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Phytosomes: Enhancing Bioavailability of Phytomedicine

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Abstract: Several plant extracts and phytoconstituents, despite having excellent bio-activity in vitro but provide less or no in vivo actions as they poorly dissolve in lipid and have large molecular size, which results in poor absorption and low bioavailability. Such plant extracts when complexed with phospholipids like phosphatidylcholine forms a new drug delivery system called Phytosome (or Herbosome). Compared to conventional herbal extracts Phytosome exhibit better pharmacokinetic and pharmacodynamic profile. The Phytosome vesicles have ability to effectively deliver the drug by topical and oral route. This technique have enhanced the bioavailability of various phytomedicine present in milk thristle, ngrape seed, green tea, olive oil, turmeric, etc. The objective of this review is to describe the advancement in phytosome technology and its application.

Keywords: Phytosomes, phospholipid, phosphatidylcholine, phytoconstituent, bioavailability, drug, therapeutic application.

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I. INTRODUCTION

For a drug to be bioavailable, it should have proper hydrophillicity as well as lipophillicity. Bioavailablity is the extent and rate at which the active constituent i.e. drug or metabolite reaches in the blood and proves clinical efficacy and also minimises the dose **(Anjana, R., *et al.*, 2017).** Most bioactive plant constituents such as flavonoids, phenolic glycosides and anthocyanins are of highly polar nature (water soluble) i.e. hydrophilic in nature. This nature poses great hinderence in absorption of drug as gastrointestine membrane (lipophilic) does not permit the passage of highly water soluble substance across it and finnaly results in poor bioavailability **(Anjana, R., *et al.*, 2017).** The phytosome is patented technology, developed by Indena S.p.A. of Italy **(Pandey, S., *et al.*, 2010)**. Phytosome is a technique where standardized plant extract or water soluble phytoconstituents (mainly polyphenolics) are complexed with phospholipids in an aprotic solvent to produce lipid compatible molecular complexes **(Tripathy, S., *et al.*, 2013).** Phytosome are better able to transition from hydrophilic environment into lipophillic environment of enterocyte cell membrane and from there to blood circulation. Phytomedicine have limited effect when taken orally. When plant extracts are administered as phytomedicine through oral routes, some of their integral components or ingredient are destroyed by gastric environment and bacteria present in gut. Polyphenolics have poor absorption due to two reasons; First, phytomolecules have multiple ring molecules that are large enough to be absorbed from intestine into blood through simple diffusion, and second, molecules have poor miscibility with oils, and lipids **(Pandey, S., *et al.*, 2010)**. Thus phytoconstituents when interacted with phospholipids improves its absorption and thus improves its bioavailability. Phospholipids are building blocks of cell membrane, making up matrix into which fits large variety of proteins, enzyme, transport protein etc. Phospholipid are miscible in both water as well as lipid environment. Thus they act as carrier for both fat soluble and water soluble nutrients, therefore employed as natural digestive aid. Phospholipids used in phytosome preparation, are Phosphatidylcholine, phosphatidylserine, phosphatidylethanolamine, and phosphatidylcholine **(Tripathy, S., *et al.*, 2013).** Phospholipid mainly employed to make phytosome is Phosphatidylcholine, derived from soybean (*Glycin max*) **(Bhattacharya, S., *et al.*, 2008)**. In Phosphatidylcholine, phosphatidyl portion is lipophillic and choline portion is hydrophilic in nature, thus phosphatidylcholine act as bifunctional compound. Phytosome results from reaction of stoichometric amount of phospholipid (mainly Phosphatidylcholine) with standardized extract or polyphenolic constituents like simple flavonoid in an aprotic solvent **(Bhattacharya, S., *et al.*, 2008)**. The hypothesis of an interaction of flavanoids with phospholipids which are ubiquitous in plants and animal, originated from the histochemical finding indicating that anthocyanosides from *vaccinium myrtillus* L. show strong affinity for specific cellular structure rich in phospholipids **(Bhattacharya, S., *et al.*, 2008)**.

PROPERTIES OF PHYTOSOME

- Phytosome is generally a polyphenolic molecule linked with at least one phospholipid molecule.
- The size of phytosome varies from 50nm to a few hundred µm.
- Phytosoms assume a micellar shape resembling a liposome when treated with water. Photon Correlation Spectroscopy (PCS) reveals these liposomal structures acquired by phytosomes **(Tripathy, S., *et al.*, 2013).**
- Phytosome complex are often freely soluble in aprotic solvents, moderately soluble in fats, insoluble in water and relatively unstable in alcohol **(Tripathy, S., *et al.*, 2013).**
- Phytosomes express their behaviour in physical or biological system because of their physical size, membrane permeability, percentage entrapment, chemical composition, quantity and quality of the materials used.
- The phytoconstituent in phytosome is tied up to polar head of phospholipid, with the help of Hydrogen-Bond between phenolic hydroxyl end of polyphenols and phosphate ion on phosphatidylcholine (phospholipid) moiety. Thus phytoconstituents becomes an integral part of the phytosome membrane.
- In phytosome the lipophilic envelop shields the polar head of polyphenolic molecule and phospholipid molecule and allows the complex to dissolve in low polarity solvents resulting in increased absorption and better bioavailability of the phytoconstituent.

DIFFERENCE BETWEEN PHYTOSOMES AND LIPOSOMES

- In liposome, hydrophillic drug molecule is entrapped within cavity or spaces between membrane, whereas, in phytosome, the hydrophillic herbal drug molecule is linked with polar head of phospholipid. Fig.1 illustrates a comparative study of phytosome with liposome.
- Chemical bond is absent in conventional liposomes, while in phytosomes phenolic hydroxyl end of phytoconstituent molecule is tied up to polar head of phospholipid by Hydrogen- Bond.
- There may be hundreds and thousands of phosphatidylcholine molecule surrounding the water soluble compound in liposome. In contrast, phosphatidylcholine and plant constituent actually form 1:1 or 2:1 molecular complex depending on the substances complexed. This results in better absorption of phytosome and better bioavailability.

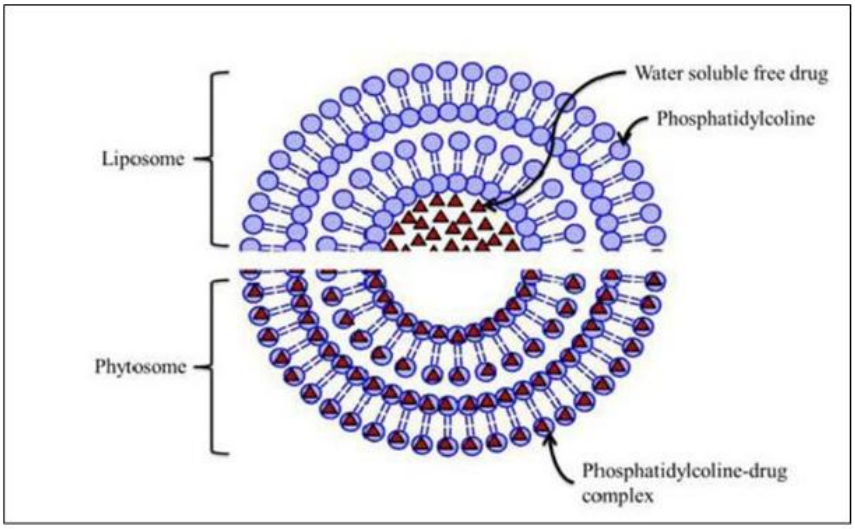

Figure 1: Comparision of liposome with phytosome, **(Tripathy, S., *et al*, 2013).**

PREPARATION METHOD OF PHYTOSOMES

Phytosomes are prepared by reacting a synthetic or natural phospholipid with a standardized plant extract in a ratio ranging from 0.5-2.0 (1:1 ratio is preferable) in aprotic solvent, such as dioxane, methylene chloride, acetone; from which novel complex can be isolated by precipitation with non solvent, usually an aliphatic hydrocarbon or by lyophilisation or by spray drying **(Tripathy, S., *et al.*, 2013).**

Phospholipids such as, Soya phosphatidyl choline, Egg phosphatidylcholine, Dipalmityl phosphatidylcholine, and Distearyl phosphatidylcholin are used. While aprotic solvent such as, Dioxane, acetone, mrthylene chloride are used for the preparation of phytosome **(Sharma, D., *et al.*, 2018).**

Different techniques are used in the preparation of phytosomes: **(Bhattacharya, S., *et al.*, 2008)**

Antisolvent Precipitation Technique Co-Solvent Lyophilisation Method Thin Layer Hydration Technique Solvent Evaporation Technique

In Antisolvent precipitation technique, specific amount of drug and phospholipid are refluxed with suitable solvent. The mixture formed is concentrated and another solvent is then added for precipitation with continuous stirring. Precipitates thus formed are then filtered and collected and stored in vacuum desiccators overnight.

In Co-solvent lyophilisation method, drug and the phospholipid are dissolved in suitable solvent separately. Both are then mixed by gentle agitation until formation of a clear mixture. The resultant homogeneous solution is then freeze-dried under vacuum and stored in air tight container.

In Thin layer hydration technique, phytoconstituents and phosphatidylcholine are dissolved in methanol, while cholesterol is dissolved in dichloromethane. The mixture is evaporated in a rotary evaporator until thin dry film is produced. Nitrogen gas is blown over thin film for complete removal of organic solvents. Film is then hydrated with distilled water.

In Solvent evaporation technique, generally both the drug and the phospholipids are placed in the same flask and refluxed with suitable solvent at fixed temperature for fixed time. The specific amount of phytoconstituent and soya lecithin are taken into a round bottom flask and refluxed with acetone at a temperature 50-60°C for 2 hrs.

CHARACTERIZATION AND EVALUATION OF PHYTOSOMES

Various in-vitro and in-vivo evalutions are applied on phytosomes. Models of in-vitro and in-vivo evaluations are selected on the basis of expected therapeutic activity of biologically active phytoconstituents present in the phytosomes **(Sharma, S., *et al.*, 2014).**

Phytosome characterization is done by physical attributes such as shape, size, distribution, drug entrapment capacity, drug release, membrane permeability; and chemical composition which govern the action of phytosome in both physical and biological system.

High Performance Liquid Chromatography (HPLC) or UV-Visible Spectroscopy method is used to determine the percentage drug entrapment by extracting the phytosomes with suitable solvent system by centrifugation and estimating its supernatant.

Photon Correlation Spectroscopy (PCS) technique is used for investigating the size of phytosome, confirmation of vesicular structure after hydration and to study surface morphology.

The Scanning Electron Microscopy (SEM) provides photomicrograph of the phytosome at suitable magnification after coating it with gold. The photomicrograph is used to study surface morphology which is important in entrapment behaviour. Transmission Electron Microscopy (TEM) is used to study internal environment of phytosome where drug is entrapped and distributed within the phospholipid mesh.

The crystallinity of the phytoconstituents is lost upon complexation. The crystallinity along with the interaction of phospholipid with phytoconstituent can be confirmed by the Differential Scanning Calorimetry (DSC) and X-Ray Diffraction (X-RD) Analysis. The crystalline drug moiety shows a sharp peak at high melting point in DSC thermogram. The phytosome show a broad peak and a melting point significantly less than that of pure drug **(Tripathy, S., *et al.*, 2013).**

The H-NMR Spectra of phytosome of various phytoconstituents show the peak of long tail part of phospholipid molecule intact, which reveals that the tail part does not take part in any chemical interactions and behave as a sheath to the central choline part attached to phytoconstituent. The C-NMR is often performed for confirmation of the type of interaction involved for the complexation **(Tripathy, S., *et al.*, 2013).**

ADVANTAGES OF PHYTOSOME

- Phytosome upgrade absorption of lipophobic polar herbal extract through oral as well as topical route showing better bioavailability.
- As absorption and bioavailability of the phytoconstituent increases the dosage requirement is reduced.
- Phytosomes have better stability profile due to presence of chemical bonds between phospholipid and phytoconstituent.
- By increasing the solubility of bile to herbal origin phytoconstituents, phytosomes enhance the liver targeting **(Kumar, A., *et al.*, 2017).**
- Phytosome possess better drug entrapment efficiency.
- Phosphatidylcholine used in preparation of phytosomes, is not merely a carrier; it also act as hepatoprotective, hence giving the synergistic effect when hepatoprotective substance are employed **(Sharma, D., *et al.*, 2018).**
- Phytosomes can be used for systemic targeting because of its ability of better transition from hydrophilic environment to fat soluble environment of enterocyte cell membrane.

- Phytosomes have great application in cosmetics because of their improved ability to penetrate skin.
- Precious phytomedicines are defended from the destruction by gastrointestinal secretions and gut bacteria.

PHYTOSOMAL PRODUCTS

PRODUCT	**PLANT SOURCE (chief constituent)**	**USE/ INDICATION**
Green Tea Phytosome Greenselect Phytosomes	*Camellia sinensis* (epigallocatechin 3-o-gallate)	Antioxidant, cardioprotective, and Protection against cancer
Ginkgo Biloba Phytosome Ginselect Phytosome	*Gingko biloba* (Ginsenosides)	Protects brain and vascular lining, Adaptogenic
Milk Thristle Phytosome Siliphos Silybin Phytosome	*Silybum marianum* (Silybin)	Antioxidant protection to liver or skin
Centella Phytosome	*Centella asiatica* (Triterpine)	Cicatrizing, trophodermic
Leucoselect Phytosome Grape Seed Pytosome	*Vitis vinifera* (Grape procyanidin)	Antioxidant
Meriva	*Curcuma longa* (Curcuminoids)	Anti-inflammatroy
Silymarin Phytosome	*Silybum marianum* (Silymarin)	antihepatotoxic
Oleaselect™ Phytosome	*Olea europaea* (Polyphenols)	Anti-inflammatory, antioxidant
Crataegus Phytosomes	*Crataegus Mexicana* (Vitexin-2'-O-rhamonoside)	Antioxidant
Visnadine	*Ammi visnaga* (Visnadine)	Circulation improver
Bilberry Mirtoselect Phytosome	*Vaccinium myritillus* (triterpine) (Anticinocide)	Potent antioxidant
Ruscogenin Phytosomes	*Ruscus aculeatus* (Steroid saponin)	Anti-inflammatory
PA2 Phytosomes	*Horse chestnut bark* (Proanthocynidin)	Antiwrinkles, UV protectant
Zanthalene Phytosomes	*Zanthoxylum bungeanum* (Zanthalene)	Soothing and anti-itching
Lymphaselect Phytosome	*Melilotus officinalis* (Triterpenes)	Indicated in insomnia
Sabalselect Phytosomes	*Serenoa repens* (Fatty acids, sterols)	Beningn prostate hyperplasia
Sericoside Phytosome	*Terminalia sericea* (Sericosides)	Skin improver and anti-inflammatory
Echinacea Phytosome	*Echinacea angustifolia* (Echinacosides)	Immunomodulators and nutraceuticals
Rexatrol	*Polygonum cupsidatum* (Resveratrol)	Antioxidant and anti-aging

ENHANCED BIOAVAILABILITY OF HERBAL EXTRACTS

Phytosomes have proved to elevate the bioavailability of various herbal extracts like milk thristle, ginkgo biloba, grape seed, green tea, etc.

A standardized extract from *Silybum marianum* (milk thristle) is excellent liver protectant but has poor bioavalability when taken orally. **SILIPHOS**, the phytosome complex of milk thristle has better absoption and improved bioavailability.

Ginkgoselect phytosome is another phytosome complex prepared from extract of *ginkgo biloba* leaves. In bioavailability study conducted with healthy human volunteers the levels of GBE constituents (flavonoids and terpenes) from the phytosomal form peaked after hours and persisted longer for at least 5 hours after oral administration. It was found that phytosomal GBE produced 2-4 times greater plasma concentration of terpenes than the non-phytosomal GBE **(Bhattacharya, S., *et al.*, 2008)**.

Grape seed phytosome called, **Leucoselect** phytosome is composed of oligomeric polyphenols (proanthocyanidins or procyanidins from grape) procyanidin flavonoid of grape have antioxidant properties and provides protection to cardiovascular system.

Greenselect phytosome contains a totally standardized polyphenolic fraction (not less than 66.5%) obtained from green tea leaves and mainly characterized by the presence of epigallocatechin and its derivatives. These compounds are potent modulators of several biochemical processes linked to the breakdown of homeostasis in major chronic-degenerative disease such as cancer and atherosclerosis **(Pandey, S., *et al.*, 2010)**.

Anthocyanosides obtained from the extracts of bilberry *(Vaccinium myritillus),* were complexed to make **Mirtoselect** phytosome. It improves capillary tone, reduces abnormal blood vessel permeability, and is potent antioxidants.

Standardized extract from *Melilotus officinalis,* used for preparation of **Lymphaselect** phytosome is particularly indicated for venous disorders, including chronic venous insufficiency of the lower limbs, and treat insomnia.

Oleaselect phytosome is prepared form the polyphenols of olive oil. They are potent antioxidants, inhibit harmful oxidation of LDL cholesterol, and have anti- inflammatory activity.

ADVANCEMENT IN PHYTOSOMES

Gold nanoparticles exhibit biological activity such as wound healing and anticancer upon living cells. *Calendula officinali*s L. has pharmacological activity, and has been utilized as anti-tumoral, anti-inflammatory, wound healing and antioxidant activities and in 200 cosmetic products in extracted form **(Demir, B., *et al.*, 2012).** A novel drug formulation encapsulating the extracts of *C. officinalis* and gold nano particles were constructed, using traditional film hydration method. The resulting phytosomes were characterized by dynamic light scattering size measurements, zeta potential and atomic force microscopy respectively. The phytosome had high encapsulation efficiency and major constituent of *C. officinalis* extract.

The AuNP-Phytosome complex exhibited more antioxidant and wound healing activity as compared to free forms of encapsulated materials **(Demir, B., *et al.*, 2012).**

Arvind Sharma and Parneet Kaur, 2013, prepared the phytosome complex of *Phyllanthus amarus* and phospholipid, and formulatd its tablet. *P. amarus* has been shown to work as antifungal, antibacterial and antiviral agent and used to treat cardiovascular problems. The tablets of *P. amarus* were prepared by dry granulation technique using different polymers. The evaluation of tablet was carried out to study the thickness, hardness, tensile strenghth, friability etc. The study indicated that all the formulations showed more than 90% of drug content during both accelerated and room temperature storage conditions.

(Dhase *et al.*, 2015), prepard the phytosome from the root extract of *Clerodendron paniculatum* L. Phytochemical studies of the extract were carried out to examine the phytoconstituents. These phytosome exhibited potent activity againt cancer cells such as MCF-7.

Luteolin-loaded phytosomes were prepared by using the solvent evaporation method. Luteolin as flavonoids compound can inhibit Nrf2 and sensitize cancer cells to chemotherapeutic agents **(Dhase *et al.*, 2015).**

The flower of *Butea monosperma* have hepatoprotective activity and used in treatment of diabetes. *B. monosperma* has low bioavailability because of its limited gastrointestinal absorption. Hepatoprotection is the ability to prevent the damage to liver. **Gahandule MB., *et al.*, 2016,** prepared the phytosomes from the extract of *B. monosperma* flower and soya lecithin. The resultant *B. monosperma* – phospholipid complex, so called phytosome showed improved absorption and better bioavailability **(Gahandule, M.B., *et al.*, 2016).**

Celastrol (CST) is the chemical compound isolated from the root extract of *Celastrus reglii.* CST is extensively studied as natural anticancer surrogate with potential activity against various types of cancer cell lines including, melanoma, human prostate cancer, pancreatic cancer cells, lung cancer, and breast MCF-7 cells. CST has limited applications due to low aqueous solubility and poor gastrointestinal absorption which results into low bioavailability. Development of self-assembled phytosomal nano-carriers (CST-PHY) for improving

CST solubility and oral bioavailability was done by, **Freag, M.S., *et al.*, 2017.** Phytosomes were prepared by interacting CST (purity 98%) and Soy Phosphatidycholine (SPC) phospholipid, at different molar ratios CST: SPC (1:1,1:2, and 1:3), by Solvent Evaporation Technique. In-vitro, in- vivo, studies and characterization of phytosomal complex were carried out and it was confirmed that CST-PHY complex enhanced the herbal drug absorption.

Antitumor activity of noval formulated form of Curcumin along with 5- fluorouracil in breast cancer was studied by **Hashemzehi, M. *et al.*, 2018.** Curcumin derived from plant Curcuma longa has proved to be potential antioxidant and anti-cancer agent in clinical trials based on its radical scavenging properties, as well as antitumorigenic activities towards some aggressive and recurrent cancers. But has poor bioavailability due to its rapid systemic elimination. It is illustrated that curcumin considerably elevates the effect of 5-fluorouracil (5FU) on HCT116R AND HCR116+ch3R cells. Curcumin combined treatment with 5-FU in breast cancer cell line (MDA-MB-231) provides protection against 5-FU induced toxicity.

The studies have confirmed that phytosomal curcumin improves its absorption 29-fold higher than traditional curcumin products **(Hashemzehi, M., *et al.*, 2018).**

Therapeutic potential of novel phytosomal curcumin and its application in combination with 5-Fluorouracil (5-FU) in mouse model of Colitis- associated colon cancer was studied**.** It was showed that phytosomal crucumin enhanced the antiproliferative activity of 5-FU in both in-vitro and in-vivo systems. Moreover, curcumin had an antioxidant activity and combination therapy with 5-FU dramatically decreased the tumor number and tumor size **(Marjaneh, R.M., *et al*., 2018).** The anti- proliferative activity of phytosomal curcumin was assessed in 2-dimensional and 3-dimensional cell culture models as well as in mouse model of colitis associated colon cancer. It was showed that phytosomal curcumin and its combination with 5-FU inhibited cell growth and invasive behaviour of Colorectal Cancer cells.

II. CONCLUSION

For any drug to be bioavailable it should be hydrophilic as well as lipophillic. Many herbal drugs possess great bioavailability in vitro but but has low or no effect in vivo due to low absorption or abnormal molecular size. Phytosomes are the complex made by interacting the bioactive compound or phytoconstituent of the herbal extract with the phospholipid (mainly phosphatidylcholine) in aprotic solvent. Phytosome is easily absorbed in lipophilic environment of gastrointestinal secretions as each phytoconstituent of herbal extract is linked to phospholipid with hydrogen bond forming the lipophilic envelop that covers the polyphenolic molecule(hydrophilic) and thereby protecting the herbal drug from gut bacteria. Extracts from many medicinal plants are complexed with phospholipid to make phytosomes with better pharmacokinetic and pharmacodynamic profile. Herbal extract and the phospholipid can be complexed in different ratio as per requirement (generally 1:1 is preffered) as the incorporation of phytoconstituent can be controlled. Apart from any phytoconstituent of herbal extract, any nanoparticle (for example gold nanoparticle) having the therapeutic value can also be incorporated into phospholipid, to enhance the therapeutic value of the phytosome. Many novel formulations of phytosomes are used effectively to treat cancer, diabetis, etc.

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