

Phytosomes: a potential phyto-phospholipid carriers for herbal drug delivery

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ABSTRACT

The potential uses of large number of herbal drugs are limited due to their poor absorption and poor bioavailability after oral administration. The bioavailability can be improved by formulating a appropriate drug delivery system, which can enhance the rate and the extent of drug absorption across the lipid biomembrane. Phospholipids based drug delivery system have been found promising for better and effective delivery of drug and providing much appropriate systematic drug delivery. 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, which is also one of the chief components of the membranes in our cells. "Phytosome" is formed by complexing the polyphenolic phytoconstituents in molar ratio with phosphatidylcholine. Phytosomes are advanced forms of herbal products that are better absorbed, utilized, and as a result produce better drug delivery than conventional herbal extracts. This article reviews the current trends in phytosomes drug delivery.

Keywords: Phytosomes, Phospholipids, Drug Delivery

INTRODUCTION

During the last century chemical and pharmacological studies have been performed on a lot of plant extracts in order to know their chemical composition and confirm the indications of traditional medicine. Most of the bioactive constituents of herbal drugs are water soluble molecules. However, water soluble phytoconstituents like many flavonoids are poorly absorbed^[1] either due to their multiple-ring large size molecules which can not be absorbed by simple diffusion, or due to their 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 phytoconstituent molecules (mainly polyphenoles) can be converted into lipid-compatible molecular complexes, which are called phytosomes. Phytosomes are more bioavailable as compared to simple herbal extracts owing to their enhanced capacity to cross the lipid rich biomembranes and finally reaching the blood^[2]. The lipid-phase substances employed to make phytoconstituents, lipid-compatible are phospholipids from soy, mainly phosphatidylcholine (PC). Phospholipids are complex molecules that are used in all known life forms to make cell membranes. The term "phyto" means plant while "some" means cell-like. What the Phytosomes process produces is a little cell,

whereby the valuable component of the herbal extract is protected from destruction by digestive secretions and gut bacteria^[3].

Phytosomes are better able to transition from a hydrophilic environment into the lipid-friendly environment of the enterocyte cell mem-

brane and from there into the cell, finally reaching the blood.

Chemical analysis indicates that in phytosome is usually a flavonoid molecule linked with at least one phosphatidylcholine molecule. A bond is formed between these two molecules, creating a hybrid molecule. This highly lipid-miscible hybrid bond is better suited to merge into the lipid phase of the enterocyte's outer cell membrane. 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. The intakes of phytosome preparations sufficient to provide reliable clinical benefit often also provide substantial phosphatidylcholine intakes. The phytosome process has been applied to many popular herbal extracts including *Ginkgo biloba*, *grape seed*, *hawthorn*, *milk thistle*, *green tea*, and *ginseng*.

Method of preparation:

Phytosomes are novel complexes which are prepared by reacting from 3-2 moles but preferably with one mole of a natural or synthetic phospholipid, such as phosphatidylcholine, phosphatidylethanolamine or phosphatidylserine with one mole of component for example-flavonolignans, 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 spray drying. In the complex formation of phytosomes the ratio between these two moieties is in the range from 0.5-2.0 moles. The most preferable ratio of phospholipid to flavonoids is 1:1^[4].

In the phytosome preparations, phospholipids are selected from the group consisting of soy lecithin, from bovine or swine brain or dermis, phosphatidylcholine, phosphatidylethanolamine, phosphatidylserine in which acyl group may be same or different and

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Table 1: Commercial Phytosome Preparations [3,6]

S.no	Phytosomes	Phytoconstituent complexed with Phosphatidylcholine	Indication
1	Silybin Phytosome TM	Silybin from Silymarin	Food Product, antioxidant for Liver and skin
2	Ginkgo Phytosome TM	24 % ginkgolflavoglycosides from <i>Ginkgo biloba</i>	Protects brain and vascular lining, Anti-skin ageing agent,
3	Panax Ginseng Phytosome TM	37.5 % ginsenosides from roots of <i>Panax ginseng</i>	Food Product
4	Green Tea Phytosome TM	epigallocatechin 3-O- gallate from <i>Camelia sinensis</i>	Food Product, Systemic antioxidant, Cancer protectant
5	Super Milk thistle Extract	Silybin from Silymarin	Food Product; antioxidant for liver and skin
6	Grape seed (PCO) phytosomes	Procyranidolic oligomers (PCOs) from grape Seeds	Food Product; protects against heart disease
7	Hawthorn Phytosomes	Flavonoids	Food Product; In heart disease or hypertension
8	Centella Phytosome	Terpenes	Vein and Skin disorders

mostly derived from palmitic, stearic, oleic and linoleic acid. Selection of flavonoids are done from the group consisting of quercetin, kaempferol, quercetin-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 operate with the solvent having a reduced dielectric constant. Starting material 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 [5]

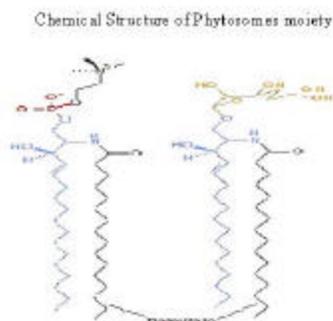
Phytosomes technology:

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 [2]. Phosphatidylcholine is a bifunctional compound, the phosphatidyl moiety being lipophilic and the choline moiety being hydrophilic in nature. Specifically the choline head of the phosphatidylcholinemolecule binds to these compounds while the lipid soluble phosphatidyl portion comprising the body and tail which then envelopes the choline bound material.

Various properties of Phytosomes:

Chemical:

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-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



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.

Phosphatidylcholine

This can be deduced from the comparison of the 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 aliphatic chains are wrapped around the active principle, producing a lipophilic envelope, which shields the polar head of the phospholipid and the catechin [7].

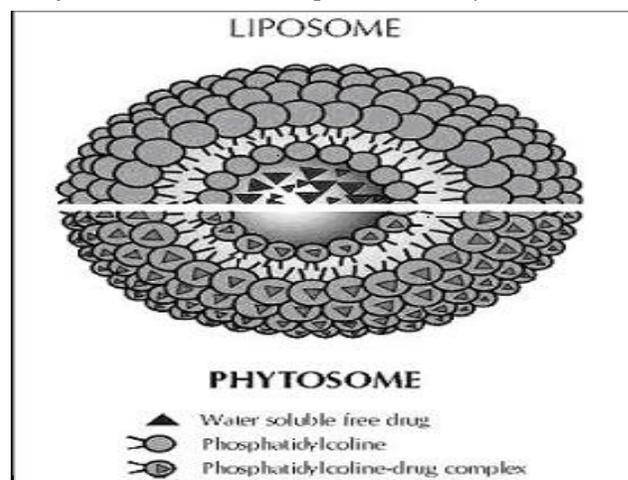
Biological:

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 [8].

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 [9].

Fig 1 Major difference between liposome and Phytosome



Liposomes are used primarily in cosmetics to deliver water-soluble substances to the skin. Mixing a water-soluble substance with phosphatidylcholine forms a liposome. No chemical bond is formed and 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^[10]. Phytosomes are not liposomes - structurally, the two are distinctly different as shown in fig. no.1. The phytosome is a unit of a few molecules this makes difference so the phytosomes being much better absorbed than liposomes. Not surprisingly, Phytosomes are also superior to liposomes in skin care products while the liposome is an aggregate of many phospholipid molecules that can enclose other phytoactive molecules but without specifically bonding to them. Liposomes are touted delivery vehicles, but for dietary supplements their promise has not been fulfilled. But for phytosome products numerous studies prove they are markedly better absorbed and have substantially greater clinical efficacy. Companies have successfully applied this technology to a number of standardized flavonoid preparations.

Merits of Phytosomes:

Phytosomes have the following merits:^[11]

- It enhances the absorption of herbal constituent and hence the bioavailability.
- By enhancing the solubility of bile to herbal constituent, facilitates the liver targeting.
- As the absorption of chief phytoconstituent is improved, its dose requirement is also reduced.
- Phosphatidylcholine used in preparation of phytosomes, besides acting as a carrier also acts as a hepatoprotective, hence giving the synergistic effect.
- Unlike liposome, chemical bonds are formed between phosphatidylcholine molecule and phytoconstituent, so the phytosomes show better stability profile.

Applications of Phytosomes

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^[12]. Silymarin primarily contains three flavonoids of the flavonol subclass (having a fully saturated C-ring). Silybin predominates, followed by silydianin and silychristin. Silybin is actually a flavonolignan, probably produced within the plant by the combination of a flavonol with a coniferyl alcohol. It is now known that silybin is the most potent of the three^[13]. Silybin protects the liver by conserving glutathione in the parenchymal cells^[12], while PC helps repair and replace cell membranes^[14]. These constituents likely offer the synergistic benefit of sparing liver cells from destruction. In its native form within the milk thistle fruit, silybin occurs primarily complexed with sugars, as a flavonyl glycoside or flavonolignan. Silybin has been extensively researched and found to have impres-

sive bioactivity, albeit limited by poor bioavailability.

Tedesco et al (2004) reported silymarin phytosome show better antihepatotoxic activity than silymarin alone and can provide protection against the toxic effects of aflatoxin B1 on performance of broiler chicks^[15].

Busby et al. (2002) reported that the use of a silymarin phytosome showed a better fetoprotectant activity from ethanol-induced behavioral deficits than uncomplexed silymarin^[16].

Yanyu et al (2006) prepared the silymarin phytosome and studied its pharmacokinetics in rats. In the study the bioavailability of silybin in rats 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^[17].

Bombardelli et al. (1991) reported Silymarin phytosomes, in which Silymarin (A standardized mixture of flavanolignans extracted from the fruits of *S. marianum*) was complexed with phospholipids. Phytosomes showed much higher specific activity and a longer lasting action than the single components, with respect to per cent reduction of odema, inhibition of myeloperoxidase activity, antioxidant and free radical scavenging properties^[18].

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^[19]. Recently Maiti et al. (2006) developed the phytosomes of curcumin and naringenin in two different studies^[20, 21]. In the first study phytosome of curcumin was developed to overcome the limitation of absorption and to investigate the protective effect of curcumin-phospholipid complex on carbon tetrachloride induced acute liver damage in rats. The complex showed enhanced aqueous or n-octanol solubility. The antioxidant activity of the complex was significantly higher than pure curcumin in all dose levels tested. In the other study the developed phytosome of naringenin produced better antioxidant activity than the free compound with a prolonged duration of action, which may be helpful in reducing the fast elimination of the molecule from body.

Conclusion

Phytosomes are advanced form of herbal extract that are better absorbed which results better than conventional herbal extract. Phytosomes have improved pharmacokinetic and pharmacological parameter, which in result can advantageously be used in treatment of acute liver diseases, either metabolic or infective origin.

Absorption of phytosome in gastro-intestinal tract is appreciably greater resulting in increased plasma level than the individual component. As mention in the literature, Phytosomes have been therapeutically used for hepatoprotective and liver diseases. After screening and selection for phytoconstituents for therapeutics use, phytosomal drug delivery can be developed for various categories like anticancer, cardiovascular and anti-inflammatory activities.

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