REVIEW ARTICLE

Enhancing bioavailability with phytosome technology: Approaches to formulation, characterization, and pharmacological assessment

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Abstract

Phytosomes are advanced herbal drug delivery systems designed to improve the bioavailability, stability, and therapeutic efficacy of plant-based phytoconstituents. Many herbal compounds, particularly polyphenols and flavonoids, suffer from low absorption due to poor lipid solubility, large molecular size, and extensive first-pass metabolism. Phytosome technology overcomes these limitations by forming a phospholipid–phytoconstituent complex, which enhances membrane permeability and gastrointestinal uptake. This review provides a comprehensive overview of the principles of phytosome technology, formulation strategies, key phospholipids used, and optimization parameters. Various characterization techniques – including fourier transform infrared spectroscopy, differential scanning calorimetry, scanning electron microscopy/transmission electron microscopy, X-ray diffraction, zeta potential analysis, particle size distribution, and entrapment efficiency – are discussed in detail. The article further highlights the pharmacokinetic and pharmacological advantages of phytosomes, featuring recent studies on antioxidant, anti-inflammatory, hepatoprotective, anticancer, and neuroprotective activities. Overall, phytosomes represent a promising platform for improving the therapeutic potential of herbal bioactives, supporting their application in modern pharmaceutical and nutraceutical formulations.

Key words: Bioavailability enhancement, characterization methods, flavonoids, formulation techniques, herbal drug delivery, nanocarrier systems, pharmacological activity, phospholipid complex, phytosomes, polyphenols

INTRODUCTION

Herbal medicines have been used for centuries for the prevention and management of various diseases. Despite their proven therapeutic potential, many plant-derived bioactive compounds exhibit poor oral bioavailability due to low aqueous and lipid solubility, instability in the gastrointestinal tract, and rapid metabolism. The pharmaceutical industry has therefore focused on developing novel drug delivery systems that can improve the absorption and clinical efficacy of herbal constituents. Among these, phytosomes – also known as phyto-phospholipid complexes – have emerged as an innovative and effective approach for enhancing the delivery of herbal actives.[1]

Phytosomes differ from conventional liposomes in that the phytoconstituent forms a molecular complex with phospholipids, creating a structure that enhances lipophilicity and facilitates better interaction with biological membranes [Figure 1]. This unique arrangement improves gastrointestinal absorption, leading to higher systemic availability and improved pharmacological responses. Phytosomes have been widely applied to several phytochemicals such as curcumin, silybin, quercetin, catechins, ginkgo flavonoids, and boswellic acids.[2]

The growing interest in phytosome technology can be attributed to its ability to overcome major challenges associated with herbal drug delivery, including poor permeability, low stability, and inconsistent therapeutic outcomes. Recent

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advancements in formulation techniques – such as solvent evaporation, anti-solvent precipitation, supercritical fluid technology, and lyophilization – have further refined the preparation and performance of phytosomes.

This review provides a detailed discussion on the formulation principles of phytosomes, commonly used phospholipids, preparation parameters, and analytical methods for characterization. It also summarizes current pharmacological findings and clinical applications, offering insights into the future prospects of phytosome-based herbal therapeutics.

RATIONALE FOR PHYTOSOME TECHNOLOGY

Many plant-derived bioactive compounds – especially flavonoids, polyphenols, terpenoids, alkaloids, and glycosides – exhibit potent pharmacological properties but fail to achieve significant therapeutic effects due to poor oral bioavailability. This limitation arises from several factors, including low lipid solubility, large molecular size, poor permeability across biological membranes**,** instability in the gastrointestinal environment, and rapid first-pass metabolism. As a result, only a small fraction of these compounds reaches systemic circulation, making their clinical translation difficult despite promising *in vitro* efficacy.[3]

Phytosome technology was developed to address these challenges by enhancing the interaction of phytoconstituents with biological membranes**.** Unlike conventional liposomes, where the drug is passively entrapped, phytosomes involve the formation of a molecular complex between phospholipids and phytoconstituents through hydrogen bonding and polar interactions. This complexation increases the lipophilicity**,** membrane affinity**,** and absorption efficiency of the herbal extract.

The rationale for adopting phytosomes technology can be summarized as follows:

Overcoming Poor Bioavailability

Most phytochemicals, such as silybin, curcumin, catechins, and quercetin, have very low oral absorption. Complexing them with phospholipids improves lipid miscibility and facilitates efficient uptake through enterocyte membranes.[4]

Enhancing Stability

Phytosomes protect sensitive phytoconstituents from chemical degradation, hydrolysis, and enzymatic metabolism within the gastrointestinal tract, thereby improving their pharmacokinetic profile.

Improving Pharmacological Efficacy

Higher plasma concentrations of the phytoconstituent lead to improved therapeutic outcomes, allowing the same herb to demonstrate stronger antioxidant, anti-inflammatory, hepatoprotective, cardio-protective, and anticancer effects.[5]

Enabling Dose Reduction

Enhanced bioavailability allows for reduced dosing compared with conventional extracts, minimizing gastrointestinal discomfort and increasing patient compliance.

Compatibility with Nutraceutical and Pharmaceutical Systems

Phytosomes have favorable physicochemical properties, making them easy to incorporate into capsules, tablets, gels, functional foods, and cosmetic formulations.

Natural, Safe, and Industry-Friendly

Phospholipids such as phosphatidylcholine are biocompatible, biodegradable, and recognized as safe, aligning with the global preference for natural, plant-based therapeutic systems.

Improved Commercialization Potential

Phytosome-based products such as Siliphos® (silybin phytosome) and Meriva® (curcumin phytosome) already demonstrate successful clinical and market acceptance, validating the technology's translational potential.[6]

PREPARATION OF PHYTOSOMES

The preparation of phytosomes involves the formation of a phyto-phospholipid complex, in which bioactive phytoconstituents interact with phospholipids (mainly phosphatidylcholine). Several techniques have been developed to prepare phytosomes with optimal stability, entrapment efficiency, particle size, and bioavailability. The most widely applied methods include solvent evaporation, anti-solvent precipitation, thin-film hydration, supercritical fluid technology, and lyophilization-based techniques.

Solvent Evaporation Method (Conventional Method)

This is the most commonly used and simplest method for phytosome preparation.

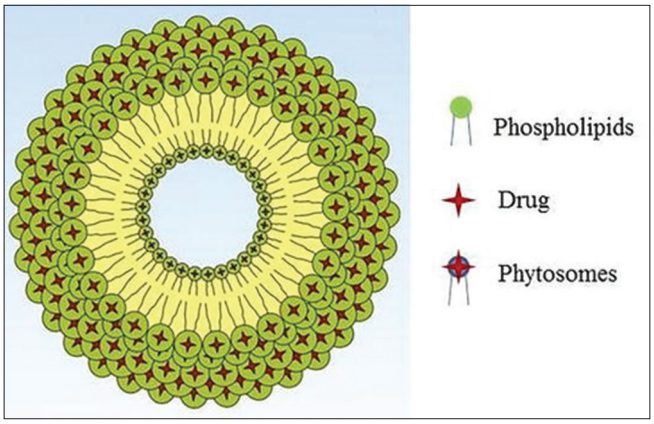

Figure 1: Structure of phytosomes

Procedure

1. The phytoconstituent and phospholipid are dissolved in a common organic solvent (e.g., ethanol, acetone, dichloromethane, chloroform).
2. The mixture is heated at 40–60°C under constant stirring to allow complex formation.
3. The solvent is removed using a rotary evaporator to obtain a thin layer of the complex.
4. The dried film is scraped, collected, and stored or further processed into dosage forms.[7]

Advantages

- Easy and scalable
- High complexation efficiency.

Limitations

- Uses organic solvents
- Requires controlled evaporation to avoid phospholipid degradation.

Anti-Solvent Precipitation Method

This method is used to obtain fine particulate phytosomes.

Procedure

1. The phytoconstituent and phospholipid are dissolved in a polar solvent (e.g., methanol, ethanol).
2. The solution is slowly added to a non-solvent (e.g., hexane) under constant stirring.
3. The addition causes precipitation of the phyto-phospholipid complex.
4. The precipitated phytosomes are filtered and dried.

Advantages

- Produces micron- to nano-sized particles
- Better control over particle size.

Limitations

- Requires solvent selection optimization.

Thin-Film Hydration Method

Commonly used for phospholipid-based vesicular systems, including phytosomes.

Procedure

1. The phytoconstituent and phospholipid are dissolved together in an organic phase.
2. The solvent is evaporated using a rotary evaporator to form a thin lipid film.
3. Hydration is done using water or buffer under gentle agitation, forming phytosomal vesicles.
4. Sonication or homogenization may be applied to reduce particle size.[8]

Advantages

- Produces stable and uniform vesicles
- Suitable for heat-sensitive phytochemicals.

Limitations

- Time-consuming
- May require size reduction processing.

Supercritical Fluid Technology (SCF Method)

Eco-friendly, advanced technique using supercritical CO_2.

Procedure

1. Phospholipid and phytoconstituent are dissolved in a suitable organic solvent.
2. Supercritical CO_2 is introduced to dissolve the solvent at high pressure.
3. Rapid depressurization leads to precipitation of the phytosome as fine particles.[9]

Advantages

- Solvent-free residues
- Produces nano-sized particles
- High purity.

Limitations

- Expensive equipment
- Requires process expertise.

Lyophilization (Freeze-Drying) Method

Often used as a final step to enhance the stability of phytosomes.

Procedure

1. A liquid phyto-phospholipid complex is prepared by solvent evaporation.
2. The complex is dispersed in water or cryoprotectants (mannitol, sucrose).

3. The dispersion is frozen and then lyophilized to obtain dry phytosomal powder.

Advantages

- Increases stability and shelf-life
- Better for thermolabile phytochemicals.

Limitations

- Additional processing cost.

EVALUATION PARAMETERS FOR PHYTOSOMES

Evaluation of phytosomes is essential to confirm the formation of the phyto-phospholipid complex, determine physico-chemical properties, and assess stability and performance. The following parameters are commonly used to characterize phytosomes:[10]

Particle Size and Particle Size Distribution

Techniques

- Dynamic light scattering
- Laser diffraction.

Importance

- Determines dispersion quality
- Smaller particle size enhances bioavailability and membrane penetration
- Polydispersity index (PDI) indicates homogeneity (<0.3 preferred).[11]

Zeta Potential

Technique

Electrophoretic mobility analysis.

Importance

- Indicates surface charge of phytosomes
- Predicts physical stability of the dispersion
- Zeta potential >±30 mV indicates good stability and low aggregation.[12]

Entrapment Efficiency (EE%)/Complexation Efficiency

Definition

Percentage of phytoconstituent successfully complexed with phospholipid.

Method

- Ultracentrifugation or dialysis
- Quantified using ultraviolet–Vis spectroscopy or high performance liquid chromatography (HPLC).[13]

Drug–Phospholipid Interaction Studies

These confirm the formation of the complex.

Fourier transform infrared spectroscopy

- Identifies hydrogen bonding between phytoconstituent and phospholipid
- Shifts in functional group peaks (–OH, C=O, P=O) confirm complex formation.

Nuclear Magnetic Resonance (NMR) (^{1}H-NMR and ^{31}P-NMR)

- Detects chemical shifts indicating molecular interactions
- Confirms stoichiometry (1:1 or 1:2 complex).

X-ray diffraction

- Determines crystalline or amorphous nature
- Loss of crystalline peaks implies successful complexation.

Thermal Analysis

Differential scanning calorimetry

- Identifies thermal transitions (melting point, glass transition)
- Disappearance or shift of endothermic peaks confirms complex formation.[14]

Thermogravimetric analysis

- Measures thermal stability and degradation patterns.

Morphological Evaluation

Scanning electron microscopy

- Reveals surface morphology and shape
- Confirms spherical/vesicular structures.

Transmission electron microscopy

- Provides nanoscale visualization
- Shows lamellarity and internal structure.[15]

CONCLUSION

Phytosomes technology represents a significant advancement in the field of herbal drug delivery, offering a scientifically proven approach to overcome the inherent limitations of many

phytoconstituents. By forming a stable phyto-phospholipid complex, phytosomes enhance the solubility, permeability, stability, and bioavailability of plant-derived bioactives that otherwise exhibit poor absorption and limited therapeutic effect. The technology not only improves pharmacokinetic behavior but also leads to superior pharmacological responses, allowing the development of more effective and patient-friendly herbal formulations.

The versatility of phytosomes in terms of formulation approaches, characterization techniques, and compatibility with various dosage forms makes them highly suitable for both pharmaceutical and nutraceutical applications. Numerous preclinical and clinical studies validate their potential in treating diverse conditions such as liver disorders, inflammation, oxidative stress, cancer, and metabolic diseases.

Despite some limitations related to production cost, solvent use, and batch variability, ongoing research and technological advancements – such as supercritical fluid processing, green chemistry approaches, and nano-phytosome innovations – continue to improve the efficiency, scalability, and safety of this platform.

Overall, phytosomes provide a promising and innovative strategy for maximizing the therapeutic potential of herbal medicines. Their integration into modern drug delivery systems bridges the gap between traditional herbal wisdom and contemporary pharmaceutical science, paving the way for the development of highly bioavailable, scientifically standardized, and clinically effective natural therapeutics.

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