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Review Article

Phytosome: Drug Delivery System for Polyphenolic Phytoconstituents

Anupama Singh[a,*], Vikas Anand Saharan[b], Manjeet Singh[a], Anil Bhandari[a]

[a]*Jodhpur National University, Boranada, Jodhpur, Rajasthan, India*
[b]*Sardar Bhagwan Singh Post Graduate Institute of Biomedical Sceinces and Research, Balawala, Dehradun, Uttarakhand, India*

Abstarct

Several plant extracts and phytoconstituents, despite having excellent bioactivity *in vitro*, demonstrate less or no *in vivo* actions due to their poor lipid solubility or improper molecular size or destruction in gut. Drug delivery system for polyphenolic phytoconstituents (phytosomes) was prepared by complexing polyphenolic phytoconstituents with phospholipid mainly phosphatidylcholine which bind components to each other on a molecular level. Bioavailability is enhanced due to their capacity to cross the lipid rich bio-membranes and to protect the valuable components of the herbal extract from destruction by digestive secretions and gut bacteria. Phytosomes have the capacity to deliver the standardized plant extracts and phytoconstituents through several routes of drug administration. Only a few natural drugs have been formulated and are available in the market as phytosomes. With wide range of applications of phytosomes numerous studies are undergoing and lots more is expected in the forthcoming years. The techniques used for such formulations are patentable and highly profitable.

Keywords: Absorption; Bioavailability; Phytoconstituents; Phytosomes; Stability.
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1. Introduction

Phytosomes, complex of natural active ingredients and phospholipid(s), increase absorption of herbal extracts or isolated active ingredients when applied topically or orally. Phytosomes are cell like structures which result from the stoichiometric reaction of the phospholipids (phosphatidylcholine, phosphatidylserine, etc.) with the standardized extract or polyphenolic constituents (like flavonoids, terpenoids, tannins, xanthones) in a non-polar solvent, which are better absorbed, utilized and as a result produce better results than conventional herbal extracts [1-3]. Phospholipids are the main building blocks of life and are one of the major components of cellular membranes. In general, they are considered as natural digestive aid and carriers for both polar and non-polar active substances [4, 5]. Most of phospholipids possess nutritional properties, like phosphatidylserine which acts as a brain cell nutrient, phosphatidylcholine which is important in liver cell regeneration. Soya

*Corresponding Author: Anupama Singh; Assistant Professor & Head, Department of Pharmacognosy, Jodhpur National University, Boranada, Jodhpur, Rajasthan, India.
Mobile: (+91)-9799398906;
E-mail: anupama.cognosy@gmail.com

phospholipids have lipid reducing effect and hydrogenated phospholipids serve as basis for preparation of stable liposomes because of their amphiphilic charater [4, 6].

Many plant extracts and phytochemical constituents possess excellent biological activity *in vitro*, but demonstrate less or no *in vivo* activity due to inherent property of drug constituents like poor lipid solubility, improper molecular size, destruction in gut, etc. [1]. These problems lead to decreased absorption. Decreased absorption problems can be alleviated by preparing complexes with phospholipids. Thus, phytosomal formulations enhance the bioavailability of active phytochemical constituents as they are now permeable and can cross the lipid rich bio-membranes quite easily, and the active components of the herbal extracts are well protected from destruction by digestive secretions and gut bacteria. Therefore, with help of phytosomal preparations, the amount of standardized plant extracts and phytoconstituents administered in body through several routes are required in less amount for good therapeutic activity [2].

With the advancements in science, the phytosomes have gained importance in various fields like pharmaceuticals, cosmeceuticals and nutraceuticals in preparing different formulations such as solutions, emulsion, creams, lotions, gels, etc. Several companies involved in production and marketing of phytosomal products are Indena, Jamieson natural resources, Thorne Research, Natural factors, and Natures herb [7]. Some of the marketed formulations are shown in Table 1.

2. Phytosome *vs* liposome: similarities and differences

A liposome is formed by mixing a water-soluble substance with phosphatidylcholine. No chemical bond is formed; molecules of phosphatidylcholine collectively surround the water-soluble substance. Hundreds or even thousands of phosphatidylcholine molecules surround the water-soluble compound. In contrast, phytosome is formed by mixing a water-soluble substance with phosphatidylcholine and here chemical bond is formed between individual plant components and phosphatidylcholine.

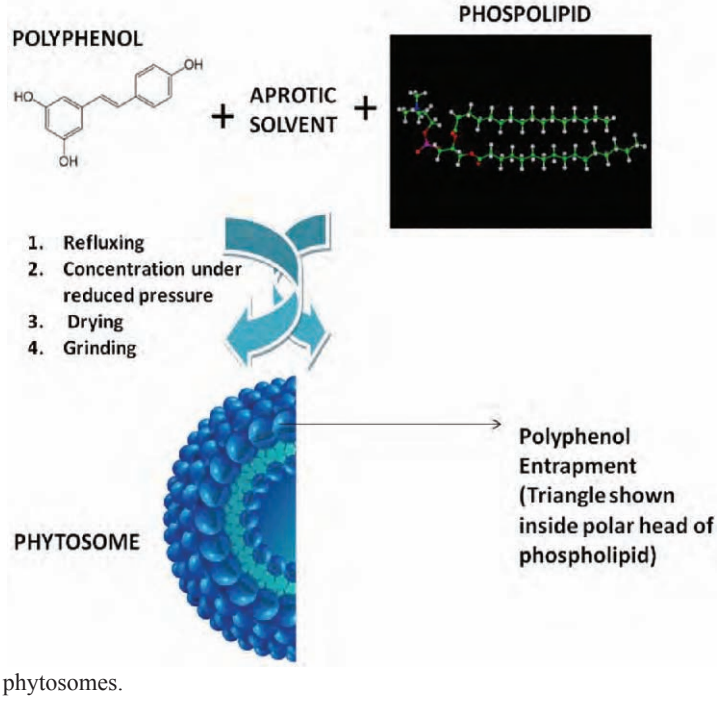

Figure 1. Preparation of phytosomes.

Soichiometric 1:1 or 2:1 complexes form which depend on the extract or phytoconstituent and the phospholipid used. This difference results in increased absorption of active constituents from phytosome than from liposomes [2, 3, 8, 9].

3. Strenghts of phytosome

- Phytosomes show better stability as chemical bond is formed between phsospholipid molecule and phytoconstituent(s).
- Dose of phytoconstituents is reduced due to more bioavailability of the phytoconstituents in the complex form.
- Duration of action is increased.
- Phytoconstituents complex with phospholipids are more stable in gastric sections and resist the action of gut bacteria.
- Enhanced permeability of phytoconstituents across the biological membranes.
- Absorption of lipid insoluble polar phytoconstituents through different routes shows better absorption, hence shows significantly higher therapeutic effects.
- Phoshatidylcholine used in the formation of phytosomes, besides acting as a carrier also possess several therapeutic properties, hence gives the synergistic effect when particular substance is given.
- Drug entrapment is not a problem with phytosome as the complex is biodegradable [2, 4, 9-11].

4. Production methodology

Phytosome, phospholipid complexes of vegetable extracts as shown in Figure 1 are prepared by adding the aqueous extracts to phospholipid dissolved in a suitable solvent such as ethyl acetate, acetone, ethanol under reflux and stirring. The resulting suspension is concentrated by reduced pressure to a thick residue which can be dried and ground. Natural, synthetic or semi-synthetic phospholipids have also been reported to form complexes with purified components of the vegetable extracts [8].

5. Principle

Phosphatidylcholine (or phosphatidylserine) is a bifunctional compound. The phosphatidyl moiety is lipophilic and the choline (serine) moiety is hydrophilic in nature. This dual solubility of the phospholipid makes it an effective emulsifier. Thus, the choline head of the phosphatidylcholine molecule binds to these compounds while the lipid soluble phosphatidyl portion comprising the body and tail which then surrounds the choline bound material. Hence, the phytoconstituents produce a lipid compatible molecular complex with phospholipids, as shown (also called as phytophospholipid complex) [9].

6. Patents of phytosome technology

Bioavailability of phenols in human volunteers was 3-5 times more when administered in complexed form with phospholipids (Oleaselected ™ Phytosome®) [12]. Phospholipids to olive fruits and leave extract ratio in the prepared complexes was in the range of 10 to 1% (w/w). Phospholipid complexes of curcumin provided five times higher peak plasma levels and AUC in male Wistar rats when compared to peak plasma levels and AUC value obtained after treatement with extract of uncomplexed curcumin [13]. Phospholipid complexes of proanthycynidins extracted from *Vitis vinifera* were prepared for use in suitable oral formulations, e.g. tablets or capsules, for treatment of atherosclerotic pathological conditions like myocardial and cerebaral infarctions [14]. The phospholipid complexes of proanthocyanidin A2 (2:1 to 1:2 ratio) were significantly more useful for the prevention and the treatment of atherosclerosis lesions in rabbit [15]. Phospholipid complexes of extracts of *Vitis vinifera*, and

Natural sources	Phytoconstituents complexed	Phytosomal products	Dose and Dosage form	Mechanism of action	Utilization	References
Silybium maranium (Milk Thistle)	Silybin, Silycristin, Isosilbin, silydianin.	Silybin Phytosome™ (Siliphos®)	120-200 mg Emulsion, gel, lotion and cream.	Prevents the destruction of glutathione in liver.	Hepatoprotective, hepatitis, cirrhosis and inflammation.	[8, 22-24]
Panax ginseng (Ginseng)	Ginsenosides	Ginseng Phytosome™	150 mg	Increases catalase, superoxide dismutase, glutathione peroxidase and glutathione reductase activities and prevent depletion of these antioxidant enzymes.	Nutraceutical, Immunomodulator .	[8]
Camellia sinensis (Tea)	Epigallocatechin, catechin, epicatechin-3-O-gallate, Epigallo catechin-3-O- gallate.	Green tea Phytosome™	400 mg	Inhibits urokinase enzyme which is responsible for increase in tumour size. Enhances the antioxidant mechanisms by increasing the activity of enzymes such as glutathione peroxidase and catalase.	Nutraceutical, Anticancer, Antioxidant, Hepatoprotective, Atherosclerosis, Anticancer, Reduces weight, Antidiabetic, Antiinflammatory.	[8, 25]
Gingko biloba (Maiden hair tree)	Gingko flavonoids, Gingoic acids of ginkgoflavonglucosides and ginkgolides	Gingkoselect Phytosome™	120 mg; Emulsion, solution, conditioner,	Enhances release of neuro-transmitters like catecholamines and inhibits catechol-O-methyl transferase and MAO. Dilatation	Cognition enhancer Raynaud's disease, antiageing, anti-	[5, 8]
	bilobalide		shampoo.	of capillaries and arterioles, thus improves delivery of nutrients to skin.	asthmic antiamnestic,	
		Ginkgo select Gingko biloba terpene Phytosome™ Gingko biloba dimeric flavonoids Phytosome™	20-25mg 1.5 % Gel, emulson Massage oils. 100-200 mg	Ginkolides inhibits the binding of platelet activating factor to its platelet membrane receptor. Gingko flavanoids inhibits cAMP phosphodiesterase enzyme thus improves lipolysis in fat cells and capillary blood flow.	antidepressant, cardio protective, dermatitis, soothing, antiinflammatory.	[8, 26]

Vitis vinifera (Grapes)	Resveratrol, quercitin, catechin, procyanidins, epicatechin.	Biovin and leucoselect Phytosome™ Masquilier's Phytosome™	50-100 mg	Protects endothelial cells from peroxynitrite induced damage and increased the endothelium-dependent NO release. Reduce the oxidant level and increases antioxidant level and enhance the resistance of LDLs and as a result causes oxidative modification.	Cardioprotective, systemic antioxidant, nutraceutical.	[5, 7, 8]
Crateegus oxyacanthoides (Hawthron)	Hyperin, quercitin.	Hawthron Phytosome™	100 mg	cAMP-independent mechanism, digitalis-like effect on the Na+/K+-ATPase in human cardiac muscle tissue Inhibits angiotensin converting enzyme.	Nutraceutical, Cardioprotective and antihypertensive	[8]
Olea europaea (Olive tree)	Verbascoside, tyrosol, hydroxytyrosol	Oleaselect Phytosome™	-	Decreases concentration of free radicals and level of lipid peroxidation.	Antioxidant, antihyperlipidimic, anticancer and	[5]
				Inhibits topoisomerase II, protein kinase C and telomerase. Selective inhibitor of 5-Lipooxygenase.	anti-inflammatory.	
Echniacea angustifolia (Cone flower)	Echinacosides and high molecular weight polysaccharide (Inulin).	Echniacea Phytosome™	-	Mechanism of action not clear but it is believed to stimulate cellular and hormonal immune defence, activates B and T lymphocytes and stimulates tissue necrosis factor.29	Nutraceutical, Immunomodulator .	[27]
Terminalia serica (Silver cluster leaf)	Sericoside	Sericoside Phytosome™	3% Gel, cream, emulsion, lotion	Reduction in capillary permeability.	Anti-aging, skin restructuring, wound healing, antioedema, anti-inflammatory.	[8, 28]
Glycyrrhiza glabra (Mulethi)	Glycyrrhetinic acid	Glycyrrhetinic acid Phytosome™	-	Glycyhrretinic acid is structuraly similar to cortisol, it potentiates the anti-inflammatory activity of cortisol by inhibiting its intracellular inactivation.	Anti-inflammatory, antierythemic, anti-irritant, skin infection.	[8]
Centella asiatica (Brahmi)	Asiatic acid, madecassic acid.	Centella triterpenoid	60-120 mg	Protective activity on microcirculation, with reduction	Skin disorders, antiulcer, wound	[8]

		Phytosome™		of abnormal increase in capillary permeability.	healing, anti-hair loss agent.	
Curcuma longa (Turmeric)	Curcumin	Curcumin Phytosome™ Curcuvet®	250 mg and 360 mg	Inhibit arachidonic acid metabolism, cyclooxygenase, lipoxygenase, cytokines, tissue necrosis factor and release of	Anti-inflammatory, osteoarthritis,	[24, 29]
		(Meriva®)		steroidal hormones. It stabilizes lysosomal membrane and cause uncoupling of oxidative phosphorylation.	anticancer	
Citrus aurantium (Bitter orange)	Naringenin.	Naringenin Phytosome™	100mg/kg	Increase the activity of glutahione peroxidase, superoxide dismutase, catalase.	Antioxidant	[8, 30]
Aesculus hippocastanum (Horse Chestnut tree)	Saponins	Escin β-sitosterol Phytosome TM	3% gel shampoo, hair conditioner, toothpaste, mouthwashe, and lotion	Modifies the vascular permeability.	Anti-oedema, and vasoactive properties	[8]
Swertia alternifolia	Xanthones 26	Swertia Phytosome™	-	-		[31]
Vaccinum myrtillus (Bilberry)	Anthocyanosides	Mirtoselect Phytosome™	-	Reduces capillary permeability and increase capillary resistance and also inhibits proteolytic enzymes.	Antioxidants, anti-inflammatory, vasoprotective, diabetic retinopathy	[5, 26]
Serenoa repens (Saw palmetto berries)	Phytosterols	Salbalselect Phytosome™	320 mg	Inhibits cyclooxygenase, 5-α reductase and lipooxygenase, smooth muscle relaxant. Inhibits specific components of the IGF-I signalling pathway, and induces JNK activation. α-	Non- Cancerous prostate enlargement	[5]
		(Meriva®)		steroidal hormones. It stabilizes lysosomal membrane and cause uncoupling of oxidative phosphorylation.	anticancer	

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Melilotus officinalis (Sweet clover)	Melilotoside, Flavanoids and terpenoids	Lymphaselect™	2 to 60 mg	Modifies the vascular permeability.	Anti-inflammatory, antioedema, thrombophlebitis.	[5]
Ammi visnaga (Khella)	Visnadine	Visnadex™	Cream, emulsion, lotion, gel	Antiphosphodiesterase activity, Concentration of cAMP increases which causes activation of lipases and improves lipolysis in fat cells.	Microcirculation improver, anticellulite	[8]
Santalum album (Sandal wood)	Ximenynic acid, ethyl ximenynate	Ximilene and Ximenoil Phytosome™	Emulsion, lotion, gel	Increases the conversion of arachidonic acid into eicosanoids in the dermis which	Microcirculation improver	[8]

				is related with a vasokinetic action and further with an increase of the microcirculation..		
Fraxinus ornus (Flowering ash)	Esculoside (Esculin)	Esculoside Phytosome™	Emulsion	Improves capillary permeability and fragility Inhibits catabolic enzymes such as hyaluronidase and collagenase, thus preserves the integrity of connective tissue.	Vasoactive, microcirculation improver, anticellulite.	[8, 32].
Radix pueriae (Kudzu root)	Puerarin	Puerarin and phospholipid complex	-	Inhibits the activation of both Hypoxia inducible factor -1 α and tumor necrosis factor - α. Increases superoxide dismutase	Antiinflammatory, cardiovascular diseases	[33-36]
(Butchers' broom)	neoruscogenin,	Phytosome™	preparation	promoting muscle contractions with a mechanism involving post junctional a-adrenergic receptors. Inhibit the enzyme elastase and hyaluronidase.	inflammatory, anti-ageing,sSunscreen agent.	
Panicum miliaceum (Millet)	Mineral salts, vitamins, unsaturated fatty acids, aminoacids	Millet Phytosome™	Topical preparation	Mineral salts, vitamins, unsaturated fatty acids which are present in it exerts a trophic activity on skin and cutaneous annexes (hair and nails)	Antistress, beauty food for skin, nails and hairs.	[8]
Vaccinium angustifolium (Blue berry)	Anthocyanosides tocotrienol complex, citrus bioflavonoid, alpha lipoic acid	VitaBlue Phytosome™			Anti-oxidant, improves vision, memory enhancer.	[8]

phospholipid complexes of standardized extract from *Centella asiatica* were incorporated in pharmaceutical and cosmetic compositions for were described for prevention of skin aging [16].

Flavanolignane-phospholipid complexes with a molar ratio of 1:1 of silybin, silidianin and silicristin were prepared for oral administration for treatment of acute or chronic liver disease of toxic, metabolic and/or infective origin or of degenerative nature, and for prevention of liver damages resulting from the use of drugs and/or luxury substances injurious to the liver [17]. The pharmacological activity of the novel flavanolignane-phospholipid complexes was more evident and demonstrated even when orally administered thus overcoming the known problems of absorption common to many phenolic substances and particularly to silymarin.

Poor absorption by oral route, poor tolerability by cutaneous/topical administration and remarkable toxicity by parenteral route limits the therapeutic utility of saponins. Complexes of saponins with phospholipids allowed overcoming these drawbacks, particularly allowing an effective absorption by oral and topical route and a high stability, due to the lipophilic characteristics attained [18]. Complex of flavonoids with phospholipids, characterized by high lipophilia and improved bio-availability and therapeutic properties as compared with free, not complexed flavonoids were prepared for use as the active principle in pharmaceutical and cosmetic compositions like tablets, capsules, creams, gels etc. [19]. Complexes of extracts from *Krameria triandra* Ruiz et av. and other plants of the Eupomatia genus, as well as some phenol constituents thereof of neo-lignane or nor-neolignane nature, with phospholipids were prepared [20] for incorporation in the traditional pharmaceutical forms for the treatment of superficial infected inflammatory processes, in torpid sores and in all the phlogistic conditions of the oral cavity.

Complexes between natural or synthetic phospholipids and bilobalide, a sesquiterpene extracted from the leaves of *Gingko biloba*, were prepared for their application as antiinflammatory agents and as agents for the treatment of disorders associated with inflammatory or traumatic neuritic processes [21]. These complexes exhibited high bioavailability compared with free bilobalide, and were suitable for incorporation into pharmaceutical formulations for systemic and topical administration.

7. Conclusions

Phytosomes results from the reaction of a stoichiometric amount of the phospholipid (phosphatidylcholine) with the standardized extract or polyphenolic constituents (like flavonoids, terpenoids, tannins, xanthones) in a non-polar solvent. Phytosomes show better absorption profile and enhances delivery of phenolic phytoconstituents to the tissues. The complexation of phenolic phytoconstituents and phospholipids makes the pheolic phytoconstituents more stable in the complex form due to liopophilic nature. Both improvement in absorption and increase of stability reduce the amount of active constituents required in formulating an appropriate dosage form when compared to the products obtained from conventional plant extracts. Hence, several excellent phenolic phytoconstituents have been successfully formulated and delivered in this way exhibiting remarkable therapeutic efficacy in animal as well as in human models. Numerous phytosomal products have been commercially introduced and churning out appreciable profits to the pharmaceutical, neutraceutical or cosmetic manufacturers.

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