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Aarthi Edulakanti
Queen's University Belfast, Northern Ireland, United Kingdom

Corresponding Author:
Aarthi Edulakanti
Queen's University Belfast, Northern Ireland, United Kingdom

Phytosomes: An emerging trend for herbal drug delivery

Aarthi Edulakanti

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Abstract
Novel drug delivery system is a new patented technology that addresses the limitations of conventional drug delivery systems. Herbal drugs have been utilized since ancient times and are considered safer than allopathic treatments. A phytosome is a complex reaction between organic products and organic phospholipids. They have better pharmacokinetic and pharmacodynamic profiles than traditional delivery systems for herbal drugs. This article discusses a comprehensive overview of phytosomes including their characteristics, advantages, and marketed products acknowledging that phytosomes have great potential as a drug delivery system.

Keywords: Phytosome, phytophospholipid, novel drug delivery system

Introduction
A novel drug delivery system is a new patented technology that addresses the drawbacks of conventional drug delivery systems. Herbal remedies were used as first aid medications since ancient times however they have become obsolete. Herbal drugs are making a resurgence for various reasons such as -

- Inflation has made everything expensive including allopathic medicines.
- Herbal treatments have long-term benefits.
- Herbal medicines are known to have fewer side effects, unlike allopathic medicines.

Limitations of herbal drugs include
- Herbal drugs are polar in nature and thus have a poor rate of absorption in the body.
- Herbal medicines delay the process of healing and thus cannot be used in emergencies.
- Most herbal drugs lack scientific evidence because clinical studies have not been performed on them.
- The other limitation of herbal drugs is that there are high chances of drug interactions with the prescribed medicines.

The development of NDDS has been given considerable attention over the past few decades. This new approach can be used to overcome limitations associated with herbal drugs [1].

Phytosomes
Phytosome is a novel technology that is developed to incorporate herbal extracts into phospholipids to produce lipid-friendly molecular complexes. Most of the phytoconstituents are polar in nature and thus, are poorly absorbed in the body. Encompassing such phytoconstituents in the phospholipid can help them transport across lipid-rich biological membranes resulting in enhanced bioavailability.

Phospholipids [1]
Phospholipids are amphiphilic compounds that include both hydrophobic and hydrophilic moieties. They are naturally found in all living organisms as the building blocks of cell membranes. Due to their amphiphilic nature, phospholipids are often used as carriers for herbal drugs in the development of phytosomes. Phospholipids also act as hepatoprotective and thus are beneficial for human health.

In phosphatidylcholine, the choline moiety is hydrophilic in nature, thus, binds with the bioactive compounds through chemical bonds such as hydrogen bonds whereas the phosphatidyl portion having lipophilic character envelopes the choline-bound material to produce a phyto-phospholipid complex.

Properties of phytosomes [1]

Chemical properties

A phytosome is a complex reaction between organic product and organic phospholipid. On conduction of various physicochemical tests on phytosomes, the studies showed that the interaction between the phospholipid and the phytoconstituent is mainly due to the formation of hydrogen bonds between the polar head of phospholipid (i.e. phosphate and ammonium groups) and the polar functional groups of the phytoconstituent. Phytosomes are lipophilic in nature. They have a sharp melting point and are freely soluble in organic solvents and moderately soluble in fats. Phytosomes assume a micellar shape when dissolved in an aqueous solvent.

Biological properties

Pharmacological studies in experimental animals and 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 in these studies [3].

Advantages of phytosomes [4-5]

- Phytosomes increase the absorption of polar herbal constituents by converting them into lipid-compatible complexes thereby improving systemic bioavailability when administered orally.
- Phytosomes enhance the skin absorption of phytoconstituents and are widely used in cosmetics for their more skin penetration and high lipid profile.
- Phytosomes increase the duration of action of herbal drugs.
- Phosphatidylcholine which is used as the carrier for herbal drugs can also act as a hepatoprotective.
- Phytosomes exhibit better pharmacokinetic and pharmacodynamic profiles than conventional plant extracts.
- Phytosomes show a better stability profile than liposomes due to the presence of chemical bonds between the phospholipid and phytoconstituent.
- Manufacture of phytosomes is economical and comparatively easy since no complex technical investment is required.
- Phospholipid utilized in phytosome formulation act as a carrier transporter for herbal drugs. Since it is an integral component of the cell membrane, it is bio-degradable and thus there is no hindrance to drug entrapment during formulation.

Disadvantages of phytosomes

- Lack of broad clinical studies.
- The active ingredients are rapidly eliminated from phytosomes.

Phytosome vs Liposome

Table 1: Differences between Phytosome and Liposome [4]

Property	Phytosome	Liposome
Chemical bonds	Hydrogen bond is present between the polar head of phospholipid and the phytoconstituent	No chemical bonds are present in liposomes.
Mechanism	Phytomedicines are anchored through chemical bonds to the polar head of phospholipid and the non-polar body of phospholipid envelops the choline-bound complex.	Active plant constituents are hosted in the inner cavity of phospholipid with little or no interaction between the plant constituents and the surrounding lipid core.
Pharmacokinetic properties	Phytosomes show a better pharmacokinetic profile than liposomes	Liposomes are inferior to phytosomes in terms of pharmacokinetic profile
Bioavailability	It has superior bioavailability than liposomes	Liposomes have less bioavailability than phytosomes

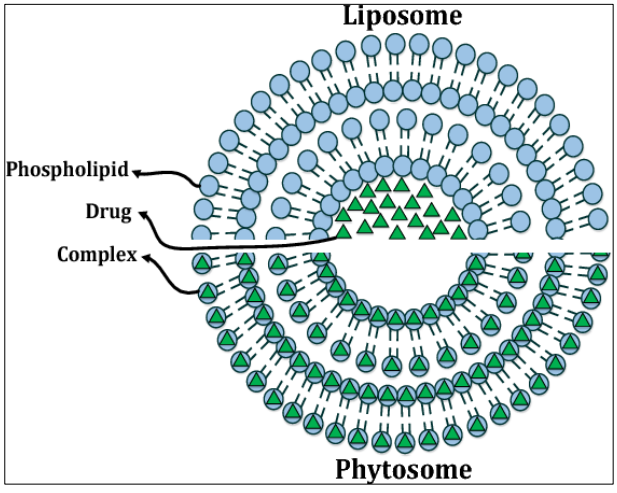

Fig 1: Phytosome vs Liposome [4]

Methods of preparation [5-7]

1. Rotary evaporation process

A specific weight of plant extract and phospholipid were combined in a round bottom flask with 20 ml of a water-miscible organic solvent such as acetone, Dichloromethane, etc and stirred for about an hour at a temperature below 40°C in the rota evaporator. To the thin film formed, anti-solvent such as n-hexane can be added. The obtained precipitate of phytosomes is stored in amber-colored glass under specified conditions.

2. Anti-solvent precipitation process

A Specific quantity of herbal extract and phospholipid is refluxed with 25 ml of an organic solvent such as dichloromethane under appropriate experimental conditions below 40 °C for 1-2 h. The obtained reaction mixture is concentrated to a minimum volume of 10 ml and then the precipitate is obtained at the bottom of flash by the addition of a low polar anti-solvent such as n-hexane. The precipitate is filtered and is stored in the desiccator. The dried precipitate is then pulverized and the powdered complex mixture is stored in an amber-colored glass bottle at room temperature.

3. Solvent ether-injection process
The method involves the reaction of phospholipid which is previously dissolved in organic solvent with the herbal extracts dissolved in an aqueous solvent. Phospholipid dissolved in diethyl ether is slowly injected drop by drop in a phytoconstituent-water mixture solution. Thus, cellular vesicles are formed. Subsequently, on the removal of solvent, the phyto-phospholipid complex is formed.

4. Novel methods
Novel methods for the phospholipid complexation including supercritical fluids are the gas solvent technique, compressed solvent process, the rapid expansion of supercritical solutions, gas antisolvent technique, and supercritical antisolvent method

Evaluation techniques [6-10]

1. Determination of particle size
The average diameter of the phytosome was measured using a particle size analyzer. For the measurement, the specific amount of formulation is diluted with the appropriate amount of Phosphate buffer saline at pH 6.8 and the diameter of the formed vesicles was determined.

2. Determination of entrapment efficiency
Phytosome complex was diluted 1-fold with 10 ml of suitable organic solvent and then centrifuged at 10,000 rpm for 1 hr at -4 ˚C using a cooling centrifuge machine. The supernatant was isolated and the amount of free herbal drug was determined by UV/Vis spectroscopy at a specific wavelength. To determine the total amount of herbal drug, 0.1 ml of the phytosome complex was diluted inorganic solvent, adjusting the volume to 10 ml. The Entrapment efficiency was calculated by using:-

Entrapment efficiency (%) = (Total amount of drug) – (amount of free drug) × 100 (Total amount of drug)

3. Determination of drug content
The drug content of the phytosome complex was determined by dissolving 100 mg of the complex in 10 ml of a suitable organic solvent such as methanol. After suitable dilution, the absorbance was determined by using a UV-Visible Spectrophotometer at a specific wavelength and the drug content was determined.

4. Scanning electron microscopy (SEM)
Scanning electron microscopy has been used to determine particle size distribution, size, shape, and surface morphology of the prepared phytosome complexes. The optimized freeze-dried phytosomes were subjected to scanning electron microscopy and are photographed.

5. FTIR Spectroscopy
FTIR spectral data were taken to determine the structure and chemical stability of phytosome complex, phospholipid, and plant drugs. Sampling was done using the KBr pellet method. The pellets were made at a pressure of 500 kg/cm^2. The prepared pellets were subjected to FTIR and the peaks obtained in the graphs were interpreted to evaluate the chemical interactions between the drug and the phospholipid.

6. **Proton-Nuclear Magnetic Resonance (1H-NMR)**: Spectroscopic studies are widely used to evaluate the formation of complexes between phytoconstituents and the phospholipids moiety, as well as to study the resultant association. This method can be used to simulate the complex formation of active phytoconstituents with the phosphatidylcholine molecule.

7. Carbon-Nuclear Magnetic Resonance (13C-NMR)
Studies showed that the carbons of the phytoconstituents were not detectable in the 13C-NMR of the phytoconstituents and the stoichiometric complex with phosphatidylcholine. The signals belonging to the glycerol and choline parts were broadened and others were shifted, but the majority of the fatty acid chain resonance has retained its original sharp line form.

8. *In vitro* drug release study
The drug release was evaluated by using the treated cellophane membrane which is mounted on one end of the open tube, containing the phytosomes. The dialysis tube was then suspended in a 500ml beaker having 250ml of phosphate buffer with pH 6.8. The solution was stirred with the magnetic stirrer at 37+(or)- 0.5 degrees Celsius. Then, 1ml sample was withdrawn at specific time intervals and an equivalent amount of fresh PBS was added to the samples. The samples were then filtered and diluted. The diluted samples were analyzed by using a UV spectrophotometer. The permeation of the complex was compared with the phytoconstituent.

Marketed formulations of Phytosomes

Table 2: Marketed formulations of Phytosomes with their source and biological activity [11-13]

S. No.	Phytosome	Source	Biological activity
1	Silybin	*Silybum marianum*	Hepatoprotective and Antioxidant
2	Greenselect®	*Centella Asiatica*	Skin Disorders
3	Rutin	*Ruta Graveolens*	Rheumatoid Arthritis
4	Curcumin	*Curcuma Longa*	Hepatoprotective
5	Leucoselect	*Vitis Vinifera*	Antioxidant
6	Naringenin	*Citrus Aurantium*	Antioxidant and Anti-inflammatory
7	Berberine	*Berberis Vulgaris*	Antidiabetic
8	Soyselect®	*Glycin Max*	Anticancer and Cardioprotective
9	Ginseng	*Panax Ginseng*	Immunomodulator
10	Hawthorn	*Crataegus Species*	Cardioprotective
11	Gingko	*Ginkgo Biloba*	Brain and Vascular Protection
12	Olive Oil	*Europaea Oil*	Anti-Inflammatory, Antioxidant, Anti-hyperlipidaemic and Cardiovascular Protection

13	Visnadine	*Ammi Visnaga*	Circulation Improver
14	Bilberry	*Vaccinium Myrtillus*	Potent Antioxidant
15	Echinacea	*Echinacea Augustifolia*	Immunomodulator

Phytosomes in clinical trials [10, 19, 20]

A study was conducted in the year 2014 to evaluate the effect of green tea extract phytosome in obese patients to counteract weight regain after a 3-month weight loss intervention.

The study has currently reached phase 4 trial and the results proved that the phytosomes formulation has a significant effect in controlling weight in obese patients.

Another research was conducted on bergamot phytosome as a potential hypocholesterolemic agent when given in combination with artichoke leaf extract. The study showed positive results proving that bergamot phytosome can be used as an adjuvant in hypercholesteraemic patients.

Recently, a study was conducted with 400mg of Quercetin Phytosome suggesting that it might be a potential immunity booster and can help in preventing the COVID-19 disease progression. The study is currently in phase 3 and the results of the study are yet to be known.

Table 3: Phytosome-based formulations in clinical trials [10, 19, 20]

Phytosome Identifier No.	Clinical Trial	Phase	Condition
Quercetin	NCT04578158	Phase 3	COVID-19
Leucoselect®	Nct04515004	Phase 2	Early-Stage Lung Cancer (I and II)
Artichoke and Bergamot	NCT04697121	Not Applicable	Hypercholesterolemia
Greenselect ®	NCT02542449	Phase 4	Obesity
Berberine	NCT05031715	Not Applicable	Glucose Metabolism Disorders
Silybin	NCT00487721	Phase 2	Prostate Cancer

Conclusion

Back in the past, plants were man's only apothecary. Herbs are rising in popularity with more and more people preferring natural extracts to conventional medicine**.** This review aims at presenting an incisive profile of phytosomes. Many phytosome formulations have already been marketed while few others are in the clinical trials stage. Thus, phytosome technology seems to have a great future as a potential drug delivery system.

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