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Phytosomes: Promising approach for the delivery of phytoconstituents

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Abstract
Herbal drugs are a great option for treating a wide range of illnesses in the modern world. Yet, their therapeutic application may be severely limited due to their limited selectivity and bioavailability. This means that the phytosome technology is a state-of-the-art approach meant to tackle the problem of limited bioavailability. The term "phyto" refer to plants, "some" refer to individual cells. This innovative formulation creates lipid-compatible molecular complexes with improved absorption and bioavailability by combining phospholipids with a standardised plant extract. The phosphatidylcholine moiety functions as the bifunctional. Phosphatidylcholine is an essential part of phytosomes, because it gives effective drug loading capacity. Compound's head, the choline moiety which is inherently hydrophilic. Compound's tail, phosphatidyl moiety is naturally lipophilic. When hydrophilic phytoconstituents bind to the choline portion of the molecule, the lipid-soluble phosphatidyl component of the phosphatidylcholine molecule envelops the choline-bound complex. This leads to the production of a phyto-phospholipid complex with higher lipid solubility. Phytosomes offer several benefits, such as higher bioavailability, better nutritional efficacy and better entrapment efficiency. This review is made to give comprehensive insights about the phytosomes, its chemical composition, mechanism of phytosome formation, advantages, method of preparation & characterization.

Keywords: Phytosomes, phospholipid, phosphatidylcholine, solubility

Introduction

In the past few decades, a lot of emphasis has been given to the development of novel drug delivery systems (NDDS) for herbal medications. Two requirements should preferably be met by the novel carriers. First and foremost, during the course of treatment, the drug should be delivered at a rate determined by the requirements of the body. Second, it ought to direct the herbal medicine's the active constituent to its site of action. None of these can be met by conventional dosage forms, including prolonged-release dosage forms.

Several fundamental factors contributing to the limited bioavailability of these compounds include their high molecular weight/size, poor plasma membrane permeability, and low solubility in water or lipid. Furthermore, in the presence of stomach fluids, the standardised extracts lose part of their components, when taken orally. This has limited the application of polyphenolic plant actives that are pharmacologically effective in treating various illnesses. In an effort to address these issues and improve the efficacy of herbal therapy, these medications have recently been added to a number of novel drug delivery methods. Formulating at the nanoscale as nanoparticles, binding with lipids as liposomes, herbosomes, or phytosomes, delivering in the form of microemulsions, altering chemical structures, delivering as prodrugs, complexing with cyclodextrins and other methods have various benefits for improving bioavailability, enhancing pharmacological activity, good stability.

In an effort to get around these issues and improve the efficacy of herbal medicine, these medications have recently been added to a number of cutting-edge delivery methods. One of the most effective way to increase the bioavailability and therapeutic efficiency of a number of poorly absorbed plant elements is to phospholipid-complement plant medications or extracts [1, 2].

The herbal extracts containing phytochemical components, such as terpenoids and flavonoids, enable them to bond with phosphatidylcholine directly [3]. Furthermore, due to the lipoidal nature of small intestine membrane, some herbal phytomolecules frequently fail to transit through it because of their weak misciblility with oils and other lipids. Any herbal product's ability to provide an effective level of the active components determines its efficacy. This difficulty is addressed by Indena's phytosome technology which significantly increases the bioavailability of specific phytomedicines. Utilising phytosomes is a cutting-edge, contemporary dose formulation technique for the delivery of herbal products [4, 5]. A phytosome is a vesicular drug delivery vehicle that has lipid and phytoconstituents. When applied topically or taken orally, herbal extracts are more readily absorbed [6].

Herbal medicines called phytosomes are delivery systems in which phytoconstituents are encapsulated in vesicles. Due to its high lipid miscibility, this hybrid is better suited to join with the lipid phase of the enterocyte phytosomes, which is a compound that is meant to increase the absorption and bioavailability of water-soluble phytoconstituents and plant extracts into lipoidal membrane. They may finally enter the bloodstream by efficient absorption from the lipophilic environment of the cell membrane into an environment that contains water. One of the finest methods to enhance the body's absorption and utilisation of herbal medicines and nutraceuticals is through phytosomes (phyto-phospholipid complexation) [6, 7].

Phytosomes

The term 'phyto' is used to describe a plant and 'somes' means cell like. An innovative form of drug delivery tool called a phytosome is utilised to encapsulate plant extracts in lipid. Consequently, phytopharmaceuticals are produced. Since the beginning of recorded history, traditional medical practices and plant-based pharmaceuticals have been used for a variety of therapeutic purposes and have been demonstrated to be quite effective at preserving one's health. The delivery of plantbased medicines has only recently advanced to the point where they may successfully treat human illnesses. Around the world, people are turning more and more towards herbal medicines as a self-medication and a way to receive medical care outside of the traditional bounds of modern medicine. Most of the chemicals that make up the bioactive components of phytomedicines are soluble in water. By mixing phospholipids with standardised herbal extracts or water-soluble phytoconsituents, lipid-compatible molecular complexes called phytosomes are produced [8].

The hydrophilic choline moiety and the lipophilic phosphatidyl moiety combine to form the bifunctional phosphatidylcholine molecule. After the phosphatidylcholine molecule's head attaches to a phytocomponent, the lipid-soluble tail of the molecule encircles the choline-bound material. Consequently, the union of the phytoconstituents and phospholipid results in the formation of the phyto-phospholipid complex, phytosomes [3, 9].

Advantages

- It increases the bioavailability of herbal constituents by improving their absorption.
- Dose requirement decreases when absorption of phytoconstituent is enhanced.
- Phosphatidylcholine molecule and the phytoconstituent create chemical bonds. Hence, the stability profile of phytosomes is superior [10].
- Improved bioavailability: better outcomes [11].
- Makes bile more soluble in herbal constituents, which makes liver targeting easier [12].
- The synergistic impact of phosphatidylcholine (which is used in the manufacture of phytosomes) comes from its dual roles as a hepatoprotective and a carrier [13].
- Phytosomes improve polar (lipophobic) herbal extract's absorption when applied topically and orally, showing improved bioavailability.
- The efficacy of drug entrapment is higher in phytosomes.
- Phytosomes may more easily shift from a hydrophilic to a fat-soluble environment. Hence,they can be employed for systemic targeting.
- Because of their enhanced skin penetration, phytosomes are highly useful in cosmetic applications.
- Additionally, precious phytomedicines are protected from destruction by gut bacteria and gastrointestinal secretions [14].

Mechanism of Phytosome formation

Plant based extracts contain polyphenols that are highly conducive to direct binding to phosphatidylcholine. When standardized extract or polyphenolic components, such as simple flavonoids, mix with phospholipids like phosphatidylcholine in an aprotic solvent, phytosomes are created [15–16]. Phosphatidylcholine is a bifunctional molecule, with a hydrophilic choline moiety and a lipophilic phosphatidyl moiety. Phosphatidylcholine specifically binds to these chemicals through its choline head, while the lipid-soluble section is the phosphatidyl component, which consists of the body and tail, envelops the choline-bound substance. Consequently, the phytomolecules and phospholipids form the phyto-phopholipid complex, a lipid-soluble molecular complex.

Certain spectroscopic approaches have indicated that phytomolecules are linked to the polar choline head of phospholipids by chemical bonding [16]. In most cases, according to precise chemical analysis, a flavonoid molecule connected to at least one phosphatidylcholine molecule often makes up the unit phytosome. A tiny microsphere or cell is created as a result. These drug-phospholipid complexes can be prepared as a pill, capsule, powder, granules, aqueous micro dispersion, lotion, gel, cream, solution, suspension, emulsion, syrup, and chewable tablet form [17].

Applications

Fig 1: Applications of phytosomes [18, 19]

Structure of phytosome

Phytosomes are complexes of phytoconstituents and phospholipids. They are produced by the physical and chemical combination of the hydrophilic active phytoconstituents and the polar head (choline moiety). Phospholipid head groups are anchored in these complexes. Fatty acid chains enclose the polar component in complexes that produce a lipophilic surface. The component of the cell membrane that forms phytosomes is phosphatidylcholine [6, 20].

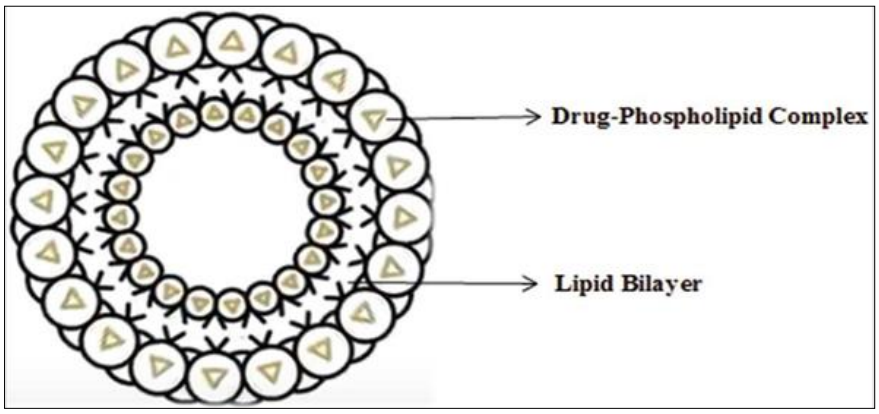

Fig 2: Structure of Phytosomes [21]

Composition of Phytosomes

Phytoconstituents

Herbal extracts contain phytoconstituents and are assessed based on their *in vitro* pharmacological activity and their *in vivo* effects. The majority of these phytoconstituents are polyphenols, terpenoids; some of them are found in polyphenolic components, which are soluble in the aqueous phase and cannot cross biological membranes. Others, like rutin and curcumin, on the other hand, have lipophilic properties and are thus insoluble in aqueous stomach contents. Phyto-phospholipid complexes enhance both the solubilization of lipophilic polyphenols in the water phase and the permeability of hydrophilic polyphenols in cell membrane. Furthermore, complex formation may protect polyphenols from hydrolysis, oxidation, and photolysis [6, 22].

Phospholipids

Phospholipids, notably sphingomyelins and glycerophospholipids, are widely dispersed and categorised based on their backbones within plants and egg yolks. Phosphatidylcholine (PC), phosphatidylethanolamine, phosphatidylglycerol (PG), phosphatidylserine (PS), phosphatidyl inositol (PI), and phosphoric acid (PA) are the main constituents of glycerophospholipids [23]. There are currently phospholipids available in the market that are manufactured commercially. PS, PE, and PC are the primary phospholipids involved in the formation of complexes with two hydrophobic hydrocarbon chains and a hydrophilic head group. The most popular phospholipid among them, Phosphatidylcholine (PC) is utilised to create phospholipid complexes because of its amphiphilic nature, which permits mild solubilization in aqueous and lipid soluble environments. The fact that PC is a crucial component of cell membrane. Hence, it functions efficiently in living organisms [6].

Methods of preparation

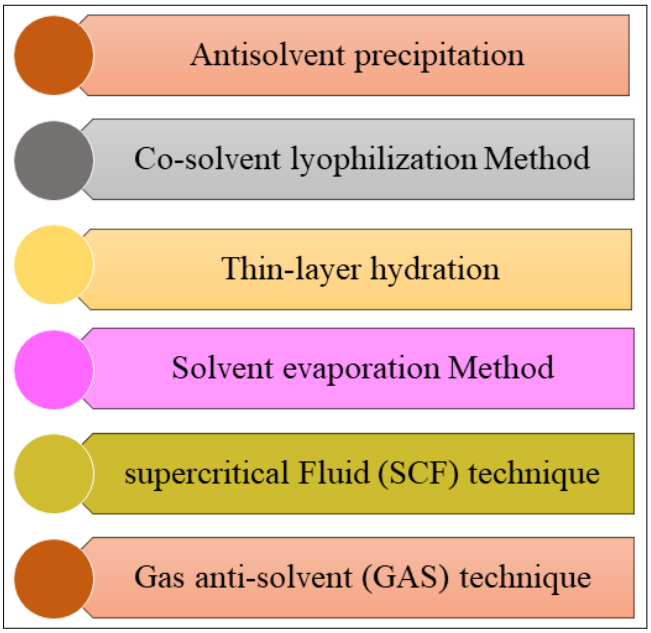

Fig 3: Methods for preparation of phytosomes

Antisolvent precipitation method

A predetermined quantity of drug and phospholipid are refluxed with an appropriate solvent in the antisolvent precipitation procedure. After the mixture has been created, it is concentrated and another solvent (n-hexane is used as the antisolvent.) is added while stirring continuously to form precipitate. The resulting precipitates are then collected, filtered, and kept overnight in vacuum desiccators [24].

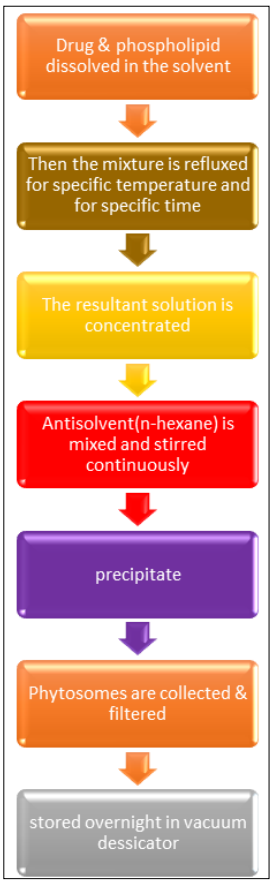

Fig 4: Flow chart: Antisolvent precipitation method

Co-solvent lyophilization method

The drug and the phospholipids are dissolved in a suitable solvent separately. After that, both are combined with moderate stirring to create a transparent mixture. After achieving homogeneity, the mixture is freeze dried under vacuum and kept in an airtight container for later use [24].

Thin-layer hydration

Cholesterol dissolved in dichloromethane and phytoconstituents and phosphatidylcholine are dissolved in methanol. A thin, dry film is then formed by evaporating the mixture in a rotary evaporator. To completely remove organic solvents from the thin coating, nitrogen gas is often blown over it. The organic solvents are then completely evaporated by vacuum drying. Then, the film is replenished with distilled water. Then the phytosomes are formed [24].

Solvent evaporation method

Typically, solvent evaporation techniques are used for preparing the complex of plant extracts or particular active principles with natural phospholipids, utilizing alcoholic or organic solvents as the reaction medium. The drug and the phospholipids are combined in a flask with an appropriate solvent system, like ethanol or tetrahydrofuran, in the most common solvent evaporation method. For a specific period of time, at a fixed temperature the reaction is permitted to proceed in order to maximize yield and drug entrapment. The resultant formulation was then refrigerated [17].

Super critical fluids (SCF) technique

Super critical fluids, or SCFs, have become a useful tool for producing particles with sizes between 5 and 2000 nm. Supercritical fluid techniques such as compressed antisolvent process (CAP), supercritical antisolvent method (SAS), rapid expansion of supercritical solutions (RESS), gas anti-solvent technique (GAS) have all been used to improve the solubility profiles of drug candidates that are poorly soluble [17, 25].

Technique for gas anti-solvent (GAS)

The drug and phospholipid solutions were treated independently with a supercritical antisolvent in the GAS approach until the desired pressure was reached. After that, the reaction vessel was maintained at a constant 38 °C and 10 mPa of pressure for three hours without being agitated [17].

Solvents used in the formulation of phytosomes

Scientists have previously employed a variety of solvents for the manufacture of phospholipid phytocomplexes. Most often, complexes of phytophospholipids have been synthesised using aprotic solvents such methylene chloride, cyclic ethers, ethyl acetate, hydrocarbons, and halogen derivatives. But because of high success rate, prototic solvents like methanol and ethanol have replaced them [6].

Characterization

1. Vesicle size and Zeta potential:

Computerised inspection system and photon correlation spectroscopy, dynamic light scattering (DLS) can be used to detect the particle size and zeta potential.

2. Visualization

Transmission electron microscopy (TEM) and scanning electron microscopy (SEM) are used to visualize phytosomes.

3. Drug content

A suitable spectroscopic method (uv spectroscopy) or a modified high performance liquid chromatographic technique can be used to quantify the amount of drug [17].

4. Transition temperature

Differential scanning calorimetry (DSC) can be used to check the vesicular lipid system transition temperature [17].

5. Stability of vesicles

Stability of Vesicles can be ascertained by evaluating their size and structure over time. Dynamic Light Scattering (DLS) measures the mean size, and transmission electron microscopy (TEM) tracks structural alterations. Practically, the stability of the complex can be verified by comparing its solid form spectrum (phytosomes) with the time-series spectrum of its microdispersion in water following lyophilization [17].

6. Fourier Transform Infrared (FTIR) spectroscopy

By comparing the phytosomes complex's spectra to that of its constituent and their mechanical mixtures, IR spectroscopy can also be used to confirm the phytosome complex formation. FTIR spectroscopy is helpful technique for managing phytosome stability when microdispersed in water [17].

7. *In vivo* and *in vitro* activity

Based on the expected therapeutic efficacy of the physiologically active phytoconstituents found in the phytosomes, models of *in-vitro* and *in-vivo* evaluations are chosen. For instance, the antioxidant and free radical

scavenging capabilities of the phytosomes can be used to evaluate the *in-vitro* antihepatotoxic efficacy. The effect of produced phytosomes on animals against thioacetamide, paracetamol, or alcohol-induced hepatoxicity can be studied for the purpose of determining antihepatotoxic activity by *in-vivo* method [17, 26].

8. Entrapment Efficiency

The ultracentrifugation method can be used to determine amount of entrapped of drug in phytosomes [17].

Conclusion

Phytosomes are the novel drug delivery systems which enhance the bioavailability and give better entrapment efficiency for the herbal drugs. This is one of the best drug delivery systems for the herbal origin drugs. Phytosomes forms the connecting link between the novel and the conventional drug delivery systems. This contains the drug of herbal origin and it is bonded with the phospholipid such as phosphatidylcholine. The resulting complex so formed has better stability, best entrapment efficiency and good drug release profile. The method of preparation of phytsomes are easy and reproducible. Many herbal drugs which are hydrophilic and not absorbed through gastrointestinal membrane can be easily made absorbable by formulating them into phytosomes. Hence, many diseases or disorders which can be treated by the herbal drugs and still can't be used because of solubility, stability and bioavailability issues. Hence, potential of the phytoconstituents to treat different diseases can be used by formulating them into phytosomes. Phytosomes holds great promises in future for the effective delivery of phytoconstituents which are not yet used due to the stability problems.

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