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Phytosomes: An advanced drug delivery system

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Abstract-

This review aims to highlight the growing usage of phytosomes as modern pharmacy technology due to their wide range of therapeutic applications and low occurrence of adverse effects. Phytosomes, a term for lipid soluble molecular complexes with enhanced bioavailability and absorption, are created using a unique proprietary method that combines standardized plant extracts with phospholipids.The two words "phyto" (which means plant) and "some" (which indicates cell-like) combine to form phytosomes. The process of solvent evaporation was used to create phytosomes. Phytosomes exhibit superior pharmacodynamic activity, augmenting the bioavailability of certain widely used herbal extracts, such as green tea and milk thistle. Numerous products, like silybum marianum and camellia sinensis, are on the market that contain phytosomal drug delivery systems. The current review highlights the technology, features, advantages, preparation techniques, assessment, and applications of phytosomes.

Keyword- **Phytosomes, Phospholipids, Solvent evaporation.**

I. Introduction-

Phytosomes provide a unique drug delivery system, one that overcomes the drawbacks of more conventional drug delivery methods with a fresh approach. The field of Ayurveda is well-established in our nation and has been gaining popularity in recent years. Its benefits include delivering herbal drugs at a predetermined rate, delivering them at the site of action, reducing their toxic effects, increasing their bioavailability in phytosomal preparations, controlling drug circulation through carrier system consolidation or molecular drug structure changes [1, 4].

Phytosome is a recently discovered and patented technique developed by an Indian company to digest standardized plant extracts. The vital active components of the medicinal plant extract are shielded from destruction by gut bacteria and digestive fluid thanks to the phytosome formulation technology, which forms a tiny, cell-like structure.[1]

Because phytosomes have a greater potential to pass through lipid-rich biomembranes and subsequently enter the bloodstream, they have a higher bioavailability than herbal extracts. Different kinds of pharmaceutical carriers, such as polymeric micelles, particulate systems, macro- and micromolecules, are included in novel drug delivery systems.[6]The innovative medicine delivery method known as phytosomes is quite popular. give the herbal medication at a predetermined rate, lessen harmful effects, deliver the medication at the site of action, increase the drug's bioavailability in phytosomal preparations, and control the drug's circulation by either combining it with a carrier system or altering its molecular structure.(Source:) Herbal medications packed into vesicles, or phytosomes, are sold in nanoscale form. The active ingredient of the medication is protected from bacterial and digestive secretion breakdown by the phytosomes, which operate as an envelope-like layer around it. A lipid-loving environment can be effectively absorbed by phytosomes. The formation of phytosomes occurs when standardized herbal extract or polyphenolic ingredients react with a stoichiometric amount of phospholipid in an aprotic solvent.

Because phosphatidylcholine molecules and phytoconstituents create chemical bonds, phytosomes are more stable. When phospholipids and standardized plant extracts or water-soluble phytoconstituents are complexed to form lipid-compatible molecular complexes, phospholipids not only serve as a carrier but also have hepatoprotective activity and nutritional value[2]. This greatly increases absorption and bioavailability. Several phospholipids are employed, including phosphatidylcholine, phosphatidylserine, phosphatidylethanolamine, and phosphatidylinositol. However, phosphatidylcholine is used extensively due to its potential therapeutic benefits in the treatment of liver disorders, hepatitis, drug-induced liver damage, and alcoholic steatosis. Phospholipids are also used in naturally occurring digestive serves as a transporter for nutrients that are both water- and fat-soluble. In addition to the stratum corneum layer of epidermis, phytosomes can easily pass through the lipophilic pathway of enterohepatic cell membranes [3]. The first plant extracts having water-soluble components that were made more bioavailable by adding phospholipids to their

composition were created by an Italian pharmaceutical and nutraceutical business. They filed for a PHYTOSOME patent for the invention.[8] Plant is referred to as "phyto," while cell-like is referred to as "some." Better physical stability and improved absorption of hydrophilic polar phytoconstituents lead to greater therapeutic effects and increased bioavailability of phytosomes. This is because phospholipids and phytoconstituents have an H-bond.(Source:) Many well-known herbal extracts have had their bioavailability successfully increased by phytosome technology, which can also be produced for a range of therapeutic applications or nutritional supplements with additional medical benefits.[1]

1. Phytosomes

Phytosomes are lipid-compatible molecular complexes with enhanced absorption and bioavailability that are created by incorporating standardized plant extracts into phospholipids using a revolutionary, patented technique. Herbosomes are another name for phytosomes. "Some" refers to something resembling a cell, and "phyto" indicates a plant.

The distribution of an effective level of the therapeutically active component is a prerequisite for the success of any herbal medicine. When applied topically or orally, their bioavailability is severely limited.

Herbal compositions called phytosomes, which are more readily absorbed than extracts, were recently introduced. Numerous botanical items' compositions, biological activity, and health-promoting properties were determined by phytochemical and phytopharmacological sciences.[4]

Effectively, a phytosome can absorb from an environment that loves water to one that loves lipids in the cell membrane before eventually reaching the bloodstream[8].

Flavonoids, tannins, glycosidic aglycones, and other water-soluble phytoconstituents are poorly absorbed because of their large molecular size, which prevents passive diffusion, or because of their poor lipid solubility, which severely restricts their ability to cross lipid-rich biological membranes and leads to poor bioavailability.[4,8]

1.1 Phytosome technology

By adding phospholipids to standardized plant extract, which improves absorption and utilization, Indena s.p.A. of Italy created the phytosome technology, which significantly increases the bioavailability of certain phytomedicines. Both in lipids and water, the polyphenols are not very soluble. Using hydrogen bonds and polar contact with the charged phosphate head of phospholipids, the polar functions of the lipophilic guest produce a unique relationship that is attempted to be demonstrated by the use of spectroscopy.[5]

The hydrophilic choline group head of phosphatidylcholine bonds with the chemical, while the hydrophobic phosphatidyl group envelops the confined region. Phosphatidylcholine is a bifunctional molecule. [3]

1.2 Advantages of phytosomes:

1)Compared to other nano drug delivery systems like solid lipid nanoparticles and nanostructure lipid carriers, phytosomes offer a simpler formulation process. [1]

2)The medicine is guaranteed to be properly delivered to particular tissues [6].

3)The clinical benefit of phytosomes is found to be much greater. [6]

4)The phytoconstituent and phosphatidylcholine molecule establish chemical linkages, which improves the stability profile of the phytosomes.[7]

5)There is no chance of medication entrapment during the formulation procedure [8].

6)Because the absorption of the active component is improved, a small dose can yield the required results.(8)

7)As a messenger and nutrient for the epidermis, phosphatidylcholine is a component of the cell film that is used in phytosome innovation. In [9]

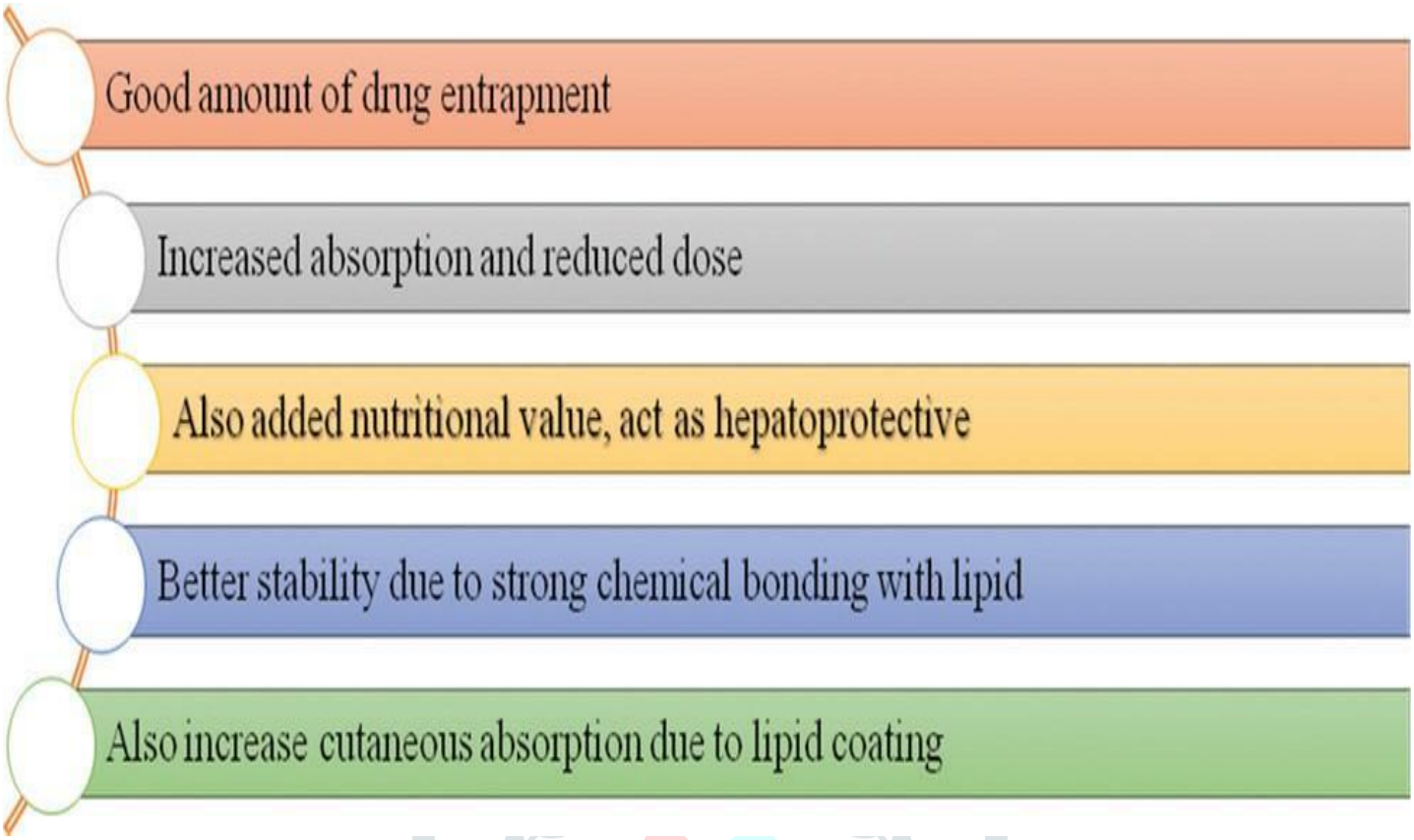
8)Phytosomes' ability to penetrate the skin is facilitated by the lipid layer enveloping the phytoconstituents, which enhances their potency.In [9]

9)In addition to being a carrier, phosphatidylcholine has nutritional benefit and hepatoprotective activity[9].

10)It enhances the oral and topical absorption of lipid-insoluble phytoconstituents. [10]

11)The components of Phytosome have all been approved for use in cosmetic and medicinal applications, making the formulation safe.[11]

12)Phytosomes lengthen the duration of action and make bile more soluble in herbal components.[12]



The benefit of phytosomes is depicted diagrammatically in Fig. 1

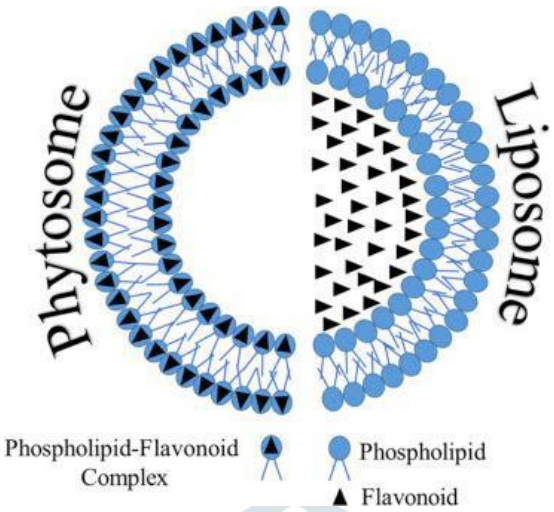


Fig no -2 Structure of Phytosome [13]

II. Preparation of phytosomes:

1. Solvent evaporation method:

The medication and phospholipids are combined in a flask with the suitable solvent system (ethanol or tetrahydrofuran) in the most widely used solvent evaporation approach. To get the most yield and drug trapping feasible, this reaction mixture is maintained at an ideal temperature for a set amount of time—hours. Created a marsupsin-phospholipid complex using a mechanical dispersion-oriented liquid anti-solvent precipitation method. They added marsupsin to double the water and soy lecithin to ether until it was dissolved by sonication. After that, the drug solution was added drop by drop while sonicating the phospholipid solution. After the resulting formultion was chilled, an analysis of the complex revealed 44% marsupsin entrapment with 20% cumulative drug release.[1, 6, 8, 12, 13, 14]

2) Anti-solvent precipitation process:

A specific amount of herbal extract and phospholipids are refluxed in a round-bottom flask with 20 ml of organic solvents, such as acetone, and temperature below 50°C for 2-3 hours. Many researchers have also used the traditional anti-solvent precipitation technique, which incorporates n-hexane as an anti-solvent to precipitate the drug phospholipids complex from an organic solvent. After reducing the reaction mixture's volume to a minimum of 10 milliliters and adding a low-polarity solvent, such as n-hexane, while stirring, precipitates are produced. The dried precipitates are ground into a powder and placed in a dark amber glass bottle to be kept at room temperature.[1, 6, 8, 12, 13)

3) **Rotational evaporation process:**

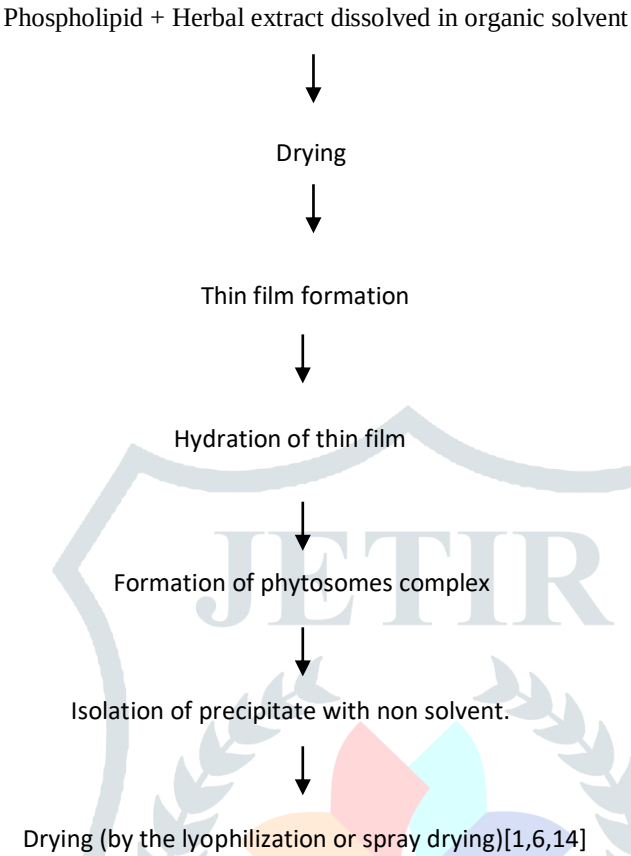
Solvent evaporation techniques are typically used to prepare the complex of plant extracts or particular active principles with dietary phospholipids, employing alcoholic or organic solvents as the reaction medium. A precise amount of herbal extract and phospholipids were combined with 30 milliliters of water-miscible organic solvent, such as acetone or tetrahydrofuran, in a glass container with a circular bottom. The mixture was then stirred for two to three hours at a temperature of no more than 50°C in a rota evaporator. Antisolvents such as n-hexane are frequently added to thin films that are produced through continuous swirling with a stirrer. The precipitate of the produced phytosomes is frequently kept at a regulated temperature and humidity in amber-colored glass containers. [1, 6, 8, 12, 14]4]

4) Ether injection technique-

This method involves dissolving the medication lipid complex in an organic solvent. Vesicles are created by gradually injecting this combination into a hot aqueous agent. Amphiphiles' condition is dependent on concentration. Amphiphiles introduce a monomer state at lower concentrations; however, when concentrations rise, a range of structures, including spherical, cylindrical, disc, cubic, and hexagonal forms, may emerge.[1]

5) Dehydration-rehydration technique:

An organic solvent is used to dissolve the phospholipid and the bioactive ingredient. A rotary vacuum evaporator is then used to entirely remove the organic solvent and the aqueous content at a lower temperature and pressure. In the round bottom flask, a thin layer comprising a conjugated combination of phospholipid and bioactive chemical would form. To totally eliminate the solvents, water is added to the mono layer. In order to create micelles, the mono layer is then rehydrated with water. After being exposed to water, the phospholipid thin layer forms micelles, which are subsequently probe-sonicated to reach the appropriate micelle size.[1]



III. Evaluation of phytosomes[1,5,6,8,12,13,15]

1)Visualization:

Transmission electron microscopy (TEM) or scanning electron microscopy (SEM) can be used to evaluate the size and form of phytosomes.

A)TEM analysis -

Using a 1000x magnification, the size of phytosomal vesicles was measured using TEM.
The complex was observed with a Transmission Electron Microscope (Hitachi, Japan) after being shook in water.

B) SEM analysis –

The particle's size and appearance were assessed using SEM. A dry sample was placed in an ion sputter on a brass stub for an electron microscope that had been coated in gold. The complex is scanned at random at 100.

2) Vesicle size and Zeta potential:

Dynamic light scattering (DLS) can be used to quantify the particle size and zeta potential utilizing photon correlation spectroscopy (PCS) and an automated inspection system.

3) Entrapment efficiency:

The Ultracentrifugation technique can be used to test the drug's entrapment efficiency by phytosomes.

4. Transition temperature: The differential scanning calorimeter can be used to find the vesicular lipid systems' transition temperature.

5. Surface tension activity measurement: Using the ring method in a Du Nouy ring tensiometer, the drug's surface tension activity in an aqueous solution is determined.

6. Vesicle stability: Analyzing the size and shape of vesicles over time can reveal information about their stability. By using transmission electron microscopy (TEM), structural alterations are observed and the mean size is determined using differential light scattering (DLS).

7. Drug content:
A suitable spectroscopic approach or a modified high-performance liquid chromatographic method can be used to quantify the drug's quantity.

IV. Properties of phytosomes[11,13]
1) Physical properties
1) The lipophilic compounds in phytosomes have a distinct melting point.
2) A protosome's average size might vary from 50 nm to several hundred μm.
3) They exhibit moderate solubility in lipids, insoluble in water, and highly soluble in non-polar solvents.
4) When Phytosomes are handled with water, miscellaneous entities resembling liposomes are generated.

2) Chemical properties
1) The spectroscopic analysis results validates the development of a hydrogen bond between the polar functions of the substrate and the phospholipids' polar head, which consists of phosphate and ammonium groups.
.
2) Long aliphatic chains are wrapped around the active principle to produce a lipophilic envelope, as indicated by the 1HNMR and 13CNMR data, which also show that the fatty chain provides unchanged signals in the complex and in free phospholipid.

V. APPLICATION OF PHYTOSOMES:
1) Enhancing Bioavailability:
Numerous studies have been conducted that demonstrate phytosomes' enhanced absorption and bioavailability as compared to traditional techniques.The majority of phytosomal research is on Silybum marianum because it has superior flavonoids that protect the liver.(family: Steraceae), the fruit of which includes flavonoids with hepatoprotective properties that are used to treat liver illnesses such as cirrhosis, hepatitis, fatty infiltration of the liver, and bile duct inflammation. Three flavonoids make up silymarin; silybin predominates and is suppressed by silychristin and silydianin. The most effective is silybin, which protects the liver by preserving glutathione in parenchymal cells [1, 8].
2) Cancer treatment:
The primary antioxidant qualities of medicinal plants' chemical constituents—flavones, isoflavones, flavonoids, anthocyanins, coumarins, lignins, catechins, and isocatechins—contribute to their potential anticancer effects.Certain plant-based chemicals have certain adverse effects and are poisonous at larger doses.[1]
3)Phytosome of green tea-
The main characteristic of green tea leaves (Theasinensis) is the presence of the polyphenolic compound epigallocatechin 3-O-gallate.
These substances are strong regulators of a number of biochemical pathways connected to the disruption of homeostasis in significant chronic degenerative illnesses like atherosclerosis and cancer.
In addition, green tea offers us several health benefits, including anti-oxidant, anti-mutagenic, anti-carcinogenic, hypocholesterolemic, and cardioprotective properties.
The oral bioavailability of green tea polyphenols is significantly increased by complexing them with phospholipids.[16]

4)Phytosomes of curcumin-
Curcumin (a flavonoid found in turmeric, Curcuma longa linn) and naringenin (a flavonoid found in grapes, Vitis vinifera) phytosomes were created by Maiti et al. in two separate investigations.
In every measured dose range, the complex's antioxidant activity was noticeably greater than that of pure curcumin. In the other study, the naringenin phytosome that was generated produced better antioxidant activity than the compound that was free and had a longer duration of action. This difference in antioxidant activity may have resulted from a slower rate at which the molecule left the body[16].

5)Phytosomes of *Gingko biloba* leaves-
Research has indicated that ginkgo phytosome, which is made from a standardized extract of Ginkgo biloba leaves, outperformed the traditional standardized plant extract (GBE, which contains 24% ginkgo flavones glycoside and 6% terpene lactones) in terms of yielding superior outcomes. Its main indications are peripheral vascular diseases and cerebral insufficiency, while it can also help with decreased cerebral circulations. Even for long-term treatment, its enhanced oral bioavailability and high tolerability make it the perfect ginkgo product.[16]

6)Phytosomes of Coated Tablet-
An oral formulation of coated tablets [Monoselect Camellia®][MonCam] containing highly bioavailable green tea extract [GreenSelect® Phytosome] was studied by Francesco et al. for the analysis of 100 overweight individuals of both genders on a hypocaloric diet. The results showed that there were no adverse effects at all, suggesting that this is a safe and effective weight loss tool[4].

7) Phytosomes of Hesperetinphytosomes-

Hesperetin and hydrogenated phosphatidylcholine were combined to create a new hesperetinphytosome by Mukerjee et al. The complex's antioxidant activity was assessed, and the results showed that the phytosomes' relative bioavailability was higher than that of the active pharmaceutical ingredient.[4]

VI. CONCLUSION-

Phytomedicines, complex chemical mixtures prepared from plants, have been used in medicine since ancient times and continue to have widespread popular use Phytosomes are advanced forms of herbal products that are better absorbed, utilized, and as a result produce better results than conventional herbal extracts. Phytosome preparation is done by non-conventional method. Absorption of phytosome in gastro-intestinal tract is appreciably greater resulting in increased plasma level than the individual component. Complex formation ratio of component and phospholipids is 1:1 and 2:1. Phytosomes forms a bridge between the convectional delivery system and novel delivery system.

The flavonoid and terpenoid components of these herbal extracts lend themselves quite well for the direct binding to phosphatidylcholine. Through study of literature reveals that phytosome show promise in reliving the pain and symptoms associated with asthma, arthritis, rheumatism, ulcers, phlebitis, edema, varicose veins, premenstrual syndrome, diabetic retinopathy and hemorrhoids. Phytosomes are used as a medicament and have wide scope in cosmetology. Many areas of phytosome are to be revealed in future in the prospect of pharmaceutical application.

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