novel drug delivery systems address the limitations of traditional drug delivery systems, such as those used in Ayurveda. By incorporating novel methods of drug delivery, herbal medicines can increase efficacy and reduce side effects. Traditional methods have been overlooked due to lack of scientific justification and processing difficulties. Herbal medicines are popular due to concerns over drug reliance, effectiveness in treating common health conditions, and the potential of natural treatments without side effects [1, 2, 6]. With the use of this novel, patented process, phospholipids and standardized plant extracts or water-soluble phytoconstituents are complexed to create lipid-compatible molecular complexes, which significantly improve absorption and bioavailability [3].

Although polar or water-soluble physiologically active chemicals are found in plants, absorption problems limit their bioavailability. Plant preparations are used for medicinal purposes in both traditional and modern medical systems [4]. Their safety, effectiveness, cultural acceptability, and low side effects have made them stand the test of time [5].

Advantages of Herbal Medicines

1. The cost of herbal medicines is significantly lower than that of conventional forms of treatment.
2. It is well known that herbal remedies are more effective than other types of medication in treating specific ailments.
3. The main advantage of using herbal medicine is that there are less adverse effects.
4. A rising issue, obesity is known to have dangerous consequences for a person's health. Without requiring a lot of time or effort, herbal therapy addresses the issue of obesity quite successfully [1, 2, 6].

Disadvantages of Herbal Medicines

1. Sometimes people move to herbal medication without realizing that the symptoms can be associated with another illness.
2. Herbal remedies healing times are typically longer than those of conventional treatments. When receiving herbal treatment, the patient needs to be more patient.
3. In certain instances, herbal medications may trigger allergic reactions in individuals [1, 2, 6].

Phytosomes

"Some" refers to cell-like, while "Phyto" indicates plant. Polar or water-soluble molecules make up the majority of the physiologically active components found in plants. [7]. Herbosomes, another name for phytosomes [8]. Studies on the pharmacokinetics and activities of the phytosomes in humans and animals have shown that they have a higher bioavailability than the simpler, non-complex plant extracts [9]. Combining phytochemicals from herbal plant extract with a phospholipid carrier to increase the pharmacological benefits of conventional chemotherapy while reducing its side effects has resulted in the development of a novel cancer therapeutic approach[10]. By combining specific plant components with phospholipid in an appropriate solvent, phytosomes are created, and because of their superior physical and chemical properties, they can be regarded as a unique entity [11].

Phytosomes are herbal drugs in the form of nanoparticles that are packed into vesicles. The primary component of the herbal extract is shielded from bacterial and digestive secretion breakdown by the phytosomes, which operate as an envelope-like coating around the drug's active ingredient [12]. Cell membrane production involves the utilization of complex chemicals called phospholipids [13]. The phospholipids phosphatidylcholine, phosphatidylserine, phosphatidylethanolamine, and phosphatidylinositol are utilized [14]. The lipophilic route of the enterohepatic cell membranes [15] and the stratum corneum layer of the skin are both easily traversed by phytosomes [16].

In order to meet contemporary food criteria, the first generation of phytosomes was created by mixing phospholipids and particular polyphenolic extract in a non-polar solvent [17].

Advantages

- A notable improvement in the drug's bioavailability transpires [3].
- Because of the establishment of chemical connections between phytoconstituents and phosphatidylcholine molecules, phytosomes exhibit superior stability [18].
- Because phytoconstituents create chemical connections with phosphatidylcholine molecules, phytosomes are more stable [19].
- A small dosage can yield the intended effects since the active component's absorption is enhanced. [20].
- The process of creating phytosomes is simple because drug entrapment is not a concern [21].
- Phytosomes provide an improved stability profile. [22].
- The solubility of bile in herbal components is enhanced by phytosomes [23].
- The phytosomes' duration of action is extended [24].
- Pharmacosomes exhibit increased drug entrapment effectiveness [25].
- Not only is phosphatidylcholine a carrier, but it also has nutritional value and hepatoprotective properties [26].
- Phytosome formulations enable the topical application of herbal ingredients for cosmetic and other purposes [27].

Figure 1: Advantages of Phytosomes

Disadvantages of phytosomes

- The breast cancer cell line MCF-7 can proliferate when exposed to phospholipids (lecithin).
- The primary drawback of phytosomes is the lixiviate of the phytoconstituent off the "some," which exhibits an unstable nature as a result of a reduction in the intended drug concentration [5].

Mechanism of PhytosomeTechnology

A stoichiometric quantity of phospholipid (phosphatidylcholine) reacts with standardized extract or polyphenolic components (simple flavonoids) in an aprotic solvent to form phytosomes.[28]The phosphatidyl and choline moieties of phosphatidylcholine are hydrophilic and lipophilic, respectively, making it a bifunctional molecule.The lipid-soluble phosphatidyl part of the phosphatidylcholine molecule, which makes up the body, envelops the choline-bound material while the choline head of the molecule binds to polyphenolic components [29,30].

According to precise chemical analysis, a flavonoid molecule connected to at least one phosphatidylcholine molecule often makes up the unit phytosome [31].

Additionally, the quick exchange of phospholipids between biological membranes and extracellular fluids can transfer the compounds into biological membranes, increasing their cellular capitation [32].

Difference between liposome and phytosome

Depending on the chemical bonds within the complex, the phosphatidylcholine and the herbal elements in the phytosme really form a 1:1 or 1:2 molecular complex. Additionally, it has been discovered that phytosomes work better than liposomes in topical and skin care products [33]. A liposome is an aggregate of several phospholipid molecules that can encapsulate other phytoactive molecules without necessarily connecting to them, whereas a phytosome is a unit of a few molecules bound together [34, 6]. Table 1 compares phytosomes with liposomes, and Fig. 1[6] shows their structural arrangement [6].

Table 1. Comparison between Liposome and Phytosome [6]

Sr. no.	Properties	Liposome	Phytosome
1.	Oral delivery	Inadequate Oral Bioavailability	Ideal For Administration Orally
2.	Bonding	Number Of Molecules, And Even Their Connectivity Is Poor	Connected To A Small Number Of Molecules, Primarily Polyphenol Extract And Phospholipids
3.	Ratio of phospholipid	Lipid Ration Is Increased Up To 10 Times Than The Chief Active Constituents	For Preparation, A 1:1 Or 1:2 Ratio Is Preferable.

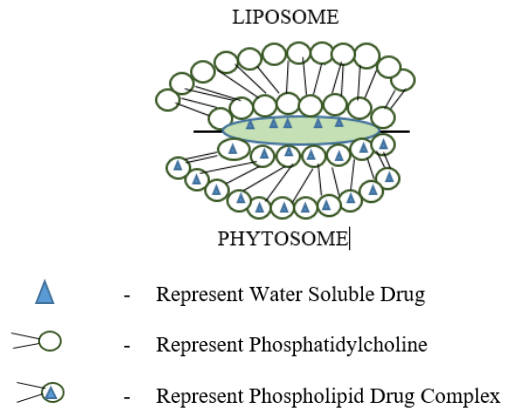

Figure2: Difference Between The Liposome and Phytosome [6].

Preparation techniques for phytosomes

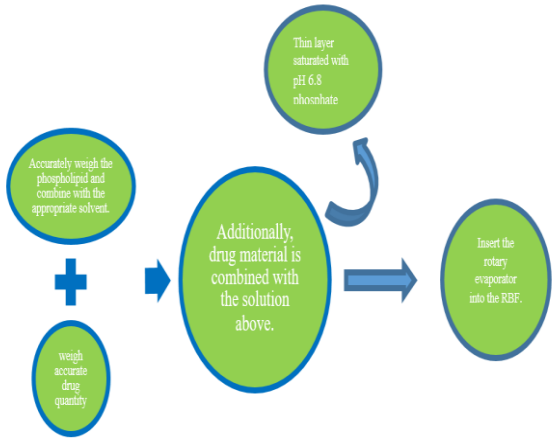

Figure 3: Preparation Method Of Phytosomes

A. Thin layer rotary evaporator method

Using thin film rotary vacuum evaporation method, phytosome vesicles were generated. In a 250 ml round bottom flask, the phytosomal complex was combined with anhydrous ethanol.A rotating evaporator had the flask fastened to it. At roughly 60˚C, the solvent will evaporate and form a thin coating around the flask. Phosphate buffer at a pH of 6.8 hydrates the film, and the lipid layer peels off to form a suspension of vesicles in the phosphate buffer. Prior to characterisation, the phytosomal suspension will be refrigerated for a full day [35].

B. Solvent evaporation method

Phospholipid, or soy lecithin, was reacted in an equal proportion with 5 milliliters of dichloromethane while being stirred until the mixture evaporated. 5 ml of n-hexane was added to the thin film with stirring after the dichloromethane had evaporated, and it was then placed in a fume hood to ensure that all of the solvent had been removed. Following the total elimination of n-hexane, the thin film was sonicated and hydrated to produce the required phytosomal complex [36].

C. Ether injection technique

This method involves dissolving the medication lipid complex in an organic solvent. Vesicles are created by gradually injecting this combination into a hot aqueous agent. Amphiphiles' condition is dependent on concentration. Amphiphiles introduce a monomer state at lower concentrations; but, when concentrations rise, a range of shapes, including round, cylindrical, disc, cubic, and hexagonal types, may emerge [5].

D. Reflux method

Reflux technique can also be used to prepare phytosomes. Phospholipid and polyphenolic extract were added to a 100 ml round-bottom flask and refluxed in dichloromethane for one hour at a temperature not to exceed 40˚C. After evaporating the clear solution, 15 milliliters of n-hexane were added till a precipitate formed. After being extracted, the precipitate was put in a desiccator [37].

Phytosome Formulations [5, 52, 53]

It is possible to build phytosome complexes for topical or oral use. The following are some potential phytosomal formulations:

Soft gelatin capsule

When creating phytosome complexes, soft gelatin capsules are a great option. Indena® suggests that for optimal capsule manufacture, a granulometry of 100% <200 µm be used. Based on Indena® expertise, different phytosome complexes respond differently when distributed in greasy automobiles and when the soft gelatin capsules containing the greasy suspension are poured.

Hard gelatin capsules

It is also possible to construct the Phytosome complex in hard gelatin capsules. Even though the phytosome complex's apparent low density appears to limit the amount of powder that can be placed into a capsule (typically no more than 300 mg for a size 0 capsule), a direct volumetric filling procedure (without precompression) can be used.

Tablets

The best production method for producing tablets with larger unitary doses and appropriate technological and biopharmaceutical qualities is dry granulation.

Topical dosage forms

Additionally, the phytosome complex can be used topically. The best way to add the phytosome complex to an emulsion is to disperse the phospholipidic complex in a tiny amount of the lipid phase and add it at low temperatures (above 40°C) to an already-formed emulsion. In the primary lipidic solvents used in topical preparations, the phytosome complexes are dispersible.

Properties of Phytosomes

1. Phytosomes range in size from 50 nm to a few hundred µm [17].
2. **Phosphatidylcholine:** Research comparing the complex's nuclear magnetic resonance signals to those of the pure precursors shows that the fatty chain's signals remain unaltered [38].
3. Phytosomes are sophisticated, more effectively absorbed herbal goods. Consequently, outperform traditional botanical herbal extracts in terms of results. Pharmacokinetic investigations or pharmacodynamic testing in experimental animals and humans have proven the higher bioavailability of the phytosome compared to the non-complexed botanical derivatives [39].
4. Freely soluble in non-polar solvents and very slightly soluble in lipids, phytosomes are lipophilic materials with a defined melting point [40].
5. The active principle, which is attached to the membrane's polar head, can be accommodated by phytosomes and becomes an essential component of the membrane [41].
6. After being exposed to water, phytosomes take on a micellar shape and develop structures that resemble liposomes but vary fundamentally [42].
7. Because of their physical size, membrane permeability, percentage of entrapment, chemical makeup, quantity, and purity of the materials employed, phytosomes display their behavior in physical or biological systems [17].

Table 2. Commercially available phytosomal product [51,4-5,17,32]

S. No.	Product name	Constituent name	Source	Uses
1.	Ginselectphytosomes	Ginsenosides	*Gingko biloba*	Adaptogenic
2.	Silymarin	Silymarin	*Silybumm arianum*	Antihepatotoxic
3.	Visnadine	Visnadine	*Ammivisnaga*	Circulation improver
4.	Grape seed phytosome	Procyanidine	*Vitisvinifera*	Cardio-protectant, anti-inflammatory, antioxidant.
5.	SwertiaPhytosome	Xenthones 26	*Swertiaalternifolia*	Anti-oxidant

Characterization of phytosomes

1. **Visualization**: Transmission electron microscopy (TEM), scanning electron microscopy (SEM), and atomic force microscopy (AFM) can all be used to visualize phytosomes [43,10].
2. **Vesicle size and zeta potential:** Transmission electron microscopy (TEM) is used to monitor structural changes in phytosomes, while dynamic light scattering (DLS) and photon correlation spectroscopy (PCS) can be used to evaluate the particle size and zeta potential of phytosomes [43,5].
3. **Crystallinity:** The hydrophilicity and hydrophobicity are balanced by the loss of crystallinity caused by the complexation of phytoactive compounds. The two main techniques commonly used are X-ray diffraction (XRD) investigations and DSC.[10]
4. **Entrapment efficiency:** The Ultracentrifugation technique can be used to test the drug's entrapment efficiency by phytosomes. [43].

   The following formula can be used to determine the percentage of drug entrapment [10].

   $$\text{Drug entrapment (\%)} = \frac{\text{Actual amount determined}}{\text{Theoretical amount present}}$$
5. **Transition temperature:** The differential scanning calorimeter (DSC) is a useful tool for determining the transition temperature of vesicular lipid systems.[44]
6. **Retention time**: From a chromatographic standpoint, the HP-TLC was characterized as an easy-to-use technique for phytosome characterisation.[10]

7. **Surface tension activity measurement:** Using a Du Nouy ring tensiometer, the drug's surface tension activity in an aqueous solution is measured using the ring method.
8. **Vesicle stability:** Vesicles' stability can be ascertained by evaluating their size and structure over time. Transmission electron microscopy (TEM) tracks structural changes while differential light scattering (DLS) measures the mean size.[45].
9. **Stability Study:** A stability research was carried out to ascertain whether a formulation could retain stability over the course of its shelf life. Stability can be assessed over several months by assessing the mean vesicle size, zeta potential, size distribution, and trap efficiency.[10]
10. **Drugcontent:**A customized high-performance liquid chromatographic approach or an appropriate spectroscopic technique can be used to quantify the drug's quantity [46].

    By precisely weighing 100 mg of phytosome loaded and dissolving it in 10 ml of solvent, the drug concentration of the phytosome can be ascertained. Absorbance can be measured using a UV Spectrophotometer after the proper dilution. [10]

Characterization techniques

A. Differential scanning calorimetry

Phosphatidylcholine, drug polyphenolic extract, drug-phospholipid complex, and a physical mixing of drug extract and phosphatidylcholine were all put in an aluminum cell and heated in a nitrogen environment to a temperature of 50–250˚C/min between 0 and 400˚C [47]. Interactions in DSC can be observed through melting points, changes in the relative peak area, transition temperature, and the emergence and disappearance of additional peaks. [10]

B. Scanning electron microscopy (SEM)

The particle's appearance and size were assessed using SEM. [43]. Dry samples can be put on a brass stub for an electron microscope and coated in gold using an ion sputter. The phytosome loaded can be digitally photographed by randomly scanning the stub at magnifications of 1000, 5000, 10,000, and 30,000 X [3].

A. Transition electron microscopy(TEM)

Using a magnification of 1000, TEM was utilized to determine the size of phytosomal vesicles [48].

B. Fourier transform infrared spectroscopy(FTIR)

The medication and phospholipid's structural integrity and chemical stability will be examined using FTIR analysis. The ranges that will be scanned are 4000-400 cm-1 [49]. The structure and chemical stability of phytosome-loaded, phospholipid-filled, polymer- and drug-containing samples can be ascertained using FTIR spectrum data. Pellets can be produced at 600 kg/cm2 pressure by crushing samples with KBr [10].

Applications of phytosomes

- The primary antioxidant qualities of medicinal plants' chemical constituents—flavones, isoflavones, flavonoids, anthocyanins, coumarins, lignins, catechins, and isocatechins—contribute to their anticancer potential. However, some plant-based chemicals have certain negative effects and are dangerous at larger doses [5].
- Strong market appeal.[3]
- Approved for use in cosmetic and pharmaceutical applications;
- Low-risk profile;
- Safe composition
- Phospholipids' toxicological characteristics are widely known.
- Delivery of large and diverse medications, including peptides and proteins [3].
- Ravorotto et al. claimed that crude silymarin is less effective than silymarinphytsome in terms of anti-hepatotoxic action [50].

Conclusion

Phytosomes, a patented technology from Italy, can improve the potency of herbal extracts by improving their water and lipid solubility. These phospholipid-based drug delivery systems offer better absorption and stability profiles compared to other methods. They have improved pharmacokinetic and pharmacological parameters, making them suitable for various therapeutic purposes such as cardiovascular, anti-inflammatory, anticancer, immunomodulator, and antidiabetic. Phytosomes have a simple formulation methodology and can be easily upgraded to a commercial scale. They have a great future for use in formulation technology and applications of hydrophilic plant compounds. These delivery systems have improved the pharmacotherapeutics and pharmacokinetics of herbal drugs and are used in nutraceuticals and cosmoceuticals to improve therapeutic effect and permeability in the skin. The formation of phytosomes is simple and reproducible, and the phospholipids used in their preparation have their own beneficial effects in the body. Overall, phytosomes offer a promising solution for herbal drug delivery systems.

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Conflicts of Interests

There are no conflicts of interest.

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Authors Contributions

All the authors have contributed equally.

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