Polyherbal Phytosome:Preparation methods ,composition and characterization of phytosomes

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Abstract: Polyherbal phytosomes represent a promising advancement combining the advantages of several herbal extracts in the field of phyto-pharmaceuticals with enhanced bioavailability and therapeutic efficacy. This review delves into the preparation methods, composition, and characterization techniques associated with polyherbal phytosomes. Preparation methodologies encompass solvent evaporation, thin-film hydration, and complexation techniques, tailored to encapsulate diverse phytoconstituents efficiently. Compositionally, these phytosomes predominantly comprise phospholipids like phosphatidylcholine, facilitating enhanced solubility and permeability of bioactive compounds. Characterization techniques, including particle size analysis, zeta potential determination, Fourier-transform infrared spectroscopy (FTIR), and differential scanning calorimetry (DSC), elucidate the physicochemical properties, stability, and interaction mechanisms within the polyherbal matrix. Furthermore, the amalgamation of multiple herbal extracts within phytosomal formulations augments synergistic therapeutic outcomes, paving the way for innovative drug delivery systems with improved bioavailability and therapeutic potential.

INTRODUCTION

Phytosomes are herbal drugs in the form of nanoparticles that are packed into vesicles. Since the phytosomes surround the drug's active ingredient with an envelope-like covering, the principal ingredient in the herbal extract is shielded from bacterial and digestive secretion destruction. Effectively, a phytosome can absorb from an environment that loves water to one that loves lipids in the cell membrane before eventually reaching the bloodstream. Its improved bioavailability and ability to treat a variety of deadly diseases Make it useful by not denaturing the active phytocompounds. In order to create phytosomes, reactions specific plant ingredients with phospholipid, which can be synthetic or natural, in the right solvent. Because of their unique combination of properties, these phyto-complexes are both physically and chemically efficient. The present study emphasises the potential applications and cutting-edge technological advancements for the advantage of conventional and herbal treatments derived from plants in the field of NDDS (1)

The pharmacological action and eventual therapeutic utility of several active ingredients found flavonoids, tannins, and terpenoids—found in therapeutic plants—are restricted because of their poor oral absorption [1]. First-pass metabolism and intestinal absorption in rats (Zhang F, Huan M, Cao W, Li K, Mei Q, Yuan C, Teng Z). and Caco-2 cells' transport kinetics of polyphenol chemicals. (2012) Plos One 7(1).) There are two reasons why active phytochemicals are not well absorbed:

1) Polyphenols' multi-ring architectures make it impossible for them to be absorbed inactively or passively.

2) The restricted solubility of active substances in water or lipids hinders their ability to cross the gastrointestinal cells' outer membrane. (2]

Numerous studies have demonstrated the good efficacy of natural products as skin antioxidants and tyrosinase inhibitors. Nevertheless, a few restrictions Based on their physical and chemical properties, including their instability, solubility, and inadequate drug penetration, prevent the intended therapeutic effect from occurring. Researchers keep coming up with methods to enhance the physicochemical characteristics in light of this. The process known as the "phytosome drug delivery system" creates a vesicle system that is capable of binding to both polar and nonpolar substances by using a double-layer phospholipid membrane. Additionally, it can lessen the surface tension between insoluble compounds and

the solvent, which is able to increase the compounds' permeability, stability, and solubility.(3)
"Some" denotes something that is cell-like, but "Phyto" refers to the plant. Phytosomes: an innovative medication delivery system for plant extracts, Nagar G. 2019. doi: 10.13040/IJPSR.0975-8232.4 Int J Pharm Sci Res. The vesicular drug delivery technology known as phytosomes, sometimes known as herbosomes, improves the absorption and bioavailability of low-soluble medications. (4)

The composition of phytosomes
Hydrogen bonding can stabilize molecules by docking the active polar moiety to a phospholipid, a key component of the membrane. Phosphatidylcholine, which is utilised in phytosomes, has a micellar shape similar to the cell membrane. (5)

COMPOSITION OF PHYTOSOMES

Phospholipids
Industry-produced phospholipid delivery methods are becoming increasingly common and play a significant role in today's society. To prepare phytosomes, additional ingredients such as chicken eggs and soy lecithin are utilised. The primary component, phospholipid, is mostly made composed of a phosphate group joining the remaining bonds and a glycerol unit joining two fatty acids.(6)
Usually, to assess the chemical makeup of vesicle components and phytochemical interactions, NMR, FTIR, and mass spectrometry are employed. Additionally, phytosome phospholipid assessment can be accomplished by spectrophotometric quantification following a reaction with an appropriate reagent.(7, 8)

Advantages of phytosomes
The benefits of phytosomes over traditional herbal formulation are as follows:
1They enhance lipid-insoluble polar plant extracts' cutaneous and oral absorption, improving their bioavailability and significantly boosting their therapeutic impact.
2. A very small amount of the active ingredient may produce the required results when its absorption improves. (9)
3. It improves topical and oral absorption of lipid-insoluble hydrophilic polar phytoconstituents while raising their bioavailability;
4enhances the absorption of bioactive substances and lowers the quantity needed;
5. Enhances bile's solubility in herbal component
6. Phospholipids are another nutritional benefit of phytosomes.
7. possesses the capacity to quickly pass through cell membranes and penetrate cells
8. Phytosomes have an excellent stability profile because the phosphatidylcholine molecule and the phytoconstituents establish chemical connections. (10)

History of Phytosomes
Because the important The phytosomes, which are parts of the herbal extract, protect against digestion secretions and gut bacteria. process is a tiny cell in and of itself. Properly named phytosomes, water-soluble phytoconstituents have the ability to transform into lipid-compatible molecular complexes.(11)
According to recent studies, phytosome technology is a ground-breaking technique for improving plant extract absorption and bioavailability at a lower dosage. In this field, several studies are being conducted. Gian F. Patriot and Ezio Bombardelli of Indena Inc., a well-known Italian manufacturer of nutraceutical ingredients, invented the phytosome technique in 1989. They found that the absorption rate of the silybin phytosome complex was a great deal greater than the standard silybin. Schandalik discovered that the phytosomal form of silybin entered the liver four times faster when he studied the hepatoprotective effects of silymarin on nine human volunteers. Studies that were similar included 232 people who had chronic hepatitis. (12,13) PC is a bioactive nutrient that has shown promise in the management of conditions affecting the liver, such as drug-induced liver damage and alcoholic hepatic steatosis. It is more than just a passive "carrier" for the phytosomes' bioactive phytoconstituents; in fact, PC intakes of a phytosomes preparation are often sufficient to yield large PC intakes that consistently result in clinical effects. (14

PHYTOSOME AND LYPOSOME DIFFERENCE

Sr.no	phytosomes	Liposomes
1	Phytosomes are linked to very few molecules (particularly phospholipid and polyphenolic extract).	There are numerous compounds connected to liposomes.
2	The best way to give phytosomes with optimal absorption is orally.	There is low oral bioavailability..
3	There is no bond forming.	chemical bond formation.
4	Depending on the material, forms either a 1:1 or 1:2 complex with plant extracts and phosphatidylcholine.	There are about a thousand or more phosphatidylcholine compounds surrounding the water soluble molecule.
5	The drug material is joined by the polar head of phospholipid.	The medication dissolves in the medium inside the membrane layer.

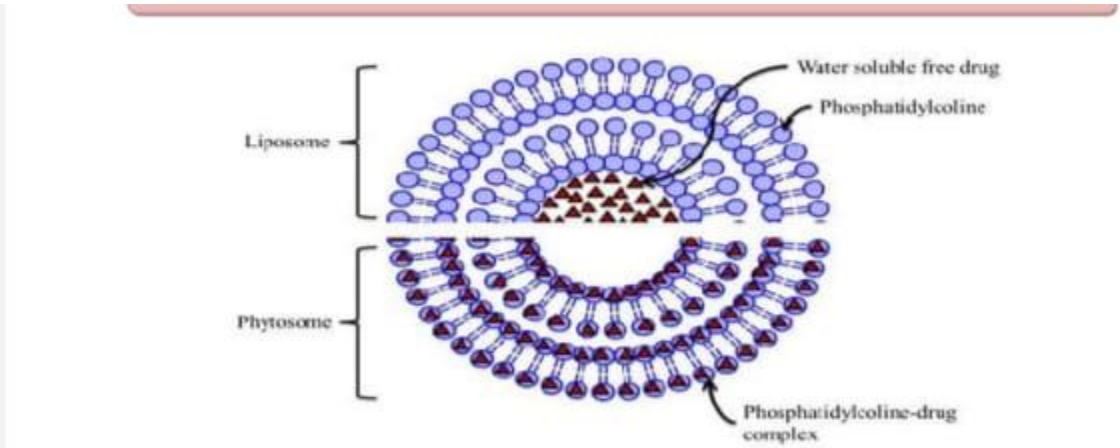

Figure 1: Difference between liposomes and phytosomes.

PREPARATION METHODS

The following methods can be used to create a phytosome.

1.formation that resists solvents. In this procedure, an organic solvent, such as 20 mL dichloromethane or acetone, will be used to dissolve phosphatidylcholine and extracts in a molar ratio. Subsequently, the combination is refluxed according to the research design at a specific temperature and time. To create a precipitate, the reflux product is concentrated and treated with an anti-solvent, like n-hexane. The precipitate was then either dried in a vacuum desiccator or made into an affiliation.

2. conjoint. Phosphatidylcholine and In an organic solvent, dissolved, is the extract. like methanol. Using a magnetic stirrer, the mixing was done by stirring.

3. Adding salt. After dissolving the extract and phosphatidylcholine in ethanol, swirl to combine. To create precipitate phytosomes, n-hexane is added to the mixture during the precipitation formation process.

4. thin-film hydrolysis. Dichloromethane was used to dissolve cholesterol, whereas methanol was used to dissolve fraction and phosphatidylcholine. A thin, dry film forms use a rotary evaporator set at 45°C to gradually evaporate the mixture until all of the solvent has evaporated, on the bottom of the container.. After that, nitrogen gas is pumped through the thin layer of lipid that has developed, and it is let to rest for a night at room temperature before undergoing hydration treatment. Aquabidest was used to hydrate the film layer at 45°C in a rotating evaporator. Sonification and homogenizer were also used to optimise the process for determining the particle size.

5. Evaporation of a solvent. After dissolving the Phosphatidylcholine and extract in ethanol, they were refluxed for two hours at 30°C and 120 rpm in a vacuum rotary evaporator. Aquadest is then used to hydrate the residue in order to create a phytosome solution. (15)

Multiflavonoids-loaded flavanosomes: formulation, characterisation, and optimisation by bulk or sequential methods. Globally Vol. 11, 3417, Journal of Nanomedicine. 10.2147/IJN.S112045 DOI (16)

Journal of Cancer Prevention in the Asian Pacific, 15(13):5311–5316. By blocking Nrf2 mediated signaling, phytosomes make human breast cancer MDAMB 231 cells more susceptible to doxorubicin.(17)

One mole of phospholipid, such as phosphatidylcholine, phosphatidylethanolamine, or phosphatidyiserine, either naturally occurring or manufactured, should be combined with another phospholipid to create phytosomes. The mixture can be made either by itself or in an aprotic solvent like acetone or dioxane with other ingredients. Following that, the complex can be separated by sparing desiccating, lyophilization, or precipitation using non-solvents like aliphatic hydrocarbons. The complex evolution of phytosomes depends on the ratio of these two moieties. varies from 0.5 to 2.0 moles.(18)

The proportion of flavonoids to phospholipids that is most preferred is Using a thin layer rotary evaporator vacuum approach, phytosome vesicles were created. In a 250 ml round-bottom flask, the phytosomal complex was combined with anhydrous ethanol. A rotating evaporator had the flask fastened 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 suspension of phytosomal cells. The phytosomal suspension will be refrigerated for a full day before being characterized [51].b. Five milliliters of phospholipid, or soy lecithin, was reacted in an equivalent volume.s of dichloromethane and polyphenolic extract. Phytosome. (19)

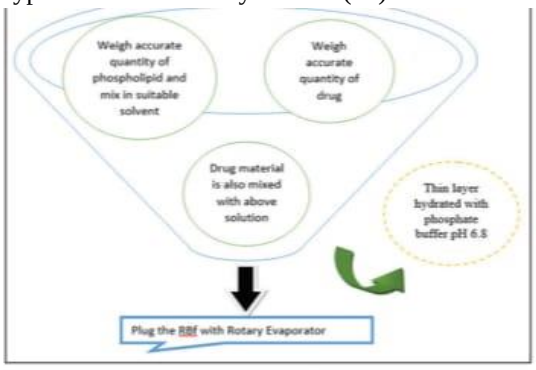

Fig. 4: Preparation method for phytosomes

ADVANCES IN PHYTOSOME TECHNOLOGY

Numerous studies have demonstrated the superiority phytosomal delivery methods in comparison to conventional herbal extracts. Some advancements in phytosomal delivery systems include the following:

a. The plant Bacopa monnieri Includes the well-known active component bacopaside, which has the ability to prevent amnesia. The production of phytosomes from bacopaside and their in vivo evaluation in rodents are the objectives of this work. The phospholipid-produced molecule's therapeutic efficacy has significantly altered in comparison to simpleB. monnnieri extract .

b. According to still another study, the berberine phospholipid complex is synthesized as a solid dispersion, which enhances the compound's flow and dissolution rates for industrial manufacture.(20)

PATENTED TECHNOLOGIES RELATED TO PHYTOSOME

The field of phytosomes has seen a number of innovative processes carried out by both industrial laboratories and academic scientists conducting research studies on phytosome formulation. These works address new developments that can be enabled by phytosomes as well as ongoing research topics. The patented technologies of phytosomes and related technologies, together with their innovations and uses, are listed below.(21)

APPLICATIONS

1. Silymarin phytosomes Since milk thistles, or Silybum marianum, are known to have exceptional flavonoids that protect the liver, most phytosomal research focuses on this plant. Yanyu et al. studied the pharmacokinetic response of rats to silymarin phytosome. Because of a noteworthy improvement Based on modifications to the lipophilic characteristics of the silybin-phospholipid complex and a rise in the biological activity of silybin, the investigations found that oral administration of the complex significantly enhanced the bioavailability of silybin in rats. Tedesco et al. (2004) state that silymarin phytosomes can protect grill chick performance from aflatoxin B1's detrimental effects and show more anti-hepatotoxic action than silymarin alone.20.

Curcumin 2 phytosomes Maiti et al. (2006) produced curcumin, a flavonoid derived from Curcuma longa, or turmeric, and naringenin, a flavonoid derived from grape fruit, Vitis vinifera, using phytosomes in two different studies. In every dosage range that was examined, the complex's antioxidant activity outperformed that of pure curcumin by a significant margin. In comparison to the free chemical, the

phytosome generated by naringenin demonstrated higher antioxidant activity in the second trial. One possible explanation for its extended duration of action is a slower pace at which the body eliminates molecules2. 3. Quercetin-phospholipid hydrosomal complex The quercetin-phospholipid Phytosomal complex was produced by Maiti et al. utilizing a procedure that was simple to duplicate. Additionally, they showed that the formulation outperformed the chemical in terms of therapeutic efficacy when used to treat rat liver damage caused by carbon tetrachloride.22. 4 In grape seeds are phytosomes Grape seed phytosomes are composed of phospholipid-complexed oligomeric polyphenols called proanthocyanidins, or procyanidines. These polyphenols come in a variety of molecular sizes. The instructor It has been demonstrated that procyanidine flavonoids from grape seeds enhance the body's ability to neutralize free radicals, activate plasma's physiological defenses, shield the heart from the damaging effects of ischemia or reperfusion, and prevent atherosclerosis. These flavonoids offer significant organ and heart protection through a complex network of mechanisms that extend beyond their antioxidant action. In a second study, rabbits were fed a high-cholesterol diet for six weeks to create conspicuous elevations in blood cholesterol and to induce atherosclerotic lesions in the aorta and carotid arteries. Phytosomes in grape seeds

5. Phytosomes in Gingko biloba leaves Studies show that ginkgo phytosomes, which are formed from a standardized extract of Ginkgo biloba leaves, yield better results than the standardised plant extract (GBE) that contains 24% ginkgo flavones glycoside and 6% terpene lactones. A bioavailability research conducted on healthy human volunteers showed that the amount of GBE components (flavonoids and terpenes) from the Phytosomal form peaked after three hours and remained for at least five hours following oral therapy. It was shown that compared to the non-phytosomal GBE, the phytosomal GBE generated 2-4 times as many terpenes in plasma. It can help with reduced cerebral circulations, although its primary symptoms include cerebral insufficiency and peripheral vascular disorders. Due to its increased tolerance and oral bioavailability, this phytosomes

The polyphenolic molecule called v Furthermore, green tea has several health advantages for humans, such as cardioprotective, antimutagenic, hypocholesterolemic, and anticarcinogenic qualities. Green tea extract polyphenols have several health benefits, however one problem is that they are not very bioavailable. Complexing green tea polyphenols with phospholipids increases their oral bioavailability by a significant amount. In healthy human volunteers, an investigation was carried out on the oral absorption of phytosomal preparation and non-complexed green tea extract.

Characterization

Vesicle size and distribution

The optimized phytosome formulation's Dynamic light scattering (DLS) and a 2.5.1 were used to calculate the vesicle size, size distribution, and zeta potential. Size and dispersion of vesicles: The zeta potential, size distribution, and vesicle size of the improved phytosome formulation were assessed using dynamic light scattering (DLS) and the computerized inspection system (Malvern Zetamaster ZEM 5002, Malvern, UK). In order to ascertain the phytosomes' electric potential, including its layer (zeta potential), the diluted system was put into a zeta potential measurement cell.

Entrapment efficiency:

The Paolino et al. approach was used to calculate the entrapment efficiency. Following preparation, the phytosomes were placed in a cooling centrifuge and centrifuged for four hours at 12000 rpm. (Remi).To extract the non-entrapped quercetin, the clear supernatant was carefully strained off, and a UV/visible spectrophotometer (Shimadzu1601) was employed to determine the supernatant's absorbance for the unentrapped Curcuma extract at λ max 420.0 nm. One milliliter of 0.1% To lyse the vesicles, Triton x 100 was applied to the silt. After that, the absorbance at 420.0 nm was measured after it was diluted to 100 milliliters using phosphate buffer saline (7.4). One milliliter of the curcuma extraction was obtained, and this was determined by looking at the amount of quercetin in the sediment and supernatant. The following formula was used to determine the percentage of entrapment. Amount of drug in sediment divided by total amount of drug added x 100 is the percent entrapment.

Drug release in vitro

Through the use of an altered Franz diffusion cell, an in vitro penetration investigation of all formulations and market preparation was conducted. The glass device known as the modified Franz diffusion cell is divided into two sections: the donor compartment, located on top, and the receptor, located below.

section. Samples are removed for estimate using a long side tube called a sampling tube that is part of the receptor. A magnetic bead was inserted along with the receptor medium into the receptor compartment. A biological membrane that had been manufactured was positioned ccc between the compartments for donors and receptors, and the joint between them was securely clamped. The formulation—which contains 2.5 mg of medication—was applied to the donor compartment's top egg membrane. After being mounted on a magnetic stirrer/heater unit, the entire assembly was turned on. The assembly was kept at 37±2°C in temperature. Every hour, samples were taken out by passing one millilitre of the receptor media through the sampling tube and at the same time

Kinetics of in-vitro Drug Release

To investigate the release kinetics of in-vitro drug release, data from in-vitro release experiments were displayed in a number of kinetic models: Plotting the results of an in-vitro release investigation with a range of kinetic models, where zero order represents the drug release percentage: Higuchi represents the percentage of drug released versus time, Korsmeyer Peppas represents the log% of drug released versus log time, and zero order represents the percentage of drug released versus time.

In vitro anti-microbial Activity

The nutritional agar culture media and the agar well diffusion method are used to carry out antimicrobiological activity. This agar media was heated in a conical flask with enough capacity after being dissolved in distilled water. The necessary amount of distilled water is added to a flask filled with dry components, and the mixture is heated to dissolve the medium entirely. After plugging the flask with the medium with cotton, it was autoclaved for 15 minutes at 15 pounds per inch, or 121 degrees Celsius. Following sterilisation, sterile petri dishes with a plane surface were filled with the media in the flask (20 ml/plate). In order to verify that the poured plates were sterile, they were allowed to harden at room temperature and then incubated at 37°C for a whole night. Prior to usage, the plates were dried at 50°C for 30 minutes. The microorganisms employed in.

Entrapment efficiency

The ultracentrifugation method shows how much of a medicine is trapped within the phospholipid mesh and can be used to calculate the phytosome entrapment efficiency of a given medicament. Almost all formulations of phytosomes include the entire medication. The results demonstrate the homogeneous binding of rutin and phosphatidylcholine.

4. Drug content

A suitable spectroscopic approach or a modified high performance liquid chromatographic technology can be employed to ascertain the drug's quantity

5. Partition coefficient determination

CHARACTERIZATION TECHNIQUES OF PHYTOSOME

In an aluminum cell, the drug polyphenolic extract, phosphatidylcholine, drug-phospholipid complex, and a physical mixing of the drug extract and phosphatidylcholine were all heated to a temperature of 50–250°C/minute from 0 to 400°C in a nitrogen environment.

SEM, or scanning electron microscopyThe particle's appearance and size were assessed using SEM. A dry sample was mounted on an ion sputter-coated brass stub for an electron microscope. scanning the complex at random speed of 100.TEM, or transition electron microscopy

by a 1000 magnification, the size of phytosomal vesicles was measured by TEM.Entrapment of drugs and loading capacityweight of the complimentary medication 100 percent entrapment efficiencyTotal drug weight = ×Analysis using Infrared spectroscopy with Fourier transform (FTIR) FTIR analysis is going to be carried out to confirm the chemical stability and structural integrity of the phospholipid medication. The phytosomal drug will be crushed with potassium bromide at a pressure of 600 kg/cm2 to create pellets. The 4000-400 cm−1 ranges will be surveyed.

Analysis of sizes and zeta potential

The Malvern Zetasizer is used to measure the particle and zeta sizes of the phytosomal complex. An argon laser is used for this zeta sizer and particle size analysis.(27, 28)

CONCLUSION

Phospholipids and naturally occurring phytochemicals are bonded together to form phytosomes, which are produced when phosphatidycholine reacts with plant extracts in an aprotic solvent. Herbal products consistently demonstrate substantial denaturation and bioavailability levels. The most suitable cutting-edge methods for herbal medications to address these kinds of problems are liposome and phytosome.Reference

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