Phytosomes: A promising system of herbal drug delivery

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ABSTRACT
Phytosomes, are the tiny structures which serve as intermediate between the conventional and novel drug delivery system. These are the cells, which are able to carry themselves from a hydrophilic to the lipid environment of the cell membrane, which ultimately reaches the blood. The hydrophilic plant constituents, which find their application in skin disorders, anti-ageing possess and different type of carcinomas are difficult in processing into conventional delivery system and hence transformed into phytosomes. Phytosomes are the complexes prepared by mixing polyphenolic phytoconstituents and phosphatidylcholine in molar ratio. Phytosomes are superior to the conventional drug delivery systems in terms of pharmacokinetic and pharmacodynamic properties. Phytosomal delivery of the extracts of Ginkgo biloba, Grape seed, Green tea, Ginseng, etc. has been profitably used. Phytosomes have been refined for therapeutic uses like cardiovascular, anti-inflammatory, immunomodulator, anticancer, antidiabetic etc. or for preventive and health reasons. In the ever-expanding pharmaceutical horizon, exploration of Phytosome technology is much needed.

Keywords: Phytosomes, immunomodulator, phosphatidylcholine.

INTRODUCTION
In order to amalgamate different water-soluble phytocconstituents into phospholipids to yield molecular complexes that are compatible with lipid, a technology had developed which also fruitfully improve their absorption and bioavailability. These molecular complexes are acknowledged as Phytosomes or Phytolipid delivery system or herbosomes in certain literature and serve as a intermediate between the conventional and novel drug delivery system [1]. These are the cells, which are able to carry themselves from a hydrophilic to a lipid environment of the cell membrane, and ultimately reach the blood. The above-described delivery system has upgraded pharmacokinetic and pharmacodynamic parameter, which is profitable in the treatment of the acute and chronic liver disease of toxic and infective source [2]. This unique delivery system mainly consolidates herbal drugs as it assist in increasing solubility, stability and pharmacological activity. Major biologically active constituents of plants are polar or water soluble molecules (like flavonoids, tannins and terpenoids) which are ailingly absorbed either because of their bulky molecular size which are unable to absorb by passive diffusion, or because of their low solubility in lipid portion; which restrain their capability to cross the lipid-rich biological membranes, culminating in poor bioavailability.[3,4]

PHYTOSOME TECHNOLOGY: [5, 6]
Phytosomes are processed by reacting stoichiometric amount of phospholipid (phosphatidylcholine) with the standardized extract (like simple flavonoids) in a non-polar solvent. The phospholipid that is most often hired is phosphatidylcholine originated from soybean. It is a dual compound, as the phosphatidyl fraction is lipophilic and the choline portion is hydrophilic in nature. The hydrophilic part (choline group) binds with water-soluble constituents and forms the body whereas lipid soluble phosphatidyl fraction forms tail and enclose the choline bound material [7, 8]. Hence, phospholipids form a molecular complex that is compatible with lipid; and referred to as
Phyto-phospholipid complex. The polar choline head of the phospholipids and molecules are bonded through chemical bonds. The phytosomal technology produces little structures, in which the plant concentrates safeguard from ruination by gastric secretions and gut bacteria attributable to the gastro protective property of phosphatidylcholine. [9, 10]

PROPERTIES OF PHYTOSOMES:
1. Chemical properties: [11, 12]
Phytosomes are the complex between botanical products and phospholipids (soy phospholipids) which is obtained by reaction of required amounts of phospholipid and the substrate in a solvent. By scrutinizing the spectroscopic data, it can be asserted that the phospholipid-substrate interaction is because of formation of hydrogen bonds between the polar head of phospholipids and the functionalities of the substrate. Phosphatidylcholine can be figured from the juxtaposition of $^{13}$C-NMR and $^1$H-NMR spectra of the complex with that of the pure forerunners. The signals of fatty chain remain unaltered. This assertion concluded that the long aliphatic chains are clothed around the main constituent, ended in the production of a lipophilic envelope, which defenses the polar head of the phospholipid and flavonoid moiety and empowers the complex to dissolve in low polar solvents. [13]

2. Biological properties:
Phytosomes are finer forms of natural products, which are more fittingly absorbed, utilized and produce superior results than conventional ones. The elevated bioavailability of phytosomes over the noncomplexed botanical derivatives has been authenticated by pharmacokinetics or pharmacodynamic trials in experimental animals and human volunteers. [14]

ADVANTAGES OF PHYTOSOME TECHNOLOGY:
This technology has reformed the nutraceuticals in addition to pharmaceutical industry in the consequential way [15, 16].
- Phosphatidylcholine, which is one of the elements of phytosome, serves the bifold role as it acts as a carrier as well as possesses health benefit.
- The constitution of phytosome is secured and is sanctioned for pharmaceutical use.
- The absorption and hence bioavailability of water-soluble constituents is elevated culminating in better therapeutic effects.
- As the bioavailability of phytoelements is enhanced, the dose required is reduced.
- The phytosomes have a better stability than liposomes because former is composed of chemical bonds.
- Phospholipids enhance the nutritional quotient of the botanical extract.
- Phytosomes products are superior in terms of market demand.
- The manufacturing process of phytosomes is simple.
- Phytosomes can easily permeate through skin and thus enhances their effectiveness.
- The water soluble phytoconstituents are shielded by phospholipid which nourishes skin apart from acting as a carrier.
- They can be used for systematic targeting as they are able to carry themselves from hydrophilic to lipophilic environment. [17]

PREPARATION OF PHYTOSOME:
Phytosomes are prepared by equimolar reaction of natural or synthetic phospholipids (phosphatidylethanolamine, phosphatidylcholine or phosphatidyserine) with one mole of component (flavolignanans) either alone or as a mixture in aprotic solvent such as acetone or dioxane, from which the complex can be alienated by precipitation with non-solvent or by spray drying. In the processing of phytosomes the ratio between these two portions should be in the range 0.5-2.0 moles but the most preferable ratio is 1:1[18,19].

In the above said method, phospholipids are selected from the group composed of soy lecithin, from swine or bovine dermis or brain, phosphatidylcholine, phosphatidylethanolamine, phosphatidyserine which contains similar or different acyl group and mostly derived from oleic, stearic and palmitic acid. Assortment of flavonoids is done from the group consisting of apigenin-7-glucoside, (+) catechin, quercetin, kaempferol, rhamnogluco side, (-) epicatechin, diosmine and 3- rhamnoside. Some liposomal drugs are prepared in the presence of the water or buffer solution whereas phytosomes requires the solvent having a reduced dielectric constant. The starting materials like flavonoids are insoluble in chloroform, ethyl ether or benzene, which after forming phytosomes results in the acceptable solubility in these solvents. This alteration in physical and chemical property is because of the formation of stable complexes, which protects them from disintegration by gut bacteria and enzymes and thus properly delivers the drug to the targeted tissues. [20, 21]
CHARACTERIZATION OF PHYTOSOME:[22,23]
The main aspect which regulate the performance of phytosomes in both biological and physical system are chemical composition and purity of the starting materials, membrane permeability, physical size and percentage entrapped solutes and hence the phytosomes are differentiated for specialties like size, shape, entrapped volume, percentage drug captured and released and chemical composition. $^1$H-NMR, $^{13}$C-NMR and IR spectroscopy is undertaken to study the complexion and molecular interactions between phosphatidylcholine and components. For the quantification of thermal effects such as fusion, loss of solvent and decomposition of the phytosome is performed by Thermal gravimetric analysis (TGA) and differential scanning colorimetry (DSC) [24, 25].

In addition to those stated above the other methods used are Thin Layer Chromatography (TLC), Infra-Red Spectroscopy, NMR spectroscopy, X-Ray Diffraction Analysis, Scanning Electron Microscopy (SEM), Transmission Electron Microscopy (TEM), Percentage drug entrapment and Photon correlation Spectroscopy (PCS). [26]

- $^1$H-NMR
The NMR spectrum is engaged for reckoning the formation of complex between the active constituents and phosphatidylcholine portion. In nonpolar solvents there is an evident change in $^1$H-NMR signal commencing from atoms included in the complex formation. The signals from protons are broadened. In phospholipids there is broadening of signals whereas the singlet correlative to the N-(CH$_3$)$_3$ of choline yields an upfield shift [27, 28].

- $^{13}$C-NMR
The $^{13}$C-NMR of phytosomes, when recorded in C$_6$D$_6$ at room temperature all the carbons of phytoconstituents are unobservable. The signals equivalent to the choline and glycerol portion is broadened whereas some are shifted and most of the resonance of the fatty acids chains maintains their initial sharp lines. [29]

- FTIR
The spectroscopic interpretation of the resultant complex can be firmly established by FTIR. It also confirms the stability by comparing the spectrum of the complex with that of the micro-dispersion in water after freeze-drying at varying time interval [30].

- HP-TLC
In HPTLC different retention factor values from the phytoconstituents are eluted with the preferred solvent system confirms the formation of a new moiety. [31]

- DSC and XRD
The pure drug, which is crystalline in nature, indicates a sharp peak as high melting point in DSC thermogram whereas resultant phytosome shows a broader peak, which indicates the loss of crystallinity and low melting point than that of pure drug. Similarly the diffraction angle (2$\theta$) of phytoconstituent, phospholipid and the phytosomes are compared which indicates loss of crystalline peaks of drugs confirming the interaction and entrapment of drug within a sheath. [32, 33]

- SEM
The SEM shows photomicrograph of the phytosomes after coating it with a very thin layer of gold. It indicates no impurity on surface and confirms the spherical shape of the phytosomes. [34]

- TEM
The TEM study investigates the enclosed elements where the drug is entangled and its distribution within the phospholipid mesh. [35]

- PCS and Percentage Drug Entrapment
Photon Correlation Spectroscopy (PCS) technique is employed for inspecting the size of the phytosome and confirming its vesicular structure after hydration. The percentage drug entrapment is resolved by extracting the phytosomes with convenient solvent systems by centrifugation and analysing the supernatant for detection of drug by either High Performance Liquid Chromatography (HPLC) method or UV-Visible spectroscopy. [36]
APPLICATIONS OF PHYTOSOMES:[37,38,39]
The primordial study of phytosomes was focused on *Silybum marianum* (Family Steraceae), whose fruit contains flavonoids known for hepatoprotective effects and has shown convincing outcomes in treating liver diseases like hepatitis, cirrhosis, fatty infiltration of the liver and inflammation of the bile duct. Silymarin chiefly contains three flavonoids out of which Silybin overrule, superseded by silychristin and silydianin. It is fact that silybin is the one which is most potent as it shields the liver by conserving glutathione in the parenchymal cells. In its native form within the milk thistle fruit, silybin predominantly occurs in complexation with sugars (such as flavonolignan or flavonyl glycoside). [40]

Francesco et al., studied an oral formulation of coated tablets (Monoselect Camellia®) (MonCam) containing greatly bioavailable green tea extract (GreenSelect® Phytosome) for analyzing overweight subjects (n=100) of both genders on a hypocaloric diet which results into the total absence of adverse effects and thus appears to be a an effective and safe tool for weight loss. [41,42]

Mukerjee et al. developed a novel hesperetin phytosome by making complex of hesperetin with hydrogenated phosphatidyl choline. The complex was then evaluated for antioxidant activity, which communicate that the phytosome had higher relative bioavailability than that of active drug entity. [42, 43, 44]

Ravarotto et al., (2004) asserted that silymarin phytosome shows better anti-hepatotoxic activity than crude silymarin. [45]

**Table I: Commercial Phytosomes Products [46,47]**

<table>
<thead>
<tr>
<th>S.No.</th>
<th>Phytosomes</th>
<th>Phytoconstituents</th>
<th>Complexed Dose</th>
<th>Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Silybin Phytosome™</td>
<td>Silybin from <em>Silybum marianum</em></td>
<td>120 mg</td>
<td>Hepatoprotective, antioxidant for liver and skin</td>
</tr>
<tr>
<td>2.</td>
<td>Ginkgo Phytosome™</td>
<td>24 % ginkgo flavonoids from <em>Ginkgo biloba</em></td>
<td>120 mg</td>
<td>Protects brain and vascular linings, anti-skin ageing</td>
</tr>
<tr>
<td>3.</td>
<td>Ginseng Phytosome™</td>
<td>37.5 % ginsenosides from <em>Panax ginseng</em></td>
<td>150 mg</td>
<td>Nutraceuticals, immunomodulator</td>
</tr>
<tr>
<td>4.</td>
<td>Green Tea Phytosome™</td>
<td>Epigallocatechin from <em>Thea sinensis</em></td>
<td>50-100 mg</td>
<td>Nutraceutical, systemic antioxidant, anticancer</td>
</tr>
<tr>
<td>5.</td>
<td>Grape Seed Phytosome™</td>
<td>Procyanidins from <em>Vitis vinifera</em></td>
<td>50-100 mg</td>
<td>Nutraceutical, systemic antioxidant, cardio-protective</td>
</tr>
<tr>
<td>6.</td>
<td>Hawthorn Phytosome™</td>
<td>Flavonoids from <em>Crateagus sp</em></td>
<td>100 mg</td>
<td>Nutraceutical, cardio-protective and antihypertensive.</td>
</tr>
<tr>
<td>7.</td>
<td>Olive oil Phytosome</td>
<td>Polyphenols from <em>Olea europaea</em></td>
<td>-</td>
<td>Antioxidant, anti-inflammatory, anti-hyperlipidemic</td>
</tr>
<tr>
<td>8.</td>
<td>Echinacea Phytosome</td>
<td>Echinacosides from <em>Echinacea augustifolia</em></td>
<td>-</td>
<td>Nutraceutical, immunomodulator</td>
</tr>
<tr>
<td>9.</td>
<td>Centella Phytosome</td>
<td>Terpenes</td>
<td>-</td>
<td>Vein and Skin disorders</td>
</tr>
<tr>
<td>11.</td>
<td>Super Milk thistle Phytosome</td>
<td>Silybin from <em>Silymarin</em></td>
<td>-</td>
<td>Food Product antioxidant for liver and skin</td>
</tr>
</tbody>
</table>

**CONCLUSION**

Phytosomes are the exceptional form of herbal extract, which serves as intermediate between the traditional and novel drug delivery systems. The phytosome nutraceuticals products become available at the site of action of liver, heart, kidney, brain at low dose in contrast to conventional plant extract. This novel technology when applied concerning plants open new scheme to seek maximum therapeutic potential of plant substance and have extensive opportunity in cosmetology and many areas are yet to be acknowledged in future in the anticipation of pharmaceutical application.

**REFERENCES**
