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Recent Trends of Phytosomes for Delivering Herbal Extract with Improved Bioavailability

Arijit Gandhi [1*], Avik Dutta [1], Avijit Pal [1], Paromita Bakshi[1]

1. Gupta College of Technological Sciences, Ashram more, G.T. Road, Asansol-713301, West Bengal, India. [E-mail: arijit.babugandhi.gandhi@gmail.com]

In the recent days, most of the prevailing diseases and nutritional disorders are treated with natural medicines. The effectiveness of any herbal medication is dependent 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 whereby 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. The present review represents the recent advances and applications of various standardized herbal extract phytosomes as a tool of drug delivery.

Keyword: Herbal extracts; Bioavailability; Phytosomes; Herbal Drug delivery.

1. 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]. 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[4].

1.1 Phytosomes

Phytosome is also called as Phytolipids delivery system which forms a bridge between the convectional delivery system and novel delivery system. It is a newly introduced patented technology developed by Indena to incorporate standardized plant extracts or water soluble phytoconstituents into phospholipids to produce lipid compatible molecular complexes, which enhances their absorption and bioavailability. The term "phyto" means plant while "some" means cell-like, often referred as herbosome in certain literature. The Phytosome technology produces a little cell, 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. in such a way it protects the valuable components of the herbal extract 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. When different phytoconstituents such as flavonoids, terpenes & saponins forms reversible complexes with phospholipids, they shown that their anti-inflammatory and vasokinetic activities are higher and long lasting than those observed after administration of same amount of substance in free form. This is mainly due to the complexation of active ingredients with phospholipids[5,6].

1.2 Phytosome technology:

The water soluble constituents (flavonoids and terpenoid) of plant extracts have the affinity to bind directly with phosphatidylcholine. A stoichiometric amount of phosphatidylcholine (phospholipid) is allowed to react with standard extract in a non-polar solvent. Phosphatidylcholine being a bifunctional compound possessing a lipophilic phosphatidyl moiety and hydrophilic choline moiety helps in improvement of bioavailability of water soluble phytoconstituents (like simple flavonoids). The hydrophilic moiety (choline group) binds with water soluble phytoconstituents and forms the body while as lipid soluble phosphatidyl moiety forms tail and envelops the choline bound material. As a result, a lipid compatible molecular complex is formed called phytosome. The molecules are bound to polar choline moiety of phosphatidyl choline through chemical bonds which can be demonstrated by specific spectroscopic techniques[7,8].

1.3 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 ^{1}H-NMR and ^{13}C-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 flavonoid molecule and enables the complex to dissolve in low polarity solvents[9].

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[10].

1.4 Advantages of phytosome technology:

The phytosome technology has revolutionized the nutraceutical industry by serving the following benefits[11,12].

- Phosphatidylcholine, one of the components of phytosome, has a dual function that it acts a carrier as well as has a health benefit such hepatoprotective effect.
- The composition of phytosome is safe and the components are approved for pharmaceutical use.
- The absorption and bioavailability of water soluble phytoconstituents is increased. This results in better therapeutic effects.
- Because the bioavailability of phytoconstituents is increased, therefore, the dosage required to produce desirable effect is reduced.
- The phytosomes have a better stability than liposomes. This is because the former consists of chemical bonds while as it is absent in the later.
- Phospholipids add to the nutritional value of the plant extract.
- High market demand for products.
- The process of manufacturing phytosomes is relatively simple.
- Phytosomes have the ability to permeate through skin with quite ease and thus enhances their effectiveness.
- The water soluble phytoconstituents are enveloped by phospholipid which prevents them from destruction by digestive enzymes and gut bacteria. It helps in proper drug delivery to targeted tissue.
- Phosphatidylcholine nourishes skin besides acting as a carrier because it is part of cell membrane.
- They can be used for systematic targeting as phytosomes are able to transit from hydrophilic environment into lipophilic environment of enterocyte cell and from there into cell.

2. Methods of preparation:

Mareno and Lampertico (1991), Jiang *el al*. (2001), Maiti *el al*. (2006) and Maiti *el al*. (2007) reported the methods of phytosome preparation. Phytosomes are prepared by, complexing polyphenolic phyto-constituents in 1:2 or 1:1 ratio with phospholipids. Phospholipids that can be used may be either vegetable or synthetic in nature. Generally phytosomes are prepared by reacting 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 (n-hexane) or lyophilization or by spray drying. The ratio between these two moieties in the complex formation of phytosomes is in the range from 0.5-2.0 moles. The most preferable ratio of phospholipid to flavonoids is 1:1. Silybin- phospholipid complex was prepared by Yanyu *el al*. (2006) using ethanol as a reaction medium. Silybin and phospholipids were resolved into the medium, after the organic solvent was removed under vacuum condition, silybin phospholipid complex was formed. 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[13-15].

In the phytosome preparations, flavonoids are selected from the group consisting of vitexine, quercetin, kaempferol, quercretin-3, luteolin, rhamnoglucoside, quercetin-3-rhamnoside, hyperoside ,diosmin, 3- rhamnoside, (+) catechin, (-) epicatechin, apigenin-7-glucoside, luteolin glucoside, ginkgonetine, isoginkgetin and bilobetine. Selection of phospholipids is done

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 mostly derived from palmitic, stearic, oleic and linoleic acid[16].

2.1 Characterization of phytosome:

The behavior of phytosomes in both physical and biological system is governed by the factors such as physical size, membrane permeability; percentage entrapped solutes, chemical composition, quantity and purity of the starting materials. Therefore, the phytosomes are characterized for physical attributes like shape, size, distribution, percentage drug capture entrapped volume, percentage drug released and chemical composition. Complexation and molecular interactions between phytoconstituents and phosphatidylcholine in solution have been studied by ^{1}H-NMR, ^{13}C-NMR, ^{31}P-NMR, as well as by IR spectroscopy. Thermal gravimetric analysis (TGA) and differential scanning calorimetry (DSC) are other techniques employed for the detection and measurement of thermal effects such as fusion, solid–solid transitions, glass transitions, loss of solvent, and decomposition to characterize a solid phytosome. Further NMR data available on the marketed phytosomes also indicates that 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 envelope the polar head of the phospholipids and the herbal extract[17-20].

2.2 Difference between phytosomes and liposomes:

Phytosome products, after numerous studies prove that they are markedly better absorbed and have substantially greater clinical efficacy over niosomes and now a day's companies have successfully applied this technology to a number of standardized flavonoid preparations. The following table shows the major differences between phytosome and liposome.

Table 1: Table showing difference between phytosome and liposome

Property	Phytosome	Liposome	References
Bonding	It is a unit of few molecules bonded together	It is an aggregate of many phospholipid molecules that encloses other phytoactive molecules without specifically bonding to them.	21
Bioavailability and Absorption	It has much better bioavailability and absorption	Its bioavailability and absorption is lesser than phytosome.	14
Arrangement of molecules	In phytosome, phospholipid (phosphatidylcholine) and an individual phytoconstituent are present in 1:1 or 2:1 ratio depending on the substance.	In liposomes, hundreds and thousands of phosphatidylcholine molecules surround the water soluble molecule.	22

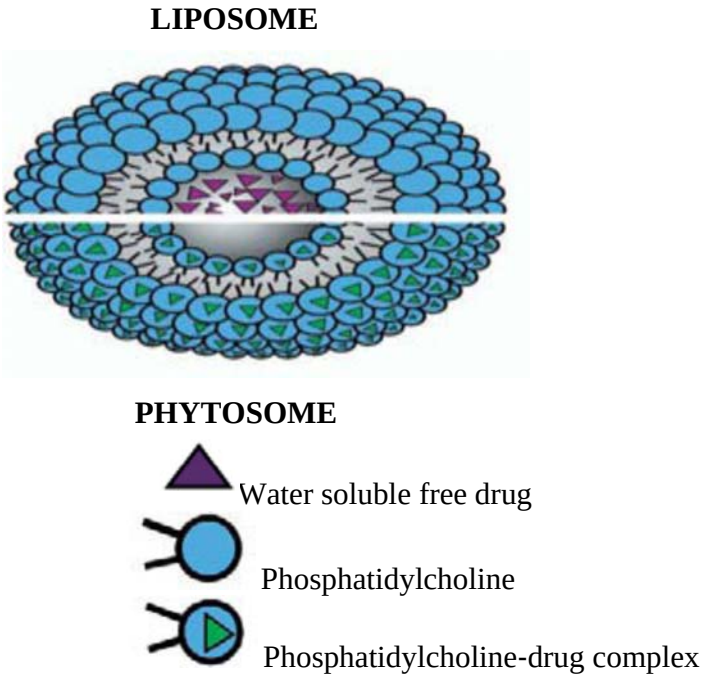

Fig 1: Major difference between liposome and phytosome. The molecular organization of the liposome (upper segment) versus many individual phytosomes (lower segment).

2.3 Improved bioavailability of phytosome and its importance:

The phytosome process has been applied to many popular herbal extracts including *Ginkgo biloba*, grape seed, hawthorn, milk thistle, green tea, and *ginseng* and recent research shows improved absorption and bioavailability with phytosomes as compared to the conventional means. Many standardized extract containing flavonoids and polyphenolics have been reported with improved bioavailability when incorporated in photosomal preparation. Silymarin is some of the most studied drug for the better delivery of silybin by forming silybin phospholipid complex. Yanyu *el 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 due to an improvement of the lipophilic property of silybin-phospholipid complex[23]. Tedesco *el al*. (2004) reported Silymarin phytosome with better anti-hepatotoxic activity than Silymarin alone and can provide protection against the toxic effects of aflatoxin B_1 on performance of broiler chicks[24]. Barzaghi *el 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[25].

Studies have shown ginkgo phytosome (prepared from the standardized extract of *Ginkgo biloba* leaves) produced better results compared to the conventional standardized extract from the plant (GBE, 24% ginkgo flavone glycoside and 6% terpene lactones). In a bioavailability study conducted with healthy human volunteers the levels of GBE constituents (flavonoids and terpene) from the phytosome form peaked after 3 hours and persisted longer for at least 5 hours after oral administration. It was found that the phytosome GBE produced a 2-4 time's greater plasma concentration of terpenes than did the

non-phytosome GBE. Its major indications are cerebral insufficiency and peripheral vascular disorders, and it also can ameliorate reduced cerebral circulation. Its improved oral bioavailability and good tolerability makes it the ideal ginkgo product even for long term treatment. Studies with ginkgo phytosome in patients with peripheral vascular disease (e.g. Raynaud's disease and intermittent circulation) have shown to produce a 30-60% greater improvement compared to regular standardized GBE[26].

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[27].

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[28].

A standardized *Green tea* extract generally contains a 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 and also got several long term beneficial activities such as antioxidant, anticarcinogenic, antimutagenic, antiatherosclerotic, hypocholesterolemic, cardioprotective, antibacterial and anticariogenic effects. Despite such potential actions, to improve their poor oral bioavailability polyphenols are complexed with phospholipids[29].

Maiti *el al*. developed the quercetin-phospholipid phytosome 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[30].

A novel hesperetin was developed by (by Mukherjee *el al*., 2008) combining and complexing hesperetin with hydrogenated phosphatidyl choline. Mukherjee *el al*. (2008) also studied its antioxidant activity and pharmacokinetic studies in $CC1_4$ intoxicated rats along. The results of the study showed the phytosome has shown high antioxidant activity. Pharmacokinetic studies have revealed the improved bioavailability of phytosomes than the parent molecule at the same dosage[31].

Recently much amount of work is going on various new standardized herbal extract to formulate into more bioavailable phytosomes. Extract of *Serenoa repens* (CO_2 extract) extract of *Vaccinium myrtillus* (Fruit extract), extract of *Coleus forskohlii*, Ximenoil and Ximenynic acid extracted from *Santalum album*, Esculoside, glycosylated coumarin obtained from *Aesculus hippocastanum*, Ruscogenins, group of saponins extracted from *Ruscus aculeatus* are highly worked upon for better bioavailability through the formation of phytosomes by patented process[32].

In this way different phytosome products have demonstrated significant therapeutic or health giving effects when compared with the conventional plant extracts.

Commercially available phytosome products:

Some commercially available phytosome products are given in table 2.

Table 2: Commercially available phytosome products[14,28,32].

Sl.no	Phytosome product	Phytoconstituent complexed with phosphatidylcholine	Dose	Indications
1	Silybin Phytosome™	Silybin from *Silybum marianum* .	120 mg	Hepatoprotective, antioxidant for liver and skin.
2	Hawthorn Phytosome™	Flavonoids from *Crataegus* sp.	100 mg	Nutraceutical .Best choice in heart disease or high blood pressure.
3	Ginseng Phytosome™	37.5 % ginsenosides from immunomodulator *Panax ginseng*	150 mg	Nutraceutical, Immunomodulator
4	Green Tea Phytosome™	Epigallocatechin from *Thea sinensis*	50 to 100 mg	Nutraceutical, Systemic antioxidant. Best choice for protection against cancer and damage to cholesterol.
5	Ginkgo Biloba Phytosome™	24 % Ginkgoflavonglycosides from *Ginkgo biloba*	120 mg	Protects brain and vascular lining; Anti-skin ageing agent. Best choice for most people over the age of 50.
6	Grape Seed Phytosome™	Procyanidins from *Vitis vinifera*	50-100 mg	Nutraceutical, systemic antioxidant. Best choice for most people under age of fifty. Also specific for the eyes, lungs, diabetes, varicose veins, and protects against heart disease.
7	Bilberry Phytosomes	Extract of *Bilberry* which provides anthocyanosides	_	Improve capillary tone, reduce abnormal Bloodvessel permeability, and are potent antioxidants.
8	Super Milk thistle Extract™	Silybin from *Silymarin* Food Product	150 mg	Antioxidant for liver and skin
9	Centella Phytosome	Terpenes	_	Used to treat Vein and Skin disorders
10	Palmetto berries Phytosomes	Fatty acids, alcohols and sterols	_	Used for the treatment of Non-cancerous Prostate enlargement.
11	Olive oil Phytosomes	Polyphenols from *Olea europaea* oil	_	Inhibit oxidation of LDL cholesterol, and also have anti-inflammatory activity.
12	Echinacea Phytosome	Echinacosides from *Echinacea angustifolia*	_	Nutraceutical, Immunomodulator
13	Sericoside Phytosome	Sericosides from *Terminalia sericea*	_	Skin Improver
14	Echinacea Phytosome	Echinacosides from *Echinacea angustifolia*	_	Immunomodulator, nutraceuticals
15	Visnadine Phytosome	Visnadine from *Ammi visnaga*	_	Circulation Improver

3. Conclusions

Phytosomes forms a bridge between the convectional 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 pharmacokinetic and pharmacological parameter, which in result can advantageously be used in various diseases. The nutraceutical products based on phytosome technology become present at the site of action of liver, kidney, brain, heart) at similar or less dose as compared to conventional plant extract. Phytosomes have wide scope in cosmetology and many areas of them are to be revealed in future in the prospect of pharmaceutical application.

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