Phytosomes

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**ABSTRACT**

The term "phyto" and "some" refer to plants and cells, respectively. Phytosomes are small structures that resemble cells. This is a more advanced herbal formulation in which the bioactive phytocomponents of herb extracts are surrounded and bonded by lipid. The majority of bioactive ingredients, such as flavonoids and glycosides, are water soluble. The phytosome is a lipid-based vesicular delivery method that can be used to encapsulate pharmaceuticals as well as plant-derived nutraceuticals including polyphenolic substances. The phytosome, as a newly introduced food-grade delivery technology, has the potential to reduce difficulties with polyphenolic compound solubility and bioavailability, making it useful in the creation of new medicinal and food formulations. This delivery platform could help pharmaceutical companies encapsulate adequate amounts of active phytoingredients for the production of new supplements. Furthermore, phytosomes can increase polyphenolic compound bioavailability through the gastrointestinal tract while decreasing administration dosage. Furthermore, the phytosome preparation procedure is simple and can be scaled up commercially. As a promising candidate for incorporating herbal-derived polyphenolic compounds into effective cancer and other disease treatments, phytosome technology is a promising encapsulation platform for future nutraceutical nano-formulation.

**Keywords** – Phytosomes; Flavonoids; Herbal;Stability

## Introduction - Phytosomes Technology

## Phytosomes enhances the absorption of lipid insoluble polar phytoconstituents through oral as well as topical route showing better bioavailability, hence significantly greater therapeutic benefit. As the absorption of active constituents is increased, so its dose requirement is reduced {1}.

Plant extracts flavonoid and terpenoid constituents lend themselves well to direct binding to phosphatidylcholine. Phytosomes are formed by reacting a stoichiometric amount of phospholipid (phosphatidylcholine) with a standardized extract or polyphenolic constituents (such as simple flavonoids) in a non-polar solvent. Phosphatidylcholine is a bifunctional compound with a lipophilic phosphatidyl moiety and a hydrophilic choline moiety. The phosphatidylcholine molecule's choline head specifically binds to these compounds, while the lipid soluble phosphatidyl portion, which includes the body and tail, then envelopes the choline bound material destruction by gastric secretions and gut bacteria.

As a result, the phytoconstituents form a lipid compatible molecular complex with phospholipids, known as the phyto-phospholipid complex. Specific spectroscopic techniques show that molecules are anchored to the polar choline head of the phospholipids via chemical bonds. According to precise chemical analysis, the unit phytosome is typically a flavonoid molecule linked to at least one phosphatidylcholine molecule. As a result, a small microsphere or cell is formed. The phytosome technology creates a small cell that protects the plant extract or its active constituent.

1. **Chemical Properties:**

Phytosomes are a combination of a natural product and natural phospholipids, such as soy phospholipids. A complex of this type is formed by reacting stoichiometric amounts of phospholipid and substrate in an appropriate solvent. The formation of hydrogen bonds between the polar head of phospholipids (i.e. phosphate and ammonium groups) and the polar functionalities of the substrate has been shown to be the main phospholipid-substrate interaction based on spectroscopic data. When treated with water, phytosomes take on a micellar shape, forming liposomal-like structures. In liposomes, the active principle is dissolved in the internal pocket or floating in the layer membrane, whereas in phytosomes, the active principle is anchored to the polar head of phospholipids, becoming an integral part of the membrane, as seen in the case of the catechindistearoyl phosphatidylcholine complex, where H-bonds form.

1. **Biological properties:**

Biological Properties Phytosome are advanced forms of herbal products that are better absorbed, utilized and as a result produce better results than conventional herbal extracts the increased bioavailability of the phytosome over the non-complexed botanical derivatives has been demonstrated by pharmacokinetics studies or by pharmacodynamic tests in experimental animals and in human subjects.

1. **Characterization of phytosomes:**

The behavior of phytosomes in both physical and biological system is governed by the factors such as physical size membrane permeability; percent entrapped solutes, chemical composition as well as the quantity and purity of the starting materials. Therefore, the phytosomes are characterized for physical attributes i.e. shape, size, its distribution, percentage drug capture entrapped volume, percentage drug released and chemical composition.

* 1. **Advantages of phytosomes:**

By forming a stable complex with phospholipids, phytosomes improve bioavailability and stability profiles, and drug delivery improves absorption from the site of action in the intestinal tract when administered as a herbal constituent alone.

* Improves liver targeting by increasing bile salt solubility.
* The required dose is reduced as active phytoconstituent absorption improves.
* PC used in phytosome preparation, in addition to acting as a carrier, also acts as a hepatoprotective, providing a synergistic effect.
* Because of their improved skin penetration and high lipid profile, phytosomes are widely used in cosmetics.
* Herbal extracts' valuable components are protected from destruction by digestive secretions and gut bacteria.
* It ensures that the drug is delivered to the appropriate tissues.
* The nutrient safety of herbal extracts does not have to be jeopardised by delivering the herbal drug via phytosomes.
* Because of the maximum absorption of the main constituents, the dose requirement has been reduced.
* Significant improvement in drug bioavailability occurs.
* Entrapment efficiency is high and predetermined because the drug is conjugated with lipids in the formation of vesicles.
* There are no issues with drug entrapment when creating phytosomes.
* Phytosomes have a higher stability profile due to chemical bonds formed between phosphatidylcholine molecules and phytoconstituents.
* Phosphatidylcholine, which is used in the phytosomes process, both nourishes and acts as a carrier.
* Phytosomes outperform liposomes in skin care products.
* Phytosomes show a significantly higher clinical benefit.
* Phosphatidylcholine is used in the preparation of phytosomes; in addition to actingas acarrier, it also acts as a hepatoprotective, resulting in a synergistic effect.
	1. **Disadvantages of phytosomes:**

Despite the numerous benefits of phytosomes, it has been reported that phospholipids (lecithin) can induce proliferation in the MCF-7 breast cancer cell line. The leaching of phytoconstituents from the ‘some' is a significant disadvantage of phytosome. Phytosomes of Curcumin In two separate studies, Maiti et al. (2006) created phytosomes of curcumin (flavonoid from Curcuma longa, turmeric) and naringenin (flavonoid from grape fruit, Vitis vinifera). In all dose levels tested, the complex's antioxidant activity was significantly higher than pure curcumin. In another study, the developed phytosome of naringenin produced better antioxidant activity than the free compound with a longer duration of action, which could be due to a decrease in the molecule's rapid elimination from the body21.

1. **Applications of phytosomes:**
2. **Silymarin Phytosomes:**

The majority of Phytosomal research has focused on Silybum marianum (milk thistles), which contains powerful liver-protecting flavonoids. Yanyu et al. (2006) synthesized silymarin phytosomes and investigated their pharmacokinetics in rats. The bioavailability of silybin in rats was significantly increased after oral administration of silybinphospholipid complex, owing to an impressive improvement in the lipophilic properties of silybinphospholipid complex and an improvement in silybin's biological effect. Tedesco et al (2004) reported that Silymarin phytosomes have greater anti-hepatotoxic activity than silymarin alone and can protect broiler chick performance from the toxic effects of aflatoxin B1.

1. **Curcumin Phytosomes:**

In two separate studies, Maiti et al. (2006) created phytosomes of curcumin (flavonoid from Curcuma longa, turmeric) and naringenin (flavonoid from grape fruit, Vitis vinifera). In all dose levels tested, the complex's antioxidant activity was significantly higher than pure curcumin. In another study, the developed phytosome of naringenin produced better antioxidant activity than the free compound, with a longer duration of action, possibly due to a decrease in the molecule's rapid elimination from the body21.

1. **Quercetin-phospholipid Phytosome:**

Complex Maiti et al. (2005) created the quercetin phospholipid Phytosomal complex using a simple and reproducible method and demonstrated that the formulation outperformed the molecule in rat liver injury caused by carbon tetrachloride.

1. **Phytosomes of grape seed:[25]**

Grape seed phytosomes is composed of oligomeric polyphenols (grape proanthocyanidins or Procyanidine from grape seed extract, *Vitis vinifera*) of varying molecular size complexed with phospholipids. The main properties of Procyanidine flavonoids of grape seed are an increase in total antioxidant capacity and stimulation of physiological defenses of plasma, protection against ischemia/reperfusion induced damages in the heart, protective effects against atherosclerosis thereby offering marked protection against the cardiovascular system and other organs through a network of mechanism that extend beyond their antioxidant effect. In another study, rabbits were fed with a high cholesterol diet for 6 weeks, to markedly elevate their blood cholesterol level and to induce atherosclerotic lesions in their aortas and carotid arteries. One group of rabbit received grape seed phytosomes in their feed for the first 6 weeks, then 4 weeks of high cholesterol diet. These developed significantly less aortic plaque than did the control group which received conventional standardized grape seed extract in similar regimen. In randomized human trial, young healthy volunteers received grape seed phytosomes once daily for 5 days. The blood TRAP (Total Radical-trapping Antioxidant Parameter) was measured at several time intervals during 1st day, then also on 5th day. Already by 30minutes after administration on 1stday, blood TRAP levels were significantly elevated over the control which received conventional standardized grape seed extract.

1. **Phytosomes of *Gingko biloba* leaves[24}:**

Studies have shown that ginkgo phytosomes (prepared from standardized extract of Ginkgo biloba leaves) produced better results compared to the conventional standardized extract from plant (GBE, 24% ginkgo flavones glycoside and 6% terpenes lactones). In a bioavailability study conducted with healthy human volunteers the level of GBE constituents (flavonoids and terpenes) from the Phytosomal form peaked after 3 hours and persisted longer for at least 5 hours after oral administration. It was found that the Phytosomal GBE produced a 2-4 times greater plasma concentration of terpenes than did the non-Phytosomal GBE. Its major indication is cerebral insufficiency and peripheral vascular disorders and it can also ameliorate reduced cerebral circulations. Its improved oral bioavailability and good tolerability makes it the ideal ginkgo product even for long term treatment. Studies with ginkgo phytosomes in patients with peripheral vascular disorders have shown to produce 30-60% greater improvement compared to regular standardized GBE. Studies were also conducted on gingko phytosomes which yielded better result as compared to the conventional form. For conducting the aforesaid studies ginkgo phytosomes was administered for 5 days in guinea pigs, in whom the bronchoconstriction was induced by three different agonists (histamine, PAF and Acetylcholine). The bronchospastic inhibition was measured at the maximum peak, expressed as variations versus the basal values. The result indicated that ginkgo phytosomes can not only counteract direct bronchoconstriction but also it possess the tendency to reduce the TXA2 mediated broncho constriction of histamine and PAF2 as phytosomal preparation was done. Antioxidant capacity the improved efficacy of ginkgo phytosomes in combating the allergen induced broncho spasm. Studies have also proved the improved efficacy of ginkgo phytosomes over the conventional standardized extract in protecting rat isolated hearts against ischemia. The above mentioned results clearly gives an indication about the upper hand that phytosomes possess over the conventional preparations, thus proving it’s utility for herbal phytoconstituents.

1. **Phytosomes of green tea:**

Green tea leaves (Theasinensis) is characterized by presence of a polyphenolic compound epigallocatechin 3-O-gallate as the key component26. These compounds are potent modulators of several biochemical process linked to the breakdown of homeostasis in major chronic-degenerative diseases such as cancer and atherosclerosis. Green tea also furnishes us with a number of beneficial activities such as antioxidant, anticarcinogenic, antimutagenic, hypocholesterolemia, and cardioprotective effects. In spite of such beneficial activities furnished by polyphenols from green tea extract the polyphenols suffer from the problem of poor bioavailability. The complexation of polyphenols derived from green tea with phospholipids strongly improves the oral bioavailability. A study on absorption of Phytosomal preparation was performed in healthy human volunteers along with non-complexed green tea extract following oral administration. Over the study period of 6 hours the plasma concentration of total flavonoids was more than doubled when comparison was done between the Phytosomal and the nonwas measured as TRAP (Total Radical Trapping Antioxidant Parameter). The peak antioxidant effect was a 20% enhancement and it showed that the phytosomes formulation had about double the total antioxidant effect.

* + - 1. **Phytosomes containing dosage forms**

Phytosome preparations can be administered orally or topically, but in order to achieve the best results in terms of formulation bioavailability, it is necessary to study the dissolution and disintegration time of dosage forms, while some examples of phytosome-containing dosage forms are given below:

1. **Soft gelatin capsules:**

Indene recommends a granulometry of 100 % < 200 μm in the suspension form vegetable or semi-synthetic oils can be used for this purpose.

1. **Hard gelatin capsules:**

Usually not more than 300 mg in a size 0 capsule, without recompression method is used to fill the hard gelatins.

1. **Tablets:**

Dry granulation represents the ideal manufacturing process to obtain tablets with higher unitary doses. Wet granulation is avoided due to adverse effect on phospholipid complex

1. **Topical dosage forms:**

The emulsion is used for this purpose to obtain the best result from phospholipid complex.

1. **Method of Preparation**

Phytosomes is prepared by different methods by interacting 3-2 moles natural or synthetic phospholipid, mainly phosphatidiccholine with one mole of phytoconstituents (Saha et al., 2013). The most preferable ratio for complexes formation between these two moieties is in the range from 0.5 to 2.0 moles.

**Solvent evaporation method**

The particular quantity of drug, polymer and phospholipids can be taken into a spherical bottom flask and reflux with specific solvent at a temperature 50-60ºc for 2 hr. The mixture may be concentrated to 5 – 10 ml to get the precipitate which can be filtered and collected. The dried precipitate phytosome loaded can be placed in amber coloured glass bottle and stored at room temperature29.

1. **Rotary evaporation technique**

The specific amount of drug and soya lecithin were dissolved in 30 ml of tetrahydrofuran in a rotary round bottom flask followed by stirring for 3 hours at a temperature not exceeding 40oC. Thin film of the sample was obtained to which n-hexane was added and continuously stirred using a magnetic stirrer. The precipitate obtained was collected, placed in amber coloured glass bottle and stored at room temperature.

1. **Antisolvent precipitation technique**

The specific amount of drug and soya lecithin were taken into a 100 ml round bottom flask and refluxed with 20 ml of dichloromethane at a temperature not exceeding 60oC for 2 h. The mixture is concentrated to 5-10 ml. Hexane (20 ml) was added carefully with continuous stirring to get the precipitate which was filtered and collected and stored in vacuum desiccators overnight. The dried precipitate is crushed in mortar and sieved through #100 meshes. Powdered complex was placed in amber collared glass bottle and stored at room temperature.

1. **Salting out method**

The phytoconstituent or standardized extract and phosphatidecholine is dissolved in an aprotic solvent, such as dioxane or acetone where the solution is being stirred overnight then the formed complex is isolated from by precipitation from non-solvent like n-hexane.

1. **Lyophilization technique**

Both natural or synthetic phospholipid and phytoconstituent is dissolved in different solvent and further solution containing phytoconstituent were added to a solution containing phospholipid followed by stirring till complex formation takes place. The formed complex is isolated by lyophilization.

The phospholipid which are used in preparation of phytosome consist of acyl group which may be same or different in phosphatidylcholine, phosphatidylserine, phosphatidyl ethanolamine and mostly derived from palmitic, stearic, oleic, and linoleic acid .In phytosome active principle becomes an integral part of the membrane as the active principle is anchored to the polar head of phospholipid.

1. **Mechanical Dispersion method**

In this method, the lipids dissolved in organic solvent are brought in contact with aqueous phase containing the drug .Initially, pc is dissolved in diethyl ether which is later slowly injected to an aqueous solution of the phytoconstituents to be encapsulated. The subsequent removal of the organic solvent under reduced pressure leads to the formation of phyto-phospholipid complex. Novel methods for the phospholipid complex preparation includes super critical fluids (SCF), which include gas anti-solvent technique (GAS) compressed anti solvent process (PCA), supercritical anti solvent method (SAS).

1. **Different additives used in the formulations of Phytosomes**

**Phospholipids:** Soya phosphatidyl choline, Egg phosphatidyl choline, Dipalmityl phosphatidyl choline, Distearyl phosphatidyl choline.

**Aprotic solvent:**Dioxane, acetone, methylene chloride

**Non solvent:** n-hexane and non-solvent i.e. aliphatic hydrocarbon

**Alcohol: Ethanol, Methanol**

**V. Characterization techniques of Phytosomes**

* 1. **Visualization**

Transmission electron microscopy and scanning electron microscopy are used for visualization of phytosomes.

1. **Transition temperature**

Differential scanning calorimetry is used to determine transition temperature of vesicular lipid system.

1. **Surface tension measurement**

Surface tension activity can be measured by ring method in a Du Nouy ring tensiometer of the drug in aqueous solution.

1. **Vesicle stability**

Assessing the size and the structure of vesicles overtime gives the idea about stability of vesicles. Structural changes are monitored by TEM and mean size is measured by DLS.

1. **Scanning electron microscopy (SEM)**

Scanning electron microscopy has been used to determine The average eparticle size distribution and surface morphology of the complexes. Samples were studied using JEOL JSM-6360 Scanning microscope (Japan). Dry samples were placed on an electron microscope brass stub and coated with gold in an ion sputter. Digital images of phytosome complex of lawsone were taken by random scanning of the stub at 1000, 5000, 10000 and 30000 X magnifications.

1. **Entrapment efficiency**

The entrapment efficiency of a phytosomal formulation can be determined by subjecting the formulation to ultracentrifugation technique.

1. **Evaluation of Phytosomes**

Spectroscopic evaluations to confirm the formation of a complex or to study the reciprocal interaction between the phyto-constituent and the phospholipids, the following spectroscopic methods are used.

1. **1H-NMR:**

Bombardelli et al studied the NMR spectra of (+)-catechin and its stoichiometric complex with distearoylphosphatidylcholine. In nonpolar solvents, there is a marked change of the 1H-NMR signal originating from the atoms involved in the formation of the complex, without any summation of the signal peculiar to the individual molecules. The signals from the protons belonging to the flavonoids are to be broadened that the proton cannot be relieved. In phospholipids, there is broadening of all the signals while the singlet corresponding to the N-(CH3)3 of choline undergo an uplift shift. Heating the sample to 60˚ results in the appearance of some new broad bands, which correspond mainly to the resonance of the flavonoid moiety.

1. **13C-NMR:**

In the spectrum of (+)-catechin and its stoichiometric complex with distearoylphosphatidylcholine, particularly when recorded in C6D6 at room temperature, all the flavonoid carbons are clearly invisible. The signals corresponding to the glycerol and choline portion of the lipid (between 60–80 ppm) are broadened and some are shifted, while most of the resonances of the fatty acid chains retain their original sharp line shape. After heating to 60˚C, all the signals belonging to the flavonoid moieties reappear, although they are still very broad and partially overlapping.

1. **FTIR:**

The formation of the complex can be also be confirmed by IR spectroscopy by comparing the spectrum of the complex with the spectrum of the individual components and their mechanical mixtures. FTIR spectroscopy is also a useful tool for the control of the stability of phytosomes when micro-dispersed in water or when incorporated in very simple cosmetic gels. From a practical point of view, the stability can be confirmed by comparing the spectrum of the complex in solid form (phytosomes) with the spectrum of its micro-dispersion in water after lyophilization, at different times. In the case of simple formulations, it is necessary to subtract the spectrum of the excipients (blank) from the spectrum of the cosmetic form at different times, comparing the remaining spectrum of the complex itself.[55

1. **Invitro – In vivo evaluations**

Models of in-vitro and in-vivo evaluations are selected on the basis of the expected therapeutic activity of biologically active phytoconstituents present in the phytosome. For example, in-vitro anti-hepatotoxic activity can be assessed by the antioxidant and free radical scavenging activity of phytosome. For assessing in vivo anti-hepatotoxic activity, the effect of prepared phytosomes on animals against thioacetamide, paracetamol or alcohol induced hepatotoxicity can be examined. Skin sensitization and tolerability studies of glycyrrhetinic acid phytosome ointment, a commercial product, describe the in-vivo safety evaluation methodology2.

1. **Marketed Formulations**

Many marketed formulations were introduced into the market for the treatment of various diseases .some of the examples are Leucoselect® phytosomes which is used as sysytemic anti- oxidant and is the best choice for the most people under the age of 50.Green select® phytosome it is used as the best choice for protection against cancer. Silybin phytosome is the best choice if the liver needs additional anti – oxidant protection. Sabalselect ® phytosome it enhances immune function in response to a toxic challenge.

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