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Phytosomes - A Novel Approach for Herbal Drug Delivery

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ABSTRACT

The potential uses of large number of herbal drugs are limited due to their poor absorption and poor bioavailability after oral administration. The bioavailability can be improved by formulating an appropriate drug delivery system, which can enhance the rate and the extent of drug absorption across the lipid biomembrane. Novel drug delivery system aims to provide some control in temporal or spatial nature of the drug release in the body. The phospholipid molecular structure includes a water-soluble head and two fat-soluble tails, because of this dual solubility, the phospholipid acts as an effective emulsifier, which is also one of the chief components of the membranes in our cells. Phytosomes are advanced forms of herbal products that are absorbed and utilized in improved manner to produce better results than conventional herbal extracts. "Phytosome" is formed by complexing the polyphenolic phytoconstituents in molar ratio with Phosphatidylcholine. As far as the potential of phytosome technology is concerned, it has a great future for use in formulation technology and applications of hydrophilic plant compounds. Many areas of phytosome are to be revealed in future in the prospect of pharmaceutical application.

HIGHLIGHTS

- Phytosomes are advanced forms of herbal products that are better absorbed, utilized and as a result produce better results than conventional herbal extracts.
- Phytosomes are produced via a patented process whereby the individual components of a herbal extract are bound to specific phospholipids.
- Phytosome has an added dimension: the proven health giving activity of the phospholipids themselves.

Keywords: Bioavailability, Phytosomes, Phospholipids, Drug delivery

Since ancient times, plant preparations were widely used and are continuing till today. The potential uses of large number of herbal drugs are limited due to their poor absorption and poor bioavailability after oral administration. The bioavailability can be improved by formulating a suitable drug delivery system that can improve the rate and extent of drug absorption across lipid membrane (Chauhan *et al*., 2009). The novel drug delivery system mainly aims to deliver drug at a rate which is needed by the body and to introduce active entity into the site of action. Various number of drug delivery systems have been emerging to achieve controlled and targeted drug delivery (Dhiman *et al*., 2012). Phospholipids based drug delivery system have been found promising for the effective and efficacious herbal drug delivery (Raju *et al*., 2011).

Phytosomes are advanced forms of herbal products that are better absorbed, utilized and as a result produce better results than conventional herbal extracts. Phytosomes are often known as herbosomes. The term "phyto" means plant while "some" means cell-like. It is a complex of a natural active ingredient and a phospholipid (Saha *et al*., 2013). Phytosome is a patented process developed by Indena in Italy, a leading supplier of nutraceutical ingredients

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like milk thistle, *Ginkgo biloba*, grape seed, green tea, hawthorn, ginseng etc., to incorporate phospholipids into standardized extracts and so vastly improve their absorption and utilization. Surfactant presence enhances adhesion of the product to the surface it comes into contact with and a better interaction of various molecules with cell structure. This aspect is of importance in pharmaceutical formulations (Sharma and Roy, 2010).

Phytosomes are produced via a patented process whereby the individual components of aherbal extract are bound to specific phospholipids. Phospholipids, the major component of cell membrane are lipid molecules where glycerol is bonded to fatty acids, while the hydroxyl group, normally one of the two primary methylenes, bears a phosphate group bound to a biogenic amine or to an amino acid. In humans and animals the phospholipids are also employed as natural digestive aids and as carriers for both fat miscible and water miscible nutrients, as they are miscible both in water and in lipid environments and are well absorbed orally (Acharya *et al*., 2011). The Phytosome process produces a little cell of whichthe active components of the herbal extract are protected from destruction by digestive secretions and gut bacteria and are able to transit from a hydrophilic environment into the lipid-friendly environment of the enterocyte cell membrane and then into the cell, finally reaching the blood(Kumar *et al*., 2017).

Water-soluble phytoconstituents like many polyphenolics and flavonoids can be converted into a lipid-compatible molecular complex with help of this technology. Phospholipids from soybean (*Glycine max*) mainly phosphatidylcholine is a lipophilic agent that complex polyphenolics and widely employed to make phytosomes (Acharya *et al.*, 2011). Precise chemical analysis indicates the unit phytosome is usually a flavonoid molecule linked with at least one phosphatidylcholine molecule (Kidd, 2002). The flavonoid and terpenoid components of the herbal extracts are well for binding to phosphatidylcholine. Specifically, the choline head binds to these compounds, while the fat-soluble portion comprising the body and tail then surrounds the choline-bound material (Priyanka *et al*., 2011).

PHYTOSOME TECHNOLOGY

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 phyto- phospholipid complex. The interaction of phyto-phospholipid complex with biological membrane is shown in figure 1. 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 phytosome technology produces a little cell, whereby the plant extract or its active constituent is protected from destruction by gastric secretions and gut bacteria (Mascarella, 1993).

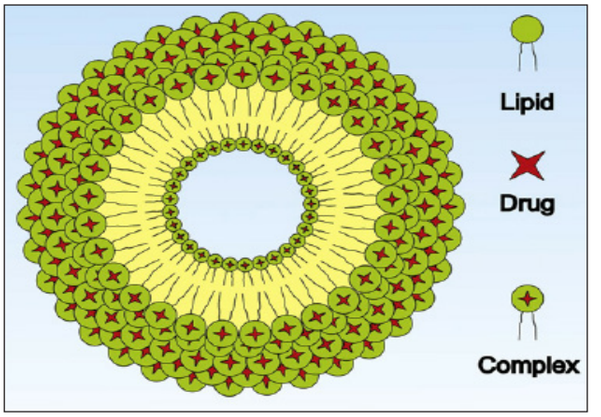

Fig. 1: Structure of phyto-phospholipid complex

Method of preparation of phytosome

Phytosomes are prepared by the reaction of 2–3 moles (preferably with one mole) of a natural or synthetic phospholipid, such as phosphatidylcholine, phosphatidyl-ethanolamine or phosphatidylserine 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. The ratio of phytosomes to phytoconstituents should be 1:1. The isolation of the complex thus formed can be done by precipitation with an aliphatic hydrocarbon

or lyophilization or spray drying (Saha *et al*., 2013). The common stages for the preparation of phytosomes are charted in Fig 2.

Quercetin-phytosome was developed by refluxing 1 mole of Quercetin with 1 mole of hydrogenated soy phosphatidylcholine (HSPC) in 20ml of dichloromethane till all the quercetin dissolved. The resulting solution was reduced to 2-3ml by volume, 10ml of n-hexane later on added to above solution to get the precipitate of the complex. Then filtration of the complex was done, later on dried under vacuum and stored in air tight container (Maiti *et al*., 2005). Similarly poor aqueous soluble curcumin was also transformed to phospholipid complex (Maiti *et al*., 2007). 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.

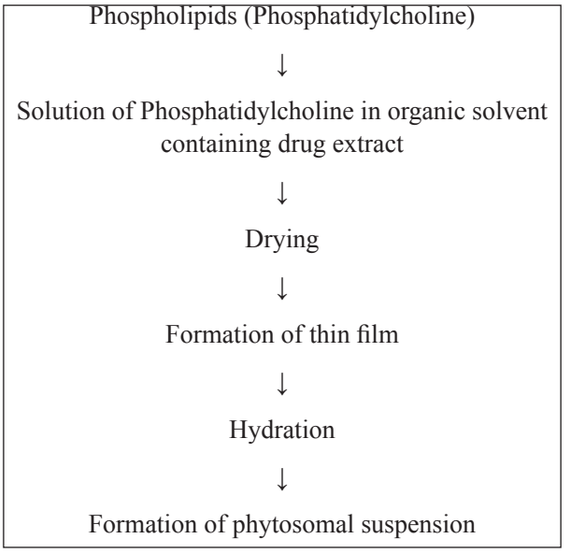

Fig. 2: Schematic presentation of phytosome preparation protocol

Solvent evaporation technique: The complex of plant extracts or specific active principles with dietary phospholipids is generally prepared by solvent evaporation techniques using alcoholic or organic solvents as reaction medium. In the more frequently used solvent evaporation technique the drug and the phospholipids are placed in the same flask containing a suitable solvent system such as tetrahydrofuran or ethanol. The reaction is allowed to be carried out at suitable fixed temperature for a fixed duration of time to get maximum possible yield and drug entrapment. Research work based on formulated marsupsin–phospholipid complex using mechanical dispersion oriented liquid antisolvent precipitation process. They dissolved soy lecithin in diethyl ether by sonication and marsupsin in double distilled water. The drug solution was then added drop wise to the phospholipids solution withsonication. The resultant formulation was then refrigerated and on analyzing, the complex showed 44% entrapment of marsupsin with 20% cumulative drug release (Sikarwar *et al*., 2008).

Herbal constituents used in phytosomal drug delivery

Flavonoids

It is recognized for antioxidant properties, flavonoids are widely distributed in food and medicinal plants. Flavonoid preparations with the greatest health giving potential and making them into phytosomal preparations, Indena scientists achieved a breakthrough in phytomedicine (Singh *et al*., 2014).

Terpenoids

They are natural products and related compounds formally derived from isoprene units containing oxygen in various functional groups

Carotenoids

This class includes carotenes, xanthophylls and certain compounds that arise from rearrangement of the skeleton or by loss of part of this structure.

Isoprenoids

Compounds formally derived from isoprene (2-methylbuta-1,3-diene), the skeleton of which can generally be discerned in repeated occurrence in the molecule. The skeleton of isoprenoids may differ from strict additively of isoprene units by loss or shift of a fragment, commonly a methyl group. The class includes both hydrocarbon and oxygenated derivatives (Swati and Sapna, 2012).

Terpenes

Hydrocarbons of biological origin having carbon skeletons formally derived from isoprene [CH_2=C(CH_3)CH=CH_2]. This class is subdivided into the C5 hemiterpenes, C10 monoterpenes, C15 sesquiterpenes, C20 diterpenes, C25 sesterterpens, C30 triterpenes, C40 tetraterpenes (carotenoids) and C5 npolyterpenes.

PROPERTIES OF PHYTOSOMES

Physio chemical properties

Phytosome is a complex between a natural product and a phospholipid. Such a complex results from the reaction of stoichiometric amounts of phospholipid with the selected polyphenol (like simple flavonoids) in a substrate. They are lipophilic substances with a definite melting point, freely soluble in nonpolar and aprotic solvents in which the hydrophilic moiety is absent. They are moderately soluble in fats and insoluble in water. When treated with water, they assume a micelle shape, forming structures which resemble liposome. In the complexes formed, the polar head of the phospholipid is participated while the fatty acid retain its high degree of mobility responsible for marked lipophilia to the new molecule.In liposomes the active principle is dissolved in an internal pocket or floats 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 (Semalty *et al*., 2007; Saha *et al*., 2013).

Biological properties

To demonstrate the biological behavior of phytosomes, there have been pharmacokinetic and pharmacodynamic studies in experimental animal and human subjects. Results from these studies shows that there is an increased bioavailability of phytosomes over the non complexed botanical derivatives (Patel *et al*., 2009).

Characterization and evaluation of Phytosomes

The behavior of phytosomes in both physical and biological system is governed by the factors such as physical size, membrane permeability, chemical composition, quantity and purity of the starting materials. Therefore, the phytosomes are characterized for physical attributes like shape, size, distribution, percentage drug capture entrapped volume, percentage drug released and chemical composition (Jain, 2005). Complexation and molecular interactions between phytoconstituents and phosphatidylcholine in solution have been studied by Proton Nuclear Magnetic Resonance Spectroscopy (H-NMR), Carbon Nuclear Magnetic Resonance Spectroscopy (C-NMR) as well as by Infra Red spectroscopy. Thermal Gravimetric Analysis (TGA) and Differential Scanning Calorimetry (DSC) are other techniques employed for the detection and measurement of thermal effects such as fusion, solid–solid transitions, glass transitions, loss of solvent and decomposition to characterize a solid phytosomes (Acharya *et al*., 2011). Further NMR data available on the marketed phytosomes also indicates that the signals of the fatty chain are almost unchanged. Such evidences inferred that the two long aliphatic chains are wrapped around the activeprinciple, producing a lipophilic envelope, which envelope the polar head of the phospholipids and the herbal extract.

CHARACTERISATION TECHNIQUES

Visualization

Visualization of phytosomes can be achieved using Transmission Electron Microscopy (TEM) and by Scanning Electron Microscopy (SEM) (Maghraby *et al*., 2000).

Vesicle size and Zeta potential

Dynamic light scattering (DLS) along with the computerized inspection system and photon correlation spectroscopy (PCS) can be used to determine the particle size and zeta potential (Fry *et al*., 1978).

Entrapment efficiency

Ultracentrifugation technique can be used for measuring the entrapment efficiency of a drug by the phytosomes (Patel *et al*., 2009).

Transition temperature

Differential scanning calorimetry is used for determination of transition temperature of the vesicular lipid systems (Cevc *et al*., 1995).

Surface tension activity measurement

The ring method in a Du Nouy ring tensiometer is used for measuring the surface tension activity of the drug in an aqueous solution (Berge *et al*., 1997).

Vesicle stability

The assessment of size and structure of the vesicles over the time determines the stability of the vesicles. DLS provides the measurement of the mean size and TEM monitors the structural changes (Dayan and Touitou, 2002).

Drug content

The amount of drug can be quantified by a modified high performance liquid chromatographic method or by a suitable spectroscopic method (Patel *et al*., 2009).

EVALUATION OF PHYTOSOMES

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 (Semalty *et al*., 2006).

Proton Nuclear Magnetic Resonance Spectroscopy (H-NMR)

The NMR spectra are employed for estimating the complex formation between the active phytoconstituents and the phosphatidylcholine molecule. The NMR spectra of (+)-catechin and its stoichiometric complex with distearoyl phosphatidylcholine has been studied by Bombardelli *et al*. (1991). In non polar solvents, there is a marked change of the H-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 protons belonging to the phytoconstituents are broadened. In phospholipids, there is broadening of signals while the singlet corresponding to the N-$(CH_3)_3$ of choline undergoes an up field shift.

Carbon Nuclear Magnetic Resonance Spectroscopy (C-NMR)

In the C-NMR of the phytoconstituents and the stoichiometric complex with the phosphatidylcholine when recorded in room temperature all the phytoconstituents carbons are invisible. The signals corresponding to the glycerol and choline portion of the lipid are broadened and some are shifted, while most of the resonance of the fatty acid chains retains their original sharp line shape.

Fourier Transform Infrared Spectroscopy (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 can also be considered as a valuable tool in confirming the stability of the phytosomal complex. The stability can be confirmed by comparing the spectrum of the complex in solid form with that of the spectrum of micro-dispersion in water after lyophilization at different times.

In vitro and *in vivo* evaluations

Models of *in vitro* and *in vivo* evaluations are selected on the basis of the expected therapeutic activity of the biologically active phytoconstituents present in the phytosomes (Semalty *et al*., 2006). For example, in vitro anti hepatotoxic activity can be assessed by the antioxidant and free radical scavenging activity of the phytosomes. For assessing anti-hepatotoxic activity *in vivo*, the effect of prepared phytosomes on animals against thioacetamide, paracetamol or alcohol induced hepatotoxicity can be examined (Abrol *et al*., 2005; Comoglio *et al*., 1995). Gazayerly *et al*. (2013) studied the antioxidant and hepatoprotective effects of silymarin phytosomes compared to milk thistle extract in carbon tetrachloride induced hepatotoxicity in rats. Skin sensitization and

tolerability studies of glycyrrhetinic acid-Phytosome® ointment, a commercial product, describe the *in vivo* safety evaluation methodology. Filburn *et al*. (2007) studied the bioavailability of a silybin- phosphatidylcholine complex in dog models to examine the pharmacokinetic parameters of this new complexed form.

BIOAVAILABILITY OF PHYTOSOMES

It is evident from many research studies that phytosomes have an improved absorption and bioavailability when compared to the conventional means. Most of the research studies are focused on *Silybum marianum* (milk thistle), the fruit of which contains a water-soluble phytoconstituent (flavonoids) which is known to have a hepatoprotective effect. But these flavonoids are poorly absorbed. The chief and most potent constituent of milk thistle is Silybin.

According to Crema *et al*. (1990) when single oral doses of Silybin directly bound to phosphatidylcholine (Silybin phytosome) are fed, its absorption was approximately seven times more than the absorption from regular milk thistle extract containing 70-80% silymarin content.

A research study was conducted by Yanyu *et al*. (2006) in which he prepared silymarin phytosome and studied its pharmacokinetics in rats. In the study, the bioavailability of silybin in rat was increased remarkably after oral administration of silybin- phospholipid complex due to an impressive improvement of the lipophilic properties of silybin- phospholipid complex and improvement of biological effect of silybin. There are various phytosomes are commercially available in the market (Table 1).

Table 1: Commercially available phytosome preparation

Sl. No.	Phytosomes	Phytoconstituents complexed	Indications
1	Silybin Phytosome	Silybin from Milk thistle seed	Hepatoprotective, antioxidant
2	Ginkgo Phytosome	Flavanoids from *Ginkgo biloba*	Anti-ageing, Protects brain and vascular lining
3	Ginseng Phytosome	Ginsenosides from *Panax ginseng*	Immunomodulator
4	Green Tea Phytosome	Epigallocatechin from *Theasinesis*	Systemic Antioxidant Anticancer
5	Curcumin Phytosome	Polyphenol from *Curcuma longa*	Cancer
6	Grape Seed Phytosome	Procyanidins from *Vitisvinifera*	Cardio-Protective Systemic Antioxidant
7	Hawthorn Phytosome	Flavanoids from *Crataegus* species	Anti hypertensive and cardioprotective
8	Olive Oil Phytosome	Polyphenols from *Oleaeuropea*	Anti-Inflammatory Anti Hyperlipidemic
9	Echinacea Phytosome	Echinacosides from *Echinacea angustifolia*	Immunomodulator, nutraceuticals
10	Sericoside Phytosome	Sericosides from *Terminalia* sericea	Skin tonic
11	Visnadine Phytosome	Visnadine from *Ammi visnaga*	Circulation improver
12	Centella Phytosome	Terpenes from *Centella asiatica*	Vein and skin disorders
13	Palmetto berries Phytosome	Fatty acids, alcohols and sterols	Non cancerous prostate enlargement, antioxidant
14	Bilberry Phytosome	Anthocyanosides extract	Antioxidants

Acharya *et al*. (2011).

CONCLUSION

Phytosomes are novel formulations which offer improved bioavailability of hydrophilic flavonoids and other similar compounds through the skin or gastrointestinal tract. The formulation methodology for phytosome is simple that can be easily upgraded to a commercial scale. The characterization methodologies and analytical techniques are well established for this type of novel formulation. Many patents and marketed formulations are already approved for innovative formulations, processes and applications of phytosomes. As far as the potential of phytosome technology is concerned, it has a great future for use in formulation technology and applications of hydrophilic plant compounds. Many areas of phytosome are to be revealed in future in the prospect of pharmaceutical application. Phytosome has an added dimension: the proven health giving activity of the phospholipids themselves.

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