RESEARCH PAPER

Phytosome-Based Drug Delivery System for Improved Bioavailability of Herbal Drugs.

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ABSTRACT
The bioactive compounds found in herbs which include polyphenols and flavonoids show strong potential for medical use but their effectiveness is limited because they cannot dissolve in water and their molecules are too large and their substances cannot pass through cell membranes. The body shows very low absorption of these substances which leads to unpredictable medical results. Phytosome technology represents a major breakthrough in herbal medicine through its development of stoichiometric complexes which combine plant extracts with phospholipids. Phytosomes establish chemical connections through hydrogen bonding which enables phytoconstituents to attach to the polar phospholipid head. The combination process creates an amphiphilic molecule which results in better intestinal absorption and improved metabolic stability. The review presents an analysis of phytosome molecular structure and modern production methods and mathematical release patterns and the latest medical research from 2024 to 2026. The study investigates potential uses of phytosomes for targeted drug delivery and personalized medical treatments. Phytosomes provide a practical solution to enhance the medicinal power of herbal treatments because they boost the body's ability to absorb & process plant-based medicines. Through the process of encapsulating plant extracts within phospholipids phytosomes present an effective solution to the challenges faced by traditional herbal products. The pharmaceutical and nutraceutical industries currently use phytosomes for drug delivery but this field has the potential to create future advancements in their delivery systems

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INTRODUCTION

Introduction: The Bioavailability Paradox in Herbal Medicine

For centuries, plant-derived secondary metabolites have been the main source of primary healthcare treatment. The most promising molecules which include curcumin and silymarin and quercetin face the "bioavailability paradox" problem. The compounds show strong effects according to in vitro tests but their effectiveness in living organisms is usually below expectations.

The primary physiological barriers include:

Intestinal Permeability: The high polarity of many flavonoids which exhibit hydrophilic properties creates challenges for their passage through intestinal enterocyte membranes which contain lipophilic components through passive diffusion.

First-Pass Metabolism: In many cases, such enzymes may help to increase the metabolism of conjugation thereby helping the body eliminate the drug before any significant systemic circulation.

Gastric Instability: The volatile oil is denatured during digestion because of heat.

The technology of phytosomes which scientists developed to solve particular problems creates a lipid-compatible protective layer that enables poor-extraction bioactive molecules to become highly bioavailable therapeutic agents. The "bioavailability paradox" is one of the most persistent frustrations in modern pharmacology. The phenomenon shows how a molecule performs perfectly in a petri dish but fails to operate effectively inside the human body. We need to study the plant compounds at their molecular level and examine their complete biological testing process to understand how phytosome technology solves this problem.

The laboratory studies demonstrate that curcumin which comes from turmeric and silymarin which comes from milk thistle and quercetin which comes from onions and apples are exceptional pharmacological compounds. The substances demonstrate strong capacity to protect against oxidative damage while also reducing inflammation and fighting cancerous cells. The results show disappointing outcomes when people take these substances through oral consumption in their natural state.

The body recognizes these molecules as invaders which need to be eliminated instead of treating them as nutrients that should be absorbed into the body. The path from mouth to target cell presents numerous challenges which completely eliminate the medicinal effectiveness of natural herbal extracts.

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The Barrier of Intestinal Permeability

The majority of bioactive flavonoids possess hydrophilic properties together with strong polar characteristics. The compound dissolves easily in tea but its gut wall permeability becomes restricted because of this property. Enterocytes form the small intestine lining which exists behind a protective lipophilic phospholipid bilayer. The intestinal wall fatty membranes block polar plant molecules from melting into their structure because "like dissolves like" principle operates. The intestinal lumen retains the substances which do not enter the bloodstream and they get excreted without producing any effects throughout the body.

The Gauntlet of Gastric Instability

The compounds need to survive through the stomachs extreme low-pH conditions before they can reach the intestines. Many herbal glycosides are chemically fragile. The high acidity of gastric juices causes premature hydrolysis and oxidation which results in complex molecules being transformed into inactive metabolites before they can function. The stomach functions as a furnace instead of an entrance point for botanical extracts.

The "First-Pass" Clearance

Even if a molecule successfully crosses the intestinal barrier, it immediately enters the hepatic portal vein, which carries it straight to the liver. The body processes its first pass of metabolism through this system. The liver contains enzymes that function to detoxify blood through various processes which include:

Glucuronidation: Attaching a sugar acid to the molecule to make it more water-soluble for excretion.

Sulfation: Adding a sulfate group to neutralize the compound.

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2. Structural Elucidation: The Phyto-Phospholipid Complex

The structural elucidation of the phyto-phospholipid complex which scientists refer to as a phytosome shows its complex molecular structure which separates it from standard drug delivery systems that use liposomes and basic physical combinations. The phytosome functions as more than a "capsule" because it exists as a solid-state dispersion that contains botanical extract and phospholipid carrier in specific stoichiometric ratios of 1:1 or 1:2. The complex achieves its absorption of secondary metabolites through this chemical interaction which enables it to overcome the natural barriers created by its polar properties.

The Molecular "Anchor"

The hydrogen bonds which form between the polar head group of phosphatidylcholine and the functional groups of phytoconstituents create the conditions for phytosome formation. The choline head of a phospholipid molecule exhibits hydrophilic properties whereas its fatty acid tails display lipophilic characteristics. The plant extract undergoes synthesis through an aprotic solvent which includes acetone and ethanol to create a chemical process that allows polyphenolic rings to bind through their phosphate groups to the lipid. The bioactive molecule which has hydrophilic properties gets protected through its central position in the structure whereas the phospholipid's fatty acid side chains extend outward to create a structure that repels water.

Phytosomes vs. Liposomes: A Structural Distinction

Phytosomes should not be confused with liposomes though both have different structural geometries.

Liposomes: The drug exists as a water-soluble compound which is contained within microscopic vesicles that have an internal aqueous core and a lipid bilayer shell. The drug exists in a state of "trapped" condition because there exists no direct chemical bond that connects the drug to the lipid.

Phytosomes: The active component of the complex and the lipid material combine to create a 1-to-1 molecular complex. The guest molecule exists as a fundamental component of the membrane structure. The botanical extract maintains its protective properties until it contacts the lipophilic surface of the intestinal cell.

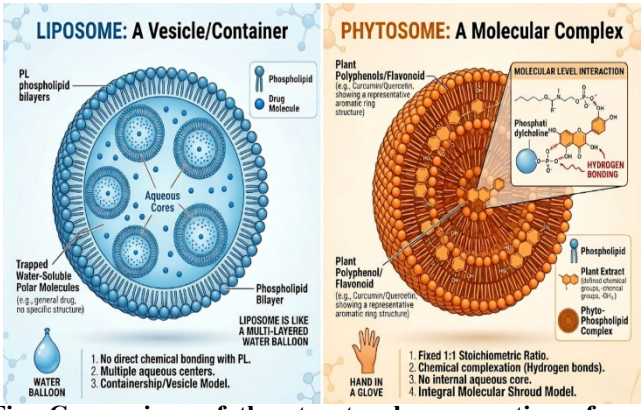

Fig: Comparison of the structural cross-section of a liposome vs a phytosome

Spectroscopic Verification

Researchers use advanced spectroscopic methods to confirm that a real phyto-phospholipid complex has formed. Nuclear Magnetic Resonance (NMR) provides the only method which can determine the structural information needed for this study. The researchers used 31P-NMR to track phosphorus atom signal changes and proton signal changes from aromatic rings to establish that the chemical link had formed instead of which a mechanical mixture had existed. The scanning electron microscope and transmission electron microscope provide researchers with details about the complex shapes which form round or rough-surfaced particles that stay intact for longer periods than their unbound counterparts. The researchers used differential scanning calorimetry to prove that the complex melts at a different temperature than its individual parts which confirms the existence of a completely different physical substance.

Functional Implications of the Structure

Your training covers information that exists until the month of October in the year 2023. The structural reconfiguration

of the system results in a transformation of the plant molecule's "biopharmaceutical profile" which exists at present. The outer layer of the complex now contains fatty substances which enable it to blend perfectly with the lipid bilayer that forms the enterocyte membranes in the small intestine. The system uses natural human fat absorption methods to deliver its powerful antioxidants and anti-inflammatory compounds into the body's bloodstream. The molecular structural changes we make transform a material which the body rejects into a substance that the body actively takes into its bloodstream.

3. Advanced Preparation Methodologies (2025 Standards)

The year 2025 has marked a decisive shift in phytosome manufacturing. The industry now uses high-precision manufacturing methods which comply with "green" standards to produce products at industrial scale. The new methods have emerged because regulatory bodies like the FDA and EMA establish stricter guidelines for solvent residues and batch-to-batch consistency. These guidelines require organizations to establish more accurate methods for controlling molecular distribution and reducing environmental impacts.

The following sections detail the current gold standards for advanced phytosome preparation as of 2025.

Supercritical Fluid Technology (SFT)

The most significant advancement in 2025 is the widespread adoption of Supercritical Carbon Dioxide (SC-CO2) as a processing medium. The method requires CO2 to reach conditions above its critical temperature of 31.1o C and its critical pressure of 73.8 bar, which enables CO2 to display both liquid density and gas diffusivity.

Supercritical Anti-Solvent (SAS) Process: Scientists dissolve plant extract materials together with phospholipids into small quantities of organic solvent which they use to spray the mixture into a chamber that contains supercritical carbon dioxide. The CO2 rapidly extracts the solvent, which causes the phyto-phospholipid complex to form spherical nanoparticles that appear as uniform particles.

The "Green" Advantage: This method eliminates the need for toxic chlorinated solvents like dichloromethane. The final phytosome powder contains no solvents because CO2 transforms back to its gaseous state at room temperature and this process meets the "Clean Label" standards which will be in effect during 2025.

Solution-Enhanced Dispersion by Supercritical Fluids (SEDS)

SEDS by far is the optimal version of SFTs that allows simple mixtures of the botanical extracts and phospholipids solution possible with coaxial nozzles. The mixture is carried in a CO2 stream...

Molecular Precision: The SEDS method enables researchers to control particle dimensions down to sub-micron measurements which typically reach between 50 and 100 nanometers. The manufacturers achieve complete polyphenol molecule attachment to phospholipid heads through their ability to control both flow rates and pressure with exact precision.

Application: Scientists now prefer this method to extract EGCG from green tea because the compound belongs to a group of highly sensitive molecules that become oxidized during extended high-temperature evaporation processes.

High-Pressure Microfluidization (HPM)

Sonication (using Sound waves) used to be traditionally established to reduce in phytosome dimensions, whereas the year 2025 standards have shifted towards a modernized procedure: Microfluidization.

The Process: The researchers use high-pressure systems which reach 30,000 psi to drive the crude phyto-phospholipid mixture through micro-channel interaction chambers. The resulting shear forces and impact break the complexes into highly stable, uniform "nanophytosomes."

Stability: The temperature control system of microfluidization provides stable conditions which scientists can use to conduct their experiments, while sonication creates hot spots that lead to sample degradation because of titanium contamination from its probe. The process produces a product with a Polydispersity Index PDI which meets essential requirements for pharmaceutical-grade applications.

One-Step Spray-Drying (OSSD)

The nutraceutical industry has reached its mass production capabilities in 2025 through the complete development of One-Step Spray-Drying technology. Phytosomes required their first step to be created in liquid form before they could be transformed into solid form through an additional complex process.

Innovation: Modern spray dryers now employ two new techniques which involve using inert nitrogen atmospheres combined with low-temperature nozzles. The system receives phospholipid and plant extract materials which operate at a stoichiometric ratio. The hydrogen bonds form mid-air while the atomized droplets dry, which creates a completed phytosomal powder that results from a single processing operation.

Industrial Scalability: This methodology has decreased production expenses between 30% and 40%, which enables the production of high-bioavailability curcumin and berberine for use in functional foods such as energy bars and beverages.

Quality Control: The "Digital Twin" Approach

The preparation process of 2025 shows only 50 percent of the complete story. The modern testing methods of today use Real-Time Release Testing (RTRT) as their main assessment tool. The hydrogen bond formation monitoring during synthesis can be tracked by manufacturers through their use of Near-Infrared (NIR) sensors and In-line Raman Spectroscopy. The system automatically adjusts flow rates and temperature when the sensors detect either a 1:1 ratio change or incorrect molecular "shroud" formation. The production process ensures that every batch meets the exact structural requirements which are essential for maximum bioavailability.

The Shift to Protic "Green" Solvents

The 2025 standards require facilities that use traditional solvent evaporation methods to transition from aprotic solvents which include acetone and dioxane to Protic Green Solvents.

Bioethanol and ethyl acetate derived from biomass fermentation have become the industry norms.

The modern solvents provide environmental safety together with improved interactions at hydrogen-bonding sites found in phospholipids, which lead to stronger complexation than the traditional solvents which contain more dangerous substances.

The advanced methodologies of 2025 have effectively moved phytosome technology from a "niche lab technique" to a cornerstone of the global health industry. The combination of supercritical fluid technologies together with high-pressure microfluidics allows us to develop botanical medicines which achieve the same level of accuracy as synthetic drugs while maintaining the safe and natural advantages of herbal products.

4. Mathematical Modeling of Release Kinetics

The transition of a phyto-phospholipid complex from a dosage form into systemic circulation occurs through a controlled physical process which scientists can describe using mathematical models. The Mathematical Modeling of Release Kinetics must be understood to predict phytosome gastrointestinal tract behavior and determine the optimal bioactive cargo release rate from the "shroud".

The Fundamental Physics of Release

Phytosomes start to hydrate and then break apart when they come into contact with water in environments that include gastric and intestinal fluids. The release process involves two steps because the phytoconstituent connects to the phospholipid through hydrogen bonds which must be broken before the molecule can move from the lipid phase to the water phase.

To model this, we look at the dissolution rate, which is generally defined by the Noyes-Whitney Equation:

$$\frac{dC}{dt} = \frac{DA(C_s - C)}{h}$$

Where:

dC/dt is the dissolution rate.

D is the diffusion coefficient of the phytosome complex.

A is the surface area of the particles.

C_s is the solubility of the compound at the solid-liquid interface.

C is the concentration in the bulk medium at time t.

h is the thickness of the stagnant diffusion layer.

The Cs value in phytosomes shows a substantial increase compared to raw extracts because the lipid complex of the phytosomes enhances the solubility of the molecule which results in continuous "driving" of the reaction.

Zero-Order vs. First-Order Kinetics

Phytosome manufacture has two competing models of controlled release, depending on the manufacturing technique used (spray drying vs. solvent evaporation).

Zero-Order Kinetics

The Zero-Order model describes drug release through a constant rate which remains unchanged during the entire process. The "holy grail" of drug delivery exists because this method maintains consistent plasma levels throughout the entire process.

$$Q_t = Q_0 + K_0 t$$

Q_t = Amount of drug dissolved in time t.

K_0 = Zero-order release constant.

Phytosomes embedded in a polymer matrix system which functions like a controlled-release tablet system can achieve this model though it remains an uncommon occurrence for raw powders to attain this outcome. The system provides a continuous "slow drip" of polyphenols which enters the bloodstream through the controlled release mechanism.

First-Order Kinetics

Most phytosomes follow First-Order Kinetics which establishes that their release rate depends on their current concentration. The release rate of phytosome material from the gut decreases as the concentration of phytosome material in the gut decreases.

$$lnQ_t = lnQ_0 - K_1 t$$

This model is typical for phytosomal suspensions where the initial "burst" of absorption is followed by a plateau as the site of absorption (the duodenum) becomes saturated.

5. Conclusion and Future Directions

Phytosome technology has reached its current stage of development which establishes new standards for clinical research methods that researchers use to study herbal medicine. The therapeutic range of plant-based substances was not known in the past because their active ingredients could not enter human cells which have a lipophilic nature that prevents hydrophilic substances from passing through. The industry successfully developed operational systems to handle botanical products by creating lipid-compatible complexes which made it possible for them to ingest these products without facing previous digestive challenges.

The scientific community needs to focus on precise medicine delivery systems which provide better results than current methods of drug absorption. The research path at present investigates "Surface-Engineered Phytosomes." The research process involves binding specific ligands to the phospholipid shell through two methods which include using monoclonal antibodies and peptides and galactose sugars as binding ligands. The ligands function as molecular GPS systems which guide the phytosomal complex to attach with receptors that show high expression on diseased tissues.

The creation of asialoglycoprotein receptor (ASGPR) targeted phytosomes has transformed chronic hepatitis and hepatocarcinoma treatments. The addition of a galactose moiety to phosphatidylcholine head enables the silybin or curcumin complex to be absorbed by hepatocytes while it decreases systemic exposure which can cause unexpected metabolic stress. Transferrin ligands demonstrate strong potential to transport neuroprotective herbal drugs such as bacosides and ginkgolides through the highly selective blood-brain barrier (BBB). The method enables scientists to concentrate substances in hippocampal regions which produces neuro-regeneration results that oral extracts cannot achieve.

In 2026, "Stimuli-Responsive" Phytosomes will make their inaugural debut. First-generation complexes use basic diffusion methods to release their payloads while current systems offer improved performance through their capability to respond to particular environmental conditions at designated locations. Recent research investigates pH-

sensitive phytosomes that maintain their structural integrity at neutral circulation pH but disintegrate in the acidic environments which occur in malignancies and injured joints. The "triggered release" process delivers bioactive compounds in their highest concentration to areas where the most severe pathological conditions exist.

The industrial sector benefits from artificial intelligence (AI) which helps industries choose stable phospholipid-to-extract ratios through molecular docking methods. The upcoming months will bring multiple "Multi-Targeting Herbosomes" which combine synergistic extracts of green tea epigallocatechin gallate (EGCG) and resveratrol into one phytosomal unit. The approach solves chronic disease systems like metabolic syndrome which need two different molecules to achieve both insulin sensitivity and oxidative stress control. The evolution from basic absorption enhancement to advanced targeted delivery systems makes phytosome technology the leading force of the 21st-century "Green Revolution" currently developing in medicine.

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