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DEVELOPMENT AND EVALUATION OF GMELINA ARBOREA BASED PHYTOSOMAL DRUG DELIVERY SYSTEM

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ABSTRACT

Phytosomes represent an advanced phytopharmaceutical drug delivery system developed to overcome the limitations associated with conventional herbal formulations, particularly poor bioavailability and low absorption of phytoconstituents. Many bioactive compounds present in medicinal plants, such as flavonoids, phenolics, glycosides, and terpenoids, exhibit significant therapeutic potential but suffer from limited membrane permeability and rapid degradation in the gastrointestinal tract. Phytosome technology involves the complexation of plant extracts or active phytoconstituents with phospholipids, resulting in enhanced stability, improved absorption, and superior therapeutic efficacy. This review highlights the concept, composition, advantages, preparation methods, characterization techniques, and evaluation parameters of phytosomes. Various preparation approaches, including solvent evaporation, reflux, and thin-film hydration methods, are discussed along with physicochemical characterization techniques such as particle size analysis, zeta potential measurement, Fourier Transform Infrared Spectroscopy (FTIR), Differential Scanning Calorimetry (DSC), Scanning Electron Microscopy (SEM), and Transmission Electron Microscopy (TEM). The review also summarizes the pharmacokinetic and pharmacodynamic benefits of phytosomes and their applications in improving the delivery of herbal bioactive compounds. Furthermore, recent clinical and therapeutic applications of phytosomes in cognitive disorders, migraine, gastrointestinal diseases, inflammatory bowel disorders, breast cancer, and prostate diseases are presented. Owing to their ability to enhance bioavailability, reduce dose requirements, improve patient compliance, and provide targeted delivery, phytosomes have emerged as a promising platform for the development of effective herbal and nutraceutical formulations. The growing interest in phytosome-based systems highlights their potential role in the future of herbal drug delivery and phytopharmaceutical research.

KEYWORD: Phytosomes; Phospholipid Complex; Herbal Drug Delivery; Bioavailability Enhancement; Phytoconstituents; Phytopharmaceuticals; Phosphatidylcholine; Novel Drug Delivery System; Herbal Medicines; Nanocarriers; Pharmacokinetics; Therapeutic Applications.

INTRODUCTION

Traditional drug and herbal medicines has been utilize curative in favor of a long-lived use that preserve health with a various of procedure. Phytosomes is a novel technology emerged in 1989.Many plant extracts has been the subject of synthetic substance and living organisms (pharmacology) investigations during the departed centenary in an effort to determine their chemical makeup whereupon validate their medicinal value. The oodles of the bioactive constituent in phytomedicine, such as flavonoids, glycosides, also phenolic, molecules are dissolve in water. However, because they are poorly absorbed, the impact of water soluble phytoconstituents is restricted (Manach *et al*., 2004).

"Some" assign to homologous a cell like, afterwards "Phyto" allude a plant. Phytosomes are a novel, cutting-edge dose formulation technique that improves absorption of herbal items and drugs, producing better results than conventional herbal extracts (Dubey *et al*., 2007; Gupta *et al*., 2007).

Their enhanced pharmacokinetic and pharmacological properties are beneficial not only for pharmaceutical and cosmetic formulations but also for the management of acute illnesses. Numerous prominent herbal extracts, such as Anchi ginseng (Panax ginseng), milk thistle in (doodh patra) India (Silybum marianum), grape seed, hawthorn, ginkgo biloba, and green tea (The sinensis), has been successfully processed using the phytosomal method. These plant extracts' flavonoid and terpenoid constituents can attach to phosphatidylcholine directly. Strong lipophilicity and improved topical absorption of complex compounds are two characteristics of the phytosomes that improve the structure, hydration, and enzyme balance of the skin.[4]

Phytosomes are herbal medications contained in vesicles that are sold in nanoscale form. The phytosomes shield the medication's active ingredient from being destroyed by germs and digestive secretions, which encase it in an envelope-like covering (Mascarella, 1993).

Advantage of phytosomes

- They increase bioavailability due to phospholipid complex, thus improve therapeutic effect. They are required in fewer doses due to high bioavailability. They improve gastrointestinal absorption. They show high stability. They are preferred over liposomes in cosmetics because of their strong lipophilicity, which results in great penetrability. Their clinical benefits are higher. Additionally, phytosomes work better in skin care products than liposomes.

There is no difficulty in drug snare while formulating Phytsomes. Due to the drug's conjugation with lipids to produce vesicles, entrapment efficiency is high and almost entirely predefined. It is evident that the medication's bioavailability has improved.

- The dose required has been reduced due to the principal ingredient's maximum absorption. Using Phytosomes to modify herbal therapy does not have to jeopardize the nutritional safety of the herbal extracts. It assures that the right tissue will receive the drug. Important components of an herbal extract are contained in phytosomes, which are microscopic cells they are shielded from gut bacteria and digestive fluids that would otherwise destroy them.
- Benefits regarding phytosomes over traditional dosage forms: Phospholipids' complexation with plant extracts increases bioavailability significantly (Bombardelli, 1991).
- They allow for improved absorption from the intestinal lumen by penetrating the non-lipophilic plant extract, which would not be feasible otherwise (Bombardelli and Spelta, 1991).
- All of the ingredients in the phytosome formulation are safe and have been authorized for usage in medical and cosmetic settings.

A comparison of phytosome and liposome

Numerous studies on phytosomes have demonstrated their superior therapeutic efficacy over liposomes in terms.

Table 1: Comparison between Phytosome and Liposome.

Sr. No.	Properties	Phytosome	Liposome	References
1.	Bonding	Associated with few molecules (mainly with Phospholipid and polyphenol extract)	Number of molecules and even they are not connected well	Franceschi and Giori, (2007)
2.	Oral drug delivery	Best for oral delivery	Connected well poor oral bioavailability.	Manach *et al*., (2004)
3.	Phospholipid ratio	Preferably 1:1, 1:2 ratio is preferred for its preparation.	Up to ten times more lipids are used than the main active ingredients.	Jain *et al*., (2010)

Methods of Preparations

- Using precise weighing, 10 millilitres of chloroform are mixed with cholesterol and phosphatidylcholine in a round-bottom flask. The flask is then sonicated for 10 minutes in a bath sonicator. A rotating evaporator is used to extract the organic solvent at 45–50°C.
- A thin layer of phospholipid mixture is created when the solvent is completely removed, and it is hydrated with the plant's methanolic extract in a rotary evaporator (at 37–40°C for an hour).
- The mixture of plant extract and lipid is hydrated, and then it is sonicated for 20 minutes in an ice bath to dissipate heat. After harvesting, the phytosomes are placed in an amber-colored bottle and kept in the freezer between 2 and 8°C.

General method of preparation

Another method, to make phytosomes, a precise amount of phospholipid—soy lecithin—is added along with plant extracts in an aprotic solvent. The primary component of soy lecithin is phosphatidylcholine, which serves two purposes. While the phosphatidyl component is a lipid soluble substance connected to the choline bound complex, the choline part is attached to the hydrophilic primary active ingredients. It causes a lipid complex to develop that is more stable and bioavailable. Another method of creating phytosomes is to react, in a ratio of 0.5 to 2.0, phospholipid, synthetic or natural, containing

standardized plant extract. A 1:1 ratio is typically favoured, though. To eliminate the new complex from the process, it can be lyophilized, spraydried, or precipitated using a non-solvent (often an aliphatic hydrocarbon). The reaction can be carried out in an aprotic solvent, such as acetone, methylene chloride, or dioxane alone, or in a natural combination.

Using a thin layer rotary evaporator vacuum approach, phytosome vesicles were created. In a 250 ml roundbottom flask, the phytosomal complex have being combined accompanised by anhydrous ethanol. A rotary evaporator has the flask attached to it. At roughly 60°C, the solvent will evaporate and form a thin coating around the flask. Phosphate buffer (7.4) is used to hydrate the film, and as the lipid layer separates, vesicle suspension is formed in the phosphate buffer. 60% amplitude probe sonication was applied to the phytosomal suspension. For a whole day, the phytosomal suspension will be kept refrigerated prior to characterisation. The reflux approach is one way to prepare phytosomes.

A 100 mL round-bottom flask containing phospholipid and polyphenolic extract has being refluxed in DCM for one hour at a temperature not to exceed 40°C. After evaporating the clear solution, 15 mL of n-hexane was added as far as hasty formed. After being extracted, the precipitate was put in a desiccators (Kareparamban *et al*., 2012).

It is recommended to weigh phospholipid and cholesterol exactly into a round-bottom flask, dissolve them in 10 mL of chloroform, and then use a bath sonicator to sonicate the mixture for 10 minutes. It is possible to remove organic solvent by exposing it to a rotating evaporator at 40°C with reduced pressure. In a rotary evaporator, a thin layer that has been completely solvent-freed is hydrated with the drug's polyphenolic extract. The phospholipid mixture was sonicated in an ice bath to release heat. The prepared phytosomes were stored in an amber-colored vial (Dhase and Saboo, 2015; Amin and Bhat, 2012).

Various phytosome technology methods

The decreased bioavailability and absorption of polyphenolic components can be attributed to two main factors. These primary components are made up of many ringed molecules that are present in sufficient amounts for the diffusion mechanism to absorb them. The second factor is that flavonoid molecules, which are the primary constituents of polyphenols, are poorly soluble in lipids. These are the barriers that stop them from passing through biological membranes and being absorbed (Kidd, 2009).

Differential scanning calorimetry

Phospholipid complex medicine, polyphenolic extract medication, and phosphatidylcholine were physically mixed and heated in an aluminium cell at a pace of 50–250°C per minute in a nitrogen atmosphere.

Scanning electron microscopy (SEM)

The particle's appearance and size were assessed using SEM. For an electron microscope, a dry sample was placed on an ion sputter-coated brass stub. Scanning the complex with a 100 arbitrary speed.

Transition electron microscopy (TEM)

By a 1000 magnification, the size of phytosomal vesicles was measured by TEM.

Drug entrapment and loading capacity

The drug phytosome complex was separated from the untrapped drug by centrifuging it for 90 minutes at 4°C at 10,000 rpm. UV spectroscopy can be used to measure the amount of free drug present.

The calculation for drug entrapment % is:

Weight of total drug – Entrapment efficiency % = $\boldsymbol{weight\ of\ free\ drug/weight\ of\ total\ drug \times 100}$

Fourier transform infrared spectroscopy (FTIR) analysis

FTIR research verifies the phospholipid medication's structural integrity and chemical stability. To make pellets, the phytosomal medication will be crushed under 600 kg/cm2 of pressure using potassium bromide. We'll survey the 4000-400 cm−1 ranges (Bombardelli *et al*., 1991; Middleton and Kandaswami, 1994).

Size analysis and zeta potential

The particle and zeta sizes of the phytosomal complex are measured using the Malvern Zetasizer. An argon laser is used in both the particle size analysis and the zeta sizer (Yanyu *et al*., 2006; Jain, 2005).

In vitro and in vivo evaluations

The qualities of the medication, its primary phytoconstituents, which are coated in a phospholipid layer, and the justification for the choice of the specific animal model for testing have an impact on both the in vitro and in vivo evaluations (Maghraby *et al*., 2000; Fry *et al*., 1978).

Measurement of surface tension activity

The drug's surface tension activity in an aqueous solution can be measured using the ring method in a Du Nouy ring tensiometer (Liposomes, 1990; Cevc *et al*., 1995).

Drug content

A suitable spectroscopic method or a modified high performance liquid chromatographic method can be used to quantify the drug's quantity (Berge *et al*., 1997).

Spectroscopic evaluations

The following spectroscopic techniques are employed to verify the complex's formation.

Assessment of phytosomes

The evaluation of phytosomes involves assessing their physicochemical properties, as well as their

pharmacokinetic and pharmacodynamic characteristics. Here are some common methods used to evaluate phytosomes.

Particle Size Analysis
Phytosome particle size can be assessed using microscopy, dynamic light scattering, or laser diffraction. This aids in comprehending the stability and physical properties of the phytosome formulation.

Morphological Characterization
The appearance and structure of phytosomes can be observed at the microscopic level using scanning electron microscopy (SEM) and transmission electron microscopy (TEM).

Fourier Transform Infrared Spectroscopy (FTIR)
By studying the interaction between the plant extract and phospholipids in the phytosome formulation, FTIR analysis can be used to learn more about the chemical composition and bonding of the two components.

Differential Scanning Calorimetry (DSC) and Thermogravimetric Analysis (TGA)
DSC and TGA can be used in order to assess the thermal behavior, stability, and phase transitions of phytosomes, which are important for understanding their physical properties (Dayan, 2002).

In vitro Dissolution Studies
Dissolution studies can be conducted to evaluate the release profile of the active constituents from phytosomes, providing insights into their dissolution behavior and potential for improved bioavailability.

Pharmacokinetic Studies
The pharmacokinetic profile of phytosomes, which includes the active components' absorption, distribution, metabolism, and excretion in relation to conventional herbal extracts, can be evaluated by in vivo investigations.

Pharmacodynamics Studies
Pharmacodynamic evaluations involve studying the biological effects and therapeutic efficacy of phytosome formulations in relevant animal models or clinical trials (Murray, 2008).

Stability Studies
Accelerated stability testing can be conducted to evaluate the physical and chemical stability of phytosomes under different storage conditions, including temperature, humidity, and light exposure.

Bioavailability Studies
Comparative bioavailability studies can be performed to determine the extent of absorption and systemic availability of the active constituents from phytosomes compared to conventional herbal extracts (Pandey and Patel, 2010).

Clinical applications of Phytosomes

The Phytosomes in Cognitive Impairment and Neuronal Damage
Numerous investigations assess the phytosome's bioavailability in relation to comparable unformulated products using animal models, with an emphasis on the active components' tissue distribution. The phytosome formulation had the best performance as an MAO inhibitor and radical scavenger using an in vitro transwell model of the blood-brain barrier, making it a good model to boost the extract's antidepressant-like effects (Mancini *et al*., 2018; Naik *et al*., 2006).

The Phytosomes in Migraine
Phytosomes in Migraine Disorders the same research team examined the effectiveness of administering 60 mg of Ginkgo biloba terpenes phytosome, 11 mg of coenzyme Q10, and 8.7 mg of vitamin B2 twice a day to fifty individuals suffering from migraine with aura in two different trials (Ahmad *et al*., 2016; Bussone *et al*., 2009).

The Phytosomes and Gut Microbiota
Lecithin-curcuminoid formulation and unformulated curcuminoids are two different curcumin-based products whose effects on human colonic metabolism were studied in a recent study.

Following the fermentation of both extracts in an in vitro fecal model, curcuminoid content was measured, potential curcuminoid breakdown was evaluated, and the primary metabolites involved in the fermentation of human feces were identified using mass spectrometry. The outcomes shown that curcuminoid catabolites were more frequently observed following the fermentation of curcuminoids prepared with lecithin (Williams *et al*., 2004; Allais *et al*., 2013).

The Phytosomes against Bowel Inflammation
The 43 patients voluntarily selected to either receive one 250 mg tablet daily or no supplements for a period of four weeks. The supplementation group saw reduced levels of rectal involvement, anaemia, malaise, watery stools, blood in stools, cramps and diffuse intestinal pain, as well as a decrease in white blood cell count. Additionally, there was less of a need for additional medications and medical testing (Bresciani *et al*., 2020; Solda *et al*., 2016).

The Phytosomes and Breast Cancer
In the first research, as part of a 4-week treatment regimen before to surgery, 12 patients with early-stage breast cancer received 44.9 mg of epigallocatechin-3-gallate. The treatment plan included taking 300 mg of a commercial lecithin formulation with green tea catechins every day (Pellegrini *et al*., 2016; Lazzeroni *et al*., 2017).

The Phytosomes Role in Prostate Diseases
The effects of phytosomes loaded with silibinin on prostate cancer were assessed in three different

investigations. In the first in vivo investigation, male TRAMP mice with a palpable prostate tumor were fed a meal containing 0.5% or 1% w/w phytosomes. Following 11 weeks, the diet reduced the prostate's weight and tumors by up to 60% in a dose-dependent manner (Singh *et al*., 2008; Flaig *et al*., 2006).

CONCLUSION

Appropriate formulations and delivery systems are needed to maximize the distribution of the beneficial components in plant products, especially those that contain flavonoids and other phenolic compounds. Hydrophilic flavonoids and other similar compounds with improved skin or gastrointestinal tract bioavailability are found in new formulations called phytosomes. Compared to other traditional formulations, they provide a number of clear advantages.

The process of creating phytosomes is easy to understand and may be quickly expanded to a commercial scale.

For this kind of innovative formulation, the analytical methods and characterisation techniques are wellestablished. Several patents have already been awarded for innovative phytosomal compositions, processes, and applications. The utilization of phytosome technology has significant potential to boost formulation technique.

Phytosomes are new substances made up of phospholipidcontaining lipophilic complexes of parts of several plants, such as ginseng, S. marianum, and G. Biloba. The process of preparing phytosomes is non-convectional.

Phytosomes can be utilized to treat liver problems originating from either metabolism or infection since they possess superior pharmacokinetic and pharmacological qualities. They also have lipolytic, vasokinetic, anti-oedema, cicatrizing, trophodermic, neutraceutical, antioxidant, cardioprotective, anti-wrinkles, and UV properties.

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