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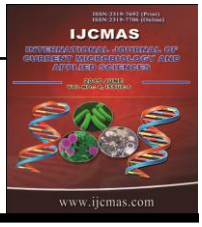

Original Research Article

Phytosome as novel delivery system for nutraceutical materials

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K e y w o r d s

Phytosomes, Plant extract, Bioavailability

A B S T R A C T

Nutraceutical materials usually show less bioactivity than optimal state. Phytosomes are better absorbed and improve bioavailability of bioingredients. They are produced by a process whereby the standardized plant extract or its constituents are bound to phospholipids, mainly phosphatidylcholine. In fact they are advanced forms of herbal formulations contains the bioactive phytoconstituents of herb extract such as flavonoids, glycosides, terpenoids, and has good ability to transition from a hydrophilic into the lipophilic environment of the outer cell membrane. It has better bioavailability and functions than the conventional herbal extracts containing dosage phytosomes enhanced bioavailability over conventional biomaterials and conventional herbal extracts. Phytosome technology has been effectively used to increase the bioavailability of herbal extracts including, green tea, milk thistle, ginseng, Ginkgo biloba, grape seed and can be developed for various therapeutic uses or dietary supplements.

Introduction

Recently good advances made on development of novel nutraceutical materials delivery systems for plant actives and extracts (Kalita *et al.*, 2013). Encapsulation is a process that entrapped one substance within another substance therefore produced particles with diameters of a few nm to a few mm. Phytosome, liposome, niosome are some encapsulation systems. Phytosomes, complex of natural bioactive materials and phospholipids, mostly phosphatidylcholine, increase absorption of herbal extracts or isolated active ingredients when applied topically or orally. The Phytosome technology applied to herbal extracts (ginkgo, milk thistle, green tea) successfully as well as phytochemicals (curcumin, silybin), with remarkable results both in animals and in human pharmacokinetic studies (Semalty *et al.*, 2010; Kidd and Head, 2005; Hoh *et al.*, 2006). Selection of flavonoids are done from the group consisting of quercetin, kaempferol, quercretin-3, rhamnoglucoside, quercetin-3-rhamnoside, hyperoside, vitexin, diosmine, 3- rhamnoside, (+) catechin, (-) epicatechin, apigenin-7-glucoside, luteolin, luteolin glucoside, ginkgonetine,

isoginkgetin and bilobetin. Phytosomes are amphiphilic substance having specific melting point, general soluble in lipids.

Greenselect® Phytosome® proved to be more bioavailable compared to the unformulated extract. The results suggest that Greenselect® Phytosome® is useful and safe for different uses. The free radical scavenging capacity of the extract accounts for most of the biological activities, Greenselect® Phytosome® is also reported to trigger other mechanisms of action.

Increasing of the antioxidant defense systems (Townsend *et al.,* 2004; Bordoni *et al.,* 2002).

Stimulation of alpha1 adrenergic stimulated glucose transport (Angeloni *et al.,* 2007).

Interference with the formation of pro-inflammatory response function cytokines (Tedeschi *et al.,* 2004).

Phospholipids used in Phytosome production are lipids that contain phosphorus, a polar and non-polar part in their structures. Phospholipids can be divided into glycerophospholipids and sphingomyelins according to the phospholipids alcohols. They mainly distributed in animals and plants, and the main sources include vegetable oils (such as soybean, cotton seed, corn, sunflower and rapeseed) and animal tissues (such as egg yolk and bovine brain).

Phytosomes are obtained by reacting 2-3 moles or 1 mole of phospholipid such as phosphatidylcholine, phosphatidyl-ethanolamine or phosphatidyl-serine with 1 mole of bioactive component (flavonoids or terpenoids) in an aprotic solvent (dioxane, acetone, methylene chloride, ethyl acetate). The solvent evaporated under vacuum or precipitation with non solvent (aliphatic hydrocarbons), lyophilization (freeze-drying) or spray drying, therefore the complex isolated (Vitamedics, 2008; Wendel Lesithin, 1995).

Difference between Liposome and Phytosome

The basic difference between liposomes and phytosomes is that in liposomes the active biomaterial is dissolved in the medium contained the cavity or in the layers of the membrane, whereas in the phytosome it is an integral part of the membrane, being the molecules stabled through chemical bonds to the polar head of the phospholipids (see Fig. 2). Liposomes are used in cosmetics to deliver water-soluble materials to the skin. A liposome is formed by mixing a water-soluble substance with phosphatidylcholine and 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 technology the phosphatidylcholine and the plant active components from a 1:1 or a 2:1 complex depending on the substance compared to liposomes. Phytosome is characterized by a high bioactive/lipid ratio with stoichiometry in the range of 1:1–1:3 between the active and the phospholipids formulation aid. This difference results in phytosomes much better absorbed that liposomes and they are superior to liposomes in skin care products.

In liposomes the active material are dissolved in the core of the complex and there is no chemical bonding between the lipid and the guest substance, but in

phytosome polar group of phospholipids interacted with hydrogen bonds and forming a unique arrangement that confirmed by spectroscopy (Husch *et al.*, 2011; Kidd, 2009; Gandhi *et al.*, 2012; Bhattacharya, 2009; Gabetta *et al.*, 1989; Kaur – pharmatutor-art).

Advantages of phytosome

- It increases the absorption of lipid insoluble hydrophilic polar phytoconstituents through oral also topical route and increasing the bioavailability;
- Improves bioactive ingredients absorption and reduces the amount requirement;
- Improves the solubility of bile to herbal constituent;
- Phytosomes also have nutritional benefit of phospholipids;
- Has ability for easily across from cell membrane and enter cell;
- Because chemical bonds are formed between phosphatidylcholine molecule and phytoconstituents, Phytosomes show good stability profile; (Kidd, 2002; Bhattacharya, 2009; Kumar *et al.*, 2010; Dayan and Touitou, 2002; Facino *et al.*, 1994).

Some flavonoids used in Phytosome production

Some biomaterials that used in phytosome formulation are representated in figure 2.

Quercetin is commonly derived from Apple, Grape, Lemon, Tomato and Onion. Also silibinin, EGCG, curcumin, rutin and isoquercetin derived from Silybum marianum, Green tea, Curcuma longa, Plant species, carpobrotus edulis Onion respectively.

Researches on phytosome

Moscarella *et al.* (1993) prepared silybin phytosome and investigated in one study of 232 patients with chronic hepatitis (viral, alcohol or drug induced) treated with it at a dose of 120 mg either twice daily or thrice daily for up to 120 days, liver function returned to normal state faster in treated patients with silybin phytosome compared to a group of controls (49 treated with commercially available silymarin, 117 untreated or given placebo).

Yanyu *et al.* (2006) prepared the silymarin phytosome and studied its pharmacokinetics in rats. They indicated the bioavailability of silybin in rats was increased significantly after oral administration of prepared silybin-phospholipid complex due to an impressive improvement of the lipophilic property of silybin-phospholipid complex and the biological effect of silybin.

Naike *et al.* (2009) investigated the 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. They indicated that total antioxidant capacity and stimulation of physiological antioxidant defenses of plasma increased, also through a network of mechanisms that extend beyond their great antioxidant potency offering marked protection for the cardiovascular system and other organs.

Hüsch *et al.* (2013) showed that lecithin formulation significantly increase the absorption of BAs and improve their tissue penetration, showing for the first time the achievement of tissue concentrations of the compounds in the range of their anti - inflammatory activity. Taken together, these results provide a rationale for investigating the clinical potential of Casperome™ in a

variety of conditions where preclinical evidence of action for BEH as been reported. Zhang *et al.* (2013) prepared a novel drug delivery system, curcumin-phytosome-loaded chitosan micro-spheres (Cur-PS-CMs) by combining polymer and lipid-based delivery systems.

Table.1 Available PHYTOSOME® complexes on the market. PHYTOSOME® and all other trademarks are owned by Indena S.p.A. Milan, Italy

	Trade name	**Phytoconstituents complex**	**Daily dose**	**Biological activity**
1	Bilberry (irtoselect) Phytosome	Anthocyanosides from Vaccinium myrtillus	-	Antioxidant, Improvement of Capillary Tone.
2	Casperome™	Banksia serrata gum Resin	-	Higher systemic availability and improving tissue distribution of boswellic acids
3	Centella phytosome	Terpenes from centella asiatica	-	Brain tonic, Vein and Skin Disorder
4	Curcumin (Merinoselect) Phytosomes	Polyphenol from Curcuma Longa	200-300 mg	Cancer Chemo preventive Agent Improved the oral bioavailability of curcuminoids, and that the plasma
5	Curbilene phytosome	Curbilene from Curcurbita pepo seeds	-	Skin care, Matting Agent
6	Echinacea phytosome	Echinacosides from Echinacea angustifolia	-	Immunomodulatory, Nutraceuticals.
7	Echinacea purpurea	Echinacea purpurea (L.) Moench - Root	-	Immunomodulator
8	Ginkgo select phytosome	Flavonoids from ginkgo biloba	120 mg	Anti aging, Protects Brain & Vascular Liling
9	Ginseng phytosome	Ginsenosides from panax Ginseng	150 mg	Nutraceutical, Immunomodulator
10	Grape seed (Leucoselect) phytosome	Procyanidins from vitis Vinifera	50-300 mg	Nutraceutical, Antioxidant, Anticancer.
11	Greenselect phytosome	Polyphenols, catechins	320 mg	Nutraceutical, weight management, healthy blood lipids, healthy in flammatory response, antioxidant capacity

Fig.1 Difference between phytosome and liposome. The molecular organization of phytosome (upper segment) liposome (lower segment)

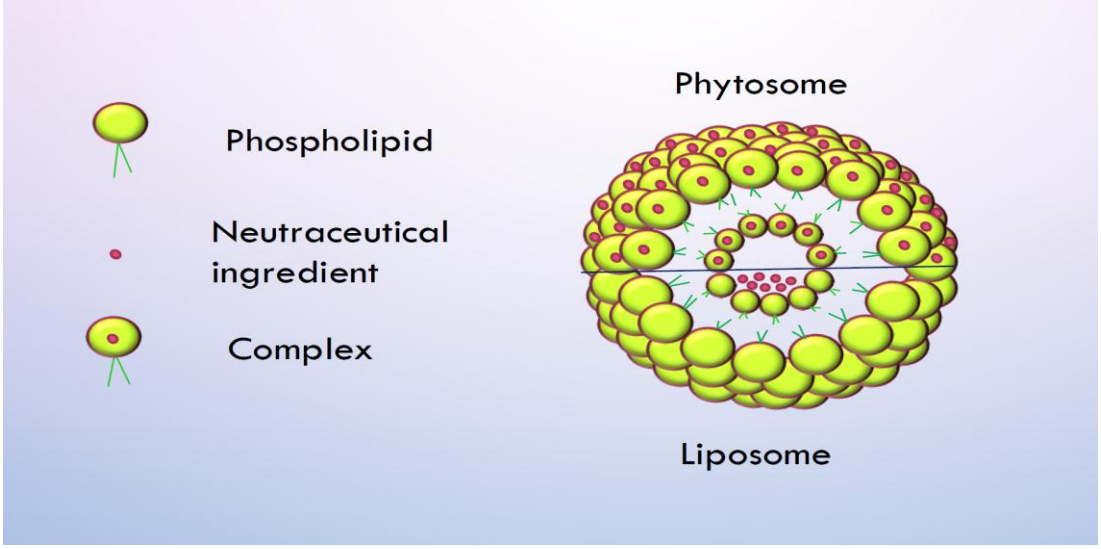
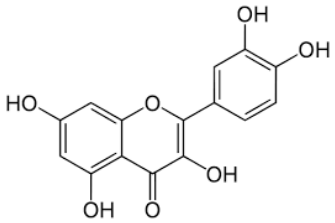
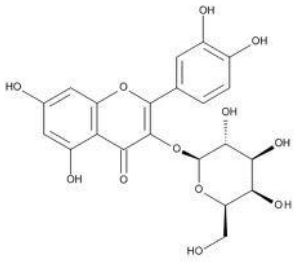
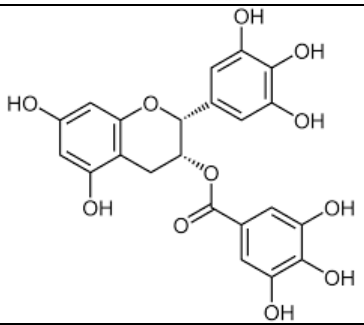
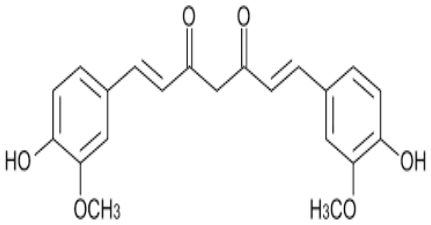
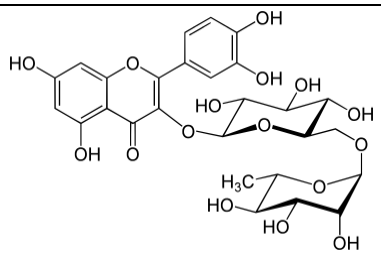


Fig.2 Flavonoids structure

Quercetin	
Isoquercetin	
EGCG	

Curcumin	
Rutin	

They reported that the new Cur-PS-CMs system combined the advantages of chitosan microspheres and phytosomes, which show better effects of promoting oral absorption and prolonging retention time of curcumin than single Cur-PSs or Cur-CMs. The PS-CMs significantly prevented degradation of bound curcumin in rat plasma and prompted absorption of curcumin compared with natural curcumin, Cur-PSs, and Cur-CMs. Therefore, the PS-CMs can be used as a sustained delivery system for lipophilic compounds with poor water-solubility and low oral bioavailability. Wu *et al.* (2014) developed a formulation to improve the oral absorption of baicalin (BA) by combining a phospholipids complex (PC) and self-emulsifying micro emulsion drug delivery system (SMEDDS), termed BA – PC – SMEDDS. BA – PC was prepared by a solvent evaporation method and evaluated by complexation percentage (CP). Physicochemical properties of BA – PC were determined. PC–SMEDDS has a good balance for lipophilicity and hydrophilicity of drugs which is critical for oral absorption. Moreover, it is worth noticing that PC – SMEDDS cannot solve the oral absorption problems associated with all BCS IV drug. Drugs with a phenolic hydroxyl group should have a high complexation percentage with PC and good oral absorption by PC – SMEDDS based on the results of their studies.

They are better absorbed which results better than conventional herbal extract, also they have improved pharmacokinetic and pharmacological characteristics, which can be used in treatment of various diseases. Phytosome aids to explore maximum therapeutic capability of phytoconstituents of polar nature exhibiting remarkable therapeutic efficacy. They have many significant advantages over other conventional formulations that cause it important delivery system. Phytosome upgraded to a commercial scale such as pharmaceutical, nutraceutical or cosmetic manufacturers. Phytosomes have many different therapeutic benefits like hepatoprotective, cardiovascular, liver diseases, anti-inflammatory, immunomodulator, anticancer and antidiabetic.

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