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Phytosomes: Novel Carrier for Bioavailability Enhancement of Phytoconstituents

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ABSTRACT
Polyphenolic Phytoconstituents of flavonoid class have been known for centuries possessing diverse health giving properties but not extensively formulated to modern dosage form due to problems in gastrointestinal absorption . A covalent complex of such Phytoconstituents with phosphatidylcholine – the principle phospholipid of biological membrane makes them significantly bioavailable and stable. The complex such developed is a patented technology and given the name Phytosomes. The term "phyto" means plant while "some" means cell-like. Phytosome is a complex of a natural active ingredient and a phospholipid. It is claimed that Phytosome increases absorption of "conventional herbal extracts" or isolated active principles. The Phytosomeprocess is that combines herbal extracts and soybean phospholipids (lecithin). Phytosome are created when the standardized extract and active ingredients of a herb are bound to the phospholipids on a molecular level. This review is an attempt to highlights the unique property of phospholipids in drug delivery,recent progress in research on the preparation, characterization, structural verification, advantages, recent patents, marketed formulation their application to enhance the bioavailability of active herbal Phytoconstituents.

KEYWORDS
Phospholipid, Bioavailability, Herbal preparations, Flavonoids

I. INTRODUCTION

Phytoconstituents are natural healers used in the world from millions & billions of years. India is a country which has a huge knowledge base of Ayurveda whose values are realized within the recent years. Over the past years, great advancements has been made for the development of Novel Drug Delivery Systems (NDDS) for various plant extracts and their active constituents. Phytosome is a novel approach of drug delivery system, is applied in herbal drugs, contains herbal drugs loaded in vesicles available in the nano form, thus, helps in increasing the effectiveness & reducing the side effect of varied herbal compounds & herbs. This are advanced herbal products produced by binding individual component of herbal extract to phytolipid mainly phosphatidylcholine resulting in a product that the conventional herbal extract. Phyto- Phospholipid complex (phytosome) results from,reaction of stoichiometryquantity of lipid (phosphatidylcholine mainly) with extract or polyphenolic constituents like simple flavonoid in an aprotic solvent. . The newly created Phytosome structures contain the active ingredients of the herb surrounded by the phospholipids. 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. An emulsifier is a material that can combine two liquids that normally will not mix well together. By combining the emulsifying action of the phospholipids with the standardized botanical extracts, the Phytosome form provides dramatically enhanced bioavailability and delivers faster and improved absorption of the active constituents of the herb in the intestinal tract. The review focuses on phytosome that proven as excellent carriers for enhancing the solubility, bioavailability of herbal active components & their applications.

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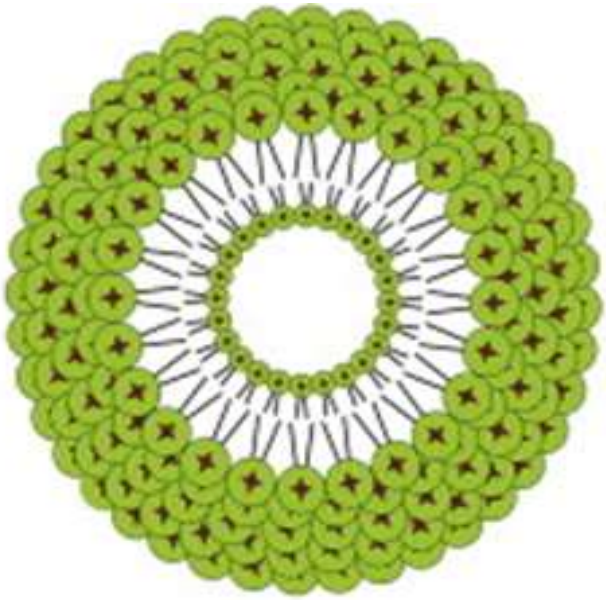


STRUCTURE AND COMPONENT

1) Phytosomes are "cell-like" structure which are a result of reaction of 2 to 3 moles of phytoconstituents with one mole of phospholipid which lead to encapsulation of phytoconstituents in individual phosphatidylcholine head.

2) Each phosphatidylcholine moiety has hydrophilic head and two lipophilic tail, making it bifunctional in nature, thus giving better absorption and eventually increase the bioavailability of herbal medicine.

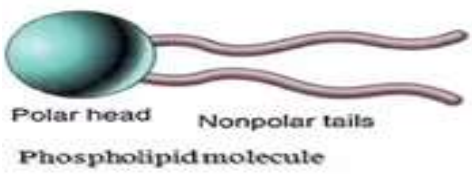
COMPONENTS INCLUDES-

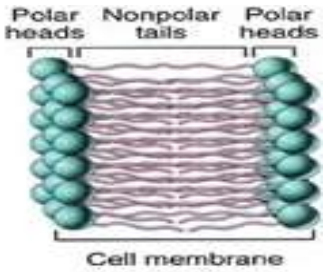
- Phospholipid
- Solvent system
- Phyto- active constituents

A. PHOSPHOLIPID :

These are class of lipid whose molecule has a hydrophilic head containing a phosphate group, and two hydrophobic tails derived from fatty acids, joined by a glycerol molecule. Also known as phosphatides.Phospholipids offer the potential to improve the bioavailability of herbal medicinal active ingredients while minimizing changes in plasma profile data, but characterization of appropriate lipid excipients for the needs of the body is a prerequisite.Phospholipids can be divided into glycerophospholipids and sphingomyelins depending on the backbone. Additionally such as phosphatidylcholine (PC), phosphatidylethanolamine (PE), phosphatidylinositol (PI), phosphatidic acid (PA), and phosphatidylserine (PS).7Phosphatidylcholine (PC), Phosphatidylethanolamine (PE), and phosphatidylserine (PS) are the main phospholipids used to prepare complexes.Among these phospholipids, Phosphatidylcholine is the used to accustomed prepare lipids complexes. The benefits of Phosphatidylcholine include

- Their amphipathic property that provides it moderate solubility in water and lipid media.
- Moreover, PC is a vital element of cell membranes
- It exhibits robust biocompatibility
- Low toxicity
- Exhibit hepatoprotective activities, and have been reported to show clinical effects in the treatment of liver diseases.





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B. SOLVENT SYSTEM:

In contrast to the phospholipids, where phosphatidylcholine is the main lipid used in the preparation of phytosomes, a wide range of solvents have been used as reaction mediums for formulating phytosomes.

The solvent system used depending on the solubility of both phytoconstituents and the phospholipids.

1) Aprotic Solven t:- Tetrahydrofuran, Aromatic hydrocarbons, halogens, methylene chloride, ethyl chloride, ethyl acetate, cyclic ethers, etc. have been used to prepare phytophospholipid complex.
2) Non-Solvents :- n-Hexane is commonly used in the formulation
3) Alcohol :- Ethanol, Methanol.

ADVANTAGES OF PHYTOSOMES

1)The bioavailability of plant extracts is enhanced due to their complexation with phospholipids and thus results in improved absorption in the intestinal tract
2) As the absorption of active constituent(s) is improved, its dose requirements are also reduced.
3) Phytophospholipid complexes possess better drug complex rate and the preparation of phytophospholipid complexes is not complicated
4)Shows better stablility characteristics, because of the formation of chemical bonds between Phytoconstituents and phospholipid molecules
5)Phosphatidylcholine, the carrier used in the preparation of phytosomes, also is a hepatoprotective, thus giving a synergistic effect when hepatoprotective substances are employed
6) Phytosomes assures proper delivery of drugs to respective tissues.
7)The nutrient safety of the herbal extracts need not be compromised by conveying the herbal drug as a means of Phytosomes also added nutritional benefits of phospholipids obtained
8)Cost effective delivery of Phytoconstituents is achieved by phytosome technology
9)Phytosomes are also superior to liposomes in skin care products.

DISADVANTAGES OF PHYTOSOMES

1)Phytoconstituents is quickly eliminated from phytosomes
2)Phospholipid (lecithin) can encourage proliferation on MCF breast cancer cell line
3) A foremost drawback of phytosomes reported as leaching of phytoconstituents off the ‘same’ which diminishes the anticipated drug concentration.

PROPERTIES OF PHYTOSOMES

A)Chemical properties:-
1) Phytosomes is a complex between a natural phospholipid (polymer).
2) The phytosome complex is obtained by reaction of suitable amounts of phospholipid and the substrate in an appropriate solvent such as glycerol.
3) On the basis of spectroscopic data, it has been shown that, due to the formation of hydrogen bonds between the polar head of phospholipid (i.e.phosphate and ammonium group) and polar functionalities of the substrate.
4)Due to their bifunctional nature, Phytosomes are better able to transition from a hydrophilic environment into the lipid-friendly environment of the outer cell membrane and from there into the cell, finally reaching the blood.
5)On interaction with water, phytosomes assumes a micellar-shape forming liposomial-like structure.
B) Biological properties:-
1) Phytosomes are ampiphillic substances, having definite melting point, commonly soluble in lipids. The low solubility in aqueous media, makes the formulation of stable emulsions and creams possible.
2) Phytosomes are advanced forms of herbal produces that are better absorbed, utilized and as a result produce better results than conventional herbal extracts.
3) Phytosomes can accommodate the active principle that is anchored to the polar head of phospholipids, which finally becomes an integral part of membrane.

DIFFERENCE BETWEEN PHYTOSOME AND LIPOSOME

SR. NO	PHYTOSOME	LIPOSOME

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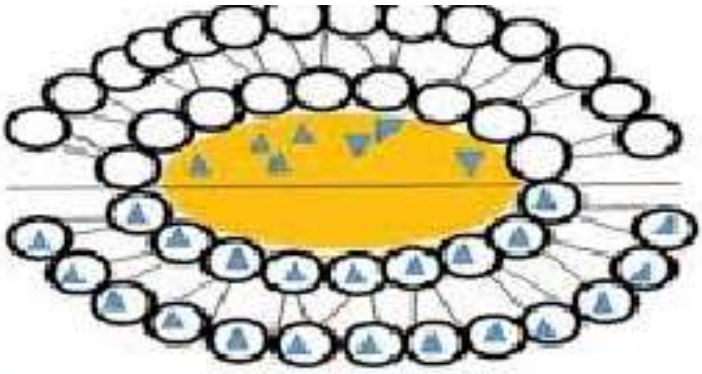
1.	In phytosome, the phosphatidylcholine and the plant components actually form a 1:1 or a 2:1 molecular complex depending on the substance(s) complexes.	A liposome is formed by mixing a water soluble substance with phosphatidylcholine in definite ratio under specific conditions.
2.	Phytosome involves chemical bonds.	Here, no chemical bond is formed; the Phosphatidylcholine molecules surround the water soluble substance.
3.	Phytosome are much better absorbed than liposomes showing better bioavailability.	Bioavailability of liposomes is less than phytosomes.

LIPOSOME



PHYTOSOMES

METHOD OF PREPARATION

Non-conventional methods are usually employed in phytosome preparation

The herbal complexes are formed by reaction between phytoconstituents or a mixture of phospholipids whose mass ratio are in 1:1.5-1:4, depending on the product.

COMMON STAGES IN PHYTOSOME FORMULATION

Phytoconstituents screening of herbal extract

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Solubility studies

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Phytoconstituents + Phospholipids + Chemical solvent

↓

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Solution of ingredient

↓

Complete vacuum drying

↓

Complex layer formation of lipid and extract

↓

Hydration the layer and thereby, collection of thin film

↓

Collection of precipitate by adding the non-solvent

↓

Removal of the solvent, subjecting to spray drying

1) Anti-solvent precipitation process**:-**

In a 100 ml round bottom flask, a specific amount of drug and phospholipid (soya lecithin)was taken and refluxed with 20 ml organic solvent below 50^0c for 2-3hr.

Reaction mixture is concentrated to minimum volume 5-10ml.Antisolvent is then carefully added with continuous stirring; resulting in the formulation of precipitates, that was further filtered and collected and stored overnight in vacuum desiccators.\

2) Solvent separation technique :-

The drug, the phospholipid are placed in the same flash containing an appropriate solvent system, such as Tetrahydrofuran or Ethanol. Reaction is carried out at an appropriate fixed temperature for a fixed duration of time in order to obtained the maximum possible yield and trapping of drug.

3) Solvent ether injection method :-

In this method lipids dissolved in organic solvent are reacted with herbal extract in aqueous phase. The bend is slowly injected into warm solvent. It results in the formation of cellular vesicles on subsequent solvent removal, leading to complex formation.

4) Rotary evaporation process :-

Specific weight of drug and phospholipids were mixed such as acetone in round bottom flask followed by stirring for 2 hours at a temperature less than 50 degree Celsius in Rota evaporator. Antisolvent such as n-hexane can be added to thin film which is obtained after uninterrupted stirring using a stirrer. Precipitateof phytosomes obtained can be stored in amber coloured container.

EVALUATION OF PHYTOSOME COMPLEXES

Transition temperature:	Thetransitiontemperatureofthe vesicular lipidsystemcanbesettledviadifferentialscanningcalorimetry.
Entrapment efficiency:	The entrapment efficiencyofaphytosomalpreparationcanbedeterminedbyexposingthepreparationto ultracentrifugation method.
Vesicle size and zeta potential:	Theparticlesizeandzetapotentialofphytosomescanbeconfirmedbydynamiclightscattering,whichusagesacomputerizedexaminationsystemandphotoncorrelationspectroscopy.

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Surface tension activity measurement:	Thesurfacetensionactivityofthedruginaqueoussolutioncanbedeterminedbytheu Nouyringtensiometer
Visualization:	Visualization of phytosomes can be accomplished using scanning electron microscopy(SEM) and by transmission electron microscopy.
Vesicle stability:	Thesteadinessofvesiclescanbemeasuredbycalculatingthesizeandstructureofthevesiclesovertime.Themeansizeiscalculatedby DLSandstructuralchangesaremonitoredbytem
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 biologically active phytoconstituents present in the phytosome.
Spectroscopic evaluation:	Toconfirmtheformationofacomplexortostudythereciprocalinteractionbetweenthephyto-constituentsandthephospholipidH1NMR,C13NMR,FTIRareused

MARKETED PREPARATION

SR. NO	PHYTOSOME PRODUCT NAME	DAILY DOSAGE	APPLICATION
1.	LEUCOSELECT PHYTOSOME	50-100 mg	Systemic antioxidant (specific). Best choice for most people under age of 40. Protection against heart disease also.
2.	GREENSELECT PHYTOSOEME	50-100 mg	Systemic antioxidant. Best choice for cancer and damage to cholesterol level.
3.	GINKGO PHYTOSOME	120 mg	Best choice for people over the age of 50. Protect brain and vascular lining.
4.	SILYBAN PHYTOSOME	150 mg	Best choice for if the liver or skin needs additional antioxidant protection.
5.	PANAX GINSEN PHYTOSOME	150 mg	As a food product
6.	SABALSELECT PHYTOSOME	-	It enhance immune function in response to a toxic challenge.

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7.	ECHNIACEA PHYTOSOMETM	Echniacea angustifolia	Nutraceuticals, immunomodulatory.
8.	ZANTHALENE PHYTOSOMETM	Zanthoxylum bungeanum	Soothing and Anti-reddening.
9.	SERICOSIDE	Terminalia serica	Anti-aging, skin restructuring.
10.	VITABLUE PHYTOSOMETM	Vaccinium angustifolium	Anti-oxidant, improves vision, memory enhancer.
11.	ESCIN ß SITOSTEROL, PHYTOSOMETM	Aesculus hippocastanum	Anti-edema and vasoactive properties
12.	NARINGENIN PHYTOSOMETM	Citrus aurantium	Antioxidant
13.	SILYBIN PHYTOSOMETM (SILIPHOS®)	Silybium maranium	Hepatoprotective, hepatitis, cirrhosis and Inflammation.
14.	CURCUMIN PHYTOSOMETM, CURCUVET®(MERIVA®)	Curcuma longa	Anti-inflammatory, osteoarthritis, anticancer

PATENTED PRPODUCT

TITLE OF PATENT	INNOVATION	PATENT NO.
Phospholipid complexes of olive fruits or leaves extracts having improved bioavailability	Phospholipid complex of olive fruits or leave extracts	EP/1844785
Compositions comprising Ginko biloba derivative for the treatment of Asthmatic and allergic conditions	Compositions containing fractions derived from Ginkgo biloba	EP1813280
Fatty acid monoesters of sorbityl furfural and compositions for cosmetic and dermatological use,	Selected from two different series of compounds in which side chain is a linear or branched C-3 to C-19 alkyl radical optionally containing at least one ethylene	EP1690862

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AREAS OF APPLICATIONS

✓ Cancer chemotherapy

Liposomes are successfully used to entrap anticancer drugs. This increases circulation life time,protects from metabolic degradation.

✓ Liposomes as carrier of drug in oral treatment

Steroids used for arthritis can be incorporated into large MlVs

Alteration in blood glucose level in diabetic animal was obtained by oral administration of liposomes was encapsulated insulin.

✓ Liposomes for topical applications

Drug like triamcilone,methotrexate, benzocaine , corticosteroids etc can be successfully incorporated as topical liposomes

✓ Liposomes for pulmonary delivery

Inhalation devices like nebulizers are use to produce an aerosol of droplets containing liposomes.

✓ Ophthalmic delivery

Drugs like Idoxuridine, Indoxol and carbochol are greater efficacy in the form of liposomes

Potential advantages of ophthalmic liposomes is their intimate contact with corneal and conjuctival surface.

ADVANCES IN PHYTOSOME TECHNOLOGY

The phytophospholipid complex which had been initially developed for its cosmetic application has now been extensively researched and developed as a novel drug carrier for systemic action. Researchers should pay more attention to carrier systems for the efficient delivery of these plant components/extracts, which can significantly improve the therapeutic capacity of delivery systems. These plant constituents/extracts may be complex with phospholipids for the efficient systematic delivery of herbal constituents. Numerous research findings suggest that a drug to phospholipid ratio other than 1:1 produces a better product in terms of physiological and pharmacological properties. The yield of phytophospholipid complexes varied significantly from about 25% to more than 90% in different studies and was attributed to different formulation factors, such as drug-to-phospholipid ratio, temperature and duration of treatment, which have been shown to affect the yield of the carrier system. Apart from passive targeting, phytophospholipid complexes could also be ideal candidates for targeted delivery by binding the cellular structures to targeting receptors and antigens. This will further elaborate the scope of use of phytophospholipid complexes in the treatment of numerous debilitating disorders

II. CONCLUSION

All that humans needs for health and healing has been provided by God in nature, the challenge of science is the find it. Polyphenolic constituents of plants such as flowers and many others have enormous medical application, but due their inability to cross the lipid barrier , there use in the treatment in the serious diseases such as cancer , lupatic diseases . Introduction into dietary phospholipid such as phytosomes complex has effectively addressedissues like unsolved uneasiness for quite a long period of time and has offered the preparation of herbal drug with adequate lipid penetrability, higher concentration and sustained therapeutic level in plasma at a slow rate of elimination. Phytosome technology has brought us one step ahead successful delivery of herbal constituents.

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