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PHYTOSOMES: A NOVEL DRUG DELIVERY SYSTEM FOR HERBAL EXTRACTS

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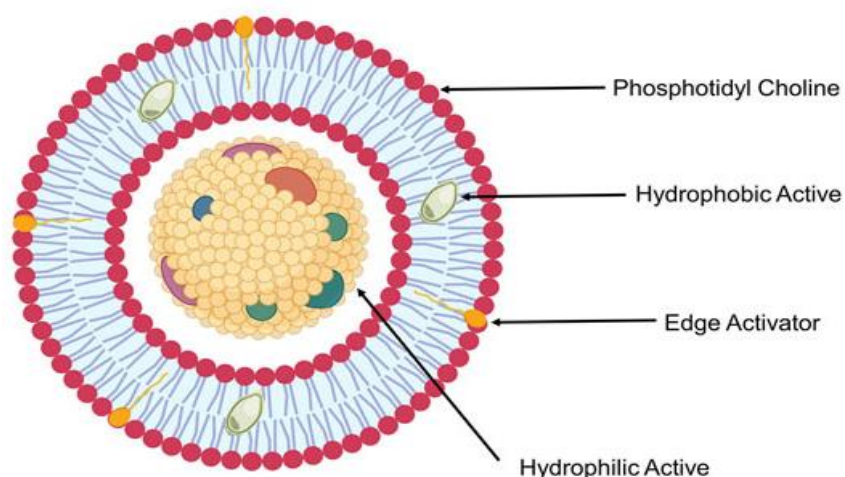
Abstract: “Phyto” denotes a plant and “some” denotes something that resembles a cell. A cutting-edge technology called a phytosome is used to make phytopharmaceuticals, which are made of herbal extracts that are surrounded and bound by lipid. The majority of phytomedicine's bioactive components are hydrophilic substances like flavonoids having hydrophilicity and compared to the conventional, phytosomes with a lipidic outermost layer exhibit better absorption, producing better bioavailability of the plant extracts. The use of phytosomes is widespread due to their enhanced pharmacological and pharmacokinetic features, employ dietary supplements therapeutically to treat acute and chronic liver disorders. The current evaluation emphasizes major discoveries of current studies on phytosomes with our own perspectives that can provide the fresh directions for herbal dosage forms, as well as technical information on phyto-phospholipid formulations to confront future challenges.

Keywords: Phytosomes; Phospholipids; Phytopharmaceuticals; Phytomedicines; Bioavailability.

Introduction: Recent intriguing candidates for the treatment of several diseases stand out as herbal medications. Natural resources fewer side effects and cheaper phytochemical expenses highlight the period of going "back to nature" and bring up new possibilities for health maintenance. Secondary metabolites, including as flavonoids and glycosides, represent the bulk of bioactive components in phytomedicines. Although these compounds are water-soluble, their limited absorption when taken orally or when applied topically limits their usefulness. Either their huge molecular size, which prevents passive absorption, or their poor lipid solubility, which severely hinders their capacity to move past the lipid-rich outer membranes of the enterocytes, the cells that line the small intestine, are the likely causes of their poor bioavailability. By binding the standardised plant extract or its contents to phospholipids, primarily phosphatidylcholine, a lipid-compatible molecular complex called a phytosome is created. Compared to traditional herbal extracts, phytosome have a better pharmacokinetic and pharmacodynamic profile. ⁽¹⁾

Novel vesicular drug delivery system: ^(2,3,4)

The goal of novel vesicular drug delivery systems is to channel the active ingredient to the site of action while delivering the medicine at a pace determined by the body's need during the treatment period. A variety of drug delivery methods have been developed in order to provide regulated and targeted drug distribution. A method of delivering the therapeutic agent is called targeted drug delivery. By lowering the relative concentration of the tissues of interest medicinal substance that enhances the therapeutic effect in the effectiveness of the remaining tissue and minimizes the adverse effects. Targeting drugs entails the delivery of medicines to receptors, organs, or any other particular body component to which one wants to administer the complete medication.

**Principle:** ⁽¹¹⁾

The substance phosphatidylcholine, also known as phosphatidylserine, is a bifunctional compound. Choline (serine) is a hydrophilic compound, whereas the phosphatidyl moiety is lipophilic. The phospholipid's twofold solubility makes it a powerful emulsifier. As a result, the phosphatidylcholine molecule's choline head bonds to these substances, and the lipid-soluble phosphatidyl part, which is made up of the body and tail, surrounds the choline-bound substance.

Advantages: ^(5,6,7,8,9)

- The bioavailability of botanical extracts is dramatically increased as a result of their complexation with phospholipid and enhanced intestinal absorption.
- They penetrate the botanical extract without lipophilia to when compared to previous methods, intestinal lumen absorption is improved conceivable.
- The Phytosome formulation and ingredients are secure and are all permitted for usage in pharmaceutical and cosmetic products.
- They have been utilized to supply flavonoids that preserve the liver because phytosomes can easily make them accessible. Additionally, phosphatidylcholine has hepatoprotective properties, and as a result, has a protective impact on the liver that is synergistic.
- When utilized as functional cosmetics, phytoconstituents and synergistic effects protect the skin from exogenous or endogenous dangers in both everyday and stressful environmental situations.
- They can also be utilized to increase the drug's penetration for transdermal and dermal administration through the skin.

- These serve as delivery platforms for vast and diverse groups of drug use (peptides, protein molecules).
- The vesicular system can be immediately commercialised because it is passive, accessible, and non-intrusive.
- Phosphatidylcholine, an essential part of cell membranes used in phytosome technology, acts as a carrier and nourishes the skin.
- As the drug forms vesicles after being conjugated with lipid, drug entrapment is not a problem during the creation of a formulation and its effectiveness is also heavily predicted.
- Because of the chemical linkages that are created between the phosphatidylcholine molecules and the phytoconstituents, they provide a superior stability profile.
- The dose requirement is reduced due to improved absorption of the main constituent. They can also be given in smaller quantities to achieve the desired results.
- Low risk profile: Since the toxicological profiles of the phytosomal components have been extensively studied and recorded in the scientific literature, there is no danger associated with the large-scale generation of drugs using this technology.

Disadvantage: ^(8,9)

- The phytoconstituent in the phytosome is quickly removed.

Phytosome Formulations : Phytosome complexes can be formulated for oral and also topical administration. Some possible phytosomal formulations are as follows,⁽¹⁰⁾

Soft gelatin capsules : The formulation of phytosome complexes is suitable with soft gelatin capsules. Oily vehicles can be used to disseminate the phytosome complex to achieve capsules made of soft gelatin that will contain suspensions. Vegetable oils or semi-synthetic oils may be employed for this.

Hard-gelatin capsules: It is also possible to create the phytosome complex as hard gelatin capsules. Despite the phytosome complex having what seems to be a low density, it is nevertheless possible to fill a capsule directly volumetrically (without precompression), but the most powder that can normally be put into a size 0 capsule is 300 mg. Although the amount of powder that may be packed into a capsule using a piston tamp filling procedure can be increased, precompression may slow down the disintegration process.

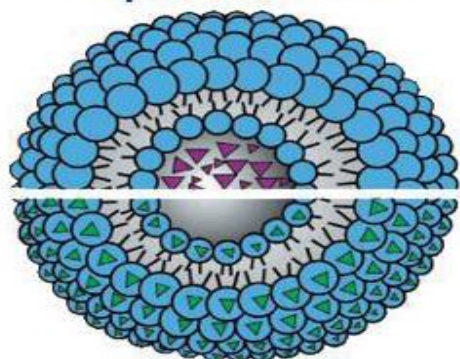
Tablets: The best production method for producing tablets with greater unitary dosages and the appropriate technological and biopharmaceutical characteristics is dry granulation. It should be noted that whenever a direct compression process is used, the phytosome complex should be diluted with 60–70% of excipients to optimise its technological properties and to produce tablets with appropriate technological and biopharmaceutical characteristics. This is due to the phytosome complex's limited flowability, potential stickiness, and low apparent density.

Topical dosage forms: The phytosome complex can also be made for topical use. The best way to incorporate the phytosome complex into an emulsion is to disperse it in a tiny amount of the lipid phase and then incorporate it into the emulsion that has already been made at low temperatures (no more than 40°C). The primary lipidic solvents used in topical preparations can disperse the phytosome complexes. The phytosome complex may also be disseminated into the watery phase and added to the final formulation at a temperature lower than 40°C in the case of formulations with a small amount of lipids. Difference between Phytosome & Liposome⁽¹¹⁾

Differences between phytosomes and liposomes:

1. The polar head of the phospholipid serves as an anchor for the molecules that make up the active chemical components of phytosomes. In liposomes, the membrane layers or cavity medium are where the active principle is dissolved. There are no chemical linkages created.
2. Depending on the substance, phosphatidylcholine and the specific plant chemical form a 1:1 or 1:2 combination in phytosome. The water-soluble molecule is surrounded by hundreds of thousands of phosphatidylcholine molecules in liposomes.

Liposome



Phytosome®



Vascular system	Description	Application
Aquasomes	These spherical 60–300 nm particles are utilised to deliver drugs and antigens. The polyhydroxyl oligomeric layer covers the noncrystalline calcium phosphate (ceramic diamond) particle core.	Specific targeting, molecular shielding
Archaesomes	Vesicles made of archaeal glycerolipids with strong adjuvant action	Poor adjuvant activity
Colloidosomes	These are hollow, elastic shells with precisely controllable permeability that are solid microcapsules made by self-assembly of colloidal particles at the interface of emulsion droplets.	Drug targeting
Cryptosomes	Surface coated lipid vesicles made of PC and a suitable phosphatidyl ethanolamine polyoxyethylene derivative	Ligand mediated drug delivery
Cubosomes	Cubosomes are bi-continuous cubic phases made up of two distinct, continuous, but not intersecting hydrophilic regions that are separated by a lipid layer that has been bent into a periodic minimum surface with zero average curvature.	Drug targeting
Discosome	Niosomes and non-ionic surfactants together	Ligand mediated drug targeting system

Emulsosomes	Emulsosomes are the polar group and lipid assembly of nanosized lipid particles were present.	Parenteral delivery of poorly water soluble drugs
Enzymosomes	Covalently immobilised enzyme on liposome surface	Targeted delivery to tumour cell
Erythrosomes	Utilizing a lipidomal system to cover a lipid bilayer with the cytoskeletons of chemically cross-linked human erythrocytes	Targeting of macromolecular drugs
Genosomes	Synthetic macromolecular system for effective gene transfer	Cell specific gene transfer
Hemosomes	Immobilizing haemoglobin with a polymerizable phospholipid results in the creation of hemoglobin-containing liposomes.	High capacity oxygen carrying system
Photosomes	The contents of photolyase-encapsulated liposomes are released by photo-triggered changes in the permeability properties of the membrane.	Photodynamic therapy
Protosomes	Multisubunit enzyme complexes with high molecular weight and catalytic activity	Compared to non-associated enzymes, catalytic activity turnover is improved.
Ufasomes	Long chain fatty acid vesicles were produced by mechanically agitating evaporated film in the presence of buffer solution.	Ligand mediated drug targeting
Vesosomes	Bilayers arranged in a nested structure around an aqueous core containing a unilamellar vesicle.	Vesosomes with many compartments offer serum's internal content better protection.
Virosomes	The liposomal bilayer of retrovirus-based lipids contains liposomes that have been injected with virus glycoproteins.	Immunological adjuvant

Preparation of phytosomes: ⁽¹¹⁾

Novel combinations of lipids and herb extracts are called phytosomes. The procedures used to create phytosomes involve the binding of phospholipid to standardized extracts of a herb's active components such as phosphatidylethanolamine (PE), phosphatidylcholine (PC), or polar end of phosphatidylserine. They prepare phytosome by combining 2-3 moles of a phospholipid, natural or artificial, with one herbal extract in a mole. The process is completed in an aprotic solvent. The complex can be separated from a solvent, like acetone or dioxane. using a non-solvent precipitant, like aliphatic hydrocarbons or by lyophilization, spray drying, etc. Within the intricate construction, the ratio of these two moieties in phytosomes ranges from 0.5 to 2.0 moles. The ratio of phospholipid to flavonoids that is preferred is 1:1.

Properties of phytosomes:

Physiological properties:

- a) A stoichiometric amount of phospholipid is reacted with the standardised plant extracts as substrate to create phytosomes. The spectroscopic data analysis indicates both the polar features of the substance and the hydrogen bond formed between the polar head.⁽¹²⁾
- b) Phytosomes range in size from 50 nm to a few hundred μm .⁽¹³⁾
- c) Phytosome takes on a micellar shape after being exposed to water spectroscopy using photon correlation and a liposome-like form (PCS) demonstrates the liposomal structures that the phytosome gained.⁽¹⁴⁾
- d) According to the H1 NMR and C13 NMR data, the fatty chain produces unchanged signals in both the complex and free phospholipid, this demonstrates the presence of lengthy aliphatic chains around the lipophilic envelope is produced by an active principle.⁽¹⁵⁾

Biological properties:

Pharmacokinetic studies or pharmacodynamic tests in experimental animals and human subjects have shown that phytosomes are novel complexes that are better absorbed and utilised; as a result, they produce more bioavailability and better results than conventional herbal extracts or non-complex extracts.⁽¹⁶⁾

Characterization and Evaluation of Phytosome⁽¹⁷⁾

Physical characteristics of phytosomes, such as shape, size, distribution, percentage of drug capture, volume of entrapped drug, percentage of drug release, and chemical make up phytosomes. Therefore, physical size, membrane permeability, the percentage of solutes that are entrapped, chemical composition, amount, and purity of the starting material all affect how phytosomes behave in both physical and biological systems.

- a) Visualization: Transmission electron microscopy can be used to see phytosomes, and the ultracentrifugation method can be used to measure them.
- b) Transition temperature: A differential scanning calorimeter can be used to determine the transition temperature of the vesicular lipid systems.
- c) Measuring surface tension activity: A Du Nouy ring tensiometer can be used to test the drug's surface tension activity in aqueous solution.
- d) Vesicle stability can be assessed by examining the evolution of the vesicles' size and structure. Transmission electron microscopy (TEM) monitors structural changes while Dynamic Light Scattering (DLS) measures the mean size (TEM).
- e) Drug content can be determined by a suitable spectroscopic approach or a modified high performance liquid chromatographic technology.
- f) Vesicle size and Zeta potential: By using a computerised inspection system and photon correlation spectroscopy, DLS can determine the particle size and zeta potential.
- g) Differential scanning calorimetry: Placed in an aluminium cell and heated to a temperature of 50-250°C/minutes from 0 to 400°C in a nitrogen atmosphere are drug polyphenolic extract, phosphatidylcholine, a physical mixture of drug extract and phosphatidylcholine, and drug-phospholipid complex.

h) Scanning electron microscopy (SEM): SEM was utilised to quantify the particle's dimensions and visual characteristics. Dry sample was applied to gold-coated brass stub of the electron microscope. Arbitrary scanning of complex at 100.

i) Drug entrapment and loading capacity: To separate phytosome from the untrapped drug, the drug phytosomes complex was centrifuged at 10,000 rpm for 90 minutes at 4°C. UV spectroscopy can be used to determine the amount of free drug present. The following formula can be used to determine the percentage of drug entrapment:

$$\text{Weight of free drug} = \frac{\text{Total drug weight} - \text{Entrapment efficiency percentage weight}}{\text{Total medication weight}} \times 100$$

J) Fourier transform infrared spectroscopy (FTIR) analysis: FTIR analysis used to examine drug and phospholipid structure and chemical stability. To create pellets, the phytosomal medication will be crushed with potassium bromide under pressure of 600 kg/cm². Between 4000-400 cm⁻¹ will be the range for scanning.

k) In vitro and in vivo assessments: These assessments rely on the characteristics of the medication, its main phytoconstituents, which are bordered by a phospholipid layer, and the rationale behind the choice of the animal model used for the assessment.

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