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Review Article

PHYTO SOMES: A NOVEL PHYTO-PHOSPHOLIPID CARRIERS FOR HERBAL DRUG DELIVERY

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ABSTRACT
Advanced biochemical and pre-clinical studies have proved the potential of plant flavonoids, polyphenolics and other hydrophilic natural compounds for the treatment of skin disorders, different types of carcinoma, anti-aging and many other areas of therapeutics and preventive medicine. The hydrophilic nature and unique chemical structure of these compounds pose major challenge because of their poor bioavailability through the skin or gut. The bioavailability can be improved by the use of delivery systems, which can enhance the rate and the extent of drug solubilizing into aqueous intestinal fluids as well as the capacity to cross the lipid rich biomembranes. Phospholipid based drug delivery systems have been found promising for the effective and efficacious herbal drug delivery. Complexing the polyphenolic phytoconstituents in molar ratio with phosphatidylcholine results into a new herbal drug delivery system- "Phytosome". Phytosomes show better pharmacokinetic and therapeutic profile than conventional herbal extracts.
KEYWORDS: Phytosomes; Polyphenolics; Herbal Drug delivery; Phospholipid complex; Herbal extracts; Bioavailability; Flavonoids

INTRODUCTION

Most of the herbal drug bioactive constituents are water soluble molecules. However, water soluble phytoconstituents like many flavonoids, polyphenolic compounds are poorly absorbed[1] either due to their multiple-ring large size molecules which cannot 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 can be converted into lipid-compatible molecular complexes, which are called phytosomes or herbosomes.

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). Phosphatidylcholine, the principal molecular building block of cell membranes, is miscible both in water and in oil or lipid environments, and is 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[3].

Phytosomes have improved pharmacokinetic and pharmacological parameters, which in result can advantageously be used in the treatment of 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[6]. PC is miscible both in the water phase and in oil/lipid phases, and is excellently absorbed when taken by mouth. PC is the principal molecular building block for cell membranes (Fig. 1), and the molecular properties that suit PC for this role also render it close to ideal for its phytosome role.

Phosphatidylcholine is registered in 53 countries. Its main application nowadays lies in the intravenous treatment and prevention of fat embolisms in polytraumatized patients in the treatment of metabolic disorders and as a liver-protecting substance[7].

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[4].

The phytosome process has been applied to many popular herbal extract including *Ginkgo biloba*, grape seed, hawthorn, milk thistle (*Silybum marianum*), green tea (*Thea sinensis*) and ginseng (*Panax ginseng*). The flavonoid and terpenoid components of these herbal extracts lend themselves quite well for the direct binding to phosphatidylcholine. The present article reviews the various aspects and the latest trends of phytosomal

research on a variety of plant materials for potential therapeutic uses.

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, 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 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 [(8)]. 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, 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[9].

MECHANISM OF PHYTOPHOSPHOLIPID COMPLEX FORMATION

The poor absorption of flavonoid nutrients is likely due to two main factors. First, these are multiple ring molecules not quite small enough to be absorbed from the intestine into the blood by simple diffusion, nor does the intestinal lining actively absorb them, as occurs with some vitamins and minerals. Second, flavonoid molecules typically have poor miscibility with oils and other lipids. This severely limits their ability to pass across the lipid-rich outer membranes of the enterocytes, the cells that line the small intestine. The phytosome technology meets this challenge. 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. 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 phytophospholipid complex. Molecules are anchored through chemical bonds to the polar choline head of the phospholipids, as can be demonstrated by specific spectroscopic techniques. Precise chemical analysis indicates the unit phytosome is usually a flavonoid molecule linked with at least one phosphatidylcholine molecule. The result is a little microsphere or cell is produced[10].

Likewise (Fig.2) 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) complexed, involving chemical bonds. This difference results in phytosome being much better absorbed than liposomes showing better bioavailability. Phytosomes also have been found superior to liposomes in topical and skin care products[11].

ADVANTAGES OF PHYTOSOMES

Phytosomes have the following advantages

- 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.
- Phytosome are widely used in cosmetics due to their more skin penetration and high lipid profile.
- Low risk profile- The toxicological profiles of the phospholipids are well documented in the scientific literature[12, 13].

- Better bioavailability: better results.

PROPERTIES OF PHYTOSOMES

Physico chemical properties

Phytosomes is a complex between a natural product and natural phospholipids, like soy phospholipids. 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 catechin distearoyl phosphatidylcholine complex, in this there is the formation of H-bonds between the phenolic hydroxyls of the flavones moiety and the phosphate ion on the phosphatidylcholine side[14].

Pharmacological 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 phytosomes over the non complexed botanical derivatives has been demonstrated by pharmacokinetics studies or by pharmacodynamic tests in experimental animals and in human subjects[15].

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[16].

EVALUATION OF PHYTOSOMES

Various spectroscopic, in-vitro and in-vivo evaluations are applied on herbosomes. These phytosomal complexes can be characterized by Transmission Electron Microscopy (TEM), 1HNMR, 13C-NMR, 31P-NMR and FT-IR. Models of in-vitro and in-vivo evaluations are selected on the basis of expected therapeutic activity of biologically active phytoconstituents present in phytosomes. Complexation increases the activity of the active principle. A chemical spectral characteristic is determined in phospholipids complexes using IR and UV spectroscopic study. Liquid chromatography/atmospheric pressure chemical ionization mass spectrometry (LC/APCI-ITMS) proved to be a very powerful tool for pharmacokinetic studies of phytochemicals. This technique is applied to evaluate the levels of ginkgolides A and B and bilobalide in plasma of volunteers after administration of *Ginkgo biloba* extracts in free (Ginkgoselect) or phospholipid complex (Ginkgoselect Phytosome) forms. The effects of Ginkgo biloba dimeric flavonoids in Phytosome form on the vasomotor activity and skin microcirculation of the cheeks, hands, limbs and female breast are studied in human subjects by Infrared-Photo-Pulse-Plethysmography, Laser Doppler Flowmetry, High Performance Contact Thermography, Computerized Videothermography, and Optic Probe Videocapillaroscopy. In-vivo studies are performed on Beagle dogs, rodents, wistar rats to compare pharmacokinetics parameters between pure extracts and its phospholipid complex[27, 28].

APPLICATION OF PHYTOSOMES

Silymarin phytosome

Most of the phytosomal studies are focused to *Silybum marianum* (milk thistle) which contains
premier liver protectant flavonoids.

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].

Tedesco et al. (2004) 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[18].

Phytosomes of curcumin

Maiti et al. (2006) developed the phytosomes of curcumin (flavonoid from turmeric, *Curcuma longa*) and naringenin(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[19,20].

Quercetin-phospholipid phytosomal complex

Maiti et al. (2005) developed the quercetinphospholipid 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[21].

Some of the marketed phytosome products are list out in the Table.1.

CONCLUSION

A Phytosome is a complex between polar polyphenolics and dietary phospholipids that shows definite physicochemical and spectroscopic features. Recent technology of drug delivery when applied to botanicals open new avenues to explore maximum therapeutic potential of plant substances of polar nature. Phytosomal complexes were first investigated for cosmetic applications, but mounting evidence of potential for drug delivery has been cumulated over the past few years, with beneficial activity in the realms of cardiovascular, anti-inflammatory, hepatoprotective and anticancer applications. Standardized plant extracts or mainly polar phytoconstituents like flavonoids, terpenoids, tannins, xanthones when complexed with phospholipids like phosphatidylcholine give rise to a new drug delivery technology called phytosome showing much better absorption profile following oral administration owing to improved lipid solubility which enables them to cross the biological membrane, resulting enhanced bioavailability. Phytosomes have improved pharmacokinetic and pharmacological parameter, which in result can advantageously be used in treatment of various acute diseases as 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.

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Table.1: SOME MARKETED PHYTOSOMES PREPERATIONS AND APPLICATIONS[9, 22, 23]

S.No	Phytosome Products	Phytoconstituents complex	Daily dosage	Indications
1	Silybin Phytosome	Silybin from *Silybum marianum*	120 mg	Hepato protective, antioxidant
2	Siliphos Milk thistle Phytosome	Silybin from *Silybum marianum*	150 mg	Antioxidant, Hepato protective
3	Grape Seed (Leucoselect) Phytosome	Procyanidins from *Vitis vinifera*	50-300 mg	Antioxidant, Anticancer
4	Ginseng Phytosome	Ginsenosides from *Panax ginseng*	150 mg	Immunomodulator
5	Hawthorn Phytosome	Flavonoids from Crataegus species	100 mg	Antihypertensive, Cardio protective
6	Sericoside Phytosome	Sericosides from *Terminalia sericea*	___	Skin improver, Anti-Wrinkles
7	Ginkgo select Phytosome	Flavonoids from *Ginkgo biloba*	120 mg	Anti ageing, Protects brain and Vascular liling
8	Olea select Phytosome	Polyphenols from *Olea europea*	___	Antihyperlipidemic, Anti inflammatory
9	Greenselect Phytosome	Epigallocatechin from *Thea sinesis*	50-300 mg	Anticancer, Antioxidant
10	Echinacea Phytosome	Echinacosides from *Echinacea angustifolia*	___	Immunomodulatory, nutraceuticals
11	Bilberry (Mertoselect) Phytosome	Anthocyanosides from *Vaccinium myrtillus*	___	Antioxidant, improvement of capillary tone
12	Palmetto (Sabalselect) Phytosome	Fatty acids, alcohols and sterols from *Serenoa repens*	___	Antioxidant, benign prostatic hyperplasia
13	Visnadine (Visnadax) Phytosome	Visnadine from *Ammi visnaga*	___	Circulation improver, Vasokinetic
14	Centella Phytosome	Terpens from *Centella asitica*	___	Brain tonic, Vein and Skin disorders
15	Glycyrrhiza Phytosome	18-beta glycyrrhetinic acid from *Glycyrrhza glabra*	___	Anti inflammatory, Soothing
16	Melilotus (Lymphaselect) Phytosome	Triterpens from *Melilotus officinalis*	___	Hypotensive, indicated in Insomnia
17	Curcumin (Merivaselect) Phytosome	Polyphenols from *Curcuma longa*	200-300 mg	Cancer chemopreventive agent
18	Mertoselect Phytosome	Polyphenols, Antcinoside from *Vaccinium myrtilus*	___	Antioxidant
19	PA_2 Phytosome	Proanthocyanidin A_2 from horse chestnut bark	___	Anti-wrinkles, UV protectant
20	Escin ß-sitosterol Phytosome	Escin ß-sitosterol from horse chestnut fruit	___	Anti-oedema
21	Ximilene and Ximenoil Phytosomes	Ximilene and Ximenoil from *Santalum album*	___	Skin smoother, Microcirculation improver
22	Zanthalene Phytosome	Zanthalene from *Zanthoxylum bungeanum*	___	Soothing, anti-irritant, Anti-itching
23	Ruscogenin Phytosome	Steroid saponins from *Ruscus aculeatus*	___	Anti inflammatory, Improver Skin circulation
24	Curbilene Phytosome	Curbilene from Cucurbita pepo seeds	___	Skin care, Matting agent
25	Esculoside Phytosome	Esculoside from *Aesculus hippocastanum*	___	Vasoactive, Anticellulite, Microcirculation improver

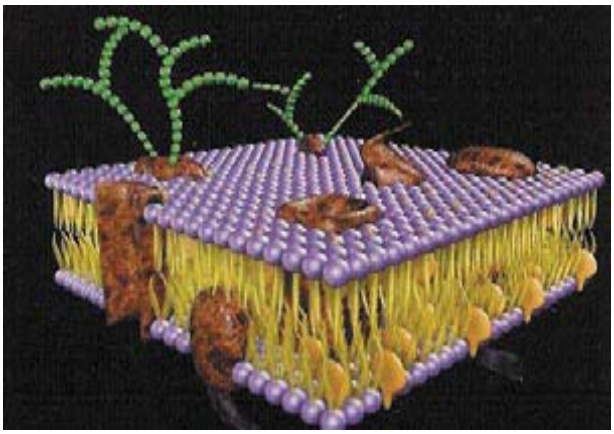

Fig. 1: Cell membranes are largely lipid phase. A double molecular layer consisting of PC and other phospholipids provides a continuous matrix into which the proteins insert.

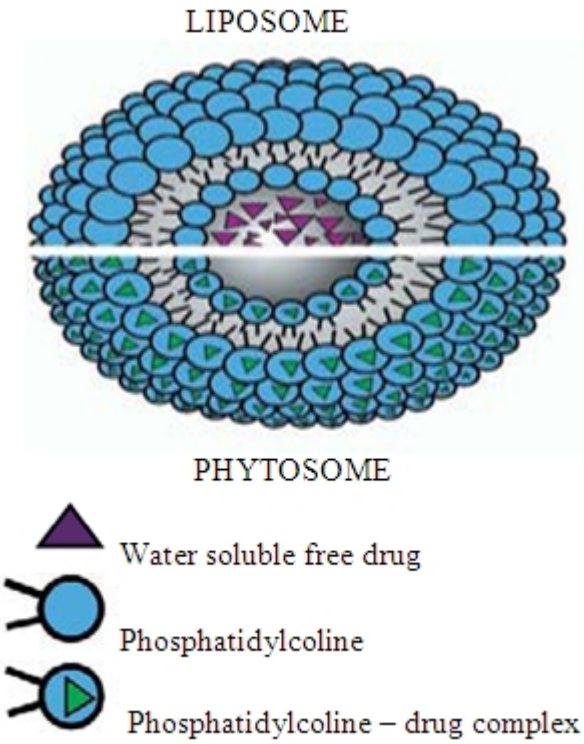

Fig.2 Major difference between liposome and phytosome. The molecular organization of the liposome (upper segment) versus many individual phytosomes (lower segment).