Advancements In Herbal Drug Delivery Systems: Expanding Horizons with Phytosome Technology

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Abstract— The integration of botanical extracts and bioactive compounds into novel drug delivery systems (NDDS) has revolutionized the field of herbal medicine and nutraceuticals. This review explores the diverse methods available for formulating unique herbal formulations, including cubosomes, transferosomes, ethosomes, liposomes, nanoemulsions, polymeric nanoparticles, and nanocapsules, all utilizing botanical and bioactive extracts. Among these innovative approaches, phytosome technology has emerged as a patented breakthrough developed by a reputable producer of herbal medicines and nutraceuticals. Phytosome technology involves the creation of lipid-compatible molecular complexes by enhancing standardized extracts of plant or water-soluble phytoconstituents with phospholipids. This novel formulation crucially enhances the drug's bioavailability and absorption compared to traditional plant actives and extract formulations.

Index Terms- Botanical extracts, Bioactive compounds, Drug delivery systems, Phytosome technology.

I. INTRODUCTION

Traditional medicine and phytomedicine have been used therapeutically for a long time to maintain health through a varietyof methods. Many plant extract have been the subject of chemical and pharmacological investigations during the past century in an effort to determine their chemical makeup and validate their medical value [(1)].

Phytosome is a patented method that provides lipid-compatible molecular complexes by incorporating standardized plant extracts or dihydrogen monoxide soluble phytoconstituents into phospholipids. Because the valuable components of the herbal extract are protected from being destroyed by gut bacteria and digestive secretions, the phytosomes process creates a touch cell. Pharmacokinetic and pharmacological parameters are enhanced by phytosomes [(2)].
The term “Phyto” means plant while “some” means cell- like [(3)]. It is also known as herbosomes. Among the phospholipids that are used are phosphatidylcholine, phosphatidylserine, phosphatidylethanolamine, and phosphatidylinositol; nevertheless, phosphatidylcholine is frequently used because of its distinct therapeutic quality. The bioactive flavonoids of the plant are not merely passively" bearers" of phosphatidylcholine. Phytosomes is also a bioactive nutrient that has been shown to be clinically effective in treating liver diseases, including as hepatitis, drug- induced liver damage, and alcoholic hepatic steatosis [(4)]. Lipid solubility and molecular size are the main factors that prevent drugs from passing through the cellular membrane and being systemically absorbed after oral or topical application. The effectiveness of any herbal product or treatment depends on howwell the active ingredients are delivered [(1)]. Phytosomes are a novel, cutting-edge dose formulation technique that improves absorption of herbal goods and medications, leading to superior outcomes compared to traditional herbal extracts [(5,6)].

The advancement of natural science has led to the rise in popularity of phytosomes in a variety of industries, including medicines, cosmetics, and nutraceuticals, where they are used to make unique products including emulsions, solutions, gels, creams, and lotions. Various firms, including Indena, Jamieson Natural Resources, Thorne Research, Natural Factors, and Natures Herb, are involved in the production and commercialization of phytosomal products [(7)].

Phytosomes are utilized to treat both acute and chronic liver diseases that have a degenerative, toxic, metabolic, or infectious cause. It can also be utilized in medicinal and cosmetic formulations, with anti-inflammatory properties. Milk thistle's silybin and other silymarin flavonolignans have the ability to prevent cancer, preserve tissue glutathione, and protect the liver. Curcumin and its associated diphenolic curcuminoids possess strong anti-

inflammatory, anti-carcinogenic, and antioxidant characteristics. Green tea flavanol catechins offer several health benefits, including weight loss through fat oxidation and antioxidant, anti-inflammatory, cardio- and neuroprotective, and anticarcinogenic properties. The complex mixture ofproanthocyanidins found in grape seeds, which includes epicatechin and catechin monomers and oligomers, counteracts oxidative stress and safeguards the cardiovascular system [8].

II. PHYTOSOME TECHNOLOGY

Phytosomes, sometimes referred to as phytolipids delivery system, serve as a bridge between innovative delivery methods and conventional delivery methods [9]. Innovation vesicular drug delivery systems are made to transport the active ingredient to the site of action while delivering the medication at a rate determined by the body's demands throughout treatment. To achieve targeted and regulated medication delivery, a plethora of innovative vesicular drug delivery systems with unique pathways of administration have been introduced. The bioactive phytoconstituents of the botanical essence complexed with phospholipids, such as phosphatidylcholine, to create lipidaggregable molecular complexes, make up the unique kindof botanical preparation known as a phytosome [10]. Phyto-constituent molecules soluble in water (mostly polyphenols) can be converted into lipid-compatible molecular complexes called phytosomes. This phytosometechnique is an approach for significantly improving bioavailability, ensuring tissue delivery that is satisfactory
(8).

In nations like India and others countries, phytosome development is still in its infancy. Thus far, this method has proven successful when applied to herbal extracts such as curcumin, ginseng, grape seeds, ginkgo Biloba, milk thistle, and other products that are often used as dietary supplements [11,12,13,]. Many compounds had shown the wide range of health benefits, but scientists were never able to fully understand them since they disintegrated too easily in the body. Thanks to this technology, the substance may be properly absorbed by the body and transportedto the right location. Hydrophilicity and lipophilicity mustbe well balanced in the herbal formulation for it to have high bioavailability. Apart from crossing bio membranes, they also need to be soluble in fluids found in the intestines. For this reason, phytosomes have higher bioavailability than a basic herbal essence [14].

III. PROPERTIES OF PHYTOSOMES CHEMICAL PROPERTIES

A phytosomes is a complex between a natural product and natural phospholipids, like soy phospholipids. Such a complex results from the reaction of stoichiometric amount of phospholipid with the selected polyphenol (like simple flavonoids) in a nonpolar solvent [15].

On the basis of their physicochemical and spectroscopic data, it has been shown that the main phospholipid-substrate interaction is due to the formation of hydrogen bonds between the polar head of phospholipids (i.e. phosphate and ammonium groups) and the polar functional groups of the substrate. They are lipophilic substances with a clear melting point, freely soluble in nonpolar solvents (in which the hydrophilic moiety was not),and moderately soluble in fats. When treated with water, phytosomes assume a micellar shape forming liposomal-like structures. In liposomes the active principle is dissolved in an internal pocket or floats in the layer membrane, while in phytosomes the active principle is anchored to the polar head ofphospholipids, becoming an integral part of the membrane [16,17].Molecules are anchored through chemical bonds to the polar head of the phospholipids, as can be demonstrated by specific spectroscopic technique [18].

IV. BIOLOGICAL PROPERTIES

Pharmacokinetic and pharmacodynamic studies in experimentalanimals and in human subjects have been used to demonstrate the biological behaviour of phytosomes. The increased bioavailability of the phytosomes over the non-complexed botanical derivatives has been evaluated from these studies [19].

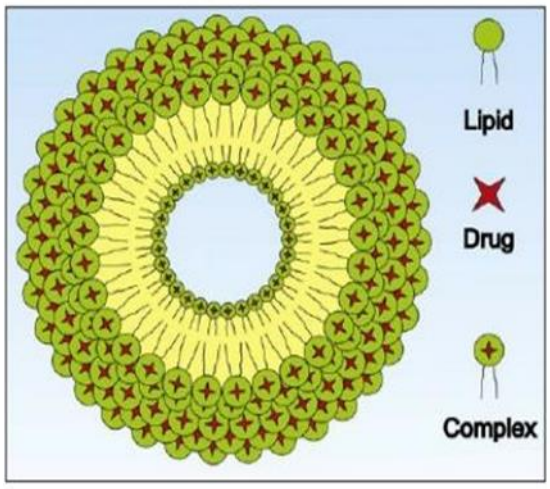


Fig.1: Structure of phytosomes complexes

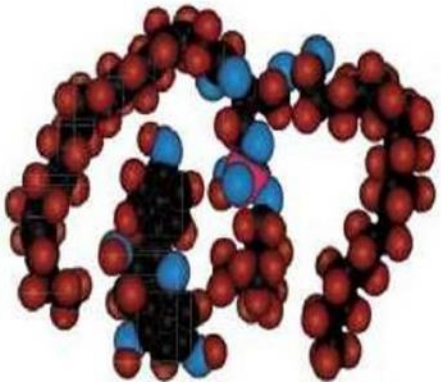
V. MECHANISM OF PHYTOSOME FORMATION

Herbal essence's polyphenolic components proved to be quite well-suited for phosphatidylcholine's direct conjugation. A stoichiometric amount of phosphatidylcholine, a phospholipid-like substance, reacts with simple flavonoids and other polyphenolic components in an aprotic solvent to form a phytosome [(20)].

Phosphatidylcholine is a multifunctional compound whose hydrophilic portion behaves like a choline and its lipophilic portion like a phosphatidyl. The lipid-soluble phosphatidyl portion, which has a body and tail and covers the choline- bound material, is the part of the phosphatidylcholine that conjugates to these molecules. As a result, the Phyto molecules produce a phospholipid-containing lipid soluble molecular complex known as the phyto-phospholipid complex. Precise spectroscopic techniques can verify that Phyto molecules are chemically bonded to the polar choline head of phospholipids [(21)].

The unit phytosome is usually a flavonoid molecule linked to at least one phosphatidylcholine molecule, according to comprehensive chemical examinations. A tiny microsphere or cell is created as a result [(22)]. The orange spectrum from phosphatidylcholine covers the red spectrum from the polyphenol in the blue phytosome spectrum. This aligns with the idea that the phosphatidylcholine molecule physically entraps the polyphenol.

Fig. 2: Schematic of the phytosome molecular complex [(8)]



PHYTOSOME	LIPOSOME
A unit of a molecule bound together is called a phytosome.	A liposome is a collection of several phospholipid molecules that have the ability to surround additional Phyto activemolecules without necessarily conjugating to them.
It is possible to tie the phytosome complex to a crucial component of thelipid membrane. where the polar head of phospholipids (i.e., the phosphate and ammonium groups) and the polar functions of the lipophilic guests engage through hydrogen bonding producing a particular pattern that spectroscopiccan validate.	Inside liposomes, the cavity's fundamental domain dissolves the active component is nochance of a chemical interaction happening between the hydrophilic material and the lipid around it.

Phospholipid and plant component are carried by phytosomes in a ratio ofeither 1:1 or 2:1, depending on the chemical or substances that are complexed involving chemical connections. Inlight of this, they have superior absorption and bioavailability.	Chemical bonds do not form within a liposome. The water-soluble material is encased in phosphatidylcholine molecules. The water-soluble substance may be surrounded by hundreds tothousands of phosphatidylcholine molecules.
Phytosomes interact with solvents that have a low dielectric constant, such as ethyl acetate, acetone, dioxane, methylene chloride, and hexane.	A buffer solution or water is used to prepare the liposomal drug complex

TABLE. 1: DEFERENCE BETWEEN PHYTOSOME ANDLIPOSOME [13]

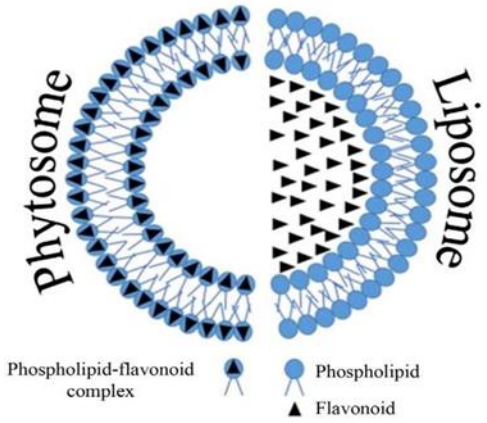


Fig. 3: DEFERENCE BETWEEN PHYTOSOME AND LIPOSOME

ADVANTAGES OF PHYTOSOMES (23)

1. Increases the solubility of bile salts, which improves liver targeting.
2. As active phytoconstituent absorption increases, the necessary dose is lowered.
3. The phytochemical components employed to prepare phytosomes have a synergistic effect in addition to serving as a carrier.
4. Phytosomes are extensively utilized in cosmetics due to their enhanced skin penetration and elevated lipid profile.
5. The beneficial elements of herbal extracts are shielded from oxidation by gut flora and digestive secretions.
6. Higher stability is a result of the chemical linkages that are established between phosphatidylcholine molecules and phytoconstituents.
7. Phosphatidylcholine serves as a transporter and nutrient throughout the phytosomes process.

VI. DISADVANTAGES OF PHYTOSOMES

1. The phytoconstituent leaves the phytosome very soon.
2. Considering all benefits, phytosomes may quickly eliminate the phytoconstituent (24)
3. Phospholipids have the ability to promote MCF-7 breast cancer cell line proliferation.
4. The main restriction of phytosomes is said to be the phytoconstituent leaching out some, which lowered the expected medication concentration (25).

PREPARATION OF PHYTOSOMES [26]

1. SOLVENT EVAPORATION METHOD

The specific amount of drug and soya lecithin were taken into a 100 ml round bottom flask and refluxed with 20 ml of acetone at a temperature 50 - 60℃ for 2 h. The mixture is concentrated to 5-10 ml to obtain the precipitate which was filtered and collected. The dried precipitate phytosomes complexes was placed in amber coloured glass bottle and stored at room temperature.

A. ROTARY EVAPORATION TECHNIQUE

The specific amount of drug, soya lecithin was dissolved in tetrahydrofuran in a rotary flask, by stirring for 3 hours at 40℃. Sample Thin film is produced upon addition of n-hexane and stirred in continuous with the help of magnetic stirrer. Precipitate is collected and stored in glass bottle at room temperature.

B. ANTI-SOLVENT PRECIPITATION TECHNIQUE

Desired quantity of drug and soya lecithin was taken in RB flask. Made reflux with dichloromethane at 60℃/2 h. Concentrated and precipitated by treating

with 20 ml of hexane. Precipitation is filtered, collected and stored. The dried precipitate is crushed, sieved and stored in amber coloured glass bottle.

2. SALTING OUT METHOD

The phytoconstituent and phosphatidylcholine is dissolved in aprotic solvents like acetone. It is continuously stirred to form complex, later isolated by using non-solvents (n-hexane).

3. MECHANICAL DISPERSION METHOD

Initially, phytosomes were made dissolved in diethyl ether, injected in water contains phyto- ingredients to be encapsulated. The organic solvent is removed under reduced pressure leads to form the complex. Novel methods for the preparation of phospholipid complex are Super Critical Fluids (SCF), Anti Solvent technique (GAS), compressed anti solvent process (PCA) and Supercritical Anti Solvent method (SAS).

4. LYOPHILIZATION TECHNIQUE

The natural or synthetic originated phospholipid and phytoconstituent were made soluble in various solvents. The phyto-ingredients were added to a phospholipid solution and stirred to get a complex. Further the complex is separated outby lyophilization. The phospholipids used in phytosomes preparation consist of acyl group which is varied in Phosphatidylcholines (PC), phosphatidylserine, phosphatidylethanolamine. In phytosome active, an integral part of the membrane because the active principle is in connection with the polar head of phospholipid

DIFFERENT ADDITIVES USED IN THE FORMULATIONS OF PHYTOSOMES:

Phospholipids: Soya phosphatidyl choline, Egg phosphatidyl choline, Dipalmityl phosphatidyl choline, Distearyl phosphatidyl choline.

Aprotic solvent: Dioxane, acetone, methylene chloride
Non solvent: n-hexane and aliphatic hydrocarbon
Alcohol: Ethanol, Methanol [27].

EVALUATION OF PHYTOSOMES

A) VISUALISATION:

Morphology of phytosomes was observed by digital microscopy transmission microscope and scanning microscope.

1) DIGITAL MICROSCOPY

Phytosome formulation was shake, with water and viewed under digital microscope at 400Xobjective lens.

2) TEM ANALYSIS

The complex was shaken with water and viewed using Transmission Electron Microscope.

3) SEM ANALYSIS

Approximately 5 µl of the phytosomal suspension was transformed to a canopy slip, which successively was mounted ona specimen tab. The samples were allowed to dry at temperature. Then the particle size of the formulation was viewed and photographer using Scanning microscope (Sigma scan, Carl Zeiss scan). The particles coated with platinum by using vacuum pressure and thus, the coated samples were viewed and photographed in JEOL JSM-6701F emission SEM.

B) PARTICLE SIZE ANALYSIS

Diameter of particles and polydispersity index was noted down by BECKMAN COULTER, DelsaTM Nano. Phytosome formulations were diluted with solvent methanol and then evaluated for particle size.

C) FTIR

Spectral data were taken to work out the structure and chemical stability of extract, PC and phytosome. Spectral scanning was exhausted the range between 4000 and 5000cm^{-1}.

D) DSC

The sample with, phospholipid and phytosome were placed within the aluminum crimp cell and heated at 100C/min from 0℃ to 4000℃ within the atmosphere of nitrogen (TA Instruments, USA, Model DSC Q10 V24.4 Build 116). Peak transit time onset temperatures wererecorded by means of an analyzer.

APPLICATION OF PHYTOSOMES

1) Enhancing Bioavailability
2) Delivery of large and diverse drugs, eg. peptides andproteins

3) Safe composition
4) Hepato-Protective
5) Approved for cosmetic and pharmaceutical applications
6) Low-risk profile
7) Toxicological properties have been well documented
8) High market attraction [28].

CONCLUSION

The restricted solubility and sensitivity to degradation of phytochemicals have resulted in their reduced utilization in medicinal products. Vesicular medication delivery methods assist in getting beyond these restrictions. Because of their capacity for entrapment, safety, and biocompatibility, vesicles present intriguing deliveryoptions at the cellular level. The combination of these phytosomes and vesicular drug transporters improves absorption and bioavailability. The only lipid-based vesicle that promotes the transport of plant-based nutraceuticals is the phytosome. An overview of phytosome applications, preparation, and assessmenttechniques is given in this paper. Clinical trials on standardised products will become more effective in the near future, drawing interest in these technologies.

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