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Review Article

PHYTOSOME: A NOVEL DRUG DELIVERY SYSTEM IN THE MIDDLE OF IMPROVED BIO-AVAILABILITY

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Abstract

Novel Drug Delivery System in the field of medicine had taken a popular attention now a day as it makes the intake, bioavaibility and overall therapeutics of a drug easier and in short period of time. In recent times the emerging technology of drug delivery and drug targeting is also being applied to Phytopharmaceuticals. 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 Phytosomes are recently introduced herbal formulations that are better absorbed, and as a result produce better bioavailability and actions than the conventional phytomolecules or botanical extracts. The term "Phyto" means plant while "some" means cell-like. It is also often known as herbosomes. Phytosome technology has been effectively used to enhance the bioavailability of many popular herbal extracts and can be developed for various therapeutic uses or dietary supplements.

Keywords: Phytosome, Phospholipids, Bioavaibility, flavonoids, herbosomes

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 phytoconsituents 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 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 physi-

cal-chemical and spectroscopic characteristics, these complexes can be considered novel entities. [6]

PHYTOSOME 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 phosphatidylcholine molecule binds to these compounds while the lipid soluble phosphatidyl portion comprising the body and tail which then envelopes the choline bound material. Hence, the phytoconstituents produce a lipid compatible molecular complex with phospholipids, also called as phyto-phospholipid complex. Molecules are anchored through chemical bonds to the polar choline head of the phospholipids, as can be demonstrated by

specific spectroscopic techniques. [7-8] Precise chemical analysis indicates the unit phytosome is usually a flavonoid molecule linked with at least one phosphatidylcholine molecule. The result is a little micro sphere or cell is produced. The phytosome 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 gastroprotective property of phosphatidylcholine. [9]

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) complexes, involving chemical bonds. This difference results in phytosome being much better absorbed than liposomes showing better bioavailability. Phytosomes have also been found superior to liposomes in topical and skin care products [10] (Fig. i).

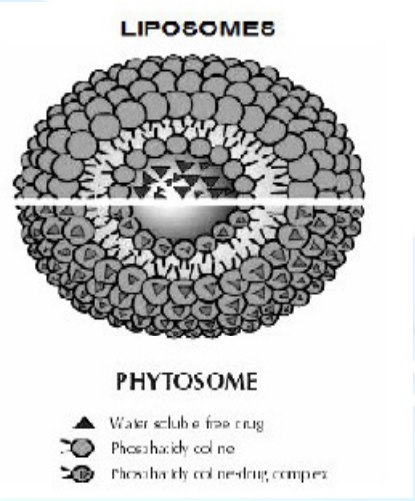

Fig.I Shows difference between liposome and phytosome; The molecular organization of the liposome (upper segment); The molecular organization of phytosomes (lower segment)

PREPARATION OF PHYTOSOME

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 phosphatidyiserine with one mole of component for exampleflavolignanans, 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 from 0.5-2.0 moles. The most preferable ratio of phospholipid to flavonoids is 1:1. [11] 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, dios-

mine, 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 materials 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. [12]

ADVANTAGES OF PHYTOSOMES

Phytosomes have the following advantages [13-14]

- It enhances the absorption of lipid insoluble polar phytoconstituents through oral as well as topical route showing better bioavailability, hence significantly greater therapeutic benefit. As the absorption of active constituent(s) 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 when hepatoprotective substances are employed. Chemical bonds are formed between phosphatidylcholine molecule and phytoconstituent, so the phytosomes show better stability profile.
- Added nutritional benefit of phospholipids.

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-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 liposomial-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 catechindistearoyl phosphatidylcholine 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 [15] (Fig. ii).

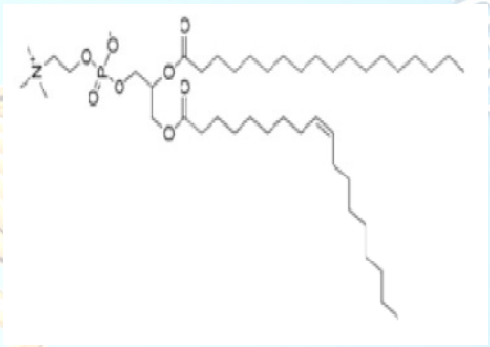

Fig.II Phophatidylcholine containing oleyl and stearoyl side chains.

- **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. [16]

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, per-

centage drug released and chemical composition. [17]

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. [18] 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. [19] Silybin protects the liver by conserving glutathione in the parenchymal cells [18], while PC helps repair and replace cell membranes. [20] 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 impressive bioactivity, albeit limited by poor bioavailability.

Francesco *et al*., (2009) studied on a recently developed oral formulation in the form of coated tablets (Monoselect Camellia®) (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. [21]

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 asustained 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. [22]

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 silybinphospholipid complex due to an impressive improvement of the lipophilic property of silybin-phospholipid complex and improvement of the biological effect of silybin. [23]

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. [24] 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. [25]

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. [14] 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. [26]

Barzaghi *et al.*, (1990) conducted a human study designed to assess the absorption of silybin when directly bound to phosphatadylcholine. 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). [27]

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). [28]

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. [29] Grape seed phytosome is composed of oligomeric polyphenols (grape proanthocyanidins or procyanidins from grape seed extract, Vitis vinifera) 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. [30]

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 benificial activities such as antioxidant, anticarcinogenic, antimutagenic, antiatherosclerotic, hypocholesterolemic, cardioprotective, antibacterial and anticariogenic effects. Despite such potential actions green tea polyphenols have very poor oral bioavailability from conventional extracts. The complexation 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 nonphytosomal extract. Antioxidant capacity was measured as TRAP (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. [31-32] Commercial product of phytosomes prepared from herbs available in market is shown in Table i.

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. This means more amount of active constituent becomes present at the site of action (liver, brain, heart, kidney etc) at similar or less dose as compared to the conventional plant extract. Hence, the therapeutic action becomes enhanced, more detectable and prolonged. Several excellent phytoconstituents have been successfully delivered in this way exhibiting remarkable therapeutic efficacy in animal as well as in human models. 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. These extracts can be standardized accordingly and may be formulated as phytosomes for systematic investigation for any improved potential to

be used rationally. In this way after screening and selection of potential extracts or constituents from plants, phytosomes can be developed for different therapeutic purposes like cardiovascuar, anti-inflammatory, immunomodulator, anticancer, antidiabetic etc or for prophylactic and health purposes as nutraceuticals, in due course.

Table I: Commercial Phytosome Products [9, 10, 32]

S. No	Phytosomes	Phytoconstituents complexed	Dose*	Indications
1	Silybin PhytosomeTM	Silybin from *Silybum marianum*	120 mg	Hepatoprotective, antioxidant for liver and skin
2	Ginkgo PhytosomeTM	24 % ginkgoflavonoids from *Ginkgo biloba*	120 mg	Protects brain and vascular linings, anti skin ageing
3	Ginseng PhytosomeTM	37.5 % ginsenosides from *Panax ginseng*	150 mg	Nutraceutical, immunomodulator
4	Green Tea PhytosomeTM	Epigallocatechin from *Thea sinesis*	50-100 mg	Nutraceutical, systemic antioxidant, anticancer
5	Grape Seed PhytosomeTM	Procyanidins from *Vitis vinifera*	50-100 mg	Nutraceutical, systemic antioxidant, cardioprotective
6	Hawthorn PhytosomeTM	Flavonoids from *Crataegus sp*	100 mg	Nutraceutical, cardioprotective and antihypertensive
7	Olive oil Phytosome	Polyphenols from *Olea europaea* oil		Antioxidant, anti-inflammatory, anti-hyperlipidemic
8	Echinacea Phytosome	Echinacosides from *Echinacea augustifolia*		Nutraceutical, immunomodulator
9	Centella Phytosome	Terpenes		Vein and Skin disorders
10	Palmetto berries Phytosomes	fatty acids, alcohols and sterols		Non-cancerous prostate enlargement.
11	Super Milk thistle Extract	Silybin from Silymarin Food Product		antioxidant for liver and skin
12	Bilberry Phytosomes	extract of bilberry which provides anthocyanosides		Improve capillary tone, reduce abnormal blood vessel permeability, and are potent antioxidants

**Specified in marketed formulation*

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