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PHYTOSOMES: AN APPROACH TO INCREASE THE BIOAVAILABILITY OF PLANT EXTRACTS

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ABSTRACT

Phytosome technology enhances the bioavailability of herbal extracts. In phytosomes technology the individual components of an herbal extract are bound to phosphatidylcholine. The emerging technology of drug delivery is being applied to phyto-pharmaceuticals for the improvement of bioavailability of herbal extracts for medicinal applications. Thorough study of literature reveals that several plant extracts (crude, partially purified or fractionated) are reported to possess different significant pharmacological or health promoting properties. Plant extracts can be standardized accordingly and may be formulated as phytosomes for systematic investigation for any improved potential use.

Keywords: Phytosomes, Phytospholipids, Plant extract, Drug delivery.

INTRODUCTION

Lipid solubility and molecular size are the major limiting factors for molecules to pass the biological membrane to be absorbed systematically following oral or topical administration. The effectiveness of any herbal product (or medication) is dependent upon delivering an effective level of the active compounds¹. Phytosomes are recently introduced advanced microspheres or cell forms of herbal products that are better absorbed, and produce better pharmacokinetic and pharmacodynamic profile than conventional herbal extracts. These are also known as herbosomes. The term "Phyto" means plant while "some" means cell-like². The phytosome structures contain the active ingredients of the standardized plant extract or its constituents bound to phospholipids, mainly phosphatidylcholine producing a lipid compatible molecular complex. Phospholipids are complex molecules that are used in all known life forms to make cell membranes. They are cell membrane building blocks, making up the matrix into which fit a large variety of proteins that are enzymes, transport proteins, receptors, and other biological energy converters. In humans and other higher animals the phospholipids are also employed as natural digestive aids and as carriers for both fat-miscible and water miscible nutrients³. Phosphatidylcholine is not only a passive "carrier" for the bioactive flavonoids of the phytosomes, but is itself a bioactive nutrient for liver disease. Flavonoids (e.g., anthocyanidins from bilberry, catechins from green tea, silymarin from milk thistle) are the most bioactive constituents of phytomedicines. Poor absorption of many flavonoids is due to two factors. First, they are having multiple-ring molecules that are too large to be absorbed by simple diffusion. Secondly flavonoid molecules typically have poor miscibility with oils and other lipids, which limited 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 phytosomes⁴. The phospholipid molecular structure includes a water-soluble head and two fat-soluble tails. Because of this dual solubility, the phospholipid acts as an effective emulsifier. By combining the emulsifying action of the phospholipids with the standardized botanical extracts, the phytosome form provides dramatically enhanced bioavailability for lipid soluble drugs explained by faster and improved absorption in the intestinal tract⁵. Phytosome protect the valuable components of the herbal extract from destruction by digestive secretions and gut bacteria⁶. Phytosomes are used in the treatment of the acute and chronic liver disease of toxic metabolic or infective origin or of degenerative nature. It can also be used in anti-inflammatory activity as well as in pharmaceutical and cosmetic compositions. Silybin and the other silymarin flavonolignans from milk thistle conserve tissue glutathione, are liver-protective, and have

anticancer potential. Curcumin and its related diphenolic curcuminoids have potent antioxidant, anti-inflammatory, and anti-carcinogenic properties. The green tea flavan-3-ol catechins have antioxidant, anti-inflammatory, cardio- and neuro-protective effects, and anti-carcinogenic benefits, with fat oxidation effects coupled to weight loss. The complex grape seed proanthocyanidin mix (including catechin and epicatechin monomers and oligomers) counters oxidative stress and protects the circulatory system (Table 1). For each of these preparations, conversion into phytosomes has improved efficacy without compromising safety. The first commercial Phytosome preparation was based on flavonolignan Silybin the major constituent of silymarin, a flavanol complex extracted from milk thistle fruit (*Silybum marianum*, family Asteraceae/ Compositae). This phytosome preparation was initially christened IDB 1016 or Silipide and subsequently recasts as Silipos[®] Phytosome[™]. Silybin phosphatidylcholine is clinically validated for its anti-inflammatory, antioxidant and liver detoxification benefits⁷.

Difference between phytosome and liposome

The fundamental difference between liposomes and phytosomes is that in liposomes the active principle is dissolved in the medium contained in the cavity or in the layers of the membrane, whereas in the phytosome it is an integral part of the membrane, being the molecules anchored through chemical bonds to the polar head of the phospholipid (Fig 1). Liposomes are used primarily in cosmetics to deliver water-soluble substances to the skin. A liposome is formed by mixing a water-soluble substance with phosphatidylcholine. No chemical bond is formed; the phosphatidylcholine molecules surround the water-soluble substance. There may be hundreds or even thousands of phosphatidylcholine molecules surrounding the water-soluble compound. In contrast, with the Phytosome process the phosphatidylcholine and the individual plant components actually form a 1:1 or a 2:1 complex depending on the substance. This difference results in Phytosomes being much better absorbed than liposomes. Phytosomes are superior to liposomes in skin care products^{7,8}.

Advantages of phytosomes

As compared to conventional herbal formulation, phytosomes have following advantages^{9,10,11,20}

1. They enhance the absorption of lipid insoluble polar botanical extract through oral as well as topical route showing better bioavailability, hence significantly greater therapeutic benefit.
2. As the absorption of active constituent(s) is improved, its small dose can produce desired results.
3. Phosphatidylcholine used in preparation of phytosomes, besides acting as a carrier also acts as a hepatoprotective,

hence giving the synergistic effect when hepatoprotective substances are employed.

4. Phytosomes show better stability profile due to formation of chemical bonds between phosphatidylcholine molecule and botanical extract.
5. 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, and thus can be used for systemic targeting.
6. Phytosome are widely used in cosmetics due to there more skin penetration and have a high lipid profile.
7. By enhancing the solubility of bile to herbal constituent, phytosomes facilitates the liver targeting.

Formulation of phytosomes

Phytosomes are prepared by reacting the herbal extract in an aprotic solvent such as methylene chloride, dioxane and ethyl acetate with the phospholipid such as phosphatidylcholine, phosphatidylethanolamine or phosphatidylserine dissolved in the same solvent. After solubilization has been completed, the complex compounds are isolated by removing the solvent under vacuum, by freeze drying or by precipitation with non solvents such as n-hexane. Thus the obtained complexes are lipophilic in character and soluble in a polar and aprotic solvent, in which the individual components of the complex are normally insoluble⁴.

Table 1: Commercial phytosome preparations ^{3, 22, 23}

S. No.	Phytosomes	Phytoconstituents complexed	Indication
1.	Centella Phytosome	Terpenes	Vein and Skin disorders
2.	Echinacea Phytosome	Echinacosides from <i>Echinacea angustifolia</i>	Nutraceutical, immunomodulator
3.	Ginkgo Phytosome™	24 % ginkgoflavonoids from <i>Ginkgo biloba</i>	Protects brain and vascular linings, anti-skin ageing
4.	Ginseng Phytosome™	37.5 % ginsenosides from <i>Panax ginseng</i>	Immunomodulator, Nutraceutical
5.	Green Tea Phytosome™	epigallocatechin 3-O- gallate from <i>Camelia sinensis</i>	Food Product, Systemic antioxidant, Cancer protectant
6.	Grape Seed Phytosome™	Procyanidins from <i>Vitis vinifera</i>	Nutraceutical, cardio-protective, systemic antioxidant.
7.	Hawthorn Phytosome™	Flavonoids from <i>Crataegus sp.</i>	Nutraceutical, cardio-protective and antihypertensive
8.	Olive oil Phytosome	Polyphenols from <i>Olea europaea</i> oil	Antioxidant, anti- inflammatory, anti-hyperlipidemic
9.	Panax Ginseng Phytosome™	37.5 % ginsenosides from roots of <i>Panax ginseng</i>	Food Product
10.	Super Milk thistle Extract	Silybin from <i>Silymarin</i>	Food Product; antioxidant for liver and skin
11.	Silybin Phytosome™	Silybin from <i>Silybium marianum</i>	Hepatoprotective, antioxidant for liver and skin
12.	Silybin Phytosome™	Silybin from <i>Silymarin</i>	Antioxidant for Liver and skin

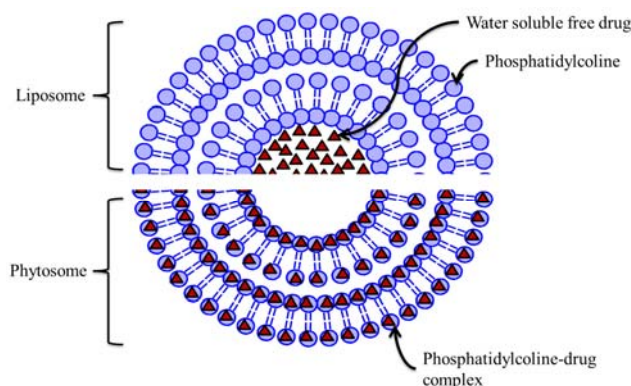


Fig. 1: Difference between phytosome and liposome. The molecular organization of phytosomes (lower segment) liposome (upper segment)

Advances in phytosome technology

In a very recent study the tissue and blood effects of high-dose silybin-phytosome in prostate cancer patients was determined. Patients received silybin-phytosome for 14-31 days (mean was 20 days) prior to surgery. Silybin blood levels were measured 1 h after the first silybin-phytosome dose with a mean value of 19.7 µM. One of the treated patients developed a grade 4 post-operative thromboembolic event. The other observed toxicities in the treatment group were mild: four subjects had diarrhea and one had asymptomatic grade 2 hyperbilirubinemia which was transient. The results indicate that high-dose oral silybin-phytosome achieves high blood concentrations transiently, but low levels of silybin are seen in prostate tissue¹².

Green Phytosome were prepared and studied in 100 obese subjects (both male and female, divided into 2 groups of 50 each). Group 1 was given hypocaloric diet with green tea phytosome. Group 2 was given only hypocaloric diet. After 90 days, parameters like weight, body mass index, low density lipid, High density lipid, total cholesterol, triglycerides, insulin, growth factor, cortisol were determined. All parameters were improved in both groups but there was more weight loss in green tea phytosome group than in diet only group (14 kg loss versus 5 kg loss). Also, no adverse effects were reported during and after trial¹³.

Another method currently being investigated is complexing curcumin with a phospholipid, known as a phytosome. The phosphatidylcholine-curcumin complex (Meriva®) is more readily

incorporated into lipophilic cell membranes, making it significantly more bioavailable than unbound curcumin. In rats, peak plasma concentration and AUC were five times higher for Meriva than for unbound curcumin¹⁴.

Phytosomes of curcumin (flavonoid from turmeric, *Curcuma longa*) and naringenin (flavonoid from grape fruit, *vitis vinifera*) showed higher antioxidant activity than pure curcumin in all dose levels tested¹⁵. In a study the bioavailability of silybin in rats was found to increase remarkably after oral administration of prepared silybin-phospholipid complex Phytosome due to an impressive improvement of the lipophilic property of silybin-phospholipid complex and improvement of the biological effect of silybin¹⁶.

Ginkgo biloba phytosome treatment was found to increase superoxide dismutase, catalase, glutathione peroxidase and glutathione reductase activities in all the brain regions compared with those treated only with sodium nitrite. *Ginkgo biloba* phytosomes were administered to Wistar rats at 50 mg/kg and 100 mg/kg for 7 and 14 days. Chemical hypoxia was induced by administration of sodium nitrite (75 mg/kg) 1 h after the last administration of treatment. Thirty minutes after sodium nitrite administration, the animals were killed and the cerebral cortex, cerebellum, hippocampus and striatum were isolated and homogenized. The supernatants were used for the estimation of the antioxidant enzymes superoxide dismutase, catalase, glutathione peroxidase and glutathione reductase¹⁷.

Herba Epimedii flavonoid phytosomes (EFP) were prepared by means of solvent evaporation technique and the accumulative dissolution of different ratios of EFP-PVP precipitates was investigated by means of dissolution release. For optimized preparation solvent-tetrahydrofuran, lecithin to PVP 2.5 times, temperature 40 °C and reaction 3 h. Oil/water apparent partition coefficient of icariin was enhanced more than 4 times by phospholipid. The accumulative dissolution of *Herba Epimedii* flavonoids of EFP-PVP precipitate was significantly higher than that of its physical mixture and *Herba Epimedii* extract tablet¹⁸.

Patients suffering from chronic hepatitis (viral, alcohol or drug induced) treated with silybin phytosome at a dose of 120 mg either twice daily or thrice daily for up to 120 days, liver function returned to normal faster in patients taking silybin phytosome compared to a group of controls (49 treated with commercially available silymarin, 117 untreated or given placebo)¹⁹.

In a study silymarin (a standardized mixture of flavanolignans extracted from the fruits of *S. marianum*) phytosomes showed much higher specific activity and a longer lasting action than the single constituents, to percent reduction of edema and inhibition of myeloperoxidase activity²⁰.

A human study was conducted to design the absorption profile of silybin when directly bound to phosphatidylcholine. Plasma levels of silybin were determined after administration of single oral doses of silybin phytosome and a similar amount of silybin from milk thistle in healthy volunteers. The results indicated that the absorption of silybin from silybin phytosome was approximately seven times greater compared to the absorption of silybin from regular milk thistle extract²¹.

CONCLUSION

Thorough study of literature different phytosome products has demonstrated significant therapeutic or health promoting properties when compared with the conventional plant extracts. Phytosomes can be developed for different therapeutic purposes like hepatoprotective, cardiovascular, liver diseases, anti-inflammatory, immunomodulator, anticancer, antidiabetic etc or for prophylactic and health purposes as nutraceuticals, in due course.

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