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PHYTOSOMES: A NEW VESICULAR DELIVERY FOR HERBAL MEDICINE

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Phytosome, Phytoconstituents, Herbal extract, Phospholipid complex, Conventional release, Bioavailability

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ABSTRACT: Phytoconstituents like flavonoids, tannins, glycosides, alkaloids and terpenoids have medicinal values. In recent years herbal medicines are developed and used to treat almost all diseases with lesser or no side effects. But the plant constituents having low half-life, poor bioavailability and stability problems because of their high particle size and high aqueous solubility. Phytosomes are the carriers for the novel drug delivery system. It consists of two words "phyto" means "plant" and "some" means "cell-like". They are used to improve the absorption, systemic bio-availability and prolongs their release by complexing with the phospholipids. It forms a weak hydrogen bond between polar heads while non-polar tail of phospholipids encloses over complex thereby imparts lipophilic character to herbal extracts. Hence increases the absorption of plant constituents than the conventional herbal extract. The current review describes the overview of phytosomes and its properties, method of preparations, evaluations of novel technologies and importance of phytosomes.

INTRODUCTION: Novel drug delivery system aims to deliver drug at a rate directed by the parts of the body using different carriers like aquasomes, liposomes, transferosomes, phytosomes, viro-somes, ethomosomes, electrosomes [1]. The poor bioavailability of plant constituents can be enhanced through their incorporation into the phospholipid-based self-assembled delivery system, *i.e.* phytosome. Biologically active constituents of plants are mostly water-soluble or polar in nature (*i.e.*, flavonoids, glycosides, tannins). Water-soluble constituents are having large sizethan lipid soluble constituents.

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The absorption of water-soluble constituents is relatively poor because of their large size. Passive diffusion is not possible due to their size limitation, and they cannot cross the lipid-rich membrane resulting in low bioavailability [2, 11]. Plant extract can cause partial or complete reduction of bioavailability, and it can cause loss of synergy of natural constituents [7]. It has been generally observed that chemical complexity is necessary for bioavailability of active constituents of crude or purified extract.

A gastric environment of the body may reduce the activity of some active constituents when taken orally. Due to this reason, the extract shows low bioavailability, and their clinical utility is doubtful [10]. To overcome these issues, botanical medicines are incorporated in novel carrier systems such as phytosomes, liposomes, nanoparticles, nano-crystals, *etc.*, for improvement of number of approaches like solubility, absorption and

bioavailability, sustained delivery [3-5]. Among these carriers phytosomes are the satisfactory vehicles for delivering the plant constituents. Phytosomes is novel technology emerged in 1989 to merger of aqueous solubility of constituents of plant with phospholipid for the preparation of a molecular complex of lipid and Phytoconstituents [8, 9]. Phytosome technology is a patented technology that involves interaction between phospholipid and water-soluble Phyto-constituents shown in **Fig. 1**, which is suitable for the oral and topical drug delivery systems. They are structurally similar to liposomes and having high configuration.

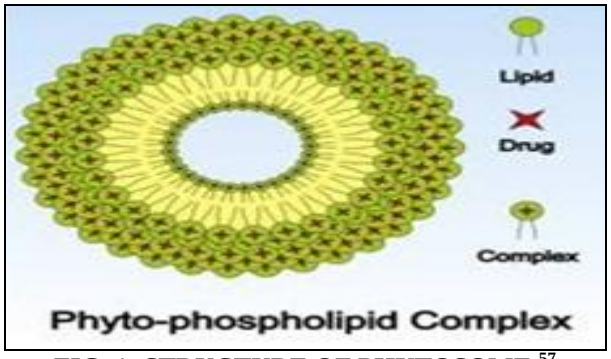

FIG. 1: STRUCTURE OF PHYTOSOME [57]

They are prepared through the attachment of individual ingredient to phosphatidylcholine (PC), resulting in a formulation having high solubility and absorption and leading to the promoted pharmacokinetic and pharmacodynamic properties compared to the conventional herbal extracts. Phytosomes are also known as phospholipid complexes. They are lipid-based novel delivery systems that are having a higher capacity for nutraceutical compounds to be added to them. As they are stable compounds chemically bound structure, plant extract can bind quite easily to phosphatidylcholine due to the presence of terpenoids and flavonoids or other phyto-constituents.

They are mainly utilized in the delivery of low solubility and low bioavailability compounds where the production methods are

1. Anti-solvent precipitation method
2. Rotary evaporation method
3. Solvent evaporation method
4. Thin film hydration method
5. Sonication method

Advantages: [12]

1- There is a dramatic improvement of the bioavailability of herbal extracts due to their complexation with phospholipid and improved absorbance in the gastric intestinal tract.

2. They permeate the non-lipophilic herbal extract to allow better absorption from the intestinal lumen, which otherwise not possible to cross the cell membrane [13].

3. The formulation of phytosomes is safe and effective, and the components have also been approved for pharmaceutical and cosmetic use.

4. Phytosomes have been used to deliver the hepatoprotective phytoconstituents because they can be easily made, and they can readily improve the bioavailability of phytoconstituents; in addition to this, phospholipid is also having hepatoprotective activity and so provides a harmonious effect for liver protection [14].

5. Phytosomal technology is economical and provide harmonious benefits when used as active constituents to protect the skin against exogenous or endogenous effects in normal as well as stressful environmental conditions [9].

6. They provide the platform for the delivery of large and diverse group of drugs (peptides, proteins, molecules).

7. They can also be used for enhanced permeation of active constituents through the skin for transdermal and dermal delivery or vesicular systems are passive, non-invasive and is available for immediate commercialization [15].

8. Phospholipid, an essential part of the cell membrane used in phytosomes technology, acts as a carrier and also nourishes the skin [16].

9. There is no problem with drug entrapment during formulation preparation. Also, the entrapment efficiency is high and moreover predetermined because the drug itself forms receives after conjugation with lipid.

10. They form a better stability profile because chemical bonds are formed between the phosphatidylcholine and Phytoconstituents.

11. The dose requirements were reduced to the improved absorption of the main constituents. They can be given as smaller quantities to achieve the desired results [16].

12. Relatively simple to manufacture rather than number of complicated technical investments required for the production of phytosomes.

14. They also have applications in the veterinary field [18-23].

Disadvantages: Phytoconstituents are rapidly eliminated from the phytosomes [16, 24].

Properties: [25-27]

Physicochemical Properties:

A. Phytosomes are the complex between plant constituents and natural or synthetic phospholipid and complex is obtained by reacting an appropriate amount of phospholipid and chief constituents in a particular solvent.

B. The interaction between the phospholipid and substrate is due to the development of hydrogen bonds between the polar head of phospholipid and the polar functionalities of the chief constituents.

C. On treatment with hydrophilic environment, phytosomes shows a cell-like structure, but in a liposome the chief constituent interacts within the internal pocket while in phytosome the chief active constituent is enveloped the polar head of phospholipid and becoming an integral part of the membrane.

D. The phytosome is a combination of a few molecular complexes which bounded together, while the liposomes are a combination of a number of phospholipids that react with chief constituents but without complete bonding with them. This can be verified with the help of various spectroscopic techniques [28].

E. phytosomes are freely soluble in non-polar solvent 12, and the formation of micelle in Polar solvents (water) and shows intermediate solubility in fats [29-32].

F. Melting point of phytosomes is clear.

G. The size of the phytosome is 50 nm to few hundred µm [33].

Biological Properties:

A. Phytosomes increase the active absorption of active molecule also increases systemic absorption when administered in orally

B. They are the advanced form of herbal products and having better efficacy compared to conventional herbal extract

C. Phytosomes has better pharmacokinetic as compared to simple herbal drugs

General Procedure for the Preparation of Phytosomes: Take the required quantity of phosphatidylcholine and extract in the ratio of 0.5:1, 1:1, 2:1 (drug: phospholipid). Among those ratios 1:1 is mostly preferred. The mixture are reacted and reflux with suitable solvent like acetone or dioxane or methylene chloride (di methyl chloride) for 2 h at 60 °C or 40°-50 °C for 3 h after that concentrate the solvent to 5- 10 ml the formed mixture is precipitated with non-solvent (ex.:n-hexane) or aliphatic hydrocarbons and dried by spray drying or by lyophilization technique and dried phytosomes are stored in amber colored bottle

Preparation Methods: [6]

1. Anti-solvent Precipitation Method: Required ratio of drug and phospholipid are reacted and refluxed with 20 ml of acetone for 2 h at 60 °C or 40-50 °C for 3 h and then concentrated to 5 to 10 ml and then add n-hexane drop wise carefully to precipitate the phytosomes and they are dried by using freeze dryer or by vacuum desiccator and the resulted powder store in amber colored bottle.

2. Rotary Evaporation Method: Specific amount of drug and soya lecithin was taken into a 100 ml of the round bottom flask and dissolved in 30 ml of tetrahydrofurantoin in a rotary round bottom flask followed by stirring for 3hrs at a temperature of not exceeding 40 °C. A thin film of the sample was obtained to which n-hexane was add continuously stirred using a magnetic stirrer. The obtained precipitate was collected, stored in an amber color glass bottle and kept at room temperature.

3. Solvent Evaporation Method: Specific amount of drug and soya lecithin were taken into a round bottom flask and dissolved in 20 ml of acetone or any other aprotic solvents and then refluxed for 2 h at 60 °C or 40-50 °C for 3 h and then concentrated the solvent for 5 to 10 ml then filter the solvent collect the precipitate and dried by using vacuum desiccator and stored in a well-closed container.

4. Thin Film Hydration Method: Phospholipid *i.e.,* soya lecithin, was reacted with polyphenolic extract in an equal ratio with 5 ml of dichloro-methane (DCM) with stirring until evaporate. Once DCM evaporated, 5 ml of n-hexane was added to the thin film with stirring and left in a fume hood for complete removal of n-hexane, the film was hydrated and sonicated for the desired phyto-somalcomplex.

5. Sonication Method: Accurately weigh the quantity of phospholipid and cholesterol in a round bottom flask and dissolve in 10 ml of chloroform, followed by sonication using a bath sonicator. Organic solvent removal can be done by subjecting it under reduced pressure in a rotary evaporator (40 °C).

After complete removal of the thin solvent, layer is formed which is hydrated with polyphenolic extract of the drug in a rotary evaporator. Phospholipid Mixture was sonicated in an amber-colored bottle.

Characterization of Phytosomes: [34-37]

1. Visualization:

A. Microscopic View: Optical microscopy was used for characterization of phytosome complex. The complex was suspended in water and a drop was placed on a glass slide and covered with coverslip. Microscopic view of phytosome was observed under different magnifications.

B. Transmission Electron Microscopy (TEM): Morphological examination was done for the prepared phytosomes. The sample was prepared by the centrifuging the phytosomal dispersion was placed onto a carbon-coated copper grip, leaving a thin film was dried and finally viewed the mean particle size of the vesicle

C. Scanning Electron Microscopy (SEM): A scanning electron microscopy study was done to determine the surface morphology, size and shape of the phytosomes.

2. Measurement of Particle Size:

• The particle size of the phytosomes was measured by a particle size analyzer. For the determination of particle size 100 µl of the sample was diluted with an appropriate volume of distilled water, and diameter of vesicle was determined.

• It can also determine by the photon correlation spectroscopy (PCS) technique used for investigating the size of the phytosome and for the confirmation of the vesicular structure and poly dispersible index is also determined by this technique

3. Vesicle Size and Zeta Potential: Dynamic light scattering (DLS) using computerized inspection system and photon correlation spectroscopy (PCS) used to determine vesicle size and zeta potential

4. Surface Tension Measurement: Surface tension was measured by zthe ring method in a du-nuoy ring tensiometer of the drug in aqueous solution.

5. Spectroscopic Evaluation:

NMR Studies (Nuclear Magnetic Resonance): It is an effective tool for the structure elucidation of molecular structure. It also helps in knowing electron distribution in molecules along with the quantum mechanical nature of bonds, based on the data formation of the phytosomes can be concluded. *e.g.,* H1-NMR, 13C-NMR

6. FTIR Studies (Fourier Transformed Infra-red Spectroscopy): FTIR spectral data can be taken to determine the structure, and chemical stability of phytosome loaded phospholipid and polymer and drug samples. The sample can be crushed with potassium bromide (KBr) to get pellets at 600 kg/cm^2 pressure. Spectral scanning may be done in the range of range between 4000-400cm^{-1}.

7. Entrapment Efficiency: Phytosomal pre-paration was subjected to centrifugation using a cooling centrifuge at 4 °C at high rpm to lyse the vesicle for the specific time period. Then clear supernatant was siphoned off carefully to separate to the non-entrapped extract and the absorbance of

supernatant for non-entrapped extract was recorded at the suitable λ_{max} using UV-visible spectro-photometer. Sediment was treated with trion-X100 solution to lyse the vesicles and diluted with suitable buffer and absorbance taken at suitable λ_{max}. Then amount of Phytoconstituents in supernatant and sediment gave a total amount of Phytoconstituents in 1 ml of phytosomal dispersion. The %entrapment efficiency was calculated by the formula

% Entrapment efficiency = (Amount of drug in sediment / Total amount of drug added) × 100

8. Drug Content: The drug content of phytosomes was determined by dissolving an accurately weighed quantity of phytosomal dispersion in 10 ml of methanol. After suitable dilution, absorbance was determined by spectroscopic methods at a suitable wavelength and drug content was determined by using formula

% Drug Content = (actual drug content in phytosomes / theoretical yield) × 100

9. *In-vitro* Drug Release Studies: The prepared phytosome was loaded in zero size capsule. *In-vitro* dissolution studies for the prepared formulation was carried out using type-2 apparatus at suitable rpm in suitable dissolution medium which is maintained at 37 ° ± 2 °C. 5ml of aliquots were withdrawn at specified interval of time intervals and assayed spectrometrically. An equal amount of fresh media was replaced after each sampling to maintain the constant volume.

10. Determination of Release Kinetics: To study the release kinetics of phytosomal formulation, data obtained from the dissolution studies were computed in different kinetic models (a) zero-order (cumulative % drug release *vs.* time) (b) first order (log cumulative % drug retained *vs.* time) (c) Higuchi (log cumulative percent drug released *vs.* square root of time) (d) Korsemayerpeppas equation (log cumulative % release *vs.* time). The regression coefficient values of different release kinetics equations were evaluated by computing the data of release profiles of phytosomal formulations

11. Stability Studies: The prepared phytosomes subjected to stability studies at 40±2 °C/75±5% RH as per ICH guidelines for a period of 3 months and evaluate the formulation for microscopic evaluation and drug release and drug entrapment and *in-vitro* drug release studies

Difference between Phytosomes and Liposomes: In phytosomesthe active constituent is embedded in the polar head of phospholipids, becoming an integral part of the membrane, while in liposomes the active constituents dissolved in the internal pocket [39,] which is shown in **Fig. 2**. After numerous studies, phytosomes are proved that they markedly improve the absorption and have substantially greater clinical efficacy over niosomes and now a day's industries have successfully applied this technology to a number of standardized flavonoid preparations. The following **Table 1** shows the major differences between phytosome and liposome [39].

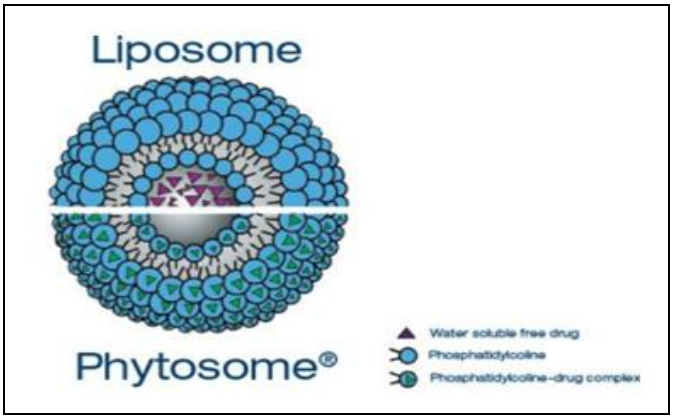

FIG. 2: MOLECULAR ORGANIZATION LIPOSOME AND PHYTOSOME [39]

TABLE 1: DIFFERENCE BETWEEN LIPOSOME AND PHYTOSOME

Property	Liposome	Phytosome
Bonding	It is an aggregate of many phospholipid molecules that encloses other photoactive molecules without specifically bonding to them	It is a unit of few molecules bonded together [10]
Bioavailability and absorption	Its bioavailability and absorption is lesser than phytosome	It has much better bioavailability and absorption [15]
Arrangement of molecules	In liposomes, hundreds and thousands of phosphatidylcholine molecules surround the water soluble molecule	In phytosome, phospholipid (phosphatidylcholine) and an individual phytoconstituents are present in 1:1 or 2:1 ratio depending on the substance [40]

Improved Bioavailability of Phytosome and its Importance: Advances in phytosomal delivery system are as follows:

- Sylimarin shows satisfactory delivery of sylibin when they are formulated as phospholipid complex. This study is an effort to formulate phytosomes of sylibin and its *in-vivo* evaluation on rats. There is a noticeable enhancement after oral administration due to an improvement of the sylibin –phospholipid complex [41].
- Tedesco *et al. (2004) studied fictitious sylimarinphytosome with great anti-hepato toxic activity than sylimarin alone and can* provide protection against the pernicious effect of aflatoxin B1 on broiler chicks [42, 43].
- Another research is on bacopside. It is an active constituent in the Bacopamonnieri plant having anti-amnesic activity. It shows conspicuous change in the therapeutic efficacy by the phytosomalformulation [44, 45].
- Barzaghi *el. al.*, (1990): A study on absorption of sylibin. This sylibin is formulated as phospholipid complex; the oral absorption of sylibin from sylibinphytosome is enhanced than the normal absorption of sylibin from milk thistle because it is bound to phospholipid. This is assessed after oral administration of the same amount of sylibinphytosome and the sylibin from milk thistle [46].
- Berberine phospholipid complex increases the solubility and dissolution rate than the berberine Phytoconstituents [47].
- Sinigrin having wound healing property this property of sinigrin is improved because they are formulated as phytosomes and results are also considered as compared to sinigrin alone [48].
- Grape seed contains proanthocyanidins / procyanidins. These are incorporated in phospholipid complex, show a role in damage-induced due to ischemia heart disease and also having the role protection in against atherosclerosis [49].
- Green tea leaves consist of Epigallocatechin 3-o-gallate. This main active constituent is incorporated in phytosomes results in improved oral bioavailability and compared to simply green tea extract [50-52].
- Further clinical studies, i.e., green tea phytosomes, which is free from caffeine having anti-obesity and anti-oxidant properties, and also having hypo lipidae-micproperty [53-55].
- Quercetin phospholipid complex shows better therapeutic efficacy in carbon tetrachloride-induced liver injury on rats [56].

CONCLUSION: The Phytoconstituents like flavonoids, glycosides, tannins, terpenoids, and glycosides are found to have medicinal value but owing to their presence of polar head, they have low solubility and low absorption rate, and poor systemic bioavailability, thereby reducing the therapeutic efficacy. These problems can be overcome by phytosomes. Phytosomes are an advanced form of herbal medicines that are absorbed better than a conventional plant extract. They are an advanced form of botanical and Phyto-constituents. That is well absorbed orally and topically owing to their presence of improved solubility, which enables to cross biological membrane resulting in enhance systemic bio-availability, *i.e.*, more active principle in the systemic circulation. Phytosome also improves pharmacokinetics and pharmacological parameters, and they having scope in cosmetology. Phytosomes superior to liposomes due to their much better absorption and stability profile.

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