

**A CONCISE REVIEW ON PHYTOSOMES: A NOVEL APPROACH FOR
PHYTOCHEMICALS**

P. Udaya Chandrika*, Dr. B. Prem Kumar, Dr. A. Srinivas Rao and M. Sri Rama Chandra

*Assistant Professor, Department of Pharmacognosy, Bhaskar Pharmacy College, Moinabad, R.R Dist.

Associate Professor, Department of Pharmacognosy, Bhaskar Pharmacy College, Moinabad, R.R Dist.

Professor, Department of Pharmacology, Bhaskar pharmacy College, Moinabad, R.R Dist.

Associate Professor, Department of Pharmacology, Bhaskar Pharmacy College, Moinabad, R.R Dist.

***Corresponding Author: P. Udaya Chandrika**

Assistant Professor, Department of Pharmacognosy, Bhaskar Pharmacy College, Moinabad, R.R Dist.

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ABSTRACT

The poor oral bioavailability of polyphenolic compound can be enhanced through the incorporation of them into phospholipid based self-assembled delivery system, i.e. popularly known as phytosome. "Phyto" means plants and "some" resembles a covering around/or a structure. Phytosome is generally prepared by reacting one or two moles of polyphenolic phytoconstituents and phospholipid. It may be either in the ratio of 1:1 and 1:2. By using phytosomes, one can also achieve enhanced rate and extent of the passage of lipophilic herbal constituents across lipid membrane that explains its character as a carrier as well as acid labile herbal drugs could also be protected in gastrointestinal tract. There are number of products available in the market that contains phytosomal drug delivery system such as Ginkgo biloba, Silybum marianum, and Camellia sinensis. The present review describes an updated overview of preparation of phytosomes, advancement in phytosomes technology, various herbal drugs for which phytosomes have been used as a carrier, its commercial availability and applications.

KEYWORDS: Phytosomes, Novel drug delivery system, Phospholipid.

INTRODUCTION

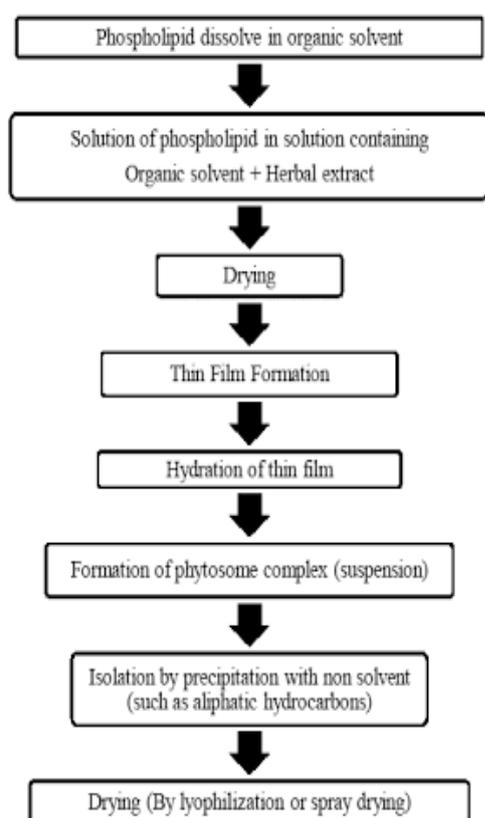
Most of the biologically active constituents of plants are polar or water soluble but due to the problem in absorption, restricts the utilization of these type of compounds which ultimately decreases the bioavailability. For improvement of bioavailability, herbal products must have proper homeostasis between hydrophilic (for absorption into gastrointestinal tract fluid) and lipophilic (to cross lipid bio membrane balance).^[1] Plant preparations are widely used in traditional as well as modern medicine system. During the traditional time, various pharmacological studies have been carried out with many plants extracts and their constituents to check their therapeutic application. Over the past year, great advancement has been made for the development of novel drug delivery system (NDDS) for various plant extracts and their active constituents. Novel drug delivery such as targeted drug delivery which directly channels the active entity on the site of action and such delivery system could offer targeted and sustained release of drug so that pharmacological effect could be achieved at lower dose. The development in the area of herbal medicine started earlier to cure human diseases with lesser side effects.^[2] A number of chief constituents of herbal medicine are easily soluble in water (glycoside, flavonoid); however, these constituents

are bounded in their potency because they may be partially soluble or hydrophobic in nature, so when applied topically shows less therapeutic efficacy.^[3] Numerous efforts have been put forward to enhance the bioavailability of such drug by formulating them to target drug delivery system such as phytosomes and liposome's are good options. The use of these techniques in formulation development process may lead to good bioavailability of herbal drugs as compare to conventional herbal extracts. Phytosomes means herbal drug loaded in vesicles, which is available in the nano form. The phytosome provide an envelope, like coating around the active constituent of drug and due to this the chief constituent of herbal extract remains safe from degradation by digestive secretion and bacteria. Phytosome is effectively able to absorb from a water loving environment into lipid loving environment of the cell membrane and finally reaching to blood circulation.^[4] It can be used in the treatment of various fatal diseases without denaturing the active phytochemicals and enhanced bioavailability. Phytosomes are obtained by reacting phospholipid (either of natural or synthetic origin) with selected botanical constituents with an appropriate solvent, and due to their physical and chemical efficiency, these phyto-complex can be considered as a novel entity.^[5]

The current review highlights the future scope and emerging technologies in the field of NDDS for the benefit of herbal and traditional medicines prepared from plant origins.

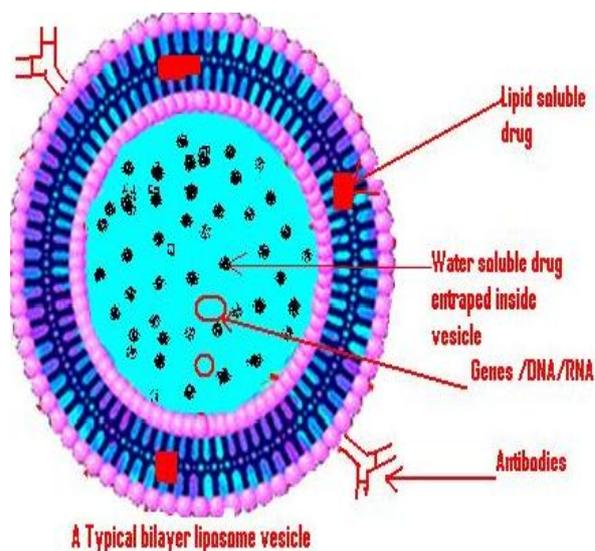
Preparation of Phytosome

Phytosomes are generally prepared by adding accurate amount of phospholipid, i.e., Soya lecithin with herbal extracts in an aprotic solvent. Soya lecithin contains main constituent, i.e., Phosphatidylcholine which is having a dual function. Phosphatidyl part is lipophilic in nature and choline part is hydrophilic in nature. The choline part attached with hydrophilic chief active constituents, where as phosphatidyl part lipid soluble compound attached with choline bound complex. It results in the formation of lipid complex with better stability and bioavailability.^[6] Fig.1.



Phospholipids^[7]

Nowadays industrially produced phospholipid delivery system has a great role and becomes more popular. The main ingredients to achieve this goal is soya, chicken egg, etc. The main key ingredients in all this are phospholipid which comprises a glycerol unit joined with two fatty acids, and the remaining linkage is joined by a phosphate group. In phytosome preparation, the main phospholipid used as phosphatidylcholine having a great role in biological membrane and also act as hepatoprotective. The molecular structure of Phosphatidylcholine is represented in Fig. 2.



Properties of Phytosomes^[8,9]

Physicochemical properties

- Phytosomes are the complex between phytoconstituents and natural phospholipid, and the complex is obtained by reacting an appropriate amount of phospholipid and chief constituents in particular solvent.
- The interaction between phospholipid and substrate is due to the development of hydrogen bonds between the polar head of phospholipid and the polar functionalities of the chief constituents.
- On treatment with hydrophilic environment phytosome shows a cell-like structure like liposomes, but in a liposome, the chief constituent interacts within the internal pocket while in phytosome the chief active constituents are enveloped the polar head of phospholipid and becoming an integral part of the membrane

Mechanism of Phytosome Technology^[10]

The lower absorption and bioavailability of polyphenolic constituents mainly due to two factors. These chief constituents are number of ringed molecule and are not too much small that it will be absorbed by diffusion process. Second factor is that flavonoid molecule or chief constituents of polyphenols have poor solubility with lipids. These are the limitations that inhibit their absorption through biological membrane. Phytosome technology is mainly result with complexation of polyphenols with phospholipid in 1:1 ratio or 1:2 results in the formation of phytosomal complex with lipid covering around the constituents.

Evaluation of phytosomes

- Visualisation: The morphology of phytosomes was observed by digital microscopy, transmission electron microscope and scanning electron microscope.

- b. i. Digital microscopy Phytosome formulation shaken in distilled water and viewed under digital microscope at 400X objective lens.
- ii. TEM analysis: The complex was shaken in distilled water and viewed using Transmission Electron Microscope (Hitachi, Japan).
- iii. SEM analysis: Approximately 5 μL of the phytosomal suspension was transformed to a cover slip, which in turn was mounted on a specimen tab. The samples were allowed to dry at room temperature. Then the particle size of the formulation was viewed and photographed using Scanning Electron Microscope (Sigma, Carl Zeiss). The particles were coated with platinum by using vacuum evaporator and thus, the coated samples were viewed and photographed in JEOL JSM-6701F Field 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. c. FTIR/FTIR (SHIMADZU, Japan) spectral data were taken to ascertain the structure and chemical stability of extract, PC and phytosome. Spectral scanning was done in the range between 4000 and 500 cm^{-1} . d. DSC Bael leaves extract, phospholipon and phytosome were placed in the aluminum crimp cell and heated at 100C/min from 0 to 400 0C in the atmosphere of nitrogen (TA Instruments, USA, Model DSC Q10 V24.4 Build 116). Peak transition onset temperatures were recorded by means of an analyzer. e. XRD analysis XRD was done on pure extract, PC and phytosome to see the crystallinity in the substance. Sample was scanned in the angular range of 50 - 800 in a PHILIPS XPert Pro X-Ray Diffractometer. Dried powder sample was kept in sample holder (20 mm \times 15mm \times 2mm) which was fitted into the instrument and X-ray was passed through the sample.

Characterization of Phytosomes

The physical attributes like shape, size, distribution, drug, entrapment capacity, drug release and chemical composition are used for their characterization. Methods used for their characterization are Melting point determination, Thin Layer Chromatography (TLC), Infra Red Spectroscopy, NMR spectroscopy, Differential Scanning Calorimetry, X-Ray Diffraction Analysis, Scanning Electron Microscopy (SEM), Transmission Electron Microscopy (TEM), Photon correlation Spectroscopy (PCS), Percentage drug entrapment etc.^[11] The melting point of the prepared phytosomes significantly vary from that of the phytoconstituents and the phospholipid, which is due to the chemical interaction between the both moiety and the change in shape of the phytosome. The HP-TLC is a simple method used for characterization of Phytosome. The phytosomes have a retention factor value different from the phytoconstituents and phospholipids when they are eluted with the suitable solvent system¹⁸, which confirms the formation of a new molecular entity. The

instrumental techniques used for the evaluation provide major informations. The FT-IR spectra of the phytoconstituent, the phospholipid and their phytosomes are compared. The free hydroxyl group interact with the choline part of phospholipid. The peak corresponding to the free hydroxyl group changes and a broad peak appears instead. The chemical shift value, presence and absence of NMR peak of particular proton can be investigated to characterize phytosome. The H-NMR Spectra of phytosomes 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 behaves as a sheath to the central choline part attached to phytoconstituent.^[12] The ¹³C-NMR is often performed for confirmation of the type of interaction involved for the complexation. The crystallinity of the phytoconstituents is lost upon complexation, which is responsible for increasing the hydrophilicity of hydrophobic phytoconstituent and balancing the hydrophilicity and lipophilicity. The crystallinity along with the interaction of phospholipid with phytoconstituent can be confirmed by the DSC and 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. The broad peak indicates the loss of crystallinity. Similarly the diffraction angle (2θ) of phospholipid, phytoconstituent and the phytosomes are compared. The general XRD study indicates loss of crystalline peaks of drugs which confirms the interaction and entrapment of drug within a sheath.^[13] The study of surface morphology is often important in identifying the entrapment behaviour, surface properties along with the presence or absence of impurities on the surface. The SEM provides photomicrograph of the phytosomes at suitable magnification after coating it with a very thin layer of gold. The surface of phytosomes generally shows no crystalline particles or any impurity on surface. The spherical bulging on the surface are generally obtained, which confirms the spherical shape of the phytosomes. The internal environment where the drug is entrapped and its distribution within the phospholipid mesh may be clearly investigated from the TEM study.^[14,15] The Photon Correlation Spectroscopy (PCS) technique is used for investigating the size of the phytosome and for confirmation of the vesicular structure after hydration and determination of size of vesicle. The polydispersity of vesicles are observed by this technique which gives an idea about distribution of various sizes of vesicular structures. The PCS study generally shows that the phytosomes upon hydration mostly forms unilamellar liposomal structures. The percentage drug entrapment can be determined by extracting the phytosomes with suitable solvent systems by centrifugation at higher rpm value for short time or a lower rpm value for longer period and estimating of the supernatant for detection of drug either by UV-Visible spectroscopy or High Performance Liquid Chromatography (HPLC) method.

Advancement & Recent Researches on Phytosomes

Numerous research is being conducted by the researchers and the recent researches reveals that the phytosome technology is a novel method for improving the absorption and bioavailability of plant extracts significantly reducing the dose level. Some plant extracts are getting more focus now-a-days due to their potential pharmacological effects, such as, silymarin, grape seed extract, quercetin, curcumin, hesperetin, ginkgo biloba extract, andrographolide.^[15,16] The suitability of this technique and increased demand of herbal medicines for various disease management.

Schandalik et al, 1992, 1994, used nine human volunteer patients and tested the hepatoprotective activity of silymarin and reported that phytosomal form of silybin possess four times greater passage through the liver.^[17,18] Similar experiment was conducted by Mascarella et al, 1993, using 232 patients with chronic hepatitis. He also reported better bioavailability of silymarin phytosome than the uncomplexed form.^[19]

Grange et al, 1999, conducted series of experiments on silymarin phytosomes and reported the better fetoprotectant activity of the phytosomal form.^[20]

Busby et al, 2002, also reported better fetoprotectant activity of silymarin phytosome than uncomplexed silymarin against ethanol-induced behavioural deficit.^[21]

Jhiang et al, 2001, prepared Herba Epimedii flavonoid phytosome (EPF) by means of solvent evaporation technique and the accumulative dissolution of different ratios of EPF-PVP precipitate was investigated by dissolution study. The study showed that the dissolution of the precipitate was significantly higher than that of its physical mixture and Herba Epimedii extract tablets.^[22]

Bombardelli et al, 2005, reported that the silymarin phytosomes showed much higher specific activity and a longer lasting action than the single constituent, with respect to percent reduction of edema, inhibition of myeloperoxidase activity, antioxidant and free radical scavenging activity.^[23]

Maiti et al, 2005, developed a quercetin phytosome by a simple and reproducible method and reported that the phytosomal complex shows better therapeutic efficacy than the uncomplexed molecule in rat liver injury induced by carbon tetrachloride.^[24] They also recently reported the enhanced bioavailability and hepatoprotective activity of andrographolide herbosome by an experiment on rats and found that the phytosomal form has an enhanced activity than that of uncomplexed andrographolide at the same dose level.^[25]

Xiao et al, 2006, Prepared silymarin phytosomes and studied its pharmacokinetics in rats and reported that the bioavailability of silybin has increased markedly in phytosomal formulation.^[21] Hepatoprotective activity of

silymarin phytosomes was found to be more than silymarin alone against aflatoxin B1, as reported by Tedesco et al, 2008, after performing the experiment on broiler chicks.^[26] Green tea extract generally contains a totally standardized polyphenolic fraction (epigallocatechin and its derivatives), having a long term beneficial activities, such as, antioxidant, anticarcinogenic, antimutagenic, antiatherosclerotic, hypocholesterolemic, cardioprotective and antibacterial effects, but having a poor oral bioavailability. But the phytosomal formulation strongly improves the oral bioavailability. Further advancement in phytosome technology has been discussed in the following section.

Feasibility of Phytosome for Transdermal Application

The enhanced bioavailability of phytoconstituents by transdermal route is a major breakthrough in the research of transdermal drug delivery systems (TDDS). TDDS involves the delivery of therapeutic agent via skin in to the systemic circulation. The stratum corneum, which is the outermost horny layer, provides the major hindrance for drug delivery due to its lipophilicity. The phytosomal form of the phytoconstituent is helpful in avoiding this barrier property. The successful research experience of around two decades of study by different researchers has been summarized below, which indicates that the phytosome technology has enough potency to be used transdermally for increasing bioavailability of phytoconstituents.

Bombardelli et al, (1991) observed that phospholipid exhibit a marked affinity for some classes of flavonoids. They developed a new series of compounds called Phytosomes, which he obtained by complexation of phospholipid with very polar botanical derivatives, i.e. complexes between a pure phospholipid and pure active principle. He first established some chemico-physical properties of phytosomes of catechin, quercetin, escin and glycyrrhetic acid and gathered some pharmacological data. He, from the beginning described phytosomes to be a good carrier for phytoconstituents across the skin.

Loggia et al, (1996) prepared Ginkgo biloba terpenes phytosomes and reported that the phytosome was effective on soothing individual contact reaction to other substances contained in topical formulation.^[27]

Zhang et al, (2008) investigated that the well known soothing activity of silymarin is increased by more than six times in silymarin phytosome in experimental models. The improvement in the activity of the phytosome form compared to the free active principle is due to a higher affinity of the complex for skin phospholipid.^[28]

Kidd (2009) reported the hydration of the superficial corneous layer is related to the liposomal like properties of the phospholipid of the complex. Ginslect

phytosomes possess a transdermic action which helps the ginseng saponin present in the phospholipid complex to penetrate into the skin.^[29]

Cao et al, (2010) formulated Oxymatrine-phospholipid complex (OMT-PLC) to improve the lipid solubility and effectiveness of OMT. The purpose of their study was to explore the utility of the combination of a microemulsion and an OMT-PLC as topical delivery vehicle for enhancing the absorption and efficacy of OMT. The solubility of OMT-PLC was determined and phase diagram of microemulsion were constructed. They developed various physicochemical properties and In Vitro and In Vitro permeability through skin. They concluded that the combination of a microemulsion and phospholipid complex represents an effective vehicle for topical delivery of OMT.^[30]

Gupta and Dixit, (2011) reported that incorporation of high amount of curcumin in topical formulation cannot provide a better bioavailability. They prepared complex of curcumin with phosphatidylcholine and characterized them on the basis of TLC, DSC, Melting point and FT-IR. They compared the activity of vesicular systems like liposome, neosome, phytovesicle. In result they got that the phytovesicles are having excellent antioxidant and antiaging properties than the other vesicular systems, that may be due to the amphiphilic nature of the complex, which greatly enhances the water and lipid miscibility of the curcumin.^[31]

Cuomo et al, (2011) investigated the relative absorption of a standardized curcuminoids mixture and its corresponding lecithin formulation (Meriva) in a randomized, double blind cross over design human study. They reported the improved absorption and a better plasma curcuminoid profile of the Meriva at a dose significantly lower than unformulated curcuminoid mixture.^[32]

Zaveri et al, (2011) have prepared the curcuminphospholipid complex in a molar ratio of (1:2) of curcumin and phospholipid. They confirmed the formation of complex by FT-IR Spectroscopy and DSC analysis. They compared the skin permeation of curcumin with the complexed curcumin and found that the complexed curcumin showed 60% greater permeation of curcumin through rat skin. They reported that the phospholipid complex has more transdermal penetration than pure curcumin.^[33]

CONCLUSION

Phytosomes or herbosomes are advanced and novel form of botanicals and phytoconstituents that are better absorbed both orally, topically and transdermally. Phytosomes have improved pharmacokinetics and pharmacological parameters and having wide scope in cosmeticology. The preparation methods of phytosomes are non-conventional, simple and reproducible. Apart from that the phospholipids used have their own

beneficial effect to the body. Many areas of phytosomes are to be reported in the future in the prospect of pharmaceutical application. The phytosome technology forms a link between the conventional delivery system of phytoconstituents and novel drug delivery systems.

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