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Phytosome: Phytolipid Drug Delivery System for Improving Bioavailability of Herbal Drug

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ABSTRACT:

Novel Drug Delivery System in the field of medicine had taken a popular attention now a days as it makes the intake, bioavailability and overall therapeutics of a drug easier and in short period of time. In current herbal drugs have been widely used because of their less side effects, cost effectiveness and easy availability. Current review deals one of the herbal Novel Drug Delivery System i.e. Phytolipid Delivery System. It is also called Phytosome. Phytosomes are little cell like structure contain the active ingredients of the herb bounded to phospholipids, mainly phosphatidylcholine. The phospholipid molecular structure includes a water-soluble head and two fat-soluble tails. Because of this dual solubility, the phospholipids act as an effective emulsifier which producing a lipid compatible molecular complex. Phytosomes are herbal formulation which has enhanced the therapeutic effect of the plant extracts and herbal lead molecule by increasing bioavailability in the target site compared to conventional herbal extract. These drug-phospholipid complexes can be formulated in the form of solution, suspension, emulsion, syrup, lotion, gel, cream, aqueous microdispersion, capsule, powder, granules and chewable tablet.

Keywords: Phytosome, Phospholipids, phosphatidylcholine, Bioavailability.

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INTRODUCTION:

Preparations of plants or parts of them were widely used in popular medicine since ancient times and till today the use of phytomedicines is widespread in most of the world's population.^[1] 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. It has often been observed that the separation and purification of the various components of an extract may lead to a partial loss of specific activity for the purified component. Phytosome is a patented technology developed by a leading manufacturer of drugs and nutraceuticals, to incorporate standardized plant extracts or water soluble phytoconstituents into phospholipids to produce lipid compatible molecular complexes, called as phytosomes and so vastly improve their absorption and bioavailability.^[2] The Phytosomes process produces a little cell because of that the valuable components of the herbal extract are protected from destruction by digestive secretions and gut bacteria. 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.^[3] Over the past century, phytochemical and phytopharmacological sciences established the compositions, biological activities and health promoting benefits of numerous plant products. Most of the biologically active constituents of plants are polar or water soluble molecules. However, water soluble phytoconstituents (like flavonoids, tannins, terpenoids etc.) are poorly absorbed either due to their large

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molecular size which cannot absorb by passive diffusion, or due to their poor lipid solubility; severely limiting their ability to pass across the lipid-rich biological membranes, resulting poor bioavailability.^[4] Phytosomes have improved pharmacokinetic and pharmacological parameter which in result can advantageously be 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.^[5] Phytosome is obtained by reacting of soy phospholipids with the selected botanical derivatives in an opportune solvent. On the basis of their physical-chemical and spectroscopic characteristics, these complexes can be considered novel entities.^[6]

PHYTOSOME TECHNOLOGY

Phytosome is also called as Phytolipids delivery system which forms a bridge between the conventional delivery system and novel delivery system. The term "phyto" means plant while "some" means cell-like. The phytosomes 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 the gastro-protective property of phosphatidylcholine. Most of the bioactive constituents of phytomedicines are water-soluble molecules (e.g. phenolics, glycosides, and flavonoids). However, water-soluble phyto-constituents are limited in their effectiveness because they are poorly absorbed^[4] when taken orally or when applied topically. Many approaches have been developed to improve the oral bioavailability, such as inclusion of solubility and bioavailability enhancers, structural modification and entrapment with the lipophilic carriers.^[7-9] Water-soluble phyto-constituent molecules (mainly polyphenols) can be converted into lipid-compatible molecular complexes, which are called phytosomes. This phytosome technology is a breakthrough model for marked enhancement of bioavailability, significantly greater clinical benefit, assured delivery to the tissues, and without compromising nutrient safety.^[2] They have improved pharmacokinetic and pharmacological parameters which are advantageous in the treatment of acute diseases as well as in pharmaceutical and cosmetic compositions.^[5]

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 nutrients. They are miscible both in water and in oil/ lipid environments, and are well absorbed orally. Phospholipids are small lipid molecules in which the glycerol is bonded only to two fatty acids, instead of three as in triglycerides, with the remaining site occupied by a phosphate group.^[10] The phospholipids mainly employed to make phytosomes, is phosphatidylcholine, derived from soybean (*Glycine max*).^[11] The phytosome process has been applied successfully too many popular herbal extracts including *Ginkgo biloba*, grape seed, hawthorn, milk thistle (*Silybummarianum*), green tea (*Theasinensis*) and ginseng (*Panax ginseng*). The flavonoids and terpenoids components of these herbal extracts are able to directly bind to phosphatidylcholine.

PROPERTIES OF PHYTOSOMES

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 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 catechindistearoylphosphotidylcholine complex, there is the formation of H-bonds between the phenolic hydroxyl ends of the phosphatidylcholine moiety. Phosphatidylcholine 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 lipophilic envelope, which shields the polar head of the phospholipid and flavonoid molecule and enables the complex to dissolve in low polarity solvents.^[12,13]

Biological properties

Phytosome are advanced forms of herbal products that are better absorbed, utilized and as a result produce better results

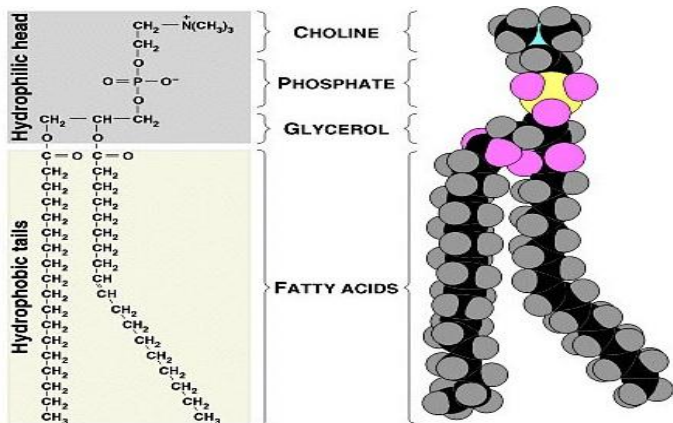


Figure 1: Structure of phosphatidylcholine(PC)

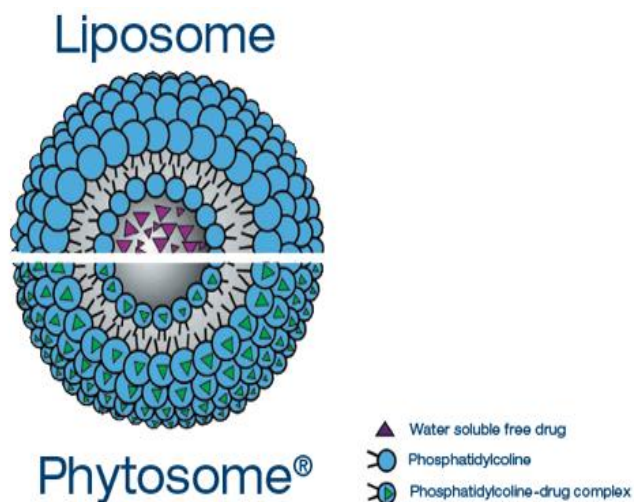


Figure 2: Major difference between liposome and phytosome

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.^[14]

PREPARATION OF PHYTOSOME

1. 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- 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 spray drying.

DEEFERENCE BETWEEN PHYTOSOME AND LIPOSOME^[9]

PYTOSOME	LIPOSOME
Phytosome is a unit of a molecules bounded together.	Liposome is an aggregate of many phospholipid molecules that can enclose other phytoactive molecules but without specifically bonding to them.
Phytosome process the phosphatidylcholine and the plant components actually form a 1:1 or a 2:1 molecular complex depending on the substances (s) complexed. Involving chemical bonds. So they better absorbed and shown better bioavailability.	In liposome 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.
Phytosome complex can somewhat be compared to an integral part of the lipid membrane. Where the polar functionalities of the lipophilic guest interact via hydrogen bonds with the polar head of a phospholipids (i.e. phosphate and ammonium groups). Forming a unique pattern which can be characterized by spectroscopy.	In liposomes. The active principles are dissolved in the central part of the cavity. With no possibility of molecular interaction between the surrounding lipid and hydrophilic substance.
Phytosomes act with the solvent having a reduced dielectric constant such as Acetone, Dioxane, Methylenechloride, Hexane and Ethylacetate etc.	Liposomal drug complex is formed in the presence of the water or buffer solution.

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.^[15]

1. Naringenin-PC complex was prepared by taking naringenin with an equimolar concentration of phosphatidylcholine (PC). The equimolar concentration of PC and naringenin were placed in a 100 mL round bottom flask and refluxed in dichloromethane for 3 h. On concentrating the solution to 5– 10 mL, 30 mL of n-hexane was added to get the complex as a precipitate followed by filtration. The precipitate was collected and placed in vacuum desiccators.^[16]
2. The required amounts of drug and phospholipids were placed in a 100 ml round-bottom flask and dissolved in anhydrous ethanol. After ethanol was evaporated off under vacuum at 40°C, the dried residues were gathered and placed in desiccators overnight, then crushed in the mortar and sieved with a 100 mesh. The resultant silybin- phospholipid complex was transferred into a glass bottle, flushed with nitrogen and stored in the room temperature.^[17]

Common steps of preparation of phytosomes

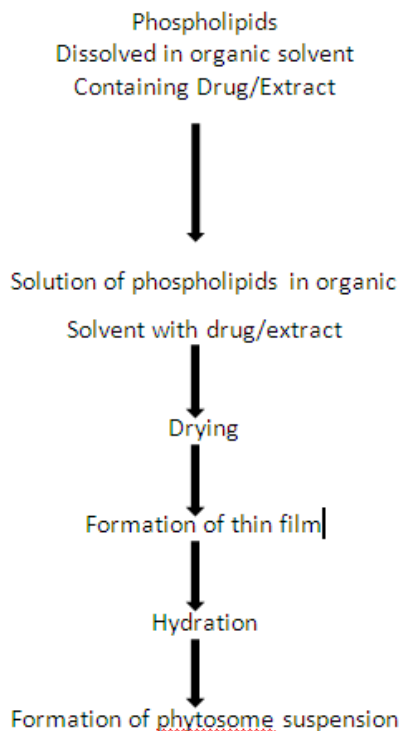


Figure 3: Common stages for preparation of phytosome^[18]

BENEFITES OF PHYTOSOMES^[19, 20, 21]

1. It enhances the absorption of lipid insoluble polar phytoconstituents through oral as well as topical route showing better bioavailability, hence significantly greater therapeutic benefit.
2. Appreciable drug entrapment.
3. Dose requirement is reduced due to absorption of chief constituent.
4. Phosphatidylcholine used in preparation of phytosomes, beside acting as carrier also acts as a hepatoprotective, hence giving the synergistic effect when hepatoprotective substances are employed.
5. Phytosomes shows better stability profile because chemical bonds are formed between phosphatidylcholine molecules and phytoconstituent.
6. Added nutritional benefit of phospholipids.
7. Application of phytoconstituents in form of phytosome improves their percutaneous absorption and act as functional cosmetics.
8. Phytosome process produces a little cell whereby the valuable components of the herbal extracts are protected from destruction by digestive secretions and gut bacteria.
9. Phytosome are been used to give liver protectant flavonoids because they were easily bioavailable.
10. Unlike liposome, chemical bonds are formed between phosphatidylcholine molecule and phytoconstituent, so the phytosome show better stability profile.
11. Their low solubility in aqueous media allows the formation of stable emulsions or creams.
12. Enhanced ability of phytosomes to cross cell membrane and enter cell.
13. Entrapment efficiency is high and more over predetermined because drug itself in conjugation with lipids is forming vesicles.

APPLICATION OF PHYTOSOME

Recent research shows improved absorption and bioavailability with phytosomes as compared to the conventional means. Grape seed phytosome is composed of oligomeric polyphenols (grape proanthocyanidins or procyanidins from grape seed extract, *Vitisvinifera*) of varying molecular size, complexed with phospholipids. The main properties of procyanidin flavonoids of grape seed are an increase in total antioxidant capacity and stimulation of physiological antioxidant defenses of plasma, protection

against ischemia/reperfusion induced damages in the heart, 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.^[22]

Francesco et al., (2009) studied on a recently developed oral formulation in the form of coated tablets (MonoselectCamellia®) (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. Besides the effect on weight and BMI, biochemical parameters (LDL, HDL, and total cholesterol, triglycerides, growth hormone, insulin-like growth factor-1, insulin, and cortisol) were improved in both groups. Leptin, not tested in the diet-only group, was reduced in patients taking MonCam. Taking into consideration the high safety profile of the product and the total absence of adverse effects observed during and after the trial, MonCam appears to be a safe and effective tool for weight loss.^[23]

Mukerjee et al., (2008) 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 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.^[24]

Yanyuet 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.^[15]

Maitiet et al., (2005) developed the quercetin-phospholipid 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.^[25]

Ravarotto 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.^[26]

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.^[27]

Grange et al., (1999) conducted a series of studies on silymarin phytosome, containing a standardized extract from the seeds of *S. marianum*, administered orally and found that it could protect the fetus from maternally ingested ethanol.^[28]

Moscarella et al., (1993) investigated in one study of 232 patients with 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).^[5]

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 edema, inhibition of myeloperoxidase activity, antioxidant and free radical scavenging properties.^[29]

Barzaghi et al., (1990) conducted a 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 results 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 (70-80 % silymarin content).^[30]

CONCLUSION

This review is an attempt to present a concise profile of phytosomes as a delivery system. Phytosomes are novel formulations which offer improved bioavailability of hydrophilic flavonoids and other similar compounds through the skin or gastrointestinal tract. They have many distinctive advantages over other conventional formulations. The formulation methodology for phytosome is simple and can be

easily upgraded to a commercial scale. The characterization methodologies and analytical techniques are well established for this type of novel formulation. Many patents are already approved for innovative formulations, processes and applications of phytosomes. As far as the potential of phytosome technology is concerned, it has a great future for use in formulation technology and applications of hydrophilic plant compounds.

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