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PHYTOSOMES: A BRIEF OVERVIEW

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ABSTRACT

Phytoconstituents have been used in medicine since ancient times due to their various pharmacological actions. Inspite having excellent bio- activity of plant extract and their phytoconstituents in vitro they have no in vivo actions due to their poor lipid solubility or inappropriate molecular size or both, which results in their poor absorption andlower bioavailability. Phytosomes are the novel formulation technology which helps to overcome these problems. Phytosomes are produced by a process whereby a standardized plant extract or its constituents are bound to phospholipids; mainly phosphotidylcholine, producing a lipid compatible complex. The phytosome technology has been applied over many popular herbal drugs such as Ginko biloba, hawthorn, olive oil, grape seed, green tea and ginseng. This article reviews the recent trends in phytosomes drug delivery.

Keywords: *Phytosomes; Bioavailability; Plant Extract; Drug Delivery.*

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INTRODUCTION

Plants or part of the plant has been used in the treatment of various diseases and disorder since ancient times.Various pharmacological and chemical studies have been carried out on a whole lot of plant extracts to know their and biological activities and chemical composition[1,2]. During the separation and purification of the various components of an extract sometimes the activity of the purified component is lost. Most of the bioactive constituent of plant extract are water-soluble molecules (eg.phenolics flavonoids and terpenoids) and due to their poor lipid solubility they are not able to cross the lipoidal biological membranes, which result in poor bioavailability[3].

Many drug delivery system and carriers has been developed to improve the bioavailability like immunoglobins, erythrocytes, reverse micelles, phytosomes, pharmacosomes etc[4].

Water soluble flavonoid molecules can be converted into lipid-compatible molecular complexes which is known as phytosomes. The meaning of " phyto" is plant and "some" is cell like. Phytosome is a novel patented technology developed to incorporate standardized plant extracts into phospholipids to give a lipid compatible molecular complexes,with improved bioavailability and absorption which is called as phytosomes (also often referred as herbosome in certain literature)[5]. Phospholipids are complex molecules which are used in the formation of cell membranes. In humans and other higher animals the phospholipids are also employed as natural digestive aids and act as carriers for both fat-miscible and water miscible nutrients which are easily absorbed orally. The phospholipid mainly used to make phytosomes, is phosphatidylcholine, obtained form soyabean (Glycine max). Phytosomes have more bioavailability as compared to conventional herbal extracts coz of their enhanced capacity to cross the lipoidal biomembrane and finally reaching the systemic circulation. Phytosome has been an emerging trend in delivery of herbal drug and nutraceuticals[6].

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THE PHYTOSOMETECHNOLOGY

The flavonoid and terpenoid constituent of plant extracts lend themselves quite well for the direct binding to phosphatidylcholine. Phytosomes are formed by the reaction of a stoichiometric amount of the phospholipid (phosphatidylcholine) with the standardized extract or polyphenolic constituents (like simple flavonoids) in a non polar solvent[7]. Phosphatidylcholine is a bifunctional compound, the phosphatidyl moiety is lipophilic and the

choline moiety is hydrophilic in nature. Specifically the choline head of the phosphatidylcholine molecule binds to polar compounds while the lipid soluble phosphatidyl part comprising the body and tail envelopes the choline bound material. Thus the phytoconstituents forms a lipid compatible molecular complex with phospholipids, called as phytophospholipid complex. Molecules are bound through chemical bonds to the polar choline head of the phospholipids, as can be demonstrated by specific spectroscopic techniques[8,9]. Precise chemical analysis shows the unit phytosome is usually a flavonoid molecule linked with at least one phosphatidylcholine molecule. The result in the formation of micro sphere or a cell. 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 because of the gastroprotective property of phosphatidylcholine[10].

PROPERTIES OF PHYTOSOMES

Physico Chemical Properties:

Phytosomes is a complex connecting natural product and natural phospholipids, like soyaphospholipids. Such a complex is obtained by reaction of stoichiometric amounts of phospholipids with the substrate in an appropriate solvent. According to the spectroscopic data the main phospholipids-substrate interaction is due to the formation of hydrogen bonds between the polar head of phospholipids (i.e. ammonium and phosphate groups) and the polar functionalities of the substrate. Phytosomes on treatment with water assumes a micellar shape forming liposomal-like structures. In liposomes the active constituent is dissolved in the internal pocket or is floating 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. For example in the case of the catechin distearoyl phosphatidylcholine complex, H-bonds is formed between the phenolic hydroxyl ends of the flavone moiety and the phosphate ion on the phosphatidylcholine moiety. Phosphatidyl choline can be deduced from the comparison of ^{1}H-NMR and ^{13}C-NMR spectra of the complex with those of the pure compound. The signals of fatty chain remain unchanged. Such evidences confirms that too long aliphatic chains are wrapped around the active principle, forming a lipophilic envelope, which shields the polar head of the phospholipid and flavonoid molecule and makes the complex soluble in low polarity solvent[11].

Biological Properties:

Phytosomes are advanced forms of herbal products that are better absorbed, utilized and thus produce better results than conventional herbal extracts. The increased bioavailability of the phytosome over the uncomplexed derivatives has been demonstrated by pharmacodynamic tests and pharmacokinetice studies in experimental animals and in human subjects[12].

ADVANTAGES OF PHYTOSOMES

The phytosome technology has transformed the nutraceutical industry by serving the following benefits[13, 14, 15, 16]

1. Phytosomes produces a little cell where the important components of herbal extracts are protected from destruction by gut bacteria and digestive secretions.
2. It assures proper delivery of drug to the respective tissues.
3. The safety of the nutrients of the herbal extract need not be compromised by conveying the herbal drug as means of phytosomes.
4. As the absorption of active component is improved, its small dose can produce desired results.
5. The bioavailability of drug is enhanced remarkably.
6. Efficiency of entrapment is high and more over predetermined because drug itself is in conjugation with lipids in forming vesicles.
7. Formulation is easy as there is no problem in drug entrapment.
8. Phytosomes shows better stability due to the formation of chemical bonds between phyto-constituents and the Phosphatidylcholine molecules .
9. Besides acting as a carrier Phosphatidylcholine used in formulating phytosome process also nourishes the skin as it is an important part of a cell membrane.
10. Phytosomes are more useful than liposomes in skin care products.
11. Phytosomes have significantly greater clinical benefit.
12. Besides acting as a carrier Phosphatidylcholine used in preparation of phytosomes also acts as a hepatoprotective resulting in synergistic effect when hepatoprotective substances are employed.
13. They are less soluble in aqueous media which allows the formation of stable emulsions or creams.
14. Liver targeting is improved by increasing the solubility in bile salt.

PREPARATION METHODS

Phytosomes are prepared by complexation of polyphenolic phytoconstituents in 1:2 or 1:1 ratio with natural or synthetic phospholipid like phosphatidylcholine, phosphatidylethanolamine or phosphatidyiserine, either alone or in an aprotic solvent, such as dioxane or acetone. The complex that is formed is isolated by precipitation with an aliphatic hydrocarbon or spray drying or lyophilization[17]. Some liposomal drug complexes are effective in the presence of water or buffer solution where the phytosomes interact with a solvent which has a reduced dielectric constant. The common stages for phytosomes preparation are charted in Fig.1[18]. Mareno and Lampertico [19], Jiang et al [20], Maiti et al [21] and

Maiti et al [22] have described the methods used for phytosome preparation. Jiang, et al. (2001) have optimized the conditions of the preparation using a uniform design and step regression and have prepared Herba Epimedii total flavonoid phytosomes (EFP) by means of solvent evaporation technique and also studied the cumulative dissolution of different ratios of EFP-PVP precipitates by means of dissolution release. The conditions for the preparation are: lecithin to PVP and solvent-tetrahydrofuran ratio - 2:5, temperature - 40°C and reaction time-3 hrs. The oil/water apparent partition coefficient of icariin was increased more than 4-fold by phospholipid. The cumulative dissolution of Herba Epimedii flavonoids of the EFP-PVP precipitate was very higher than that of its physical mixture and a Herba Epimedii extract tablet. Yanyu et al (2006) prepared a silybin-phospholipid complex using ethanol as a solvent. Silybin and phospholipids were resolved into the medium, after removing the organic solvent under vacuum condition, and a silybin-phospholipid complex was formed [23].

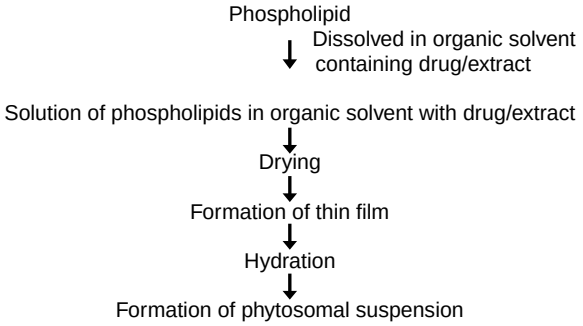

Fig. 1 : *Common stages for preparation of Phytosome [18].*

CHARACTERIZATION OF PHYTOSOME

The behaviour of phytosomes in both physical and biological system is governed by the factors such as membrane permeability, physical size, chemical composition, percentage entrapped solutes, quantity and purity of the starting material. Molecular interactions and complexation between phytoconstituents and phosphatidylcholine in solution have been studied by 13C-NMR, 1H-NMR, 31P-NMR, as well as by IR spectroscopy. Thermal gravimetric analysis (TGA) and differential scanning calorimetry (DSC) are some other techniques employed for the detection and measurement of thermal effects such as fusion, glass transitions, solid–solid transitions, loss of solvent, and decomposition to characterize a solid phytosome. Further NMR data available on the marketed phytosomes also shows that the signals of the fatty chain are almost unchanged. Such evidences dipicts that the two long aliphatic chains are wrapped around the active principle, giving a lipophilic envelope, which covers the polar head of the phospholipids and the herbal extract [24-26].

DIFFERENCE BETWEEN LIPOSOMES AND PHYTOSOMES

Like phytosomes, a liposome is formed by mixing a water soluble constituent with phosphatidylcholine in definite ratio under specific conditions. Here, no chemical bond is formed; the phosphatidylcholine molecules just surround the water soluble substance. There may be hundreds and thousands of phosphatidylcholine molecules which are surrounding the water-soluble compound. In contrast, with the phytosome the phosphatidylcholine and the plant components actually form a 1:1 or 2:1 molecular complex depending on the chemical bonds involved in the complex. This difference makes the phytosome much better absorbed than liposomes showing better bioavailability. Phytosomes have also been found to be superior to liposomes in topical and skin care products (Fig. 2) [27].

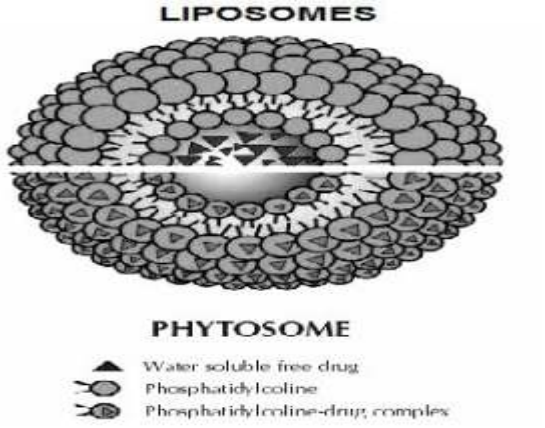

Fig. 2: *Difference between liposome and phytosome [27].*
The molecular organization of the liposome (upper segment)
The molecular organization of phytosomes (lower segment)

SOME PATENTED TECHNOLOGIES RELATED TO PHYTOSOMES

There are a number of innovative processes and formulation research studies carried out in the field of phytosomes by number of academic scientist as well as by industrial laboratories. Some patents for phytosomes and other related technologies along with their applications and innovations are listed in the below table.

ENHANCED BIOAVAILABILITY

Many researches have been done which shows improved absorption and bioavailability of phytosomes in comparison to the conventional methods. Most of the phytosomal studies are carried out on Silybum marianum (milk thistle) which contains liver-protectant flavonoids. The fruit of the milk thistle plant contains flavonoids which have hepatoprotective property[36,37]. Silybin is the most potent constituent of silymarin, the flavonoid complex from milk thistle. A standardized extract from Silybum marianum (milk thistle) is an wonderful liver protectant but is very poorly absorbed orally.

Table 1: *Some Patented Technologies :*

Title of patent	Innovation	Patent No.	Reference
Phospholipid complexes of olive fruits or leaves extract shaving improved bioavailability	Phospholipids complexes of olive fruits or leaves extracts or compositions containing it having improved bioavailability.	EP/1844785	28
Compositions comprising Ginko 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	29
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	30
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	31
Treatment of skin, and wound repair, with thymosin beta 4	Compositions and methods for treatment of skin utilizing thymosin β4	US/2007/ 0015698	32
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	33
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	34
Complexes of saponins with phospho-lipids and pharmaceutical and cosmetic compositions containing them	Complexex of saponins with natural or synthetic phospholipids have high lipophilia and improved bioavailability and are suitable for use as active principle in pharmaceutical, cosmetic, dermatologic compositions.	Ep0283713	35

Yanyu et al., prepared the silymarin phytosome and has shown its pharmacokinetics in rats. A study showing that after oral administration of prepared Silybin phospholipid complex, the bioavailability of Silybin in rats was increased drastically because of the increased lipophilic property of Silybin-phospholipid complex which further improved the biological effect of Silybin [38].

Tedesco et al., reported Silymarin phytosome showed improved anti-hepatotoxic activity than silymarin alone. Silymarin phytosome protects the toxic effects of aflatoxin B1 on performance of broiler chicks [39].

Busby et al., mentioned that the Silymarin phytosome showed a better fetoprotectant activity from ethanol-induced behavioral deficits than uncomplexed silymarin [40].

Grange et al., conducted various studies on silymarin phytosome having a standardized extract from the seeds of S. marianum, and was found to protect the fetus from maternally ingested ethanol when administered orally[41].

Bombardelli et al., reported Silymarin phytosomes, in which silymarin (a standardized mixture of extracted flavanolignans) was complexed with phospholipids. Phytosomes showed prolonged action and much higher specific activity in comparison to single constituents, with respect to percent reduction of odema, antioxidant, inhibition of myeloperoxidase activity and free radical scavenging properties [42].

Barzaghi et al., assessed the absorption of Silybin bound to phosphatidylcholine. Plasma Silybin levels were determined after the admistration of single oral dose of Silybin phytosome. The results shows that the absorption of Silybin from Silybin phytosome was approximately seven times higher as compared to the absorption of Silybin from regular milk thistle extract [43].

Moscarella et al., performed a human study on 232 patients with chronic hepatitis (alcohol viral or drug induced). They were treated with Silybin phytosome at a dose of 120 mg either twice or thrice daily, the body function returned to normal faster in the patients taking Silybin phytosome as compared to a group of patient taking commercially available silymarin, 117 controls (49 treated with for up to 120 days, liver untreated or given placebo) [44].

Studies have shown ginkgo phytosome showed better results than the conventional standardized extract from the plant. In a bioavailability study done with healthy human volunteers it was found that the phytosomal GBE produced greater plasma concentration of terpenes than the non-phytosomal GBE. Its improved oral bioavailability and excellent tolerability makes it the ideal Ginkgo product for long term treatment. Its major indications are peripheral vascular disorders and cerebral insufficiency[45,46].

Grape seed phytosome is prepared from grape seed extract containing oligomeric polyphenols complexed with phospholipids. The main properties of procyanidin flavonoids of grape seed is that they increase the total antioxidant activity provide prevention against artherosclerosis protection agaist ischemia induced damage of the heart.[47,48]

Green tea extract contains a totally standardized polyphenolic fraction containing epigallocatechin obtained from green tea leaves (Thea sinensis) . These compounds are used in cancer and atherosclerosis The phytosome of green tea extract is more bioavailable than the conventional extract.

One of the major drawback is that green tea polyphenols have very poor oral bioavailability from conventional extracts. The complex formation of polyphenols from green tea with phospholipids strongly improves their poor oral bioavailability [49].

Maiti et al., developed the quercetin phospholipid phytosomal complex which showed better pharmacological action than the conventional extract [50]. Recently phytosomes of curcumin (flavonoid from turmeric) and naringenin (flavonoid from grape fruit) were studied [51]. The antioxidant activity of the quercetin phytosome was significantly higher than pure quercetin in all dose levels tested. Extract of Serenoa repens ,extract of Vaccinium myrtillus, extract of Coleus forskohlii and Ximenynic acid extracted from Santalum album, Esculoside, glycosylated coumarin obtained from Aesculus hippocastanum, Ruscogenins, group of saponins extracted from Ruscus aculeatus are worked upon for better bioavailability through the formation of phytosomes by patented process [52].

Table 2: *Therapeutic applications of different phytosomes with their dose* [53-56].

Phytosomes	Phytoconstituent complexed with PC	Daily dosage	Indication
Leucoselect ® phytosome	Procyanidolic oligomers (PCOs) from grape seeds	50–100mg	Systemic antioxidant, specific. Best choice for most people under age of fifty. Also specific for the eyes, lungs, diabetes, varicose veins, and protection against heart disease.
Greenselect ® phytosome	Epigallocatechin 3-O-gallate from Camelia sinensis (Green tea)	50–100mg	Systemic antioxidant. Best choice for protection against cancer and damage to cholesterol
Ginkgoselect ® phytosome	24 % ginkgo flavono glycosides from Ginkgo biloba	120 mg	Best choice for most people over the age of 50. Protects brain and vascular lining 57.
Silybin phytosome	Silybin from silymarin (milk thistle)	150 mg	Best choice if the liver or skin needs additional antioxidant protection
Hawthorn phytosome	Flavonoids	100 mg	Best choice in heart disease
Panax ginseng phytosome	37.5% ginsenosides from roots of Panax ginseng	150mg	As a Food Product
Glycyrrhiza phytosome	18-beta glycyrrhetinic acid	–	These improve capillary tone, reduce abnormal blood vessel permeability & are potent antioxidants. They hold great potential for the management of retinal blood vessel problems and venous insufficiency.
Mirtoselect ® phytosome	Anthocyanosides from an extract of Bilberry	–	It delivers fatty acids, alcohols and sterols that benefit prostate health. Also beneficial for non-cancerous prostate enlargement
Sabalselect ® phytosome	An extract of saw palmet to berries through supercritical CO2 (carbon dioxide) extraction	–	It enhances immune function in response to a toxic challenge
PolinaceaTM phytosome	Echinacosides and a unique high-molecular weight Polysaccharide from Echinacea angustifolia	–	As potent antioxidants, inhibit harmful oxidation of LDL cholesterol, and also have anti-inflammatory activity.
OleaselectTM phytosome	Polyphenols from olive oil	–	Indicated for venous disorders, including chronic venous insufficiency of the lower limbs.
LymphaselectTM phytosome	A standardized extract of Melilotus officinalis	–	

CONCLUSION

Polyphenolics polar phytoconstituents, when complexed with phospholipids like phosphotidylcholine give rise to a new delivery system called Phytosomes. Phytosomes have improved pharmacokinetic and pharmacological parameter, which enable them to be used for different therapeutic purposes like cardiovascular, anti-inflammatory, immunomodulator, anticancer, antidibetic etc. Like liposomes, Phytosomes products show their potential in cosmetics as anti-skin aging agents and for the use of other non-pathogenic skin conditions. The phytosome technology forms a link between the conventional delivery system and novel drug delivery systems of the phytoconstituents.

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