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A Review on Phytosomes: Preparation, Evaluation and Applications

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Abstract: *"Phyto" means plant, and "some" implies cell-like. These two words combine to form phytosomes. Phytosomes were made using the solvent evaporation technique. It could fall between the 1:1 and 1:2 ratio range. Various drug delivery mechanisms, including liposomes, niosomes, transferosomes, ethosomes, phytosomes, colloidosomes, and others, were employed by the phytosomes. Acid-labile herbal medications may also be protected throughout the gastrointestinal system by employing phytosomes, which also improve the rate and extent of the transit of lipophilic herbal ingredients across lipid membranes, explaining their role as a carrier. There are several products on the market that use phytosomal drug delivery, including Camellia sinensis, Silybum marianum, and Ginkgo biloba. In addition to the formulation process, the study includes the chemical and biological properties of phytosomes. Phytosome evaluation and characterization technologies provide insight into several methods that are useful for screening for distinct phytosome characteristics. This page offers a number of basic research methods for the creation and optimization of phytosomes in addition to details on their benefits and physiochemical characteristics.*

Keywords: Phytosomes, Herbal extract, Novel drug delivery system, Phospholipid, Bioavailability

I. INTRODUCTION

For many years, people have employed medicinal plants and the therapeutic compounds they contain to treat a wide range of illnesses. Since modern medicine is unable to adequately treat all human ailments, synthetic drug safety and assurance are gaining more attention, and many natural products have been shown to perform better than synthetic drugs without side effects, the use of herbal medications is on the rise. Because the phytosomes method creates a contact cell, the valuable ingredients in the herbal extract are protected from being broken down by gut bacteria and digestive secretions. The pharmacokinetic and pharmacological parameters of phytosomes are enhanced[2]. Phytosomes and liposomes are two effective drug delivery systems that have been developed in an attempt to increase the bioavailability of such drugs. When compared to traditional herbal extracts, the application of these formulation development approaches may result in herbal medications with higher bioavailability. Both pharmaceutical and cosmetic formulations as well as the treatment of acute illnesses benefit from their improved pharmacokinetic and pharmacological qualities.

COMPARISON BETWEEN PHYTOSOME AND LIPOSOME

Many studies have been conducted on phytosomes, and the results indicate that they are superior than liposomes in terms of bioavailability, absorption, and therapeutic efficacy. A comparison of liposomes and phytosomes. In phospholipid-flavonoid compounds, the active principle is an essential component of the membrane, while in liposomes, it dissolves in the cavity medium or in the membrane layers.

PHOSPHOLIPIDS:

These days, industrially manufactured phospholipid delivery systems are becoming more and more common. The key components needed to accomplish this are soy, chicken eggs, etc. Phospholipid, which consists of a glycerol unit coupled with two fatty acids and the remaining linkage attached by a phosphate group, is the primary component of all of this.

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Phosphatidylcholine, the primary phospholipid utilized in the creation of phytosomes, plays a significant role in biological membranes and has hepatoprotective properties.

PHYTO-CONSTITUENTS:

Types

1) Alkaloids: The wide class of secondary metabolites known as alkaloids is basic in nature and made up of amino acids with heterocyclic nitrogen structures. Pharmaceuticals, remedies, and bitter-tasting substances are their main use. Since they are naturally poisonous, their main function is to protect plants from insects, herbivores, and microbes.

2) Phenolics: Plants contain phenolic compounds that can polymerize into larger molecules like proanthocyanidins and lignin's. Because it can shield plants from damage caused by oxidative stress.

3) Saponins: The reason they are dubbed "saponins" is that they frequently create stable soaps in aqueous solutions. An effective antibacterial agent could be thought of as saponins.

4) Glycosides: Glycosides are composed of two constituents: carbohydrates and non-carbohydrates. Glycone is the part of this that doesn't include carbohydrates, whereas glycone is the part that does. They are separated into several classes, such as anthraquinone, coumarin, aldehyde glycoside, flavonoids, cyanophore, and saponin.

6) Tannins: With their ability to scavenge free radicals, create transition metal complexes, block the peroxidase enzyme, and halt lipid peroxidation, tannins offer antioxidant qualities. Their bitter taste and polyphenols, which precipitate proteins, are what give them the name "astringents."

How to select Herbal extract?

Among the many benefits of herbal extracts include photoprotection, anti-aging, moisturizing, antioxidant, astringent, anti-irritating, and antibacterial qualities. Herbal extracts are chosen based on their nature, availability, estimation technique, stability, and usefulness. When creating new formulations, solubility is a crucial factor. The ideal formulation is determined by whether the substance is hydrophilic or lipophilic.

Anatomy of Phytosomes:

The structural components are:

A. Plant Extracts: Plants are the source of these active substances. These could be extracts from plants or herbs, or they could be other natural materials with therapeutic qualities.

B. Phospholipids: One class of lipids that are vital to cell membranes are phospholipids. Phospholipids like phosphatidylcholine are utilized in phytosomes to encapsulate plant extracts. These phospholipids can create a protective layer around the plant extract because of their hydrophilic (which attracts water) head and hydrophobic (which repels water) tail. The phospholipid molecules hydrophilic head is what makes it water soluble because it attracts water molecules. Hydrophobic tail, this portion of the phospholipid molecule is lipid-soluble because it attracts fat molecules and repels water. Phospholipids hydrophilic heads attach to the plant extract's hydrophilic chemicals, while their hydrophobic tails encircle the extract's lipophilic (fat-soluble) constituents.

II. PROPERTIES OF PHYTOSOMES

Physicochemical Properties: Organic phospholipids, like soy phospholipids, and a natural material combine to form a phytophospholipid complex. To make this complex, phospholipids and the substrate in the appropriate solvent are reacted at stoichiometric quantities. The polar head of the phospholipid and the polar functions of the main ingredients form hydrogen bonds, which facilitate the interaction between the phospholipid and substrate. Like liposomes, phytosomes exhibit a cell-like structure when exposed to a hydrophilic environment. However, the primary active ingredients in a liposome interact within the internal pocket, whereas in a phytosome, they are encased in the polar head of phospholipid and become an essential component of the membrane.

Biological Properties: Phytosome enhances the systemic bioavailability and active absorption of active ingredients when given orally. Compared to conventional herbal extracts, these herbal products are more sophisticated and efficient. Phytosomes have better pharmacokinetics than simple herbal remedies.

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Chemical properties: Phytosomes are complex interactions between organic products and organic phospholipids. Phytosomes are naturally lipophilic. Their melting point is high, they dissolve readily in organic solvents, and they are only weakly soluble in lipids. The shape of phytosomes is a micellar material when they dissolve in an aqueous solvent.

III. ADVANTAGES OF PHYTOSOMES

Phytosomes furnishes with the following advantages[16,17]

1) It guarantees that the medication will be delivered to the right tissues.
2) Transporting the herbal medication via phytosomes does not have to jeopardize the nutritional safety of the herbal extracts.
3) Because of the minor constituent's maximal absorption, the dose required has been lowered.
4) The drug's bioavailability is markedly improved.
5) The medication itself is conjugating with lipids to form vesicles, which results in a very high and more than intended entrapment capacity.
6) There are no issues with drug entrapment throughout the Phytosome formulation process. Because of the novel chemical interactions that are formed between the herbal
phytoconstituents and phosphatidylcholine molecules, phytosomes have an excellent stability profile.

IV. DISADVANTAGE OF PHYTOSOMES

1) Considering all the benefits, phytosomes have the potential to quickly eliminate the phytoconstituent.
2) Phospholipid can promote MCF-7 breast cancer cell line proliferation.
3) Leaching of the phytoconstituent off part of the phytosomes is said to be the main constraint, which decreased the expected medication concentration.

V. PREPARATION OF PHYTOSOMES

Mainly 4 type

1- Solvent evaporation method

Integrating the phytoconstituents and PC in a flask with organic solvent is part of the solvent evaporation process. This reaction mixture is maintained at an ideal temperature, typically 40°C, for a set period of one hour in order to maximize drug entrapment within the phytosomes that are created. 100 mesh sieves are used to separate the thin film phytosomes, which are then kept overnight in desiccators[6,7].

2- Mechanical Dispersion method

Lipids dissolved in organic solvents are brought into contact with the drug-containing aqueous phase throughout the tests. The Phyto-phospholipid complex is created when the organic solvent is subsequently removed under lower pressure. Supercritical fluids (SCF), which include gas anti-solvent technique (GAS), compressed anti-solvent process (PCA), and supercritical anti-solvent method (SAS), are recent approaches for the synthesis of phospholipid involute.

3-Salting out technique

One crucial step in the manufacture of phytosomes is to dissolve phospholipid complex and the plant extract in an appropriate organic solvent. Then, n-hexane is added until the extract- phospholipid complex precipitates[9].

4. Lyophilization methods

The process of lyophilization in DMSO, DSN was completely dissolved. After the SPC solution was dissolved in 1.5% weight/volume of t-butyl alcohol, the resultant DSN solution (2.5% weight/volume) was added, and the mixture was stirred for three hours using a magnetic stirrer until complex formation occurred. After that, lyophilization was used to isolate the complex. The DSN:SPC involute (yield 90.4%, weight/weight) that was obtained after the samples were removed from the freeze drier was kept in a desiccator over P2O5 at 4°C until testing. SPC type (Lipoid® S100, Lipoid® S75, and Lipoid® S PC-3), drug phospholipid ratio (1:1, 1:2, and 1:4), and co-solvent type of chemical (methanol, ethanol, chloroform, acetone, and TBA) were among the variables whose effects were evaluated for the culled development process. It is common practice to create phytosome complexes using unconventional techniques. When natural or

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synthesized phospholipids react with active ingredients or herbal extracts in acrostic organic solvents, modernistic herbal complexes are created[10,11].

Common stages in formulation of phytosomes. Various methods of preparation are as follows:

1) Anti-solvent precipitation process: At experimental circumstances below 50°C for two to three hours, a specific number of phospholipids and herbal extract is refluxed with 20 millilitres of organic solvents, such as acetone. The reaction mixture is diluted to a minimum volume of 10 millilitres, and then a low-polarity solvent, such as n-hexane, is added while stirring to produce precipitates. Desiccators hold the filtered precipitates. The dried precipitates are ground up, and the involute powder is kept at room temperature in a glass bottle with a dark amber hue[12].

2) Rotary evaporation process: Phospholipids and a specific weight of herbal extract were combined with 30 milliliters of water and a miscible organic solvent, such as acetone, in a round-bottom glass container. The mixture was then stirred for two hours at a temperature of 50°C in a rota evaporator. Thin films that are produced following continuous stirring with a stirrer are frequently treated with antisolvents such as n-hexane [13]. The produced phytosome precipitate is frequently kept at a regulated temperature and humidity in an amber-colored glass container.

Ether-soluble phospholipids are gradually added drop by drop to a phytoconstituent solution that will be encapsulated. It causes involute development by causing cellular vesicles to form upon subsequent solvent abstraction [14]. Phytosome structure is influenced by concentration. In the mono state, amphiphiles are created at lower concentrations, but as concentration rises, various morphologies such as round, cylindrical, disc, and cubic or hexagonal vesicles may also emerge.

VI. EVALUATION OF PHYTOSOMES

1)Visualization: Both scanning electron microscopy (SEM) and transmission electron microscopy (TEM) can be used to visualize phytosomes.

2) Vesicle size and Zeta potential: By employing photon correlation spectroscopy and a computerized inspection system, dynamic light scattering (DLS) can be used to determine the particle size and zeta potential.

3) Entrapment efficiency: The ultracentrifugation method can be used to gauge how well a medication is entrapped by phytosomes.

4) Transition temperature: Using differential scanning calorimetry, the transition temperature of the vesicular lipid systems may be ascertained.

5) Surface tension activity measurement: A Du Nouy ring tensiometer can be used to assess the drug surface tension activity in aqueous solution using the ring method.

6) Vesicle stability: The size and structure of the vesicles can be evaluated over time to ascertain their stability. TEM tracks changes in structure, while DLS measures mean size.

7) Drug content: A customized high performance liquid chromatographic method or an appropriate spectroscopic method can be used to quantify the amount of medication.

8) Spectroscopic evaluations: Spectroscopic techniques are employed to verify the complex formation or investigate the mutual interaction between the phytoconstituent and the phospholipids.

9) Fourier transform infrared spectroscopy analysis: IR spectroscopy can also verify the complex synthesis by comparing the complex spectrum to those of its constituent parts and their mechanical mixes. Another helpful technique for managing the stability of phytosomes when they are micro dispersed in water or added to really basic cosmetic gels is FTIR spectroscopy. Comparing the spectra of the complex in solid form (phytosomes) with the spectrum of its micro-dispersion in water following lyophilization at various intervals allows one to verify the stability from a practical standpoint. Simple formulations include subtracting the excipients (blank) spectrum from the cosmetic form's spectrum at various points in time, then comparing the complex residual spectrum.

10) In vitro drug release study:

To evaluate the drug release, the treated cellophane membrane was attached to one end of the open tube containing the phytosomes. A 500 ml beaker filled with 250 ml of pH 6.8 phosphate buffer was then used to suspend the dialysis tube. At 37+/-0.5 degrees Celsius, the solution was stirred with a magnetic stirrer. Then, at pre-arranged intervals, a 1 milliliter sample was removed and combined with an equivalent volume of fresh PBS. Afterward, the samples underwent filtration

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and dilution. The samples that were diluted were evaluated using a UV spectrophotometer. A comparison was made between the penetration of the complex and the phytoconstituent.

VII. APPLICATIONS OF PHYTOSOMES

1) Because of its fruit, which contains flavonoids with hepatoprotective qualities and has shown promising results in treating liver diseases like cirrhosis, hepatitis, fatty infiltration of the liver, and bile duct inflammation, *Silybummarianum* (family: Steraceae) was the focus of the first phytosome research. Silymarin is composed of three flavonoids, with silybin being the predominant one and being inhibited c and silydianin. The strongest is silybin, which preserves glutathione in parenchymal cells, protecting the liver[2].

2) Improved solubility: Phytosomes also make phytoconstituents more soluble. A lot of phytoconstituents have low water solubility, which may restrict how well they are absorbed in the digestive system.

3) Increased stability: In comparison to traditional herbal extracts, phytosomes also provide increased stability. The active ingredient is shielded from being broken down by the stomach fluids and intestinal enzymes by the phospholipid shield in the phytosome structure.

4) Enhanced bioavailability: Phytosomes main benefit is their capacity to increase phytoconstituents bioavailability. Although many phytoconstituents have medicinal promise, their bioavailability is limited by their quick metabolism and poor absorption.

5) Delivery of phytoactives with precision: Phytosomes capacity to distribute drugs with precision is another important benefit. By delivering medications to particular bodily areas, phytosomes might enhance therapeutic effects and lessen adverse effects.

6) Potential of Phytosomes as a novel medication delivery system: Numerous ailments, such as cancer, heart disease, and liver disease, are treated with phytosomes. There are several other uses for phytosomes, such as anti-inflammatory, lipolytic, vasokinetic, and anti-edema agents. It also serves as a nutraceutical, immunomodulator, antioxidant, etc.

Table 1: Marketed formulations of Phytosomes[6,11]

S.NO	Phytosome	Biological Activity	Source
1	Berbine	Antidiabetic	*Berberis Vulgaris*
2	Olive oil	Anti-Inflammatory, Antioxidant, Anti-hyperlipidaemic	*Europaea Oil*
3	Ginseng	Immunomodulator	*Panax Ginseng*
4	Gingko	Brain and Vascular Protection	*Ginkgo Biloba*
5	Centella	Cicatrizing, trophodermic	*Centellaasiatica*
6	Sericoside	Skin improvers	*Terminalia sericea*
7	Silymarin	Antihepatotoxic	*Silybummarianum*

VIII. CONCLUSION

This review addresses phytosomes, which increase the bioavailability of water-soluble herbal ingredients via the gastrointestinal system and skin. For phyto-constituents that are more readily absorbed orally, transdermally, or topically, phytosomes—also referred to as herbsomes—are vesicular drug delivery vehicles. Their enhanced pharmacological and pharmacokinetic characteristics make them viable candidates for targeted medication administration. There are several aspects of phytosomes that need to be discussed in relation to the potential for pharmacological use in the future. Novel medication delivery techniques and the conventional method of delivering phytoconstituents are connected by phytosome technology. An effort was made to investigate the ongoing studies about phytosomes and their uses, such as anti-oxidant, anti-cancer, and wound-healing properties. Researchers that want to investigate a vesicular drug delivery system that includes an efficient drug on track site without its metabolism will find the information gathered here helpful. Despite the fact that there are many different phytosome products on the market, many other phytoconstituents that have the potential to treat serious illnesses have not been incorporated into phytosome technology.

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