INTERNATIONAL JOURNAL OF INSTITUTIONAL PHARMACY AND LIFE SCIENCES

Pharmaceutical Sciences

Review Article……!!!

Received: 23-08-2011; Accepted: 19-09-2011; Published Online: 19-09-2011

PHYTOSOME: A NOVAL APPROACH FOR PHYTOMEDICINE

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Keywords:

Phytosomes, Phosphatidylcholine, Phytoconstituents , Bioavailability

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ABSTRACT

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. Phytomedicines, complex chemical mixtures prepared from plants, have been used for health maintenance since ancient times. But many phytomedicines are limited in their effectiveness because they are poorly absorbed when taken by mouth. Advanced biochemical and pre-clinical studies have proved the potential of plant flavonoids 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. Phytosomes are produced by a process where by 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. The paper provides details of the formulation methodology for phytosome and the characterization and evaluation technologies used for phytosomes.

INTRODUCTION

Since ancient times the therapeutic uses of traditional medicines and phytomedicines have proved very popular for health maintenance by various means. The advancement in the field of herbal drug delivery started recently with the aim to manage human diseases efficiently. Every nation is seeking health care beyond the traditional boundaries of modern medicine; turning to self medication in the form of herbal remedies[1, 2]. Most of the bioactive constituents of phytomedicines are water-soluble molecules (*e.g.* phenolics, glycosides, and flavonoids). However, watersoluble phytoconstituents are limited in their effectiveness because they are poorly absorbed [3] when taken orally or when applied topically. Many approaches have been developed to improve the oral bioavailability, such as inclusion of solubility and bioavailability enhancers, structural modification and entrapment with the lipophilic carriers [3,4,5]. So, extensive research in the field of herbal drug delivery systems as a means of improving the therapeutic indices of drugs is inevitable. The term "phyto" means plant while "some" means cell-like. The use of phytosomes is a new advanced modern dosage formulation technology to deliver herbal products and drugs by improved better absorption and, as a result, produce better results than those obtained by conventional herbal extracts [6,7].Phytosomes are not liposome ,structually the two are distinctly different The phytosome is a unit of a few molecules bonded together ,while liposomes is an aggregate of many phospholipids molecules than an enclose other phytoactive molecules but without specially bonding to them.Phytosome technology is a break through model for

1) Marketed enhancement of bioavailability
2) Significantly greater clinical benefit
3) No compromise of nutrient safety

DIFFERENCE BETWEEN PHYTOSOMES AND LIPOSOMES

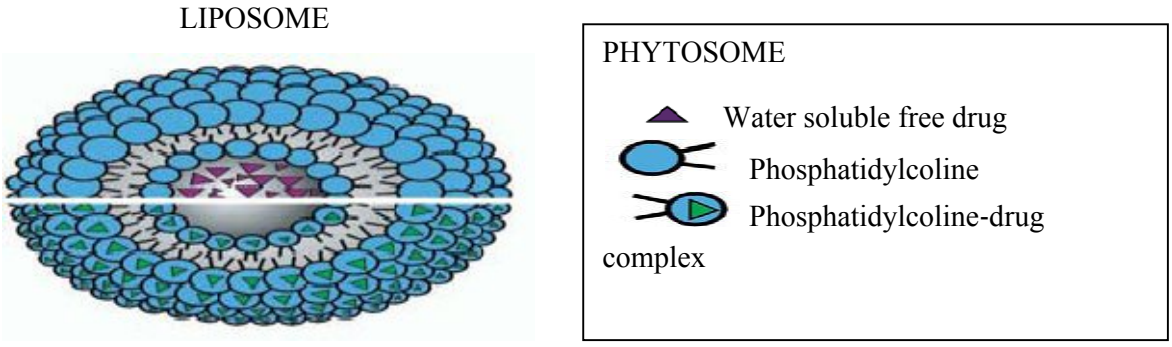

Fig. 1: Major difference between liposome and phytosome. The molecular organization of the liposome (upper segment) versus many individual phytosomes (lower segment)

CHARACTERIZATION OF PHYTOSOMES

The behaviour of phytosomes in both physical and biological system is governed by the factors such as physical size, membrane permeability, percentage of 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 release and chemical composition[8].

METHOD OF PREPARATION

Phytosomes are formulated by patented processes in which the standardized extract (having a standardized content of active principles) and/or active ingredients of herbs (like flavoliganans and terpenoids) are bound to the phospholipids like phosphatidylcholine (PC) through a polar end. The phytosome process produces small cells which protect the valuable components of the herbal extract from destruction by digestive secretions and gut bacteria [6]. They improve transition of constituents from the water phase to the enterocytes of the gut wall and ultimately they reach the circulation. The phytoactive components of these herbal extracts are well suited to direct binding to phosphatidylcholine from soy. Phosphatidylcholine is also the principle molecular building block of cell membranes and is miscible with both water and oil/lipid mixtures, and is well absorbed orally. Phospholipids are small lipid molecules in which the glycerol is bound to only two fatty acids, instead of three as in triglycerides, with the remaining site is occupied by a phosphate group [9].Specifically, the choline head of the phosphatidylcholine molecule binds to phytoconstituents while the fat-soluble phosphatidyl portion, comprising the body and tail, then envelopes the choline-bound material. This results in small microspheres or the production of cells known as phytosomes [6,10] Thus, phytosomes are also considered as a phytolipid delivery system [7].Phytosomes are prepared by reacting 3–2 moles (preferably with one mole) of a natural or synthetic phospholipid, such as phosphatidylcholine, phosphatidylethanolamine or phosphatidyiserine, with one mole of phytoconstituents either alone or in the natural mixture in an aprotic solvent, such as dioxane or acetone, in a 1:2 or 1:1 ratio [11] The optimum ratio of phospholipid to phytoconstituent is 1:1. The complex thus formed can be isolated by precipitation with an aliphatic hydrocarbon or lyophilization or spray drying [12]. Some liposomal drug complexes operate in the presence of water or buffer solution where the phytosomes interact with a solvent with a reduced dielectric constant. The Jiang, *et al*. (2001) have optimized the preparation conditions using a uniform design and step

regression and have prepared *Herba Epimedii* total flavonoid phytosomes (EFP) by means of solvent evaporation and investigated the cumulative dissolution of different ratios of EFP-PVP precipitates by means of dissolution release. The optimized preparation conditions are as follows: solvent-tetrahydrofuran, lecithin to PVP ratio— 2.5, temperature—40˚C and reaction time-3 hrs. The oil/water apparent partition coefficient of icariin was enhanced more than 4-fold by phospholipid. The cumulative dissolution of *Herba Epimedii* flavonoids of the EFP-PVP precipitate was significantly higher than that of its physical mixture and a *Herba epimedii* extract tablet [13] Yanyu *et al* (2006) prepared a silybin-phospholipid complex using ethanol as a reaction medium. Silybin and phospholipids were resolved into the medium, after the organic solvent was removed under vacuum condition, and a silybin-phospholipid complex was formed [16]

EVALUATION OF PHYTOSOMES

The behavior of phytosomes in both physical and biological systems is governed by factors such as the physical size, membrane permeability, percentage of entrapped solutes, and chemical composition as well as the quantity and purity of the starting materials. Therefore, phytosomes can be characterized in terms of their physical attributes i.e. shape, size, distribution,percentage drug captured, entrapped volume, percentage drug released and chemical composition [17].

1. Different evolution techniques used for phytosomes

a) Visualization

Visualization of phytosomes can be achieved using transmission electron microscopy (TEM) and by scanning electron microscopy (SEM) [18].

b) Vesicle size and Zeta potential

The particle size and zeta potential can be determined by dynamic light scattering (DLS) using a computerized inspection system and photon correlation spectroscopy

c) Entrapment efficiency

The entrapment efficiency of a drug by phytosomes can be measured by the ultracentrifugation technique [19]

d) Transition temperature

The transition temperature of the vesicular lipid systems can be determined by differential scanning calorimetry [20].

e) Surface tension activity measurement The surface tension activity of the drug in aqueous solution can be measured by the ring method in a Du Nouy ring tensiometer [21]

f) Vesicle stability

The stability of vesicles can be determined by assessing the size and structure of the vesicles overtime. Mean size is measured by DLS and structural changes are monitored by TEM [22].

g) Drug content

The amount of drug can be quantified by a modified high performance liquid chromatographic method or by a suitable spectroscopic method [23]

2) *Spectroscopic evaluations*

To confirm the formation of a complex or to study the reciprocal interaction between the phytoconstituent and the phospholipids, the following spectroscopic methods are used [24]

A) 1H-NMR

The NMR spectra of (+)-catechin and its stoichiometric complex with distearoylphosphatidylcholine have been studied by Bombardelli *et al* [25]. In nonpolar solvents, there is a marked change of the 1H-NMR signal originating from the atoms involved in the formation of the complex, without any summation of the signal peculiar to the individual molecules. The signals from the protons belonging to the flavonoids are to be broadened that the proton cannot be relieved. In phospholipids, there is broadening of all the signals while the singlet corresponding to the N-(CH3)3 of choline undergoes an uplift shift. Heating the sample to 60˚ results in the appearance of some new broad bands, which correspond mainly to the resonance of the flavonoid moiety.

B) 13C-NMR

13C-NMR spectrum of (+)-catechin and its stoichiometric complex with distearoylphosphatidylcholine, particularly when recorded in C6D6 at room temperature, all the flavonoid carbons are clearly invisible. The signals corresponding to the glycerol and choline portion of the lipid (between 60–80 ppm) are broadened and some are shifted, while most of the resonances of the fatty acid chains retain their original sharp line shape. After heating to 60˚, all the signals belonging to the flavonoid moieties reappear, although they are still very broad and partially overlapping.

C) FTIR

The formation of the complex can be also be confirmed by IR spectroscopy by comparing the spectrum of the complex with the spectrum of the individual components and their mechanical mixtures. FTIR spectroscopy is also a useful tool for the control of the stability of phytosomes when micro-dispersed in water or when incorporated in very simple cosmetic gels. From a practical point of view, the stability can be confirmed by comparing the

spectrum of the complex in solid form (phytosomes) with the spectrum of its micro-dispersion in water after lyophilization, at different times. In the case of simple formulations, it is necessary to subtract the spectrum of the excipients (blank) from the spectrum of the cosmetic form at different times, comparing the remaining spectrum of the complex itself.

MERITS OF PHYTOSOMES

1) It enhances the absorption of herbal constituent and hence the bioavailability.
2) By enhancing the solubility of bile to herbal constituent, facilitates the liver targeting.
3) As the absorption of chief phytoconstituent is improved, its dose requirement is also reduced.
4) Phosphatidylcholine used in preparation of phytosomes, besides acting as a carrier also acts as a hepatoprotective, hence giving the synergistic effect.
5) Unlike liposome, chemical bonds are formed between phosphatidylcholine molecule and phytoconstituent, so the phytosomes show better stability profile.
6) The formulation of phytosomes is safe and the components have all been approved for pharmaceutical and cosmetic use [26,27].
7) They can be also used for enhanced permeation of drug through skin for transdermal and dermal delivery [28].
8) They can be widely used in cosmetics due to their improved skin penetration and have a high lipid profile. Phytosomal formulations can be used as functional cosmetics [27].

HERBAL DRUGS AND THEIR PHYTOSOMES

S.No	Herbal Drug	Phytosome	Phytoconstituents complexed with phosphatidylcholine	Indications
1)	*Ginkgobiloba*	Ginkgoselect® Phytosome	(a) Dimeric Flavonoids[29] (b) terpenoids (gikgolides and bilobalide)[30,31]	(a)Vasoactive agent (b)Anti-inflammatory agents
2)	*Silybum marianum*	Silybin Phytosome TM	(a)Flavolignan (Silybin)[32,33]	(a)Antioxidant and Hepatoproptective

			(b)Flavanolignan (Silymarin) [34]	(b)Anti-inflammatory
3)	*Crataegus oxyacantha*	Hawthorne Phytosomes	Flavonoids [35,36,37,38]	Antioxidant, cardioprotective,
4)	*Camellia sinensis*	Greenselect® Phytosome	Catechins and their gallate derivatives. [39]	Antioxidant, cardioprotective
5)	*Panax ginseng*	Ginselect TM	Saponins [39,40,41]	Anti-aging
6)	*Terminalia Serica*	Sericosides Phytosome	Sericosides [42]	Skin restructuring,capillary protecting,wound healing,antioedema, anti-inflammatory.
7)	*Vaccinium myrtillus*	Mirtoselect ® Phytosome	Antcinocide [43]	Antioxidant
8)	*Vitis vinifera*	Leucoselect ® Phytosome	Monomeric flavan-3-ols together with their polymer procyanidins[44,45]	Cardiovascular protectant,antiinflammatory, antioxidant.
9)	*Serenoa repens(Bartr)*	Sabalselect ® Phytosome	Phytosterols	Non-cancerous prostate enlargement.
10)	*Melilotus officinalis*	LymphaselectTM Phytosome	Coumarin	Effective in the symptomatic treatment of chronic venous insufficiency, varicosities, hemorrhoids, thrombophlebitis, post-surgicaledema formation, and of severe lymphatic disorders such as lymphedema.
11)	*Olea europaea*	Oleaselect TM Phytosome	Polyphenols	Antioxidant, inhibit harmful oxidation of LDL cholesterol anti-inflammatory .
12)	*Echinacea angustifolia*	PolinaceaTM	Echinacosides, inulin [46]	Enhances immune function in response to a toxic challenge

The following phytosome preparations have been demonstrated safe and effective:

SILIPHOSTM Milk Thistle phytosome

The liver is especially responsible for processing potentially toxic substances such as alcohol, pharmaceuticals and drugs of abuse, pollutants, excess hormones, and others. The detoxication process can deplete essential biomolecules and damage the liver. A standardized extract from *Silybum marianum* (milk thistle) is an excellent liver protectant but very poorly absorbed. Phytosome complex of milk thistle (called SILIPHOS) is far better absorbed, as well as safe and effective in subjects with impairment of liver function that ranges from mild to severe.

Other Indena Phytosome extracts include:

***Ginkgoselect*®** Phytosome is a more fully absorbable form of the standardized extract of *Ginkgo biloba* leaves. 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.

***Leucoselect*®** Phytosome is composed of oligomeric polyphenols (grapeprocyanidins) of varying molecular size, complexed with phospholipids.The markedly improved oral bioavailability of these procyanidin flavonoids offers marked protection for the cardiovascular system and other organs through a network of mechanisms that extend beyond their great antioxidant

potency.

***Greenselect*®** Phytosome contains a totally standardized polyphenolic fraction (not less than 66.5 percent) obtained from green tea leaves and mainly characterized by the presence of epigallocatechin and its derivatives. 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. The complexation of green tea polyphenols with phospholipids strongly improves their poor oral bioavailability.

***Mirtoselect*®** Phytosome contains an extract of bilberry which provides anthocyanosides. These improve capillary tone, reduce abnormal blood vessel permeability, and are potent antioxidants. They hold great potential for the management of retinal blood vessel problems and venous insufficiency.

***Sabalselect*®** PHYTOSOME includes an extract prepared from saw palmetto berries through supercritical CO2 (carbon dioxide) extraction. It delivers fatty acids, alcohols and sterols that

benefit prostate health. In particular this extract may benefit non-cancerous prostate enlargement.

***Lymphaselect*TM** Phytosome includes a standardized extract from Melilotus officinalis. This preparation is particularly indicated for venousdisorders, including chronic venous insufficiency of the lower limbs.

***Oleaselect*TM** Phytosome is a newer preparation from olive oil polyphenols. These are potent free radical scavengers (antioxidants), inhibit harmful oxidation of LDL cholesterol, and also have anti-inflammatory activity.

***Polinacea*TM** is an immunomodulating preparation made from *Echinacea angustifolia*. It includes echinacosides and a unique high-molecular weight polysaccharide. This preparation especially enhances immune function in response to a toxic challenge[48,49].

CONCLUSION

Phytosomes are novel compounds comprising of lipophilic complexes of components of various plants like *Silybum Marianum, Ginkgo Biloba, ginseng* etc which offer improved bioavailability of hydrophilic flavonoids and other similar compounds through the skin or gastrointestinal tract. They have many distinctive advantages over other conventional formulations scale. The characterization methodologies and analytical techniques are well established for this type of novel formulation. Phytosomes enables pharmaceutical manufacturers to provide new pharmaceutical products using water soluble drugs and provides new developments in medical industry. Phytosome technology enables cost effective delivery and synergistic benefits from the phospholipid nutraceuticals intrinsic to life.

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