

Phytosomes: A Revolutionary Approach to Enhancing Bioavailability of Herbal Actives

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ABSTRACT

The term "phyto" mentions to plants, and "some" refers to cells, with the combination often termed "herbosomes." Phytosome technology is a patented method where standardized plant extracts or water-soluble phytoconstituents are combined with phospholipids to create lipid-compatible molecular complexes. This process significantly enhances the absorption and bioavailability of the active ingredients. Recent research has focused on developing the transdermal route for delivering phytoconstituents, which is becoming increasingly promising in the setting of chronic and acute conditions such as irritation, cancer, and metabolic disorders. Despite the therapeutic potential of plant-derived products, these often face challenges such as instability and poor bioavailability due to their hydrophilic or lipophilic nature, which prevents them from effectively crossing biological membranes. Phytosome technology addresses these issues by improving the solubility and stability of plant extracts, facilitating better absorption and increasing their effectiveness. By enhancing the lipophilicity of hydrophilic compounds or the hydrophilicity of lipophilic ones, phytosomes make it possible for these phytoconstituents to cross biological barriers more efficiently. The topical application of phytosomes for cosmetic purposes has already shown positive results, and there is a growing market for products incorporating phytosome delivery systems, such as those containing Ginkgo biloba, Silybum marianum, and Camellia sinensis. This review examines the advancements in phytosome technology, particularly for transdermal drug delivery, and compares it with liposome technology. It highlights the potential of phytosome-based systems to improve the bioavailability and therapeutic efficacy of polyphenolic compounds, addressing the challenges of poor absorption and low bioavailability typically seen with traditional plant extract formulations.

Keywords:-Bioavailability, phospholipids, phytochemical delivery systems, phytosome, polyphenols.

INTRODUCTION

Plants and their various parts have been utilized in traditional medicine for centuries to treat a wide range of diseases and disorders. Extensive pharmacological and chemical studies on plant extracts have revealed the therapeutic potential of their bioactive components. However, during the isolation and purification of these

components, the biological activity often diminishes due to changes in their molecular structure or their inability to effectively interact with biological membranes. Most of the bioactive ingredients of plants, such as flavonoids, phenolics, and terpenoids, are water-soluble, but their poor lipid solubility limits their ability to cross lipid-based

biological membranes. This leads to challenges in their absorption and,

consequently, their bioavailability[1,2,3].

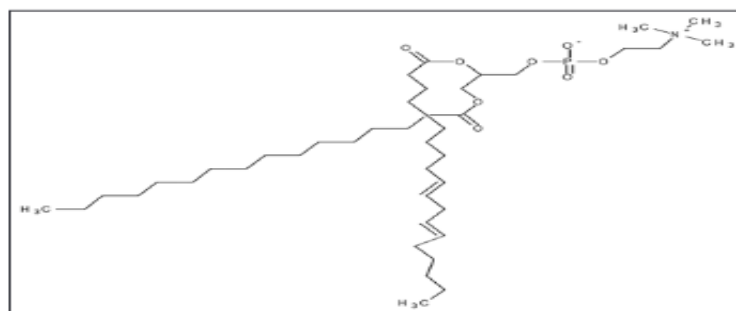


Fig.1:-Molecular structure of phosphatidylcholine[4].

In response to these challenges, various drug delivery systems have been developed to improve the bioavailability of plant-derived compounds, including liposomes, phytosomes, pharmacosomes, and micelles. Phytosomes, in specific, represent a novel approach that improves the absorption and bioavailability of herbal extracts. The term "phyto" refers to plants, and "some" refers to cell-like structures. Phytosomes are lipid-compatible

molecular complexes formed by binding standardized plant extracts or their bioactive constituents to phospholipids, such as phosphatidylcholine, the most commonly used phospholipid. This process enhances the solubility and stability of the plant compounds, allowing them to more effectively cross biological membranes and reach systemic circulation^{2,3}

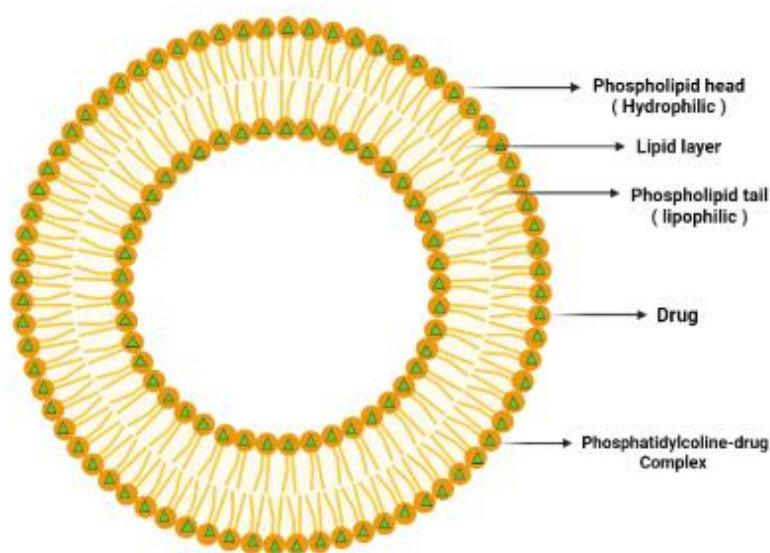


Fig.2:- Structure of Phytosome[4].

Phytosome technology has been positively applied to several well-known herbal drugs, including Ginkgo biloba, hawthorn, olive oil, grape seed, green tea, and ginseng. These formulations offer

improved bioavailability compared to conventional herbal extracts, thereby maximizing their therapeutic effects. Phytosomes are also beneficial in topical applications, where they enhance the

delivery of active ingredients through the skin. This review explores the advancements in phytosome-based drug delivery systems, with a focus on their role in improving the bioavailability of plant-derived compounds and their potential applications in modern herbal medicine [1,2,3]

PHYTOSOME TECHNOLOGY

Phytosome technology, developed by Indena S.p.A. of Italy, represents a significant advancement in improving the bioavailability of plant-derived compounds. This technology involves joining phospholipids, such as phosphatidylcholine, into consistent plant extracts, forming lipid-compatible complexes known as phytosomes. Phosphatidylcholine is a bifunctional molecule with both hydrophilic (choline) and hydrophobic (phosphatidyl) parts, which enables it to bind to polar compounds through its choline head while its lipid-soluble tail envelops the phytoconstituent. The resulting phytosome complex enhances the absorption and stability of active ingredients by facilitating their ability to cross lipid-based biological membranes, significantly improving their bioavailability and therapeutic efficacy. Initially, the first generation of phytosomes was prepared using non-polar solvents, but recent advancements have seen the use of hydro-ethanolic solvents to meet current food and pharmaceutical standards. This evolution has led to more versatile phytosome formulations for both oral and topical applications[5,6,7]

ADVANTAGES OF PHYTOSOMES

The advantages of phytosome technology over conventional herbal formulations are numerous. First, phytosomes require smaller doses due to their enhanced absorption, leading to increased efficiency and reduced dosage. Additionally, they exhibit superior drug entrapment

efficiency, better stability, and the ability to target specific sites within the body. The phospholipid carrier itself, phosphatidylcholine, also has hepatoprotective properties and nutritional value, providing additional therapeutic benefits. Furthermore, phytosomes offer gastroprotective properties, ensuring that plant-derived compounds are shielded from degradation by gastric acids and gut bacteria, allowing them to reach systemic circulation intact. This makes phytosomes highly effective for both oral delivery and topical applications, such as in cosmetics, where they facilitate the efficient delivery of active ingredients through the skin. With requests in herbal medicine, nutraceuticals, and cosmetics, phytosomes signify a talented solution for improving the bioavailability and efficacy of plant-based therapeutics[8,9]

PROPERTIES OF PHYTOSOMES

Physico-Chemical Properties

Phytosomes are formed through the reaction of a stoichiometric number of phospholipids with standardized plant extracts, creating a complex where the phospholipid interacts with the phytoconstituents. Spectroscopic data discloses that this interaction primarily involves the creation of hydrogen bonds between the polar head groups of the phospholipid (such as the phosphate and ammonium groups) and the polar functional groups of the plant extract. The size of phytosomes can vary widely, ranging from 50 nm to several micrometers, depending on the specific formulation. When exposed to water, phytosomes adopt a micellar structure similar to liposomes, as confirmed by Photon Correlation Spectroscopy (PCS). The ¹H NMR and ¹³C NMR spectroscopy indicate that the long aliphatic chains of phospholipids remain largely unchanged in the complex, suggesting that these chains wrap around the active compound, forming a lipophilic envelope. Regarding

solubility, phytosomes are typically soluble in aprotic solvents, moderately soluble in fats, and insoluble in water, with limited stability in alcohol. However, when lipophilic compounds like curcumin are complexed with phospholipids, their water solubility improves significantly^{10,11,12}

Biological Properties:

Phytosomes represent a novel formulation that offers significantly better bioavailability compared to traditional herbal extracts. This is due to their enhanced absorption and utilization, which has been demonstrated in both pharmacokinetic studies and pharmacodynamic tests involving experimental animals and human subjects. The biological behavior of phytosomes is influenced by factors such as their physical size, membrane permeability, entrapment efficiency, and the purity of the materials used in their preparation. It is important to distinguish phytosomes from liposomes although both are lipid-based vesicles, liposomes primarily serve to entrap hydrophilic drug molecules within their internal cavity, often involving multiple phospholipid molecules. In contrast, phytosomes are formed through the interaction of 1-4 phospholipid molecules with the phytoconstituents, chemically anchoring the active ingredients to the phospholipids. This results in greater membrane permeability and stability, making phytosomes a superior alternative to liposomes for improving the delivery of plant-derived compounds^{13,14}

Preparation of phytosome

Phytosomes are typically prepared by reacting an accurate number of phospholipids, such as soya lecithin, with herbal extracts in an aprotic solvent. Phosphatidylcholine, a key constituent of soya lecithin, has dual properties: the hydrophilic choline part interacts with water-soluble phytoconstituents, while the lipophilic phosphatidyl portion binds with the lipid-soluble compounds. This

interaction leads to the formation of a lipid-based complex that enhances the stability and bioavailability of the phytoconstituents. The process can also involve mixing synthetic or natural phospholipids with standardized plant extracts in a ratio typically ranging from 0.5:1 to 2:1, with a 1:1 ratio being most common. The reaction is usually carried out in aprotic solvents like dioxane, methylene chloride, or acetone, after which the phytosome complex is isolated by precipitation with a non-solvent, such as an aliphatic hydrocarbon, or through methods like lyophilization or spray drying [15,16]

One of the most common techniques for preparing phytosomes involves the thin-layer rotary evaporator method. In this method, the phospholipid and the herbal extract are mixed in anhydrous ethanol within a round-bottom flask, which is then attached to a rotary evaporator. The solvent is evaporated at approximately 60°C, forming a thin film around the flask. The film is then hydrated with a phosphate buffer (pH 7.4), causing the lipid layer to peel off and form a vesicle suspension. The resulting suspension undergoes probe sonication at 60% amplitude to achieve uniformity and is stored in the refrigerator for 24 hours before characterization. Another method includes refluxing the polyphenolic extract and phospholipid in dichloromethane (DCM) for one hour at a temperature not exceeding 40°C, followed by solvent evaporation and precipitation with n-hexane to obtain the phytosome complex. Alternatively, a method using chloroform to dissolve phospholipids and cholesterol, followed by sonication and solvent removal under reduced pressure in a rotary evaporator, can also be employed to prepare phytosomes. Once the solvent is removed, the resulting thin layer is hydrated with the polyphenolic extract and subjected to further sonication in an ice bath for heat dissipation [17,18]

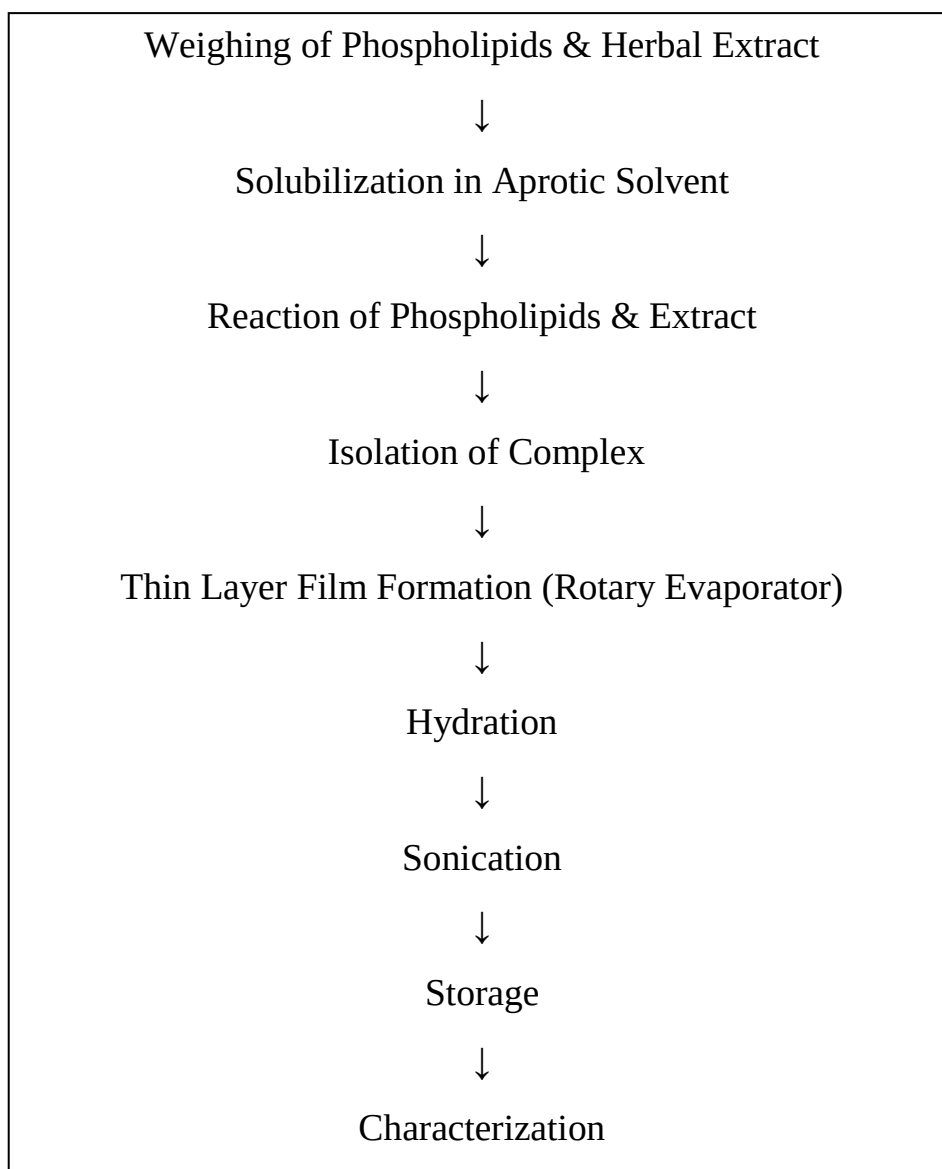


Fig.3:-Flow chart of Preparation of phytosome

Difference between liposomes and Phytosomes[19,20,21]

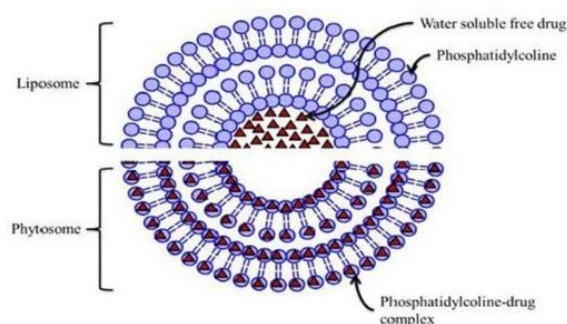


Fig.4:-Illustration on comparative account of phytosomes and liposomes

Aspect	Liposomes	Phytosomes
Definition	Liposomes are lipid vesicles that encapsulate water-soluble molecules in their aqueous core.	Phytosomes are lipid-based molecular complexes where phytoconstituents are bound to phospholipids.
Structure	Consist of a phospholipid bilayer surrounding an aqueous core.	Formed by the complexation of phospholipids with phytoconstituents (e.g., flavonoids) via hydrogen bonds.
Phospholipid Role	Phospholipids act as a barrier to encapsulate hydrophilic drugs or molecules.	Phospholipids form a complex with phytoconstituents, improving their stability and bioavailability.
Primary Function	Encapsulate hydrophilic drugs for controlled release.	Improve the solubility, stability, and bioavailability of plant extracts or phytoconstituents.
Size	Typically ranges from 50 nm to several micrometers.	Generally ranges from 50 nm to a few hundred nanometers.
Formulation	Liposomes are primarily used for hydrophilic drug delivery.	Phytosomes are specifically designed for enhancing the absorption of hydrophilic plant extracts through lipid membranes.
Membrane Composition	Composed of phospholipid bilayers.	Composed of phospholipids (e.g., phosphatidylcholine) forming a complex with the plant extract.
Encapsulation Type	Entrapment of hydrophilic compounds in the aqueous core.	Chemical complexation of lipophilic or hydrophilic phytoconstituents with phospholipids.
Targeted Delivery	Primarily used for targeted delivery of drugs, especially hydrophilic ones.	Designed for enhanced absorption, often for oral and transdermal drug delivery.
Solubility	Liposomes are generally used to solubilize water-soluble drugs.	Phytosomes improve the solubility of both lipophilic and hydrophilic plant extracts, aiding in bioavailability.
Bioavailability	Limited bioavailability due to difficulty in crossing biological membranes.	Higher bioavailability due to the lipid-compatible complex, aiding better membrane penetration.
Stability	Stability can be an issue; subject to oxidation and leakage of the encapsulated substance.	Improved stability compared to free plant extracts due to the interaction with phospholipids.
Common Applications	Drug delivery, vaccine formulations, cosmetic products.	Herbal medicine, nutraceuticals, topical applications, and cosmetic products.
Example	Used for delivery of chemotherapeutic agents, gene therapy.	Commonly used for flavonoids like quercetin, curcumin, and Ginkgo biloba.

MECHANISM OF PHYTOSOME TECHNOLOGY

The mechanism of phytosome technology addresses the challenges of low absorption and bioavailability associated with polyphenolic compounds, particularly flavonoids. The first major factor contributing to poor absorption is the molecular structure of polyphenols, which often consists of multiple ringed structures that are too large to be efficiently absorbed by simple diffusion through biological membranes. The second factor is the poor solubility of flavonoid molecules in lipids, which hinders their ability to cross lipid-based biological membranes. Phytosome technology overcomes these limitations by forming a complex between phospholipids and the polyphenolic compounds. The phospholipid, such as phosphatidylcholine, has both hydrophilic and lipophilic properties, enabling it to bind with both hydrophilic and lipophilic components of the polyphenols. This complex improves the solubility and stability of the active ingredients, making them more compatible with lipid membranes, and thereby enhancing their absorption across the intestinal lining or through the skin. The resulting phytosome complex, with its improved lipid compatibility, facilitates better bioavailability and targeted delivery of the active polyphenolic constituents[22,23,24]

CHARACTERIZATION TECHNIQUES OF PHYTOSOME

$$\text{Entrapment Efficiency (\%)} = \frac{\text{Weight of total drug} - \text{Weight of free drug}}{\text{Weight of total drug}} \times 100$$

Fourier Transform Infrared Spectroscopy (FTIR)

FTIR analysis was performed to evaluate the structural integrity and chemical stability of the drug and phospholipid. The drug-phospholipid complex was mixed with potassium bromide to form pellets, which were subjected to a pressure of 600

Differential Scanning Calorimetry (DSC)

In this study, a drug polyphenolic extract, phosphatidylcholine, a physical mixture of the drug extract with phosphatidylcholine, and a drug-phospholipid complex were placed in an aluminium cell and heated from 0 to 400°C at a rate of 50-250°C/min in a nitrogen atmosphere[25]

Scanning Electron Microscopy (SEM)

SEM was employed to observe the particle size and morphology. A dry sample was spanning on an electron microscope brass stub, which was then coated with gold using an ion sputter. The sample was randomly scanned under a 100x magnification to assess its structure[26,27]

Transmission Electron Microscopy (TEM)

TEM was utilized to assess the size of the phytosomal vesicles at 1000x magnification, providing insight into their morphology[28]

Drug Entrapment and Loading Capacity

The drug phytosomal complex felt centrifugation at 10,000 rpm for 90 minutes at 4°C to separate the phytosome from the free drug. The concentration of the un-trapped drug was measured using ultraviolet (UV) spectroscopy[29,30] The drug entrapment efficiency (EE) was calculated using the following formula:

kg/cm². The scanning range for FTIR was set between 4000 to 400 cm⁻¹[31]

Size Analysis and Zeta Potential

The particle size and zeta potential of the phytosomal complex were measured using a Malvern Zetasizer, employing an argon laser for characterization[32]

In Vitro and In Vivo Evaluation

The in vitro and in vivo evaluations were based on the characteristics of the drug, its principal phytoconstituents, and their interaction with the phospholipid layer. The choice of animal model for evaluation was determined according to the specific properties of the drug and the phytosomal formulation [33]

CONCLUSION

In conclusion, phytosome technology represents a significant advancement in enhancing the bioavailability and stability of plant-derived bioactive compounds, particularly polyphenolic constituents like flavonoids, which are known for their pharmacological efficacy. Traditional plant extracts often suffer from poor absorption and low bioavailability due to their large molecular size and limited lipid solubility. By complexing these phytoconstituents with phospholipids, phytosome technology recovers their solubility, stability, and permeability, allowing for better absorption through biological membranes. The unique interaction between the hydrophilic and lipophilic components of phosphatidylcholine and polyphenols results in a lipid-compatible molecular complex that significantly enhances the delivery of these compounds, either through oral or transdermal routes.

Phytosomes offer several advantages over conventional herbal formulations, including improved pharmacokinetic properties, increased drug entrapment efficiency, and better targeting to specific sites. This technology has proven effective in the development of nutraceuticals and pharmaceutical formulations, providing a promising solution for overcoming the limitations of traditional herbal medicine. Furthermore, phytosomes have shown potential for various applications, including in the cosmetic industry, where they are used for the effective delivery of herbal extracts to the skin. Overall,

phytosome technology not only enhances the therapeutic efficacy of polyphenolic compounds but also broadens their clinical and commercial applications, making it a valuable tool in modern drug delivery systems and natural product formulations.

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