Review Article

Phytosome: A Brief Overview
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Abstract: In the recent days, most of the prevailing diseases and nutritional disorders are treated with natural medicines. Several plant extracts and phyto constituents, despite having excellent bioactivity in vitro demonstrate less or no in vivo actions due to their poor lipid solubility or improper molecular size or both, resulting in poor absorption and bioavailability. So, much work has been directed towards the development of new concept in herbal delivery system i.e., “phytosomes” which are better absorbed, utilized and as a result produce better results than conventional herbal extracts. Phytosomes often known as herbosomes. The term “phyto” means plant while “some” means cell-like. Phytosomes are little cell like structure. Phytosome is composed of phospholipids, mainly phosphatidylcholine, producing a lipid compatible molecular complex with other constituents. Phytosomal complexes were first investigated for cosmetic applications. But PHYTOSOME process was developed and patented by Indena, a leading supplier of nutraceutical ingredients like milk thistle, ginkgo biloba, grape seed, green tea, hawthorn, ginseng etc. Recently, green tea and one of its active components EGCG has received attention from major supplement brands for weight management supplements. Phytosomes are superior to liposomes due to Complex formation ratio of component and phospholipids is 2:1 and 1:1 respectively, much better absorption and stability profile. Phytosome is anti-inflammatory as well as antioxidant. In experimental animal models it improved resistance to atherosclerotic lesion development, enhanced a protective prostaglandin, and protected ventricular heart pump muscle against damage from circulatory deprivation. Development of phytosomes is at the budding stages in India and abroad. It has a lot of potential in the field of medicine, pharmaceuticals and cosmetics.

Keywords: Phytosomes, medicine, Drug Development, Phospholipids

INTRODUCTION

Phytosome is a patented process developed by Indena, to incorporate phospholipids into standardized extracts and so vastly improve their absorption and utilization. Phytosomes are advanced herbal products produced by binding individual component of herbal extract to phosphatidylcholine resulting in a product that is better absorbed and produces better results than the conventional herbal extracts. Many phytoconstituents have multiple rings and, therefore, cannot be absorbed from the intestine into the blood by simple diffusion. Also, some herbal phytomolecules are poorly miscible with oils and other lipids and often fail to pass through the small intestine because of its lipoidal nature. The effectiveness of any herbal product is dependent upon delivering an effective level of the active compounds. Phytosome has an added dimension; the proven health giving activity of the phospholipids themselves. The phytosome process has been applied to many popular herbal extracts including Ginkgo biloba, grape seed, hawthorn, olive fruits and leaves, milk thistle, green tea, ginseng, kushenin, maruspin and curcumin. The flavonoid and terpenoid components of these herbal extracts are able to directly bind to phosphatidylcholine. Increased bioavailability of the phytosomes over the simpler, non-complexed plant extract has been demonstrated by pharmacokinetics and activity studies, conducted in animals as well as human beings. These compounds can be considered novel entities on the basis of their physiochemical and spectroscopic characteristics. Presently phytosomes are used primarily in cosmetics to deliver water soluble substances to the skin. This technology is also useful in pharmaceutical formulations intended for treatment of oral cavity in which the contact times are very short because phospholipid allows a greater adhesion of the product itself to the surfaces it comes into contact with [1, 2, 3]

Most of the bioactive constituents of phytomedicines are flavonoids (e.g. anthocyanidins from bilberry, catechins from green leaf, silymarin from milk thistle). However, many flavonoids are poorly absorbed [4]. The poor absorption of flavonoid nutrients is likely due to two factors. First, they are multiplexing molecules too large to be absorbed by simple diffusion, while they are not absorbed actively, as occurs with some vitamins and minerals. Second, flavonoid molecules typically have poor miscibility with oils and other lipids, severely limiting their ability to pass across the lipid-rich outer membranes of the enterocytes of the small intestine. Water-soluble flavonoid molecules can be converted into lipid-compatible molecular complexes, aptly called phytosomes. Phytosomes are better able to transition from a hydrophilic environment into the lipid-friendly environment of the enterocyte cell membrane and from there into the cell. Finally reaching the blood [5]. Phosphatidylcholine is not
merely a passive "carrier" for the bioactive flavonoids of the phytosomes. But is itself a bioactive nutrient with documented clinical efficacy for liver disease, including alcoholic hepatic steatosis. Drug-induced liver damage, and hepatitis.*Phytosomes are not liposomes; structurally, the two are distinctly different. The phytosome is a unit of several molecules bonded together, while the liposome is an aggregate of many phospholipid molecules that can enclose active phytomolecules. But without specifically bonding to them.

Milk Thistle: The First Phytosomes:

The first commercial phytosome preparation was based on the flavonoid silybin, the major constituent of silymarin. A flavonol complex extracted from the milk thistle fruit (Silybum marianum, family Asteraceae/Compositae). This phytosome preparation was initially christened IDB 1016 or Silipide [7, 8, 9] and subsequently recast as Siliphos* Phytosome™. [7] Silybinphosphatidylcholine is clinically validated for its antioxidant, anti-inflammatory, and liver detoxification benefits [10].

Advantages of Phytosomes:
The phytosome technology has revolutionized the nutraceutical industry by serving the following benefits:

1. Phytosomes produces a little cell where the valuable components of herbal extracts are protected from destruction by digestive secretions and gut bacteria.
2. It assures proper delivery of drug to the respective tissues.

Properties of Phytosomes:

Chemical Properties:

Phytosomes is a complex between a natural product and natural phospholipids, like soy phospholipids. Such a complex results from the reaction of stoichiometric amounts of phospholipid with the selected polyphenol (like simple flavonoids) in a nonpolar solvent. [15] On the basis of their physicochemical and spectroscopic data, it has been shown that the main phospholipid-substrate interaction is due to the formation of hydrogen bonds between the polar head of phospholipids (i.e. phosphate and ammonium groups) and the polar functional groups of
the substrate. They are lipophilic substances with a clear melting point, freely soluble in nonpolar solvents (in which the hydrophilic moiety was not), and moderately soluble in fats. When treated with water, phytosomes assume a micellar shape forming liposomal-like structures. In liposomes the active principle is dissolved in an internal pocket or floats in the layer membrane, while in phytosomes the active principle is anchored to the polar head of phospholipids, becoming an integral part of the membrane. [16, 17, 18]

**Biological properties:**

Phytosomes 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 pharmacokinetic studies or by pharmacodynamics tests in experimental animals and in human subjects [19].

**Bioavailability of Phytosomes:**

It is evident from many research studies that phytosomes have an improved absorption and bioavailability when compared to the conventional means. Most of the research studies are focused on *Silybum marianum* (milk thistle), the fruit of which contains a water-soluble phytoconstituent (flavonoids) which is known to have a hepatoprotective effect. But these flavonoids are poorly absorbed. The chief and most potent constituent of milk thistle is Silybin. A brief summary of some of the research studies is given as:

- According to Crema et al., 1990, when single oral doses of Silybin directly bound to phosphatidylcholine (Silybin phytosome) are fed, its absorption was approximately seven times more than the absorption from regular milk thistle extract containing 70-80% silymarin content).
- A research study was conducted by (Yanyu et al., 2006) in which he prepared silymarin phytosome and has shown its pharmacokinetics in rats. The phytosome was administrated to rats orally. The results showed that the bioavailability and biological effects of Silybin was increased remarkably.
- Some of the studies have reported the better results produced by consuming ginkgo phytosome than the conventional gingko extract. A bioavailability study was conducted on healthy human volunteers in which it was found that the levels of flavonoids and terpenes (GBE constituents) peaked after 3 hours and persisted longer last for 5 hours. One study shows that some patients suffering from Reynaud’s disease and intermittent circulation were fed with ginkgo phytosome which was shown to produce a 30-60% greater improvement compared to regular standardized GBE (*Ginkgo biloba* extract). [20]

**Phytosome Technology:**

The flavonoid and terpenoid constituents of plant extracts lend themselves quite well for the direct binding to phosphatidylcholine. Phytosomes results from the reaction of a stoichiometric amount of the phospholipid (phosphatidylcholine) with the standardized extract or polyphenolic constituents (like simple flavonoids) in a non-polar solvent [21]. Phosphatidylcholine is a bifunctional compound, the phosphatidyl moiety being lipophilic and the choline moiety being hydrophilic in nature. Specifically the choline head of the phosphatidylcholine molecule binds to these compounds while the lipid soluble phosphatidyl portion comprising the body and tail which then envelopes the choline bound material. Hence, the phytococonstituents produce a lipid compatible molecular complex with phospholipids, also called as phyto-phospholipid complex. Molecules are anchored through chemical bonds to the polar choline head of the phospholipids, as can be demonstrated by specific spectroscopic techniques [22, 23]. Precise chemical analysis indicates the unit phytosome is usually a flavonoid molecule linked with at least one phosphatidylcholine molecule. The result is a little micro sphere or cell is produced. The term “phyto” means plant while “some” means cell-like. The phytosome technology produces a little cell, whereby the plant extract or its active constituent is protected from destruction by gastric secretions and gut bacteria owing to Likewise phytosomes, a liposome is formed by mixing a water soluble substance with phosphatidylcholine in definite ratio under specific conditions. Here, 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. In contrast, with the phytosome process the phosphatidylcholine and the plant components actually form a 1:1 or a 2:1 molecular complex depending on the substance(s) complexed, involving chemical bonds. This difference results in phytosome being much better absorbed than liposomes showing better bioavailability. Phytosomes have also been found superior to liposomes in topical and skin care products [26].

**Method of Preparation:**

Phytosomes are prepared by reacting 3–2 moles (preferably with one mole) of a natural or synthetic phospholipid, such as phosphatidylcholine, phosphatidyl- ethanolamine or phosphatidylserine, with one mole of phytoconstituents either alone or in the natural mixture in an aprotic solvent, such as dioxane or acetone, in a 1:2 or 1:1 ratio. [22] The optimum ratio of phospholipid to phytoconstituent is 1:1. The complex thus formed can be isolated by precipitation with an aliphatic hydrocarbon or lyophilization or spray drying. [26].
Some liposomal drug complexes operate in the presence of water or buffer solution where the phytosomes interact with a solvent with a reduced dielectric constant. The common stages for the preparation of phytosomes are charted in Fig. 2. Mareno and Lampertico [25], Jiang et al [28], Maiti et al [29] have described the methods used for phytosome preparation. Jiang, et al. (2001) have optimized the preparation conditions using a uniform design and step regression and have prepared Herba Epimedii total flavonoid phytosomes (EFP) by means of solvent evaporation and investigated the cumulative dissolution of different ratios of EFP-PVP precipitates by means of dissolution release. The optimized preparation conditions are as follows: solvent-tetrahydrofuran, lecithin to PVP ratio—2.5, temperature—40°C and reaction time—3 hrs. The oil/water apparent partition coefficient of icariin was enhanced more than 4-fold by phospholipid. The cumulative dissolution of Herba Epimedii flavonoids of the EFP-PVP precipitate was significantly higher than that of its physical mixture and a Herba epimedii extract tablet [28]. Yanyu et al (2006) prepared a silybin-phospholipid complex using ethanol as a reaction medium. Silybin and phospholipids were resolved into the medium, after the organic solvent was removed under vacuum condition, and a silybin-phospholipid complex was formed [30].

**Formulation of Phytosome:**

Phytosome® complexes can be formulated both orally and topically. In order to obtain the best performances of this technological innovation both in terms of formulating manageability and enhanced bioavailability (as appropriate disintegration and dissolution time of oral forms, for instance)

**Soft gelatin capsules:** Soft gelatin capsules represent an ideal solution to formulate Phytosome® complexes. The Phytosome® complex can be dispersed in oily vehicles to obtain suspensions to be filled in soft gelatin capsules. Vegetable or semi-synthetic oils can be used to this purpose. Indena recommend a granulometry of 100% <200 μm to best perform capsule production. According to Indena experience, not all the Phytosome® complexes behave in the same way when dispersed in oily vehicles and when the oily suspension is filled in the soft gelatin capsules; for this reasons preliminary feasibility trials should be performed to select the most suitable vehicle.

**Hard gelatin capsules:** The Phytosome® complex can be formulated in hard gelatin capsules as well. A direct volumetric filling process (without precompression) can be applied, even if the apparently low density of the Phytosome® complex seems to limit the maximum amount of powder that can be filled into a capsule (usually not more than 300 mg for a size 0 capsule). With a piston tamp capsule filling process, however, it is possible to increase the amount of powder which can be filled in a capsule, but precompression might affect the disintegration time. Indena recommend to carefully monitor the related parameters during product/ process development. A preliminary dry granulation process is advisable define the best manufacturing process.

**Tablets:** Dry granulation represents the ideal manufacturing process to obtain tablets with higher unitary doses and with suitable technological and biopharmaceutical properties. However, due to the limited flowability, potential stickiness and low apparent density of the Phytosome® complex, a direct compression process can be applied only for low unitary doses; note that whenever a direct compression process is applied, the Phytosome® complex should be diluted with 60-70% of excipients to optimize its technological properties and to obtain tablets with appropriate technological and biopharmaceutical characteristics. On the other hand, wet granulation should be avoided due to the negative effect of water and heat (granulation/ drying) on the stability of the phospholipid complex.
Topical dosage forms: The Phytosome® complex can be formulated topically as well. The ideal process to incorporate the Phytosome® complex in emulsion is to disperse the phospholipidic complex in a small amount of the lipidic phase and add it to the already created emulsion at low temperatures (not higher than 40°C). The Phytosome® complexes are dispersible in the main lipidic solvents employed in topical formulations. In case of formulations containing a limited amount of lipids, the Phytosome® complex might also be dispersed into the watery phase, and again added to the final formulation at temperature lower than 40°C.

SOME PATENTED TECHNOLOGIES RELATED TO PHYTOSOMES:

There are a number of innovative processes and formulation research studies in the field of phytosomes carried out by a number of academic scientist as well as by industrial laboratories. Some patents for phytosomes and other related technologies along with their applications and innovations are listed in Table 1.

Table 1: Some patented technologies related to phytosome.

<table>
<thead>
<tr>
<th>Title of patent</th>
<th>Innovation</th>
<th>Patent No.</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phospholipid complexes of olive fruits or leaves extracts having improved bioavailability</td>
<td>Phospholipids complexes of olive fruits or leaves extracts or compositions containing it having improved bioavailability.</td>
<td>EP/1844785</td>
<td>[31]</td>
</tr>
<tr>
<td>Compositions comprising Ginkgo biloba derivatives for the treatment of asthmatic and allergic conditions</td>
<td>Compositions containing fractions deriving from Ginkgo biloba, useful for the treatment of asthmatic and allergic conditions</td>
<td>EP1813280</td>
<td>[32]</td>
</tr>
<tr>
<td>Fatty acid monoesters of sorbityl furfural and compositions for cosmetic and dermatological use</td>
<td>Fatty acid monoesters of sorbityl furfural selected from two different series of compounds in which side chain is a linear or branched C3-C19 alkyl radical optionally containing at least one ethylenic unsaturation</td>
<td>EP1690862</td>
<td>[33]</td>
</tr>
<tr>
<td>Cosmetic and dermatological composition for the treatment of aging or photodamaged skin</td>
<td>Composition for topical treatment of the skin comprises a substance that stimulates collagen synthesis and a substance that enhances the interaction between extracellular matrix and fibroblasts</td>
<td>EP1640041</td>
<td>[34]</td>
</tr>
<tr>
<td>Soluble isoflavone compositions</td>
<td>Isoflavone compositions exhibiting improved solubility (e.g., light transmittance), taste, color, and texture characteristics, and methods for making the same.</td>
<td>WO/2004/045541</td>
<td>[36]</td>
</tr>
<tr>
<td>An anti-oxidant preparation based on plant extracts for the treatment of circulation and adiposity problems</td>
<td>Preparation based on plant extracts which has an anti-oxidant effect and is particularly useful in treatment of circulation problems such as phlebitis, varicose veins, arteriosclerosis, hemorrhoids and high blood pressure</td>
<td>EP1214084</td>
<td>[37]</td>
</tr>
<tr>
<td>Complexes of saponins with phospholipids and pharmaceutical and cosmetic compositions containing them</td>
<td>Complexes of saponins with natural or synthetic phospholipids have high lipophilia and improved bioavailability and are suitable for use as active principle in pharmaceutical, dermatologic and cosmetic compositions</td>
<td>EP0283713</td>
<td>[38]</td>
</tr>
</tbody>
</table>

Evaluation of Phytosomes:

Various spectroscopic and in-vitro and in-vivo evaluations are applied on phytosomes. The following are the characterization techniques used for phytosomes in characterizing its physical attributes-

1. **Entrapment efficiency**: The entrapment efficiency of a phytosomal formulation can be determined by subjecting the formulation to ultracentrifugation technique. [39]
2. Transition temperature: The transition temperature of vesicular lipid system can be determined by differential scanning calorimetry [40, 41].

3. **Vesicle size and Zeta potential:** The particle size and zeta potential of phytosomes can be determined by dynamic light scattering which uses a computerized inspection system and photon correlation spectroscopy [42, 43].

4. **Surface tension activity measurement:** The surface tension activity of drug in aqueous solution can be measured by ring method Du Nouy ring tensiometer [44].

5. **Spectroscopic evaluation:** The spectroscopic evaluations are widely employed in order to confirm the formation of complex between phytoconstituents and the phospholipid moiety as well as to study the corresponding interaction between the two.

The widely employed methods are listed below-

**1H NMR:** The complex formation between the active phytoconstituents and the phosphatidylcholine molecule can be estimated by this method. Bombardelli studied the NMR spectra of phytosome complex in nonpolar solvents. There is a marked change in H NMR signal originating from atoms involved in the formation of complex, without any summation of the signal peculiar to individual molecules. The signals from protons belonging to the phytoconstituents are broadened. In phospholipids there is broadening of signals while the singlet corresponding to the N-(CH3)3 of choline undergoes an upfield shift [43, 45].

**13C NMR:** In the 13C NMR of the phytoconstituents and the stoichiometric complex with the phosphatidylcholine when recorded in CD3OD at room temperature all the phytoconstituents carbons were invisible. The signals corresponding to the glycerol and choline portion are broadened and some are shifted, while most of the resonance of the fatty acids chains retain their original sharp line shape [43, 45].

**FTIR:** The spectroscopic evaluation of the formed complex can be confirmed by FTIR simply by comparing the spectrum of the complex and the individual components and that of the mechanical mixtures. FTIR can also be considered as a valuable tool in confirming the stability of the phytosomal complex. The stability can be confirmed by comparing the spectrum of the complex in solid form with that of the spectrum of micro-dispersion in water after lyophilization at different times [43, 45].

**In-vivo** studies are performed on Beagle dogs, rodents, wistar rats to compare pharmacokinetics parameters between pure extracts and its phospholipid complex [46, 47].

**APPLICATION:** To examine the various advantages of phytosomes, especially their ability to enhance the bioavailability of polar phytoconstituents, various therapeutic applications of phytosomes have been explored. The details of the type of phytosomes, active constituents, the daily dose and specific indications are given in Table 2.

<table>
<thead>
<tr>
<th>Phytosomes</th>
<th>Phytoconstituent complexed with PC</th>
<th>Daily dosage</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Leucoselect® phytosome</em></td>
<td>Procyanidolic oligomers (PCOs) from grape seeds</td>
<td>50–100 mg</td>
<td>Systemic antioxidant, specific. Best choice for most people under age of fifty. Also specific for the eyes, lungs, diabetes, varicose veins, and protection against heart disease.</td>
</tr>
<tr>
<td><em>Greenselect® phytosome</em></td>
<td>Epigallocatechin 3-O-gallate from <em>camellia sinensis</em> (Green tea)</td>
<td>50–100 mg</td>
<td>Systemic antioxidant. Best choice for protection against cancer and damage to cholesterol</td>
</tr>
<tr>
<td><em>Ginkgoselect® phytosome</em></td>
<td>24% ginkgo flavono glycosides from <em>Ginkgo biloba</em></td>
<td>120 mg</td>
<td>Best choice for most people over the age of 50. Protects brain and vascular lining [52]</td>
</tr>
<tr>
<td>Silybin phytosome</td>
<td>Silybin from silymarin (milk thistle)</td>
<td>120 mg</td>
<td>Best choice if the liver or skin needs additional antioxidant protection</td>
</tr>
<tr>
<td><em>SiliphosTM milk thistle phytosome</em></td>
<td>Silybin from silymarin (milk thistle)</td>
<td>150 mg</td>
<td>Good choice for liver or skin support [53]</td>
</tr>
<tr>
<td>Hawthorn phytosome</td>
<td>Flavanoids</td>
<td>100 mg</td>
<td>Best choice in heart disease</td>
</tr>
<tr>
<td><em>Panax ginseng phytosome</em></td>
<td>37.5% ginsenosides from roots of <em>Panax ginseng</em></td>
<td>150 mg</td>
<td>As a Food Product</td>
</tr>
<tr>
<td>Glycyrrhiza phytosome</td>
<td>18-beta glycyrrhetinic acid</td>
<td>_</td>
<td>Anti-inflammatory Activity [54]</td>
</tr>
</tbody>
</table>

Table 2: Therapeutic applications of different phytosomes with their dose. [48, 49, 50, 51]
Most of the phytosomal studies are focused to Silybum marianum which contains premier liver-protectant flavonoids. The fruit of the milk thistle plant (S. marianum, Family Steraceae) contains flavonoids known for hepatoprotective effects. Silymarin has been shown to have positive effects in treating liver diseases of various kinds, including hepatitis, cirrhosis, fatty infiltration of the liver (chemical and alcohol induced fatty liver) and inflammation of the bile duct. The antioxidant capacity of silymarin substantially boosts the liver’s resistance to toxic insults while PC helps repair and replace cell membranes [55].

Francesco et al., (2009) studied on a recently developed oral formulation in the form of coated tablets (Monoselect Camellia®) (MonCam) containing highly bioavailable green tea extract (GreenSelect® Phytosome) was tested in obese subjects (n=100) of both genders on a hypocaloric diet. Fifty subjects were assigned to the green tea extract plus hypocaloric diet, while the other 50 subjects followed the hypocaloric diet only. After 90 days of treatment, significant weight loss and decreased body mass index (BMI) were observed in the group taking the herbal extract (14 kg loss in the green tea group compared to a 5 kg loss in the diet-only group); waistline was reduced only in male subjects [55].

Maiti et al. developed the quercetinphospholipid phytosomal complex by a simple and reproducible method and also showed that the formulation exerted better therapeutic efficacy as compared to the non-phytosomal conventional preparation in rat liver injury induced by carbon tetrachloride [56].

Green tea leaves (Theasinensis) is characterized by presence of a polyphenolic compound epigallocatechin 3-O-gallate as the key component. 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, hypocholesterolemic, cardioprotective effects. Inspite 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.

**Conclusion:**

The poor absorption and the poor bioavailability associated with the polar phytoconstituents limits its use. These hindrances can be tackled by formulating an appropriate drug delivery system. Phospholipid based drug delivery system have been found promising for better and effective delivery of drug and can enhance the rate and extent of drug absorption across the lipoidal biomembrane. Phytosome are one of the phospholipid based drug delivery system with a better absorption and stability profile as compared to other phospholipid based drug delivery system like liposome. Presently phytosomes are used primarily in cosmetics to deliver water soluble substances to the skin. The technology can effectively deliver the product by topical and oral route. Technology is having a lot of commercial application. Phytosomes enables pharmaceutical manufacturers to provide new pharmaceutical products using water soluble drugs and provides new developments in medical industry.

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