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Full Length Research Paper

Phytosome: An emerging trend in herbal drug treatment

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Herbal medicines have been widely used all over the world since ancient times and have been recognized by physicians and patients for their better therapeutic value as they have no or fewer adverse effects as compared with modern medicines. Phytosome is a novel approach to drug delivery system that addresses the limitations of the traditional drug delivery systems. Phytosomes are advanced forms of herbal products that are better absorbed, utilized, and as a result produce better results than conventional herbal extracts. The newly created phytosome structures contain the active ingredients of the herb bounded to phospholipids. 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 tract.This article summarizes various drug delivery technologies for herbal actives, which are gaining more attention for better therapeutic response. The bioavailability can be improved by phytosomal drug delivery system, which can enhance the rate and the extent of drug absorption across the lipoid biomembrane, which have been found promising for better and effective delivery of drug and providing much appropriate systematic drug delivery. This article reviews the current trends in phytosomes drug delivery.

Key words: Phospholipid, botanical extract, emulsifier, bioavaibility, lipoid biomembrane.

INTRODUCTION

Phytosomes are cell like structure “Phyto” means plant while “some” means cell like and phytosome is a novel approach to drug delivery system that addresses the limitations of the traditional drug delivery systems. Phytosomes contains the bioactive phytoconstituents of herb extracts surrounded and bound by lipid. Phytosomes are developed by incorporating standardized plant extract or water soluble phytoconstituents into phospholipids to produce lipid compatible molecular complexes called phytosomes and so vastly improve their absorption and bioavailability. Phytosome process produces a little cell because valuable components of herbal extract are protected from destruction by digestive secretion and gut bacteria. Phytosomes are better able to transform from a hydrophillic enviroment into the lipid friendly environment of the enterocyte cell membrane and from there into the cell finally reaching the blood (Manach et al., 2004). 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 tract (Bombardelli et al., 1989). Phytosome have improve pharmacokinetic and pharmacological parameter which in result can advantageously be used in treatment of acute and chronic liver disease of toxic metabolic or infective origin (Mascarella, 1993) The Phytosome process has been applied to many popular herbal extracts including *Ginkgo biloba*, grape seed, hawthorn, milk thistle, green tea, and ginseng. The flavonoid and terpenoid components of these herbal extracts lend themselves quite well for the direct binding to phosphatidylcholine. Specifically, the choline head of the phosphatidylcholine molecule binds to these compounds, while the fat-soluble phosphatidyl portion

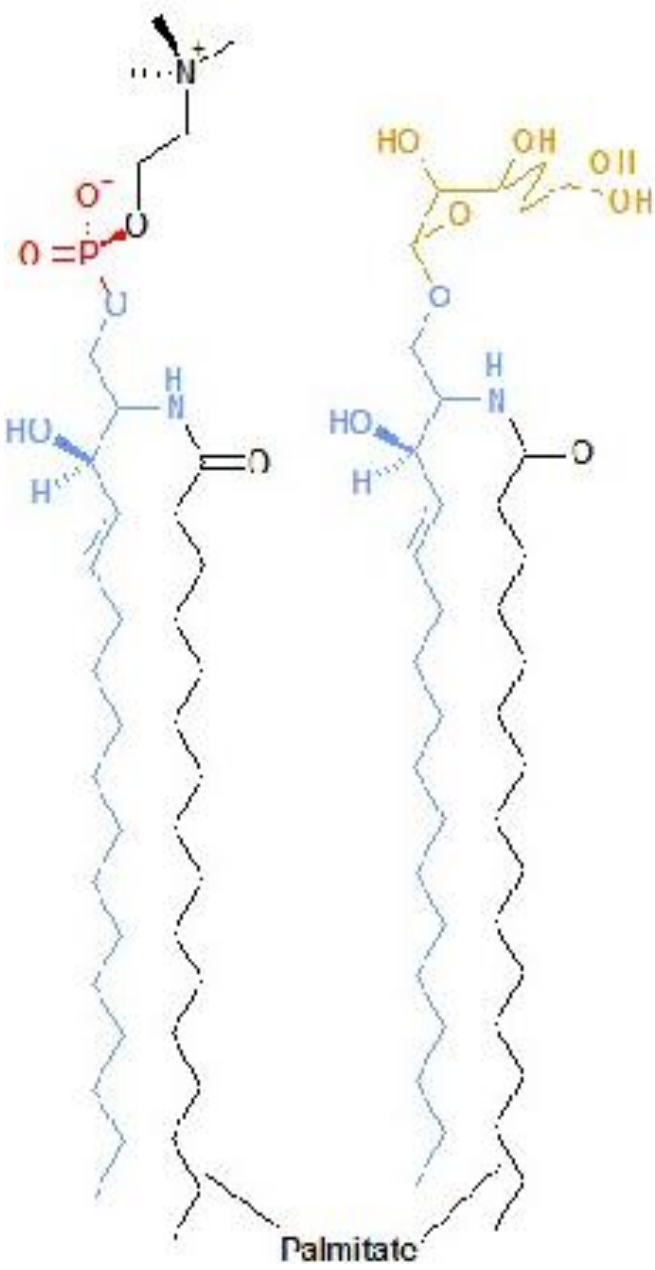

Figure 1. Phosphatidylcholine.

comprising the body and tail then envelopes the choline-bound material. The result is a little micro sphere or cell is produced.

Phytosomes (Phospholipid-herbal extract complexes) can be considered as novel entities.

PREPARATION OF PHYTOSOME

Phytosomes are novel complexes which are prepared by reacting from 2 to 3 mol but preferably with one mole of a natural or synthetic phospholipid, such as phosphatidylcholine, phosphatidylethanolamine or phosphatidyiserine with one mole of component for example, flavolignanans, either alone or in the natural mixture in aprotic solvent such as dioxane or acetone from which complex can be isolated by precipitation with non solvent such as aliphatic hydrocarbons or lyophilization or by spary drying. In the complex formation of phytosomes the ratio between these two moieties is in the range of 0.5 to 2.0 mol. The most preferred ratio of phospholipid to flavonoids is 1:1 (Jose and Bombardelli 1987).

In the phytosome preparations, phospholipids are selected from the group consisting of soy lecithin, from bovine or swine brain or dermis, phosphatidylcholine, phosphatidylethanolamine, phosphatidyiserine in which acyl group may be same or different and mostly derived from palmitic, stearic, oleic and linoleic acid. Selection of flavonoids are done from the group consisting of quercetin, kaempferol, quercretin-3, rhamnoglucoside, quercetin-3-rhamnoside, hyperoside, vitexine, diosmine, 3- rhamnoside, (+) catechin, (-) epicatechin, apigenin-7-glucoside, luteolin, luteolinglucoside, ginkgonetine, isoginkgonetine and bilobetine. Some liposomal drugs complex operate in the presence of the water or buffer solution where as phytosomes, they operate with the solvent having a reduced dielectric constant. Starting materials of component like flavonoids are insoluble in chloroform, ethyl ether or benzene. They become extremely soluble in these solvents after forming phytosomes. This chemical and physical property change is due to the formation of a true stable complex (Sharma and Sikarwar, 2005).

Properties of phytosomes

Chemical properties

Phytosomes is a complex between a natural product and natural phospholipids, like soy phospholipids. Such a complex is obtained by reaction of stoichiometric amounts of phospholipid and the substrate in an appropriate solvent. On the basis of spectroscopic data it has been shown that the main phospholipid and substrate interaction is due to the formation of hydrogen bonds between the polar head of phospholipids (that is, phosphate and ammonium groups) and the polar functionalities of the substrate. When treated with water, phytosomes assumes a micellar shape forming liposomal-like structures. In liposomes the active principle is dissolved in the internal pocket or it is floating 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 for example in the case of the catechindistearoylphosphatidylcholine complex, in this, there is the formation of H-bonds between the phenolic hydroxyls of the flavone moiety and the phosphate ion on the phosphatidylcholine side.

This can be deduced from the comparison of the Nuclear Magnetic Resonance (NMR) of the complex with those of the pure precursors. The signals of the fatty chain are almost unchanged. Such evidences inferred that the two long aliphatics chains are wrapped around the active principle, producing a lipophilic envelope, which shields the polar head of the phospholipid and the catechin in Figure 1 (Bombardelli, 1991).

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 (Franco and Bombardelli, 1998).

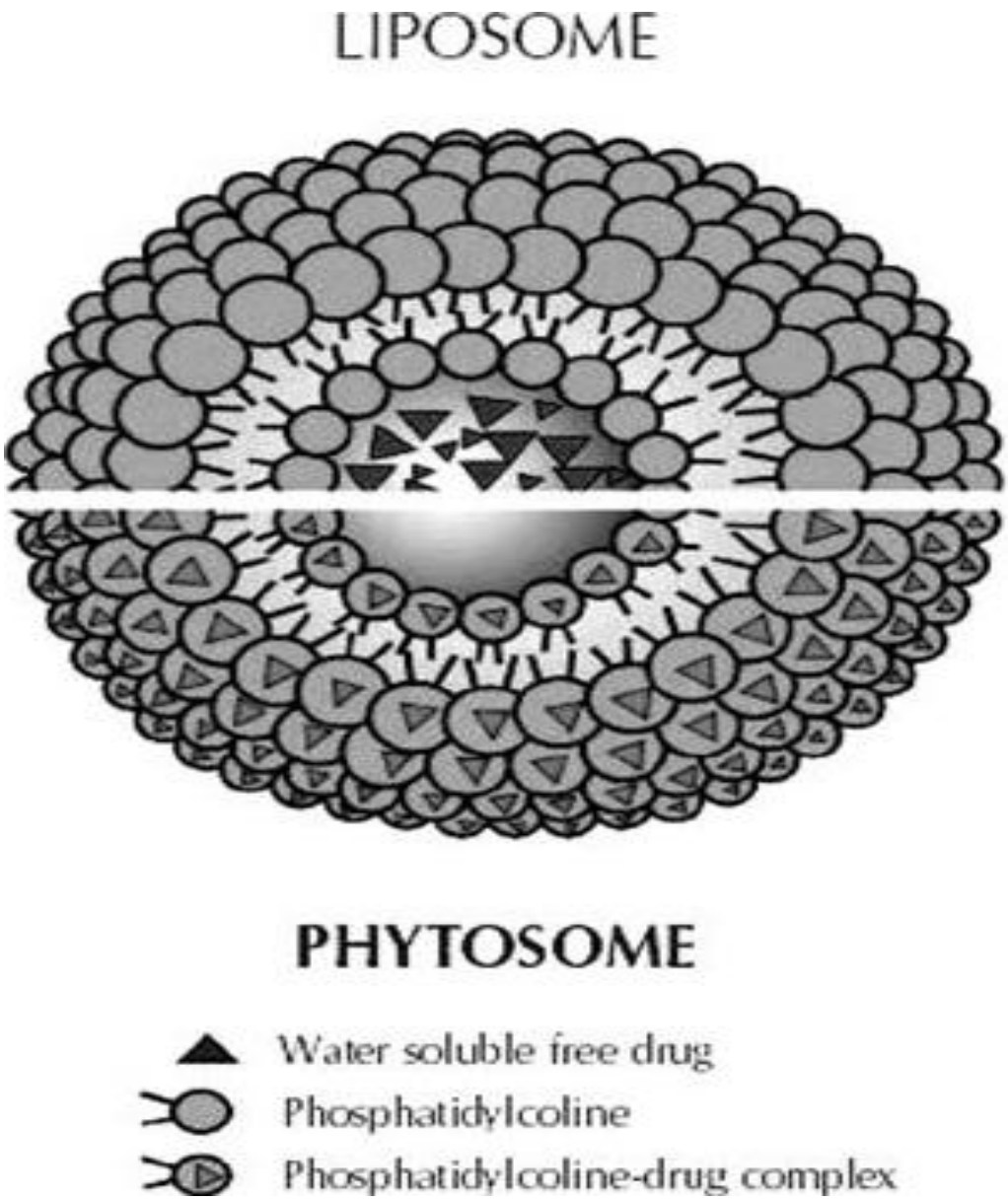

Figure 2. Major difference between liposome and phytosome. The molecular organization of the liposome (upper segment) versus many individual phytosomes (lower segment).

Difference between phytosome and liposome

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 (hydrogen bonds). This difference results in phytosome, showing better bioavailability and being much better absorbed than liposomes. Phytosomes have also been found superior to liposomes in topical and skin care (cosmetic) products in Figure 2 (Sharma and Sikarwar, 2005).

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 such as, shape, size, its distribution, percentage drug capture entrapped volume, percentage drug released and

chemical composition (Jain, 2005).

Advantages over the conventional dosage form

The various advantages of phytosome are mentioned as:

1. Phytosome as better bioavailable botanical extracts, dramatically enhance bioavailablity due to their complex with phospholipids and delivers faster and improved absorption in intestinal tract, hence significantly greater therapeutic effect.
2. Phytosome permeates the non-lipophillic botanical extract to be better absorbed in intestinal lumen.
3. As the absorption of active constituents improves, decreases dose requirement and desired results can be achieved.
4. Phytosomes are widely used in cosmetics due to there more skin penetration and high lipid profile.
5. Unlike liposome, chemical bonds are form between phosphatidylcholine molecule and phytoconstituents the phytosomes show better stability profile.
6. Phosphatidylcholine used in preparation of phytosomes, besides acting as a carrier also acts as a hepatoprotective; hence giving synergistic effect when hepatoprotective agents are employed
7. It enhances the absorption of herbal constituent and hence the bioavailability.
8. It gives nutritional benefit of phospholipid.

Commercial phytosome preparation

Commercial product of phytosomes prepared from plant extracts which are available in the market is shown in Table 1.

APPLICATION OF PHYTOSOME

Phytosome are used in treatment of various diseases like liver disease and heart disease. It is also used as antinflamatory, lipolytic, vasokinetic, anti-oedema, cicatrizing, trophodermic, neutraceutical immunomo-dulator, antioxidant for skin and liver, cardioprotective, anti-wrinkles and UV protectant.

The fruit of milk thistle plant contain flavonoid known for hepatoprotective effect. Silymarin has been shown to have positive effect in treating liver diseases of various kinds, including hepatitis, cirrhosis, fatty filtration of liver and inflammation of bile duct. The antioxidant capacity of silymarin substantially boosts the liver resistance to toxic results. Silymarin primarily contains three flavonoids of the flavonol subclass silybin followed by silidainin and silychristin. Silybin is most potent than the other two (Hikino et al., 1984). Silybin protect the liver by conserving glutathione into the Parenchyma Cells (Valenzuela., et.al 1989). While Parenchyma cell (PC) helps repair and replace cell membrane (Kid et al., 1996). These constituents likely offer the synergistic benefit of sparing liver cell from destruction. Yanyu et al. (2006) prepared the silymarin phytosome and studied its pharmacokinetics in rats. In the study the bioavailability of silybin in rat was increased remarkably after oral administration of prepared silybin-phospholipid complex due to an impressive improvement of the lipophilic property of silybin-phospholipid complex and improvement of the biological effect of silybin. Tedesco et al. (2004), reported silymarin phytosome show better antihepatotoxic effect than silymarin alone and can prove protection against the toxic effect of aflatoxin B1 on performance of broiler chicks.

Mukerjee et al. (2008) developed a novel hesperetin phytosome by complexing hesperetin with hydrogenated phosphatidylcholine. This complex was then evaluated for antioxidant activity in CCL4 intoxicated rats along with pharmacokinetic studies. It was found that the phytosome had a sustained release property for over 24 h and enhanced antioxidant activity. Pharmacokinetic study revealed that the phytosome had higher relative bioavailability than that of parent molecule at the same dose level. Bombardelli and Mustichl (1991) reported silymarin phytosomes in which silymarin was complexed with phospholipids. It shows much higher specific activity and a longer lasting action than the single components, with respect to percent reduction of oedema, inhibition of myeloperoxidase activity, antioxidant and free radical scavenging properties.

Maiti et al. (2005) developed the quercetin-phospholipids complex by a simple and reproducible method and also showed that the formulation exerted better therapeutic efficacy than the molecule in rat liver injury induced by carbon tetrachloride.

Barzaghi et al. (1990) conducted human study designed to assess the absorption of silybin when directly bound to phosphatidylcholine. Plasma silybin levels were determined after administration of single oral doses of silybin phytosome and a similar amount of silybin from milk thistle in healthy volunteers. The result indicated that the absorption of silybin from silybin phytosome is approximately seven times greater compared to the absorption of silybin from regular milk thistle extract.

Grange et al. (1999) conducted a series of studies on silymarin phytosome, containing a standardized extract from the seeds of *Silybum marinum*, administered orally and found that it could protect the fetus from maternally egested ethanol.

Grape seed phytosome composed of oligomeric polyphenols of varying molecular size, complexed with phospholipids. The main properties of procyanidin flavonoids of grape seed are, increase in total antioxidant capacity and stimulation of physiological antioxidant defenses of plasma, protection against ischemia/refusion

Table 1. Commercial phytosome preparation.

S/N	Phytosomes	Phytoconstituents complex with phosphatidylcholine	Doses(mg)	Indication
01	Silybin phytosome TM	Silybin from *Silybum marianum*	120	Food product, hepatoprotective, antioxidant for skin and liver
02	Ginkgo phytosome TM	24% Ginkgo flavonglycosides from *Ginkgo biloba*	120	Protect brain and vascular lining, antiageing agent
03	Ginseng phytosome TM	37.5% Ginsenoside from panax ginseng	150	Food product, neutraceutical immunomodulator
04	Green tea phytosome TM	Epigallocatechin3-O-gallate from *Camelia sinesis*	50 to100	Neutraceutical, systemic antioxidant, anticancer
06	Grape seed(PCO) phytosome TM	Procyanidine from *Vitis vinifera*	50 to100	Neutraceutical, systemic antioxidant, cardioprotective
07	Hawthorn phytosome TM	Flavonoids from *Crataegus* sp.	–	Food product, hypertension and other heart diseases
08	Centella phytosome	Terpenes	–	Vein and skin disorders
09	Olive oil phytosome	Polyphenols from *Olea europoea* sp.	–	Antioxidant, antinflamatory, antihyperlipidemic
10	Echinacea phytosome	Echinacosides from *Echinacea angustifolia*	–	Neutraceutical, immunomodulator
11	Curcumin phytosome	Curcumin from *Curcuma longa*	250	Antioxidant, antinflamatory
12	18ß-glycyrrhetinic acid phytosome	18ß-glycyrrhetinic acid from *licorice rhizome*	–	Soothing
13	Centella phytosome®	Triterpenes from *Centella asiatica* leaf	–	Cicatrizing, trophodermic
14	Crataegus phytosome®	Vitexin-2″-O-rhamnoside from hawthorn flower	–	Antioxidant
15	Escin ß-sitosterol phytosome®	Escin ß-sitosterol from horse chestnut fruit	–	Anti-oedema
16	Ginkgo biloba Terpenes phytosome®	Ginkgolides and bilobalide from *Ginkgo biloba* leaf	120	Soothing
17	Ginkgo biloba Dimeric Flavonoids phytosome®	Dimeric flavonoids from *Ginkgo biloba* leaf	–	Lipolytic, vasokinetic
18	PA_2 phytosome®	Proanthocyanidin A_2 from horse chestnut bark	–	Anti-wrinkles, UV protectant
19	Sericoside phytosome®	Sericoside from *Terminalia sericea* bark root		Anti-wrinkles
20	Silymarin phytosome®	Silymarin from milk thistle seed		Antihepatotoxic
21	Virtiva®	Ginkgo flavonglycosides, ginkgolides, bilobalide from *Ginkgo biloba* leaf		Vasokinetic
22	Visnadex®	Visnadin from Amni visnaga umbel		Vasokinetic

induced damages in the heart, and protective effects against atherosclerosis thereby offering marked protection for the cardiovascular system and other organs through a network of mechanisms that extend beyond their great antioxidant potency (Schwitters and Masquelier, 1993). Green tea has got several long term beneficial activities such as antioxidant, anticarcinogenic, antimutagenic, antiatherosclerotic, hypocholesterolemic, cardioprotective and antibacterial effect. Despite such potential action green tea polyphenols have very poor oral bioavailability from conventional extracts. The complexion of green tea polyphenols with phospholipids strongly improves their poor oral bioavailability. A study on absorption of phytosomal preparations was performed in healthy volunteers along with non complexed green tea extract following oral administration. During the study period of 6 h the plasma concentration of total flavonoids was more than doubled when coming from the phytosomal versus the nonphytosomal extract. Antioxidant capacity was measured as total radical-trapping antioxidant parameter. The peak antioxidant effect was a 20% enhancement and it showed that the phytosome formulation had about double the total antioxidant effect (www.phospholipids online.com)

Conclusion

Phytosomes are novel compounds comprising of lipophillic complexes of components of various plants like *S. marianum, G. Biloba, ginseng* etc. with phospholipids. Phytosome preparation is done by non-convectional method. Absorption of phytosome in gastro-intestinal tract is appreciably greater resulting in increased plasma level than the individual component. Complex formation ratio of component and phospholipids is 1:1 and 2:1. Phytosomes are used as a medicament and have wide scope in cosmetology. Many areas of phytosome are to be revealed in future in the prospect of pharmaceutical application. Phytosomes forms a bridge between the conventional delivery system and novel delivery system. Phytosomes are advanced form of herbal extract that are better absorbed which results better than conventional herbal extract. Phytosomes have improved pharma-cokinetic and pharmacological parameter, which in result can advantageously be used in treatment of liver diseases, either metabolic or infective origin, and gives therapeutic effect like lipolytic, vasokinetic, anti-oedema, cicatrizing, trophodermic, neutraceutical , antioxidant for skin and liver, cardioprotective, Anti-wrinkles and UV protectant. After screening and selection of potential extracts or constituents from plant, phytosomes can be developed for different therapeutic effect like antidiabetic, immunomodulator, anticancer, antinflamatory, heart diseases and for various therapeutic purposes in future.

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