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Review Article

FORMULATION, CHARACTERIZATION AND APPLICATIONS OF PHYTOSOMES DERIVED FROM MEDICINAL PLANTS: A COMPREHENSIVE REVIEW

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ABSTRACT

This study explores the formulation and characterization of phytosomes derived from medicinal plants, investigating their structural intricacies, the mechanism behind phytosome technology, and the advantages they offer over conventional dosage forms. Phytosomes, formed by the interaction of plant constituents with phospholipids, enhance bioavailability and therapeutic efficacy. The preparation involves meticulous techniques, and the resulting formulations show promising applications in various therapeutic areas. The accompanying table provides a concise overview of different phytosome formulations. Overall, phytosomes represent an innovative strategy in herbal drug delivery systems.

Key words: Phytosomes, Review, Formulation, Medicinal plants

INTRODUCTION

One of the most significant sources of medicine is plants. The oldest form of medicine in the world is derived from medicinal plants. All communities have historically employed plants, and in developing countries, the majority of people receive their primary medical treatment from plant-based traditional medicine. In Indian medical systems like Ayurveda, Unani, and Siddha as well as various other regional systems like Chinese and Tibetan medicine, traditional medicinal herbs have a historic record of use (Vadi *et al.,* 2017). Research on medicinal plants has advanced significantly in the last few years. The isolation of novel compounds the source of many powerful medications is its primary goal. The majority of the plants are used to make herbal remedies, which are utilized to treat the medical needs of around 80% of the world's population. Numerous studies have documented the biological properties of a range of therapeutic plants (Gnanamani *et al.,* 2003). It is common for indigenous people in rural parts of many developing nations to use medicinal plants (Shittu *et al.,* 2007). Traditional information about medicinal plants, how the locals use them, and how to prepare drugs nowadays is crucial for drug development, community health, and the preservation of traditional animal and plant cultures. Native American wisdom first surfaced when people began learning how to employ therapeutic plants (Birhane *et al*., 2011).

Herbal medicine is an integral aspect of all indigenous peoples' traditions and is widely used in Ayurveda, homeopathic, naturopathic, Native American Indian, and traditional oriental medicine. Additionally, it's believed that about 74% of the 119 pharmaceutical medications made from plants are used in modern medicine in ways closely related to their traditional uses by local populations as plant remedies.

In developing nations like India, traditional medicines have a bright future as a readily available supply of potent therapeutic substances to treat a variety of ailments (Jagtap *et al*., 2023).

The potential of the extensive Ayurvedic knowledge base in our nation has only just come to light. Nevertheless, the medication's potency is diminished because the patient is being given the medication via an antiquated and conventional drug delivery mechanism. Given the stomach's extremely acidic pH, there's a good chance that a lot of the chemicals in herbal extracts will be broken down. The liver may process other substances before they enter the bloodstream. Because of this, the blood may not receive the necessary dosage of the medication. There won't be any therapeutic benefit if the medication doesn't reach the blood at the so-called "minimum effective level."

Pharmaceuticals made with conventional substances derived from plants rather than synthetic ones are known as phytopharmaceuticals. The body metabolizes natural chemicals more readily and easily. Because of this, they have fewer, if any, adverse effects and have a higher bloodstream absorption rate, which leads to more comprehensive and successful therapies. Chemical-based pharmaceuticals are more likely to have unfavorable side effects. There are certain chemical compounds that the human body will reject because they do not occur naturally. These rejections manifest as side effects, ranging in severity from slight headaches to potentially fatal ones. While phytopharmaceuticals have little or no negative effects, it's vital to remember that they may interact chemically with other prescription medications. Compared to plants, they can also be more easily standardized because they are single, pure chemicals, which makes it easier to include them into contemporary medication delivery systems (Gavhane, 2021).

A novel drug delivery system (NDDS) is a fresh strategy for delivering pharmaceutical chemicals in the body where they are needed to safely produce the intended pharmacological effects. It involves creative creation, formulations, new technology, and novel approaches.

To reduce drug loss and degradation, avoid negative side effects, and boost drug bioavailability and the percentage of the drug accumulated in the needed zone, a number of drug delivery and targeting systems are presently being developed. Soluble polymers, microparticles composed of insoluble or biodegradable natural and synthetic polymers, microcapsules, cells, cell ghosts, lipoproteins, liposomes, and micelles are a few examples of drug carriers.

The carriers can be designed to degrade gradually, respond to stimuli (such as changes in pH or temperature), or even be targeted (for example, by conjugating them with certain antibodies that target particular traits of the target area). The capacity to guide the drug-loaded system to the desired location is known as targeting. Two basic techniques can be recognized for addressing the intended areas for drug release: (i) passive and (ii) active targeting. The preferential accumulation of chemotherapy drugs in solid tumors due to the increased vascular permeability of tumor tissues over healthy tissue is an illustration of passive targeting.

Surface functionalization of drug carriers with ligands that are specifically recognized by receptors on the surface of the cells of interest is one tactic that can enable active targeting. Given the potential for great selectivity in ligand-receptor interactions, this may enable more accurate targeting of the target region (Kumar *et al*., 2021).

Novel drug delivery technologies are now only commonly used for allopathic medications, but they have drawbacks of their own. Instead, it would be better to use tried-and-true Ayurvedic herbal drug formulations that are safe, effective, and herbal.

Numerous research have looked into lipid-based drug delivery systems, and they have demonstrated promise for targeted and controlled drug delivery. Pharmacosomes are drug-containing amphophilic phospholipid complexes that attach to phospholipids and contain active hydrogen. They give the medication superior biopharmaceutical qualities, which raises its bioavailability. Phytosomes are new substances made up of phospholipid-containing lipophilic complexes of plant-derived components, such as Fagonia Arabica. Another name for them is the phytolipid delivery system. Their medicinal effects and enhanced bioavailability are accompanied by their high lipophilicity. These are sophisticated herbal extracts with enhanced pharmacokinetic and pharmacological properties, which make them useful for treating acute liver disorders of either infectious or metabolic origin. Using a patented procedure, specific components of the herbal extract, such as terpenoids and flavonolignans, are molecularly attached to phospholipids, such as phosphatidylcholine, through a polar end to form phytosomes. Phytosomes have a broad application in cosmetics and are utilized as a medication (Pawar and Bhangale, 2015).

A revolutionary drug delivery system aims to distribute the medication at a rate that is dictated by the body's requirements during the course of treatment, while also guiding the active component to the site of action. Advances in the vesicular drug delivery sector have made it possible to design systems that facilitate controlled or extended release of conventional drugs, as well as drug targeting. A phytosome is produced by attaching the plant extract or its components to phospholipids (Sindhumol *et al*., 2010).

The term "phytosome" refers to a lipid-compatible molecular complex that is created by incorporating standardized plant extract or water soluble bioactive plant constituent into phospholipids. This increases the absorption and bioavailability of the bioactive phytoconstituents of the herb extract that are bounded by lipids (Rajak *et al*., 2023; Deleanu *et al*., 2023).When it comes to their ability to pass through the intestinal lipid barrier, phytosomes are more adept than herbal extracts (Karimi *et al*., 2015).

A phytosome is created by combining a standardized extract or polyphenolic component with a stoichiometric quantity of phospholipid in a nonpolar solvent. The extracts' phytochemical constituents, flavonoids and terpenoids, enable their direct complexation with phosphatidylcholine. The bifunctionalphosphatidylcholine molecule is composed of the hydrophilic and lipophilic phosphatidyl moiety. The lipid-soluble phosphatidyl portion's body and tail surround the choline-bound material, while the phosphatidylcholine molecule's choline head

binds to phytocomponents. As a result, the phytoconstituents and phospholipid combine to produce the phytophospholipid complex, a lipid-compatible molecular complex (Pawar and Bhangale, 2015).

Structure of phyto-phospholipid complexes

Phyto-phospholipid complexes are produced by interactions between active components and the polar head of phospholipids (Khan *et al.,* 2013). The two long fatty acid chains are not involved in the creation of phospholipid complexes, but interactions between phospholipids and active ingredients allow phospholipid complexes to play a crucial role in which the phospholipid head group is anchored. In order to create a lipophilic surface, the two long fatty acid chains can migrate and enclose the polar portion of complexes. When diluted in water, phyto-phospholipid complexes form agglomerates that resemble tiny cells that resemble liposomes in certain ways (Ghanbarzadeh *et al.,* 2016).

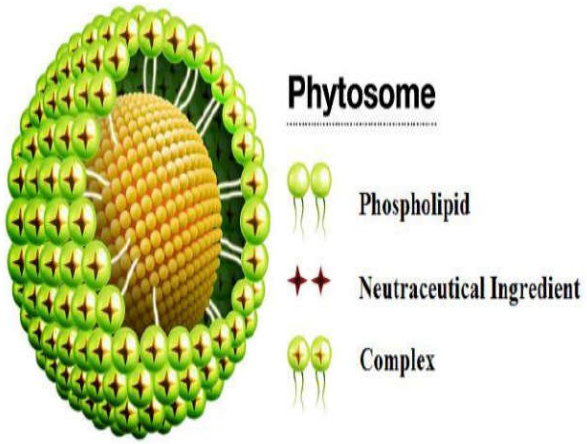

Figure 1: Structure of Phytosome

Mechanism of phytosome technology

There are two basic reasons for the reduced absorption and bioavailability of polyphenolic components. These main ingredients consist of several ringed molecules that aren't too little to be absorbed through diffusion. The second factor is the low solubility of flavonoid molecules, or the main components of polyphenols, with lipids. These are the restrictions preventing them from being absorbed through biological membranes. The primary outcome of phytosome technology is the complexation of polyphenols with phospholipid in a 1:1 or 1:2 ratio, which forms a phytosomal complex with a lipid layer around the components (Aggarwal *et al*., 2012).

Preparation of phytosome

1- Solvent evaporation method: The PC and phytoconstituents are integrated during the solvent evaporation process in a flask holding organic solvent. For a set duration of one hour, this reaction mixture is maintained at its ideal temperature of 40°C in order to maximize drug entrapment within the phytosomes that are created. After being separated using 100 mesh screens, thin film phytosomes are kept in desiccators for the night (Ravarotto, 2004).

2- Mechanical Dispersion method: In the tests, the drug-containing aqueous phase is introduced to the lipids that have been dissolved in an organic solvent. The phyto-phospholipid complex is formed as a result of the subsequent elimination of the organic solvent under lower pressure. Supercritical fluids (SCF), such as the gas anti-solvent technique (GAS), compressed anti solvent procedure (PCA), and supercritical anti solvent method (SAS), are new ways for phospholipid involute production.

3-Salting out technique: An essential procedure for preparing phytosomes involves dissolving PC and the plant extract in an appropriate organic solvent, followed by the

addition of n-hexane until the extract-PC combination precipitates (Barzaghi *et al*., 1990).

4-lyophilization methods: The process of lyophilization DSN was plenarily dissolved in DMSO. After adding the obtained DSN solution (2.5% weight/volume) to the solution of SPC dissolved in 1.5% weight/volume of t-butylalcohal, the mixture was stirred for three hours using a magnetic stirrer until complex formation occurred. After that, the complex was separated via lyophilization. The resulting DSN: SPC in volute (yield 90.4%, weight/weight) was stored in a desiccator over P_2O_5 at 4°C until testing after the samples were abstracted from the freeze drier.

Anti-solvent precipitation process: Under particular experimental settings, below 50°C, a certain amount of herbal extract and phospholipids are refluxed with 20 ml of organic solvents such as acetone for two to three hours. 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. In desiccators, filtered precipitates are kept. The dried precipitates are ground into a powder and placed in a dark amber glass bottle to be kept at room temperature (Patel *et al*., 2013).

Rotary evaporation process: In a round-bottom glass container, a specified weight of herbal extract and phospholipids were combined with 30 ml of water miscible organic solvent, such as acetone, and stirred for two hours at a temperature of no more than 50°C in a rotator evaporator. Antisolvent like n-hexane are commonly applied to thin layer which is generated after continual swirling employing a stirrer. The precipitate of the phytosomes is often kept at a regulated temperature and humidity in amber-colored glass containers (Jain *et al*., 2013).

Advantages over the conventional dosage form

The several benefits of phytosomes are listed as (Suryawanshi, 2011):

1. Phytosomes, which are more accessible botanical extracts, have a far stronger therapeutic effect because they absorb nutrients in the intestinal tract more quickly and effectively and because they combine with phospholipids to greatly increase bioavailability.
2. The non-lipophillic botanical extract is penetrated by the phytosome, which improves absorption in the intestinal lumen.
3. The dose needed to obtain the intended effects can be lowered if the active ingredients' absorption improves.
4. Because of their high lipid profile and greater skin penetration, phytosomes are commonly employed in cosmetics.
5. The stability profile of phytosomes is superior to that of liposomes because of the formation of chemical interactions between the phosphatidylcholine molecule and the phytoconstituents.
6. In addition to serving as a carrier in the production of phytosomes, phosphatidylcholine also has hepatoprotective properties; this means that the use of hepatoprotective drugs can have a synergistic impact.
7. It increases the bioavailability of herbal constituents by improving their absorption.
8. It provides phospholipid's nutritional advantages.

Disadvantage of phytosomes

Phospholipid can promote proliferation on MCF-7 breast cancer cell line; phytosomes' primary limitation is reported as leaching of the phytoconstituent off the some, which reduced the anticipated drug concentration (Reddy, 2011). Despite all of these benefits, phytosomes may quickly exclude the phytoconstituents (Gandhi *et al.,* 2012).

Characterization techniques of phytosome

1. Determination of percentage yield: Using the following formula, the percentage yield of the phytosome complex was determined (Singh and Narke, 2015):

Percentage Yield = (Practical yield) / (Theoretical yield)× 100

2. Determination of entrapment efficiency: The phytosome is separated from the free drug by centrifuging the drug phytosomal complex for ninety minutes at four degrees Celsius and 10,000 rpm. Determine the amount of free drug present using UV spectroscopy (Kumar *et al.,* 2017).

To calculate the percentage of drug entrapment, use the formula,

Entrapment efficiency (%) = (Total amount of drug) – (amount of free drug) / (Total amount of drug)× 100

3. Determination of particle size: The average diameter of the phospholipid complex was measured at a given scattering angle of 90° using a Nanophox.

4. Zeta potential: The zeta sizes of the phytosomal complex are determined using the Malvern Zetasizer.

5. Scanning electron microscopy (SEM): SEM was used to evaluate the particle's appearance and size.

6. Differential scanning calorimetry (DSC): Phosphatidylcholine, a physical mixture of drug extract and phosphatidylcholine, drug-phospholipid complex and drug polyphenolic extract were all added to an aluminium cell and heated to a temperature of 400°C at a pace of 50– 250°C per minute in the nitrogen atmosphere. Using an analyzer, the peak transition onset temperatures were noted.

7. Determination of drug content: The drug concentration of the phytosome complex was determined by accurately dissolving 100 mg of the chemical in 10 ml of solvent. The drug content was determined from the dilution absorbance using a UV spectrophotometer.

8. FTIR: The chemical stability and phospholipid structure of the medication will be investigated using FTIR analysis. The phytosomal medicine will be crushed with potassium bromide at a pressure of 600 kg/cm2 in order to form pellets. The range that will be scanned is 4000-400 cm1.

9. Transition electron microscopy (TEM): Using a 1000x magnification, the size of phytosomal vesicles was assessed using TEM.

10. Solubility test: Pour 10 milliliters of the solvent into glass jars. After agitating the mixture for 24 hours on a rotator shaker to eliminate excess extract, it was centrifuged for 15 minutes. To filter the supernatant, a membrane filter was employed. Subsequently, 1 milliliter of filtrate was diluted with 9 milliliters of an appropriate solvent. UV spectrophotometer analysis was performed, and the absorbance of concentration was calculated using a calibration curve (Gahandule *et al*., 2016).

11. X-ray: With X-ray diffraction, one may today investigate the microstructure of a variety of amorphous and crystal materials. Usually, phosphatidylcholine and phosphatidylcholine-phytophospho lipid

complexes are the subjects of X-ray diffraction. X-ray diffraction of an active component and physical mixture shows strong crystalline peaks indicating a high crystal form. However, the lack of a crystalline peak in phyto-phospholipid complexes with active components indicates that the components of these complexes have an amorphous or molecular structure (Lu *et al*., 2019).

12. Stability studies: The physical stability of the optimized formulation was assessed for six months under three distinct situations (Patel and Anu, 2022). Stability tests were carried out at four different temperatures: four degrees Celsius, twenty-eight degrees Celsius, and forty degrees Celsius (Anwar and Farhana, 2018).

Application of phytosome

Improving the degree of bioavailabilitydelivery of big and varied medications, such as proteins and peptides, secure synthesis, Hepato-Defending, Accepted for use in pharmaceutical and cosmetic purposes, low-risk configuration, The features of toxicology have been extensively studied and strong market appeal (Gaurav *et al*., 2021).

CONCLUSION

Phytosomes are new substances made up of lipophillic complexes of phospholipid-containing parts of several Fagonia Arabica plants. The process of preparing phytosomes is non-convectional. Compared to the individual component, there is a noticeable increase in the absorption of phytosome in the gastrointestinal system, which raises the plasma level. Phytosomes have many applications in cosmetology and are utilized as a medication. There is still much to learn about phytosomes in terms of potential medicinal uses. Between the traditional distribution system and the innovative delivery mechanism, phytosomes provide a link. Phytosomes are a sophisticated herbal extract type that exhibits superior absorption properties compared to traditional herbal extracts.

DECLARATION OF INTEREST

The authors declare no conflicts of interests. The authors alone are responsible for the content and writing of this article.

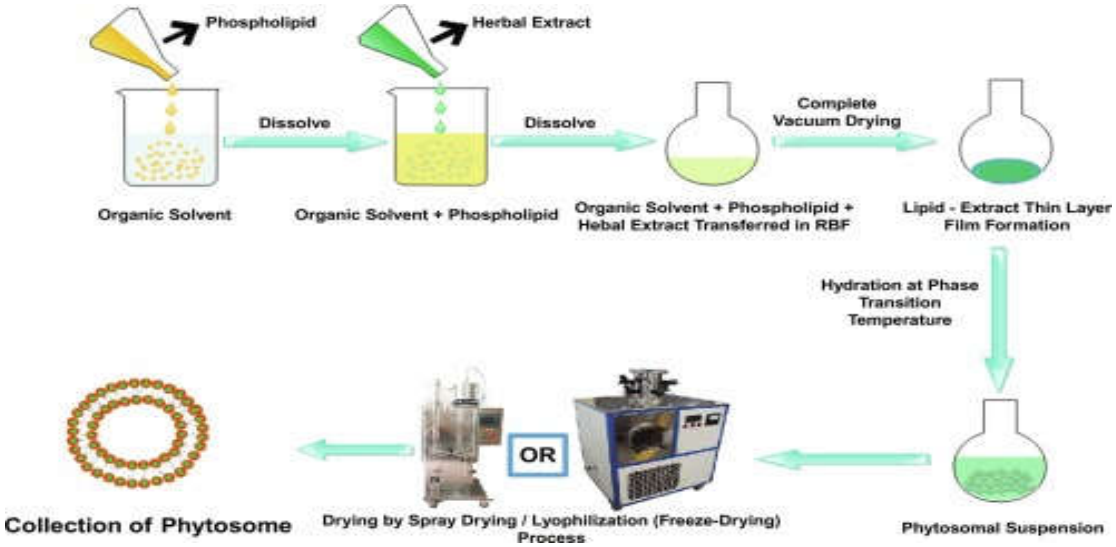

Figure 2: Preparation of Phytosoms

Table 1: Formulations of phytosomes of some medicinal plants

Name	Excipients used	Methods of preparation	References
Momordica charantia.	Phospholipon 90 G, Phosphate Buffer pH 7.4	Thin layer hydration method	Sasongko *et al*., (2019)
Polyscias fruticosa	Soy lecithin and acetone	Solvent evaporation method	Divakar *et al*., (2024)
Commiphora mukul	Soya lecithin	Solvent evaporation technique	Dudekula *et al*., (2024)
Phyllanthus emblica L.	Methanol and phospholipids	Solvent evaporation, antisolvent, and film formation.	Ridwan *et al*., (2023)
Morinda citrifolia	Dichloromethane and Ethanol	Vacuum rotary evaporator.	Burjwal *et al*., (2023)
Rosa alba L.	Dichloromethane, phospholipids and cholesterol	Reflux method	Mandal *et al*., (2023)
Manjistha	Lecithin and Carbopol 934	Solvent evaporation method	Taleuzzaman *et al*., (2023)
Andrographis paniculata	Soya phospholipid, methanol and dichloromethane.	Thin film hydration technique/method	Saini *et al*., (2023)
Carvacrol	Carbopol 934, ethyl alcohol, disodium hydrogen phosphate and potassium dihydrogen phosphate	Thin-film hydration, cosolvency, and salting out	Tafish *et al*., (2023)
Adiantum capillus-veneris	Dichloromethane	Anti-solvent precipitation method	Jagtap *et al*., (2023)
Tinospora cordifolia	Cholesterol, Span 60 and Soya lecithin	Reverse phase solvent evaporation method.	Kumar *et al*., (2023)
Tabernaemontana divaricata	Lecithin, 0.2% hypochlorite solution and ethanol	Solvent evaporation method	Solanki *et al*., (2023)
Centella asiatica	Methanol, Ethanol N-Octanol or Dimethyl sulfoxide	Reflex method	Kaur *et al*., (2023)

Ginger Rhizomes	90% ethanol, soy phosphatidylcholine	Thin-layer hydration method	Deleanu *et al*., (2023)
Nicotiana tabacum	Phosphatidylcholine, poloxamer407 and polyurethane-62	solvent displacement method	Chittasupho *et al*., (2023)
Tradescantia pallida	Span 60 and 3,5-dinitrosalicylic acid	Sequential solid-liquid hot extraction method	Imtiaz *et al*., (2023)
Punica granatum L.	Phosphatidylcholine, gamma-oryzanol , streptomycin and penicillin	Thin film hydration /sonication method	Andishmand *et al*., (2024)
Callistemon citrinus	Soybean phosphatidylcholine,	Thin layer sonication method	Ortega *et al*., (2023)
Andrographis paniculata	soy lecithin and cholesterol	Thin-film hydration technique	Singh *et al*., (2023)
Camellia sinensis	97% phospholipids, phosphatidylcholine	Thin layer hydration method.	Anwar *et* al., (2018)
Morinda lucida	phospholipon 90 H	Solvent evaporation method	Calister *et al*., (2020)
Andrographis paniculata	Soya-lecithin, Dichloromethane,hexane	Anti-solvent precipitation technique.	Saini *et al*., (2022)
Phyllanthus amarus and **Bixa orellana**	lecithin and cholesterol	Thin film hydration method	Sarathe, (2022)
Mangifera Indica	Soya lecithin, Dichloromethane (DCM)	Antisolvent precipitation technique, rotary evaporation technique and solvent evaporation technique.	Dubey and Shirsat, (2020)
Murraya koenigii	Soya lecithin, Cholesterol and Span	Antisolvent Precipitation Technique	Rani *et al*., (2022)
Pentaclethra Macrophylla	Phospholipon® 90G	Solvent evaporation method	Nnamani *et al*., (2020)

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