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**Review Article**

# Phytosome and its therapeutic aspects

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## ABSTRACT

The bioavailability of plant actives can be enhanced through the incorporation of them into phospholipid based self-assembled delivery system, named phytosome. Phytosome is generally prepared by reacting one or two moles of phytoconstituents and phospholipid. It may be either in the ratio of 1:1 and 1:2. The phytoconstituents which posses a number of activities such as anticancer, antioxidant, wound healing etc. This formulation aids to enhances the solubility and bioavailability of polyphenolics. The major concern of phytosome is that it can able to deliver the plant actives with lesser side effects than that of the conventional dosage forms. This review gives an outlook on phytosome and its therapeutic activities.

**Keywords:** Phytosomes, Phosphatidyl choline, phytoconstituents, herbal drug delivery.

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## INTRODUCTION

Herbal medicines have been known since ancient time for their safety, efficacy and folk acceptability. They are believed to have better compatibility with the human body since the chemical constituents present in them are a part of the physiological functions of living flora. [1] The therapeutic aspects of phyto-medicines made useful in terms of health maintenance by various means. The advancement in the field of herbal drug delivery was developed with the aim to manage human disease efficiently. [2] Most of these biologically active constituents of plants show poor bioavailability due to their large molecular size, and presence of multiple rings. Due to their poor lipid solubility, they exhibit the limited ability to pass across the lipid-rich biological membranes. [3] Drug delivery systems (DDS) are capable of designing drugs with increased bioavailability and release of drug in the controlled manner. It helps to minimize the drug degradation or presystemic metabolism of plant actives, also prevent the side effects arising due to the accumulation of drugs to the non-targeted areas. [3,4]

The effective distribution of phytoconstituents can be achieved with the aid of novel drug delivery technology. It is done by incorporating the drug (plant actives) in a suitable carrier system. This mechanism aids in increasing solubility, stability, protection from toxicity, pharmacological activity and sustained delivery. [5] Novel drug delivery system encompasses the use of different types of pharmaceutical carriers. They are particulate systems, nanospheres, polymeric micelles, and vesicular systems like liposomes, sphingosomes, niosomes, transfersomes, aquasomes, ufasomes, and so forth. The vesicular system consists of one or more concentric lipid bilayer, in which the amphiphillic blocks are confronted with water. [6]

## PHYTOSOME

Phytosome is a patented technology which was developed by an Italian pharmaceutical and neutraceutical company named Indena. They encapsulate the plant actives in phospholipid in order to enhance its bioavailability. [7] The term "phyto" means plant and "some" means cell like. [8] Phytosomes produces a little cell like structure and they protect the plant actives from the gut bacteria and digestive enzymes. Phytosome posses better pharmacokinetic and pharmacological parameter. It exhibits an enhanced bioavailability of phytoconstituents in comparison with the conventional herbal extracts. Normally, the active herbal constituents posses poor solubility and poor bioavailability which in turn hinders the proper delivery of the phytoconstituents. This can be overcome with the aid of phytosome technology.[9] Phytosomes, commonly known as herbosomes and it break through the barriers put forth by the conventional drug delivery systems in the terms of bioavailability and stability of plant actives. Phytosome technology helps to achieve the benefits like minimizing the toxic effects, dose reduction, increase in retention time and therapeutic index. [10]

## PHOSPHOLIPID

Phospholipid is the key component of the phytosomes. Phospholipids are the chief components of the cell membrane and it serves as the carrier of plant actives. Phosphatidylcholine is the prominent phospholipid used in the preparation of phytosome. [11] Phosphatidylcholine which posses dual function in which the phosphatidyl part is lipophilic in nature and choline part is hydrophillic in nature. The choline part holds the hydrophilic portion of chief active constituents, where as phosphatidyl part holds the lipophilic portion of the phytoconstituent and attached with choline bound complex. It results in the phytocomplex formation with better bioavailability and stability. [12]

## PROPERTIES OF PHYTOSOMES

### Physicochemical properties

a. Phytosomes are the complex that is obtained by reacting an appropriate amount of phospholipid and active constituent in particular solvent.
b. The complex formation observed in phytosome is due to the development of hydrogen bonds between the polar head of phospholipid and the polar functionalities of the chief constituents.
c. On contact with hydrophilic environment phytosome exhibits a micellar shaped cell like structure and tends to resemble the liposomes.[13]
d. The size range of phytosome which ranges from 50nm to a few hundred µm.[14]

### Biological properties

a. Phytosome increases the absorption of active ingredients and also increase the systemic bioavailability when administered orally.
b. They exhibits better efficacy and pharmacokinetic as per compare to conventional herbal extract. [15]

## ADVANTAGES

- Impressive enhancement in the bioavailability and the intestinal absorption of phytoconstituents.[16]
- Cost effective delivery of phytoconstituents.
- Entrapment efficiency is high.
- Offer better stability profile due to the presence of the chemical bonds found in between the phosphatidylcholine and phytoconstituents.

- Dose requirement can be minimized due to better absorption of phytoconstituents.[17]
- Enhanced permeation of drug in transdermal and dermal drug delivery.
- Phytosome vesicular system is passive and non-invasive.[18]
- Low risk profile: This technique has no large scale development risk since the toxicological effects of phytosome are well depicted in the systematic texts.[19]
- Comparatively easy to manufacture the phytosomal complexes and lack of complicated technical investments.

The herbosomes have gained importance in various fields which includes the pharmaceuticals, cosmaceuticals and nutraceuticals. The phytosomes can be given through oral as well as topical route. It can be formulated as soft and hard gelatin capsules, tablets, topical dosage solutions, emulsion, creams, lotions, gels, etc.

## DISADVANTAGE

- There occurs a rapid elimination of phytoconstituents from the phytosomes

## METHOD OF PREPARATION

**Antisolvent evaporation technique:** The specific amount of phytoconstituent and soya lecithin were taken into a 100 ml round bottom flask and subjected for the reflux process with 20 ml of dichloromethane at a temperature not exceeding 60ºC for 2 hours. Concentrate the mixture to 5-10 ml. Hexane (20 ml) was added carefully with continuous stirring to get the precipitate which was filtered and collected and stored in vacuum desiccators overnight. The dried precipitate is crushed in mortar and sieved through #100 meshes. Powdered complex was stored in amber colored glass bottle and stored at room temperature. [20]

**Rotary evaporation technique:** The specific amount of phytoconstituent and soya lecithin were dissolved in 30 ml of tetrahydrofuran in a rotary round bottom flask followed by stirring for 3 hours at a temperature not exceeding 40ºC. Thin film of the sample was obtained and the n-hexane was added into it and subjected for continuous stirring process by using a magnetic stirrer. The precipitate obtained was collected, placed in amber colored glass bottle and stored at room temperature [21]

**Solvent evaporation method:** The specific amount of phytoconstituent and soya lecithin were taken into a 100 ml round bottom flask and subjected for reflux process with 20 ml of acetone at a temperature 50 - 60ºC for 2 hours. The mixture is concentrated to 5-10 ml to obtain the precipitate which was filtered and collected. The dried precipitate of phytosome complex was placed in amber colored glass bottle and stored at room temperature.

## CHARACTERIZATION OF PHYTOSOMES:

The phytosomes can be characterized in both the physical and biological systems. It includes the factors such as physical size, membrane permeability, percentage of entrapped solutes and chemical composition of the preparing materials which in turn influences the performance of phytosomes.

**Visualization techniques:** Visualization of phytosome can be performed by using transmission electron microscopy and scanning electron microscopy. [22]

**Vesicle size and Zetapotential:** The particle size and zetapotential of the phytosome can be determined with the aid of dynamic light scattering and photon correlation spectroscopy. [23]

**Entrapment efficiency:** The entrapment efficiency of phytosomes can be found out with the aid of ultracentrifugation technique. [24]

**Drug content:** The amount of drug content in the prepared phytosome can be found out with the high performance liquid chromatography or with UV spectroscopic analysis. [25]

**Transition temperature:** The transition temperature of phyto-phospholipid complex can be determined with the differential scanning calorimetry. [26]

**Spectroscopic evaluations:** The purpose of spectroscopic analysis is to determine the complex formation of phytoconstituent with that of the phospholipid component. It is done by $^{1}$H-NMR, $^{13}$C-NMR and IR spectroscopy. [27]

**In vitro and in vivo evaluations**: The in-vitro and in-vivo assessments are designated on the basis of the predictable therapeutic action of phytoconstituents present in the phytosomes. [28] The in vitro antihepatotoxic activity can be found out by the antioxidant and free radical scavenging activity of the phytosomes. For calculating antihepatotoxic activity by in-vivo method, the result of synthesized phytosomes on animals in contrast to thioacetamide, paracetamol or alcohol-induced hepatoxicity can be evaluated. [29,30] Skin sensitization effects as well as tolerability studies of glycyrrhizic acid-Phytosome® ointment which is a commercial product, describes the in vivo safety evaluation methodology [31]

## THERAPEUTIC APPLICATIONS OF PHYTOSOME

**Targeted drug delivery:** Phytosomes can be used as an effective tool in the targeted drug delivery. The specificity towards targeted diseased cells can be increased as in the case of curcumin or grape seed phytosomes which exhibits the anticancer and

cardioprotectant activities respectively. Cell specificity could be targeted for better and faster healing and recovery of the patient. The phytosomes can be converted as a carrier for the targeted cell therapy incorporation with PEG (poly-ethylene glycol derived lipids) into the phytosome preparation. It is subjected for conjugation with the Fab' fragments of different desired monoclonal antibodies to the PEG molecules.[32] The selection of monocolonal antibodies were based on the type of disease and the type of cell targets.[33]

**Enhancer of bioavailability:** Evodiamine is a quinoline alkaloid, (Evodia rutaecarpa) which shows a number of pharmacological activities, such as anti-tumor, anti-inflammatory, antiobesity, thermoregulatory effects and wide range of anti-tumor activity. The phytosomes of Evodiamine proved to have higher rate of in vitro dissolution, better absorption and bioavailability. The prolonged action time and increased bioavailability was observed due to extended release of the drug from the phytosome and moreover, they reduce the first-pass metabolism of Evodiamine. The bioavailability and T1/2 of Evodiamine was 1772.35 µg h-1 L-1 and 1.33 hours respectively. The bioavailability andT1/2 of its phytosomal form was 3787.24 µg h-1 L-1 and 2.07 hours respectively. [34] The Oleaselect phytosomes were synthesized from the olive fruit extract. It possesses anti-hypertensive, diuretic, antiatherosclerotic, anti-oxidant and hypoglycemic activities. The group subjected for the treatment with Oleaselect phytosomes showed a higher percentage of HT (hydroxytyrosol) and HVAlc (homovanillyl alcohol) level which indicates the rate of increase in oral bioavaiability with that of the group which consumes the uncomplexed extract. [35]

**Hepatoprotective activity:** Phytosome can be used as an effective measure in the delivery of liver protecting flavanoids. The main component phosphatidylcholine itself exhibits the hepatoprotective action, by increasing the solubility of bile to the plant actives. Thus the phytosomes enhances the liver targeted drug delivery.[36]Silymarin (milk thistle) conjugated phytosomes exhibit hepatoprotective activity.[37] It was stated with the study that is carried out against the highly potent aflatoxin B1 on the broiler chicks performance. The activity of silybin phytosome was studied in a group of 232 patients with chronic hepatitis (alcohol, drug, viral induced). A fixed dose of 120mg was given for about 2-3 times a day, for 120 days. The result of this treatment shows that the liver functions were changed into normal condition in a faster manner with that of the control group containing 117 patients which were subjected for the intake of placebo and some were remain untreated. And about 49 patients were administered with the commercially available silybin. [38] The effect of Ginkgo select phytosome on Rifampicin induced hepatotoxicity was studied. This phytosome exhibits hepatoprotective action which is due to its antioxidant and free radical scavenging activity. [39] The quercetin-phospholipid complex exhibits a hepatoprotective action in case of carbon tetra chloride induced liver injury in rats.[40]

**Antioxidant activity:** The Silybum marianum plant possesses an antioxidant and free radical scavenging activity against carbon tetrachloride and paracetamol induced oxidative damage in liver. The Silipide plant active present in the silibin-phosphatidylcholine complex protects the liver cells by inhibiting the lipid peroxidation through the scavenging of reactive $O_2$ species. The continuation of this study in patients with hepatitis B and C viruses with the silpide for 2 months shows the appreciable reduction of serum malondialdehyde level of patients. It indicates the anti-lipoperoxidant activity of silipide against the free radical attack in humans [41]. The metal phytosome prepared with the extract of Calendula officinalis exhibit antioxidant activity. They carried out the in vitro cell based anti oxidant assay on Vero cell line. The results depicts that the cell viability is about 81% for the complex of metal phytosome loaded with plant extract and about 35% for the uncomplexed plant extract[42]. Grape seed phytosome were given to the healthy human volunteers as a part of human trial which is carried out on a randomized manner in which one is given per day for 5 days. TRAP(Total radical trapping antioxidant parameter) level in the blood was recorded for 30 mins after administration and it is found to be elevated in comparison with that of control group and conventional standardized grape seed[43]

**Anticancer therapy:** The plant actives like flavonoids, anthocyanins, coumarins, lignans, catechins of herbal plants mainly exhibits the antioxidant properties which in turn responsible for the anticancer potential. The plant active compounds shows toxicity at higher concentrations and causes certain side effects. The conventional therapies for cancer like chemotherapy and radiotherapy possess a number of side effects which include myelosuppression and neurological, cardiac, pulmonary, and renal toxicities. [44] The entrapment of these plant derived drugs within a suitable carrier enhances its solubility and permeability and it will improve the potent anticancer activity. The research work carried out with the methanolic extract of *Terminalia arjuna* bark and its phytosome in the antiproliferative activity on human breast cancer cell line MCF-7 by MTT assay. The IC50 values obtained with the

extract and its phytosome were 25µg/ml and 15µg/ml respectively and it shows that they exhibit more antiproliferative activity in comparison with uncomplexed drug. [45] Silybin (silibinin) - (Silybum marianum) is a natural polyphenol which shows high antioxidant and anti-cancer activities and they blocks VEGF, EGFR, COX-2 and TNF. The comparative study of silybin and silybin-phosphatidylcholine complex by MTT assay method, which indicates silybin-phytosomal copmplex shows 2.5-3 times more inhibitory activity on cell growth than that of silybin in the T47D cell line. [46]

**Antidiabetic activity:** The rutin –phospholipid complex, phyto formulation were evaluated for its antidiabetic activity in a streptozotocin induced diabetic model. The normoglycemic rats were subjected to the administration of higher and lower doses of rutin and rutin phosphated complex. The result shows that there is significant reduction in AUC glucose level that is achieved with the rutin-phospholipid complex form. The effect of rutin and rutin phosphate complex (50 and 100 mg/ kg) in streptozotocin induced diabetic rats for 1 day and 15 days was studied in both studies, the phytosomal complex of rutin exhibits the dose dependent percentage reduction of serum glucose level in comparison with the diabetic control group.[47]

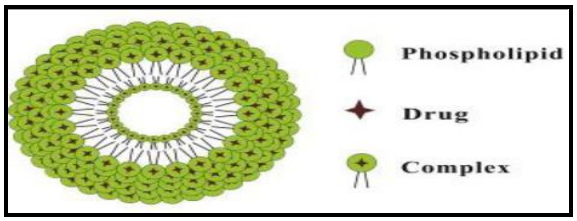
**Fetoprotectant activity:** The studies reported on the usage of phytosomal technology in case of fetoprotectant activity is made with the silimarin phytosomes through the oral administration. It is implemented against the behavioural deficits induced by the ingestion of ethanol in the maternal period. [48]

**Transdermal activity:** Rutin is the one of the most common flavonoid (Ruta graveolens) used to treat capillary fragility, hypertension, hepatic and blood cholesterol, cataract, cardiovascular activity, antioxidant, anti-inflammatory, antithrombotic, antineoplastic, and antiplatelet activity. The rutin phytosomes exhibits better penetrability through the impermeable stratum corneum with that of its free form. The skin uptake of Rutin phytosomes was observed to be 33 ± 1.33 % whereas that of Rutin was 13 ± 0.87 %. 27. [49] The phytosomes which is prepared with the saponins and plant extracts exhibits the capillary permeability, vasal protection and as an uv-protectant. They were used in the development of cosmetic pharmaceutical formulations and they exhibit the moisturizing effect on the cutis. These compositions can be used for oral administration in the form of tablets, capsules, syrups, granules, solutions (containing 1-500 mg dose of the complex) for the treatment of inflammatory conditions and permeability. [50]

**Wound healing Activity:** The wound healing activity of Sinigrin, which is present in the plant of Brassicaceae family and it is subjected for the evaluation as alone and as a phytosome complex on HaCaT cells. The sinigrin–phytosome complex exhibits a complete recovery of wound (100%) whereas the uncomplexed plant active displayed only 71% healing. [51]The efficacy of ethanolic extracts of Wrightia arborea leaves and its phytosomes were evaluated for the wound healing property. The phytosomes shows about 90.40% healing with that of the ethanolic extract alone which healed only 65.63% of the wound. [52] The better lipid penetrability of the lipid coating of phytosome complex enhances the permeation through the skin which in turn helps in the wound healing activity.

## CONCLUSION

The ongoing research works of phytosomes and its applications in various activities such as anti-cancer, hepatoprotectivity, anti-diabetic, wound healing, anti-oxidant, etc. proves that it is an efficient drug delivery system to deliver the plant actives. It can be presumed that this technology can assist in improving bioavailability by enhancing solubility, permeability, and by improving metabolic stability in GIT and can be used as an effective tool for the delivery of the chief constituents of herbal origin. It increases the significance of phytosome technology. This delivery system improves the pharmacotherapeutics and pharmacokinetics of herbal drugs. It is also utilized in preparation of nutraceuticals and cosmaceuticals for improving therapeutic effect and permeability in the skin.




**PHOSPHOLIPID: DRUG (1:1 or 2:1)**

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