PHYTOSOME: A NOVEL DOSAGE FORM FOR HERBAL DRUG DELIVERY

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Phytosome is a complex of a natural active ingredient and phospholipids. The term 'Phyto' means plant while 'some' means cell like structure. It is claimed that phytosome increases absorption of "conventional herbal extracts" or isolated active principles both orally as well as topically. In this era phytosome gain popularity as a potential drug delivery device due to excessive demand and utility of herbs or herb based medicines. This advance technology offers amenities like improved absorption, enhanced delivery & increased bioavailability of herbal extracts. These drug-phospholipid complexes can be fabricated in the form of solution, suspension, emulsion, syrup, lotion, gel, cream, aqueous micro dispersions. Standardized plant extracts, mainly polar phytoconstituents like flavonoids, terpenoids, tannins, xanthones shall be introduced in form of phytosome.

Key words: Phytosome, Phosphatidylcholine (PC), Phospholipid, Phytoconstituents

INTRODUCTION

Herbs are serving as sources of potent medicine form the ancient time. In the recent era it has been found that use of some phyto medicines are increasing due to its efficacy and comparative low toxicity profile as well less side effect as compare to conventional synthetic medicines.The World Health Organization (WHO) estimates that 80 percent of the population of some Asian and African countries presently use phyto medicine for some aspect of primary health care. Studies in the United States and Europe have shown that use of phyto medicine increasing in recent years as scientific evidence about the effectiveness of herbal medicine has become more widely available.[2,3]

The clinically and pharmacologically tested bioactive group of compounds like alkaloids, flavonoids, polyphenolic components randomly used for effective management of different ill health condition either in crud form or in the form of formulations. It is fact that development of phyto formulation is tedious due to the solubility and compatibility issue of active constitutes with other formulation variables[4]. Many pharmacologically active phytochemicals or herbal extracts exhibits poor in-vivo response despite of the extraordinary potential *in-vitro* results due to unpredictable physiochemical behaviour of active constitutes, ultimately resulting in poor absorption and poor bioavailability[5]. The bioavailability can be improved with the use of different novel delivery systems like liposomes, niosomes and phytosomes which can enhance the rate of release as well as the capacity to cross the lipidal biomembranes. Among the vesicular systems phytosome shows comparatively better acceptance and potency.

Phytosomes are advanced delivery system most popularly use to deliver phyto constituents or herbal product in vesicular encapsulated form. It is mainly developed by binding individual component of herbal extract to phosphatidylcholine resulting a product that is better absorbed and produces better results than the conventional one. The major component of this delivery system is phospholipid's molecular[5]. They are shows unique structural arrangement includes a polar head & two non polar tails that provide a facility of dual solubility. The phospholipid acts as an effective emulsifier, also having easy access through the biomembrane. There are many phytoconstitutes that are successfully incorporated into phytosome including Ginkgo Biloba, Grape seed Hawthorn, Milk thistle, Green tea & Ginsengs. This review shall provide detail information regarding the concept of phytosome and its various prospects as delivery system.

Advantage of Phytosome: [1, 6-8]

- It enhances the absorption of lipid insoluble polar phytoconstituent through oral as well as topical route showing better bioavailability.

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- This technology offers a stable and cost effective delivery of phytoconstituent. Due to improve absorption capabilities it shows better efficacy in comparatively low dose.
- The phosphatidylcholine used in preparation of phytosome besides acting as a carrier it also act as a hepatoprotective agent hence produce synergistic effect for hepatoprotective substances
- The vesicular structure of phytosome helps to protect valuable component of herbal extracts from destruction by digestive secretions & gut bacteria.
- Phytosome can be used for systemic targeting. It is widely used in cosmetic technology due to its more skin penetration ability & high lipid permeability.

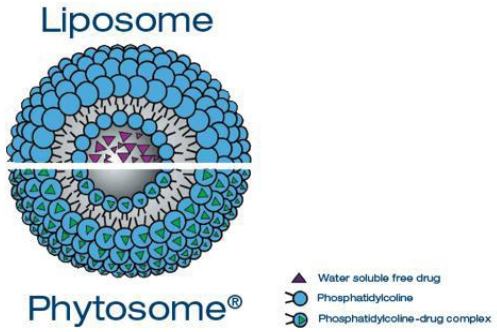

Fig I Comparison between transverse Section of Liposome and Phytosome

Properties of Phytosome[9]:

(1) The term phytosome is used to define a complex between a natural product & phospholipids, like soy lipid that are obtained by the reaction of stoichiometric amounts of phospholipids and phytoconstituent in an appropriate solvent. Spectroscopic data reveals that the interaction phospholipids substrate is due to the formation of hydrogen bonds between the polar head of the phospholipids & the polar functionalities of the substrate.

(2) Nuclear magnetic resonance study of the phospholipids complex with some of pure precursor indicates that the signals of fatty chain are almost unchanged. Such evidences inferred that two long aliphatic chains are wrapped around the active principle, producing a lipophilic envelop that shields the polar head of the phospholipids.

(3) Phytosome are lipophilic substance with a definite melting point, freely soluble in non polar solvents & moderately soluble in fats.

(4) When treated with water, they assume a miceller shape, forming structure that resembles liposomes exhibiting fundamental differences.

Difference between Phytosome & Liposome[13]:

(1) In Phytosome active chemical constituents molecules are anchored through chemical bonds to the polar head of phospholipid. In liposome the active principle is dissolved in the medium of the cavity or in the layers of membrane. No chemical bonds are formed.

(2) In Phytosome phosphatidylcholine and the individual plant compound form 1:1 or 1:2 complex depending on the substance. In liposome hundreds and thousands of phosphatidylcholine molecules surrounds the water soluble molecule**.**

Different form of Phytosome Formulations[14]

Phytosome complex can be formulated in both oral dosage form & topical dosage form.

Soft gelatin capsule The phytosome complex can be dispersed in oily vehicle to obtain suspension to be filled in soft gelatin capsule. Vegetable and semi synthetic oil can be used.

Hard gelatin capsule The Phytosome complex can be formulated in hard gelatin capsule.

Tablets The Phytosome complex can be formulated in tablet dosages form.

Topical dosage form The Phytosome complex can be formulated topically as well. The ideal process to incorporate the phytosome complex in emulsion is to disperse the phospholipid complex in a small amount of lipid phase and add it to the already created emulsion at low temperature the phytosome complexes

are dispersible in the solvent employed for topical formulation.

Phytosome In Cosmetic[15] The phytosome have a marked lipophilic character and improve topical absorption of complex molecules which show improved specific activity in the skin function such as hydration, collagen structure, enzyme balance etc. Topical absorption of biologically active phytoconstituents provides local application at the site of requirement. The phytosome process intensifies herbal compounds by improving absorption increasing bioavailability& enhancing delivery to tissue. By combining the emulsifying action of the phospholipid with the standardized botanical extracts, the phytosome form provides dramatically enhanced bioavailability and delivers faster & improved absorption through skin.

Therefore application of natural molecule in form of phytosome improves its absorption, nourishes the skin & act as functional cosmetic. Functional cosmetics are topical cosmetic pharmaceutical hybrids intended to enhance the beauty through ingredients that provide additional health related function or benefits.

The dual application of phytosome as topical pharmaceutical agent & cosmetic with improved efficacy & safety results in proper utilization of herbals that is too in cost effective manner.

Different Method of Preparation of Phytosomes[7]

Phytosomes are prepared by reacting 2-3 moles of a natural or synthetic phospholipid, such as phosphatidylcholine, phosphatidylethanolamine or phosphatidylserine with one mole of phytoconstituents either alone or in the natural mixture in aprotic solvent such as dioxane or acetone in a1:1 or 1:2 ratio . 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.

Zhi Peng Chen *et al* reported the method of preparation of complex of Ginkgo biloba extract & phospholipid. They weighed ginkgo biloba extract & phospholipid equivalently and dissolved in anhydrous ethanol and then the mixture was magnetically stirred for 2 hr. at room temperature. Afterwards ethanol was evaporated off under vacuum at 40º C. The dried residues were gathered and placed in the desiccator overnight[16].

Vinod *et al* reported the method of preparation of Naringenin Phospholipid complex, According to the method equimolar concentration of Phosphatidylcholine and naringenin were placed in 100 ml round bottom flask and refluxed in dichloromethane for 3 hr. On concentrating the solution to 5-10 ml, 30 ml of n-hexane was added to get the complex as a precipitate followed by filtration. According to another method reported drug (silybin) and phospholipid were placed in a100 ml round bottom flask and dissolved in anhydrous ethanol. After ethanol was evaporated off under vaccum at 40º C the dried residues were gathered & placed in desiccators[17].

Shrikant *et al* reported the mechanical dispersion method for preparation of marsupsin-phospholipid complex. In this methhhod phospholipid is dissolved in a suitable solvent & active ingredient is added drop by drop while sonicating the solution .They also reported the method of preparation of curcumin phytosome. Curcumin phospholipid complexes are prepared by adding the phospholipid to the ethanol solution of the hydrochloric extract of turmeric rhizome under reflux & with stirring. The prepared complex can be isolated by precipitation with nonsolvent, lyophilization, spray reagent or vaccum drying[18].

Sowjanya *et al* reported the method of preparation of silybin phospholipid complex. According to them silybin & phospholipids were resolved into the medium after the organic solvent was removed under vaccum condition silybin phospholipids complex was formed.[2]

Shalini *et al* reported the solvent evaporation method for preparation of phytosome. Phytosome of gingsenoside, puerarin & kushenin are prepared by this method. Phospholipid is dissolved in a suitable solvent & active ingredient is added drop by drop while sonicating the solution[13].

Characterization of Phytosome

Morphological Studies [19]:

Penetration of the skin barrier is size dependent, and nano-sized particles are more likely to enter more deeply into the skin than larger ones, hence, particle or vesicular size determination is an important aspect in designing the formulation for topical application. The average diameters of vesicles or particles are mainly determined by dynamic light scattering using a Zetasizer. The scanning electron microscope another important device which play vital role to determined the morphological characteristics of vesicular delivery systems. It produce images by probing the specimen with a focused electron beam that is scanned across a rectangular area of the specimen; the produce images are good representations of the 3-dimensional shape of the sample. It is considered as an important evaluation parameter for phytosome preparation.

The ability to determine the positions of atoms within materials has made the transmission electron microscope (TEM), an important tool in the research and development of nanotechnologies and vesicular drug delivery system. TEM analysis plays a vital role in for phytosome preparations.

Entrapment Efficiency [20]:

Entrapment efficiency is the percentage of the initial drug or active constituent incorporated into vesicular systems. Entrapment efficiency is can be estimated by centrifugation method. The prepared formulations are placed in centrifugation tube and centrifuged at 14,000 rpm for 30 min. The supernatant (1 mL) is withdrawn and diluted with phosphate-buffered solution (PBS) (pH 7.4) or distilled water. The concentration of entrapped phytoconstituent (drug) is then determined by UV spectrophotometer at a wavelength at which the maximum peak (λ max) is obtained for that constituent.

$$\%\ entrapment = \frac{total\ drug - diffused\ drug}{Total\ drug} \times 100$$

***In-Vitro* Drug Release[20]:**

Drug release can be observed using the dialysis method at room temperature. After reconstituting the freeze-dried formulation in distilled water/PBS, an aliquot of each formulation (0.1 mL) is placed in a dialysis tube (molecular weight cutoff dialysis membrane: 12,000-14,000 Mw,), which is tightly sealed. The tube is immersed in 200 mL release medium, PBS (pH 7.4), to maintain sink condition and stirred at 300 rpm on a magnetic stirrer. Samples (0.5 mL) are taken at predetermined time intervals for 24 h, and replenished with an equal volume of fresh medium. The concentration of drug is determined by HPLC or UV after appropriate dilution with acetonitrile without further treatment.

For Topical Formulations *in Vitro* Sun Protection Factor Determination by UV Spectrophotometer [19]

Ratio of UV doses protected to unprotected gives the sun protection factor (SPF). The *in vitro* method measures the reduction of the irradiation by measuring the transmittance after passing through a film of product. The most common *in vitro* technique involves measuring the spectral transmittance at UV wavelengths from 280 to 400 nm. The observed absorbance values at 5 nm intervals are calculated using the following formula:

$$SPF_{spectrop\ hotometric} = CF \times \sum_{290}^{320} EE(\lambda) \times I(\lambda) \times Abs(\lambda)$$

Where CF = correction factor (10), EE (λ) = erythmogenic effect of radiation with wavelength λ, Abs (λ) = spectrophotometric absorbance values at wavelength λ. The values of EE X I are constants. The aliquots prepared were scanned between 290 and 320 nm and the obtained absorbance values were multiplied with the respective EE (λ) X I (λ) values. Then their summation was taken and multiplied with the correction factor.

Transition Temperature[18]: The transition temperature of the vesicular lipid systems can be determined by differential scanning calorimetry.

Surface Tension Activity Measurement[21]

The surface tension activity of the drug in aqueous solution can be measured by the ring method in a Du Nouy ring tensiometer.

Vesicle Stability[22]

The stability of vesicles can be determined by assessing the size and structure of the vesicles over time. The mean size is measured by DLS and structural changes are monitored by TEM.

Table 2: Some Patented Phytosome Technology[35]

Title of patent	Innovation	Patent No
Phospholipid complexes of olive fruits or leaves extracts having improved bioavailability	Phospholipids complexes of olive fruits or leaves extracts or compositions containing it having improved bioavailability.	EP/1844785
Compositions comprising Ginkgo biloba derivatives for the treatment of asthmatic and allergic conditions	Compositions containing fractions deriving from Ginkgo biloba, useful for the treatment of asthmatic and allergic conditions	EP1813280
Fatty acid monoesters of sorbityl furfural and compositions for cosmetic and dermatological use.	Fatty acid monoesters of sorbityl furfural selected from two diff series of compounds in which side chain is a linear or branched C3 –C19 alkyl radical optionally containing at least one ethylenic unsaturation	EP1690862
Cosmetic and dermatological composition for the treatment of aging or photo damaged skin	Composition for topical treatment of the skin comprises a substance that stimulates collagen synthesis and a substance that enhances the interaction between extracellular matrix and fibroblasts Cosmetic or dermatological composition for topical treatment	EP1640041
Treatment of skin, and wound repair, with thymosin β4	Compositions and methods for treatment of skin utilizing thymosin β4.	US/2007/ 015698
Soluble isoflavone compositions	Isoflavone compositions exhibiting improved solubility (e.g., light transmittance), taste, color, and texture characteristics, and methods for making the same	WO/2004/ 045541
An anti-oxidant preparation based on plant extracts for the treatment of circulation and adiposity problems	Preparation based on plant extracts which has an anti-oxidant effect and is particularly useful in treatment of circulation problems such as phlebitis, varicose veins, arteriosclerosis, haemorrhoids and high blood pressure	EP1214084
Complexes of saponin with phospholipids and pharmaceutical and cosmetic compositions containing them	Complexes of saponins with natural or synthetic phospholipid have high lipophilia and improved bioavailability and are suitable for use as active principle in pharmaceutical, dermatologic and cosmetic compositions.	EP0283713

Research Carried Out On Phytosome to Increase the Bioavailability:

Recent research shows improved absorption and bioavailability with phytosomes as compared to the conventional means. Most of the phytosomal studies

are focused to *Silybum marianum* (milk thistle) which contains premier liver-protectant flavonoids. Yanyu *et al*. prepared the sily marin phytosome and studied its pharmacokinetics in rats. In this 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[23].

Tedesco *et al*. reported silymarin phytosome show better antihepatotoxic activity than silymarin alone and can provide protection against the toxic effects of aflatoxin B1 on performance of broilerchicks. Busby *et al* reported that the use of a silymarin phytosome showed a better photoprotectant activity from ethanol-inducedbehavioural deficits than uncomplexed silymarin. Grange *et al*.conducted a series of studies on silymarin phytosome, containing a standardized extract from the seeds of *S. marianum*, administered orally and found that it could protect the fetus from maternally ingested ethanol[24].

Bombardelli *et al*. reported Silymarin phytosomes, in which silymarin (a standardized mixture of flavanolignans extracted from the fruits of *S. marianum*) was complexes with phospholipids.Phytosomes showed much higher specific activity and a longer lasting action than the single constituents, with respect to percent reduction of edema, inhibition of myeloperoxidase activity, antioxidant and free radical scavenging properties **[25].**

Zhi-peng Chen *et al* studied the improvement of oral bioavailability of Ginkgo biloba extract (GBE) through preparing G. biloba extract phospholipid complexes (GBP) and G. biloba extract solid dispersions (GBS). Firstly they prepared the GBP and GBS and studied their physicochemical properties by differential scanning calorimetry (DSC), powder X-ray diffraction (XRD) and dissolution. Then they studied the pharmacokinetic characteristics and bioavailability in rats. The results showed that the bioavailability of quercetin, kaempferol and isorhamnetin in rats was increased remarkably after oral administration of GBP and GBS comparing with GBE. The bioavailabilities of GBP increased more than that of GBS[16].

Comoglio *et al* studied that ethanol metabolism by cytochrome P4502El (CYP2El) produces free radical intermediates, identified as hydroxyl ethyl radicals. They observed that ***in vitro*** addition or in ***vivo*** pretreatment of rats with Silipide. A new l:l complex of silybin with phosphatidyl-choline, was able to decrease the spin trapping of hydroxyl ethyl radicals in microsomes from chronic alcohol-fed rats[26].

Suresh *et al* studied the protective effects of Ginkgoselect Phytosome (GBP) on Rifampicin (RMP) induced hepatotoxicity and the probable mechanism involved in this protection was investigated in rats. They studied that flavonoids of Ginkgo biloba easily absorbed when administered in the form of Ginkgo select Phytosome [27].

Jia *et al* studied the potential of nanostructured lipid carriers (NLCs) for the intravenous delivery of silybin, a poorly water-soluble antihepatopathy agent. In vitro release test, silybin-NLC exhibited a biphasic drug release pattern with burst release at the initial stage and sustained release afterwards. Compared with silybin solution, silybin-NLC showed higher AUC values and prolonged residence time of drug in the blood circulation [28].

Yan Lu *et al* prepared a new formulation of clarithromycin emulsion (ClaE) with the clarithromycin–phospholipid complex which was analyzed by DSC. The results showed that ClaE has enough physicochemical stability to undergo sterilization and storage. The pharmacokinetic study showed that both ClaE and ClaS fitted a three-compartment model, their pharmacokinetic curves were similar and the main parameters showed no significant difference except Vss. ClaE has a great potential for clinical applications and industrial-scale production [29].

Giovanni B *et al* evaluate the effect of a standardized formulation of a polyphenolic extract of grapes (Leucoselect-Phytosome [LP]) on low-density

lipoprotein (LDL) susceptibility to oxidation in a group of heavy smokers. Compliance was good, and no adverse effects were recorded. Subjects did not show significant modification of total cholesterol (TC), triglycerides (TG), high-density lipoprotein-cholesterol (HDL-C) and LDL-C during LP treatment. The antioxidant potential of grape seed extract polyphenols may prove effective in a model of oxidative stress[30].

Ramadan *et al* developed a novel phenolipids formulation containing a complex of quercetin and soy lecithin. Antioxidant and antiradical characteristics of native soy lecithin and phenolipids' formulations (complexes of quercetin and lecithin, 1:99 and 3:97, w/w) in the protection of triolein and sunflower oil (SFO) models stored under accelerated oxidative conditions for 15 day at 60˚C were studied. Progress of oxidation was monitored by recording the ultraviolet absorptivity and measuring the formation of oxidative products (peroxide value). The antiradical action of different lipid matrices against DPPH· and galvinoxyl radicals was screened during Shaal oven test[31].

Parsaea *et al* prepared and studied the topical performance of some new lipid-based formulations of diclofenac, diclofenac aqueous gel containing mixed micelles (sodium cholate:egg lecithin molar ratio 0.55) diclofenac lotion that contains soya lecithin, ethanol and buffer and diclofenac lipogel containing egg lecithin, isopropyl myristate, propylene glycol and ethanol. Drug release profile and diffusion coefficients were compared with brand formulation. The results showed that diclofenac lotion and lipogel maybe more suitable formulations than the conventional topical dosage form [32].

Semalty *et al* studied that poor and/or erratic oral bioavailability of polyphenolics can be improved using the Phytosome delivery system, a strategy that enhances the rate and the extent of solubilization into aqueous intestinal fluids and the capacity to cross biomembranes. Phospholipids show affinity for polyphenolics and form supramolecular adducts having a definite stoichiometry. They studied the preparation and characterization of Phytosome complexes and their activity in various medicinal (cardiovascular, anti-inflammatory, hepatoprotective, anticancer) and cosmetic (skin aging) realms of application[33].

Kashaw *et al* studied that liver an imperative organ has a crucial in the metabolism of xenobiotics that causes it to succumb to numerous hepatic diseases. Synthetic drugs exploited in the treatment of liver diseases are incompetent and may sometimes lead to serious side-effects. Many herbs have been proven to be effectual as hepatoprotective agents while many more are claimed to be hepatoprotective but lack any such scientific evidence to support such claims. Developing a satisfactory herbal therapy to treat severe liver diseases requires systematic investigation of properties such as antiviral action (Hepatitis B, Hepatitis C), anti-hepatotoxicity (antioxidants), and stimulation of liver cell regeneration activity. They reviews the scope of herbal plants as well as novel delivery systems like liposomes and phytosomes for the treatment of hepatotoxicity and liver related disorders [34].

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Received	11th April 2014
Revised	25th May 2014
Accepted	4th June 2014

J. App. Pharm. Res., 2 (2); 2014: 44 – 52