The effectiveness of any herbal medication is dependant on the delivery of effective level of the therapeutically active compound. But a severe limitation exists in their bioavailability when administered orally or by topical applications. Phytosomes are recently introduced herbal formulations that are better absorbed and as a result produced better bioavailability and actions than the conventional phyto molecules or botanical extracts. Phytosomes are produced by a process where by the standardized plant extract or its constituents are bound to phospholipids, mainly phosphatidylcholine producing a lipid compatible molecular complex. Phytosome exhibit better pharmacokinetic and pharmacodynamic profile than conventional herbal extracts.

**Key words:** Phytosomes, Phosphatidyl choline, Liposomes

**INTRODUCTION**

The advancement in the field of herbal drug delivery started recently with the aim to manage human diseases efficiently. Every nation is seeking healthcare beyond the traditional boundaries of modern medicine; turning to self-medication in the form of herbal remedies. Nowadays, expensive research in novel drug delivery systems is going on to improve the therapeutic efficacy of the existing natural molecules. Toxicity and limited absorption of different phytococonstituents obtained from herbs are major problems in exploring their real potentials against different diseases. So, extensive research in the field of herbal drug delivery systems as a means of improving the therapeutic indices of drugs is inevitable.

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. The Phytosome process produces a little cell because of the valuable components of the herbal extract are protected from destruction by digestive secretions and gut bacteria. Phytosomes are better able to transit from a hydrophilic environment into the lipid-friendly environment of the enterocyte cell membrane and from there into the cell, finally reaching the blood. Most of the bioactive constituents of phytomedicines are flavonoids (e.g., anthocyanidins from bilberry, catechins from green tea, silimarin from milk thistle). However, many flavonoids are poorly absorbed; the poor absorption of flavonoid nutrients is likely 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 phytosomes. The term “phyto” means plant while “some” means cell like. Phytosomes is a newly introduced patented technology developed to incorporate standardized plant extracts or water soluble phytoconstituents into phospholipids to produce lipid compatible molecular complexes; aptly called phytosomes. The term "phyto" means plant while "some" means cell like. Phytosomes are novel complexes which are prepared by reacting from 2-3 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

**Preparation of phytosomes**

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two moieties is in the range from 0.5–2.0 moles. The most preferable ratio of phospholipids to flavonoids is 1:1.7.

In the phytosome preparations, phospholipids are selected from the group consisting of soy lecithin, from bovine or swine brain or dermis, phosphatidylcholine, phosphatidylethanolamine, phosphatidylinositol 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, quercitin-3, rhamnoglucoside, quercetin-3-rhamnose, hyperoside, virexine, disoxide, 3-rhamnose, (±) catechin, (±) epicatechin, apigenin-7-glucoside, luteolin, luteolinguicoside, ginkgetone, isoginkgetone 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 8.

PROPERTIES OF PHYTOSOMES

1) Physico 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 phospholipids and the substrate in an appropriate solvent. On the basis of spectroscopic data it has been shown that the main phospholipids-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, there is the formation of H-bonds between the phenolic hydroxyl ends of the flavones moiety and the phosphate ion on the phosphatidylcholine moiety. Phosphatidyl choline can be deduced from the comparison of 1H-NMR and 13C-NMR spectra of the complex with those of the pure precursors. The signals of fatty chain remain almost unchanged. Such evidence inferred that the too long aliphatic chains are wrapped around the active principle, producing a lipophilic envelope, which shields the polar head of the phospholipid and flavanoid molecule and enables the complex to dissolve in low polarity solvents9,10.

![Figure 2.Structure of phosphatidyl choline](image)

2) 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 pharmacodynamic tests in experimental animals and in human subjects 11.

CHARACTERIZATION OF PHYTOSOMES

The behaviour of phytosomes in both physical and biological system is governed by the factors such as physical size, membrane permeability, percentage of 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 release and chemical composition 12.

![Figure 3.Major difference between liposome and phytosome. The molecular organization of the liposome (upper segment) versus many individual phytosomes (lower segment)](image)

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 from a 1:1 or a 2:1 complex depending on the substance 13. Phytosomes are not liposomes; structurally the two are distinctly different as shown in fig. no.3. The phytosome is a unit of 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. The phytosomes technology is a breakthrough model for4.

- Marked enhancement of bioavailability
- Significantly greater clinical benefit
- Assured delivery to the tissues
- No compromise of nutrient safety

ADVANTAGES OF PHYTOSOMES

Phytosomes have the following advantages14,15,16,17.

1) It enhances the absorption of lipid insoluble polar phytoconstitutents through oral as well as topical route showing better bioavailability, hence significantly greater therapeutic benefit.

2) Appreciable drug entrapment.
3) As the absorption of active constituent(s) is improved, its dose requirement is also reduced.

4) 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.

5) Chemical bonds are formed between phosphatidylcholine molecule and phytoconstituent, so the phytosomes show better stability profile.

6) Application of phytoconstituents in form of phytosome improves their percutaneous absorption and act as functional cosmetics.

Recent research shows improved absorption and bioavailability with phytosomes as compared to the conventional means. Most of the phytosomal studies are focused to *Silybum marianum* (milk thistle) which contains premier liver protectant flavonoids. The fruit of the milk thistle plant contains flavonoids known for hepato protective effects. Silybin is the chief and most potent constituent of the milk thistle plant contains flavonoids known for its hepatoprotective effects. Silybin is the chief and most potent constituent of the milk thistle plant contains flavonoids known for hepato protective effects. Silybin is the chief and most potent constituent of the milk thistle plant contains flavonoids known for hepato protective effects. Silybin is the chief and most potent constituent of the milk thistle plant contains flavonoids known for hepato protective effects. Silybin is the chief and most potent constituent of the milk thistle plant contains flavonoids known for hepato protective effects. Silybin is the chief and most potent constituent of the milk thistle plant contains flavonoids known for hepato protective effects. Silybin is the chief and most potent constituent of the milk thistle plant contains flavonoids known for hepato protective effects.

Yanyu et al. 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.

Tedesco et al. reported silymarin phytosome show better anti hepatotoxic activity than silymarin alone and can provide protection against the toxic effects of aflatoxin B1 on performance of broiler chicks. Busby et al reported that the use of a silymarin phytosome showed a better foot protec tant activity from ethanol-induced behavioural deficits than uncomplexed silymarin.

Grange et al. conducted a series of studies on silymarin phytosome, containing a standardized extract from *Silybum marianum* is an excellent liver protectant but very poorly absorbed orally. These data demonstrate a four times greater passage through the liver for phytosomal silybin compared to the non-phytosomal extract. Antioxidant capacity and free radical scavenging properties are potent modulators of several biochemical processes linked to the breakdown of homeostasis in major chronic-degenerative diseases such as cancer and atherosclerosis.

In another study, rabbits were fed with a high cholesterol diet for 6 weeks, to markedly elevate their blood cholesterol and induce atherosclerotic lesions in their aortas and carotid arteries. One group of rabbits received grape seed phytosome in their feed for the first 6 weeks, then 4 weeks of the high-cholesterol diet. These developed significantly less aortic plaque than did the control groups which received conventional standardized grape seed extract in similar regimen. In a randomized human trial, young healthy volunteers received grape seed phytosome 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 30 minutes after administration on 1st day, blood TRAP levels were significantly elevated over the control which received conventional standardized grape seed extract.

Green tea extract generally contains a totally standardized polyphenolic fraction (not less than 66.5 % containing epigallocatechin and its derivatives) obtained from green tea leaves (Thea sinensis) and mainly characterized by the presence of epigallocatechin 3-O-gallate, the key compound. These compounds are potent modulators of several biochemical processes linked to the breakdown of homeostasis in major chronic-degenerative diseases such as cancer and atherosclerosis. Green tea has got several long term beneficial activities such as antioxidant, anticancerogenic, antimutagenic, antiatherosclerotic, hypcholesterolemic, cardioprotective, antibacterial and anticariogenic effects. Despite such potential actions green tea polyphenols have very poor oral bioavailability from conventional extracts. The complexity of green tea polyphenols with phospholipids strongly improves their poor oral bioavailability. A study on absorption of phytosomal preparations 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 coming from the phytosomal versus the non-phytosomal extract.

Maiti et al. developed the quercetin-phospholipid phytosomal 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.
Matti et al. developed the phytosomes of curcumin (flavonoid from turmeric, Curcuma longa) and naringenin (a flavonoid from grape fruit, Vitis vinifera) in two different studies. 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 due to decrease in the rapid elimination of the molecule from body.

Hesperetin is a potent phytomolecule abundant in citrus fruits, such as grapefruit and oranges. In spite of several therapeutic benefits viz, antioxidant, lipid-lowering, anti-carcinogenic activities their shorter half life and lower clearance from the body restricts its use. To overcome this limitation, recently Mukerjee et al. developed a novel hesperetin phytosome by complexing hesperetin with hydrogenated phosphatidyl choline. 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 hr and enhanced antioxidant activity. Pharmacokinetic study revealed that the phytosome had higher relative bioavailability than that of parent molecule at the same dose level.

In this way different phytosome products have demonstrated significant therapeutic or health giving effects when compared with the conventional plant extracts. Some commercially available phytosome products are summarized in the Table 1.

**CONCLUSION**

Phytosomes are novel compounds comprising of lipophilic complexes of components of various plants like Silybum Marianum, Ginkgo Biloba, ginseng etc with phospholipids. Preparation of phytosomes is usually carried out by non conventional method. Absorption of phytosome in gastro intestinal tract is appreciably greater resulting in increased plasma level than the individual component.

<table>
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<tr>
<th>Table 1: Commercially available phytosome products</th>
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<tr>
<td><strong>Product</strong></td>
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<tr>
<td>Ginkoselect phytosome</td>
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<td>Green tea phytosome</td>
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<tr>
<td>Grapeseed phytosome</td>
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<tr>
<td>Panax ginseng phytosome</td>
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<td>Hawthorn phytosome</td>
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<td>Milk thistle phytosome</td>
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