PHYTOSOMES: FROM HERBAL DRUG DELIVERY TO TARGETED CLINICAL THERAPY

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ABSTRACT
Conventional herbal extracts, despite their excellent biological activities, display poor bioavailability and poor lipid solubility, ascribing to their large molecular size and hydrophilic nature which adversely affects their therapeutic potential. This lack of bioavailability can be greatly improved by using different delivery systems, one such being the use of phytosomes. This phospholipid-based delivery system has proven to be a promising technique for delivery and enhanced efficacy of the herbal or phytochemical extracts, as well as demonstrating improved pharmacokinetic and pharmacodynamic profile when compared to the conventional herbal extracts. This delivery system has shown remarkable potential of herbal extract delivery, when administered orally or topically and may further be made to be used as a means of targeted intravenous cell therapy by employing the use of desired monoclonal antibodies with the standardised phytosome formulations.

KEYWORDS: phytosomes, phosphatidylcholine, bioavailability, amphiphilic, phytoconstituents, liposomes.

INTRODUCTION
In the wake of many deadly diseases, such as, cancer, diabetes, viral disease inflections, cardiovascular diseases and many more, plaguing the earth, the paradigm of clinical medicine is fast shifting towards herbal of phytochemical compounds, ascribing to their decreased cytotoxicity, lesser side-effects, anti-aging and anti-inflammatory actions. However, most
of these bio-active plant components are hydrophilic (polar) or water soluble in nature and have a large molecular size, greatly limiting their passive diffusion as well as their ability to transverse the lipid membranes of biological cells, resulting in their poor absorbance and a marked decrease in their bioavailability.[2]

To overcome this hurdle of photochemical absorption, these hydrophilic phytoconstituents are converted into hydrophobic or lipid-soluble entities, referred to as herbosomes or phytosomes, “phyto” meaning “plant” and “some” meaning “cell-like”. Phytosomes have increased bioavailability owing to their enhanced ability to cross cellular membranes and into the blood.[3] They also display greatly improved pharmacokinetic and pharmacodynamic activities, making them ideal in treating many acute and chronic ailments, as well as in pharmaceutical and many cosmetic compositions.[1,4] The lipid-phase substances or phospholipids employed in the synthesis of phytosomes are mainly phosphatidylcholine (PC), extracted from soybean (*Glycine max*).[5] Being the main molecular building block of cell membranes, PC is both water and lipid soluble and is also well absorbed when administered orally. It is a bi-functional compound in nature, with phosphatidyl being lipophilic and choline being hydrophilic.[4] PC is mainly employed for the prevention and intravenous treatment of fat embolisms in polytraumatized patients while treating disorders of metabolism as well as a substance for the protection of liver in case of both, acute and chronic liver disease in metabolic toxicity.[6]

Synthesised using PC, these phytosomes have proven to be highly efficient in the protection of pharmaceutically active herbal extracts against gastric secretions and gut bacteria.[7] This process of using phytosomes as efficient delivery vehicles have been successfully applied to a number of herbal extracts and preparations such as ginseng (*Panax ginseng*), milk thistle (*Silybum marianum*), grape seed, green tea, hawthorn, *Ginko biloba* and many more, while the active flavonoids and terpenoids present in the phytochemical or herbal extract bind directly to phosphatidylcholine[1], producing a lipid soluble compound with phospholipids present in PC, called, phyto-phospholipid complex.

Due to the rising momentum of phytosomal technology worldwide, this review article will discuss the latest trends, potential therapeutic applications and possible aspects of targeted drug delivery of various herbal formulations via phytosomes.
Characteristics and bioavailability
Phytosome technology is a registered trademark of Indena S.P.A, Italy. It was developed with the aim of incorporating plant extracts or water soluble phytoconstituents into phospholipid based molecular complexes that are lipophilic and therefore have a greater bioavailability and absorption in the body.

Phytosomes are said to structurally resemble cells and it is this structural arrangement combined with the gastroprotective abilities of phosphatidylcholine that protects them from the deleterious effects of the digestive enzymes and secretions of the gut, not to mention the various gut microbiota. Furthermore, phytosomes have an improved ability to migrate from a hydrophilic environment to a more lipophilic environment thereby facilitating better entry into the cell.

Most phytoconstituents are water soluble compounds (in other words, they are hydrophilic and soluble in polar solvents) e.g. flavonoids, glycosides, phenolics etc. The drawback with this feature is that these compounds have a reduced ability to interact with lipid-based membranes, if not are incapable of doing so, resulting in a reduced bioavailability when consumed orally or applied topically. This can be attributed to either their large molecular size (in the case flavonoids, multiple rings molecules accounts for the large size) for which passive diffusion becomes difficult or to their severely low lipid miscibility which prevents them from passing the lipid rich outer membranes of the enterocytes.

Phytosomes on the other hand have improved pharmacological profiles and increased bioavailabilities making them a potential high efficiency drug delivery method.

General preparation procedures and phytosome components
A phytosome is developed by reacting phospholipids with the desired plant extract in a stoichiometric ratio appropriate solvent (preferably non-polar). The phospholipids that can be used to synthesize phytosomes are phosphatidylcholine, phosphatidylethanolamine or phosphatidylserine which can be either synthetic or naturally derived. These can be obtained from soy lecithins found in bovine or swine brain or dermis and where the acyl groups have been preferably derived from palmitic, stearic, oleic and linoleic acid. The phytoconstituents used can be flavonoids, terpenoids etc.; flavonoids are primarily used examples are quercetin, kaempferol, catechin, epicatechin etc. Aprotic or non-polar solvents such as dioxane,
acetone, ethyl acetate, methylene chloride are used when necessary depending on the protocol followed.[7,10]

Phytosome are synthesized by combining 2-3 moles of the phospholipid with 1 mole of the phytoconstituent resulting in a 2:1 or 3:1 ratio. However, the use of 1 mole of phospholipid is preferred so as to produce a ratio of 1:1 between phospholipids and phytoconstituents.[13]

Phosphatidylcholine is the phospholipid most often used, it forms a major building block of the plasma membrane, it can act as a chaperone for polyphenolics[14] and it possess both lipophilic and hydrophilic counterparts, the phosphatidyl moiety being lipophilic and the choline moiety being hydrophilic. The choline moiety (phosphate and ammonium groups) is responsible for binding the phytoconstituent molecule via hydrogen bonds which can be examined using spectroscopic analysis[15,16], whilst the phosphatidyl moiety, making up both the body and tail, encompasses the choline-phytoconstituent complex by wrapping its aliphatic chains around the active principle as depicted by H\textsuperscript{1}NMR and C\textsuperscript{13}NMR data.[17] The desired phytoconstituents are therefore transformed into lipid compatible molecular complexes also referred to as a phyto-phospholipid complex.[7] This amphiphilic nature and resultant dual solubility, culminates to a drastically enhanced bioavailability due to swifter and amplified absorption through the intestinal tract.[10]

Gupta and Dixit, 2011 conducted a study wherein they evaluated three vesicular systems, liposomes, niosomes and phyto-vesicles containing curcumin.[18] They reported that the phyto-vesicles had exceptional antioxidant and anti-aging properties which could be attributed to the amphiphilic nature of the complex. Bombardelli and Mustich, 1991 conducted an evaluation of silymarin phytosomes and reported that they had increased specific activity and longer lasting action than individual components.[19] This further corroborates the overall benefits of phytosomes.

Once the phytosome complex is formed the solubilities greatly differ that of the phytoconstituent, it is now soluble in aprotic solvents, moderately soluble in fats and insoluble in water. Phytosomes are somewhat emulsified when mixed with water as indicated by the formation of micellar-like structures.[20] This poor water solubility allows for the production of stable emulsions and creams.[21] However, some phytosomes show an increased solubility in water such as phytosome containing curcumin.[22]
Liposomes versus phytosomes

Liposomes may seem very similar to phytosomes but there are many characteristic distinctions. Similar to phytosomes, liposomes are prepared using similar processes of mixing phosphatidylcholine and a water soluble compound in a specific stoichiometric ratio. However, unlike phytosomes, the choline moieties do not form chemical bonds with the water soluble molecules, instead the phosphatidylcholine molecules completely envelop them creating a lipid bilayer surrounding a core containing the water soluble molecules. As a result there may be thousands of phosphatidylcholine molecules surrounding the phytocomponent. In a phytosome, the choline moieties are chemically bonded via hydrogen bonds to the phytocomponents effectively anchoring them into the membrane resulting in the formation of 2:1 or 1:1 ratio between phosphatidylcholine and the phytocomponents.

Some liposomal drug complexes can function in water of buffer solutions (i.e. liquid that possess a high dielectric constant), on the other hand phytosomes are developed to function in solvent that possess low dielectric constants.

Liposomes are reported to be less effective in topical and skin care products than their phytosome counterparts. A diagram of a liposome and phytosome has been depicted in Fig. 1 and Fig. 2 respectively.

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Fig.1- Structure of a liposome containing therapeutic molecules: the figure depicts the structure of liposome with the phosphatidylcholine lipid bilayer, containing in its core, hydrophilic drug or therapeutic molecules.
Fig. 2- Structure of a phytosome: prepared by the reaction between phospholipids (phosphatidylcholine being the most commonly employed one) and the desired herbal extract, the figure depicts a typical phyto-phospholipid complex, where the bioavailability and the uptake of the therapeutic moiety is drastically increased as the herbal extract is made lipophilic by it bonding with the choline head in the phytosome.

Advantages and disadvantages
1. The first and most apparent benefit is the drastically increased bioavailability of the phytoconstituents because their association with phospholipids resulting in an improved absorption and distribution of the phytoconstituent.\(^{[24]}\)
2. The formulation and components used for the synthesis of phytosomes are harmless and therefore fit for commercial use. Moreover, this technology has a low risk profile; the toxicology evaluations of the various components have been well documented.\(^{[23]}\)
3. Phytosomes are particularly helpful in maintaining liver functioning and upkeep. In addition to increasing the bioavailability of flavonoids used to ensure proper liver function, phosphatidylcholine exhibits protective abilities which further helps ensure a healthy liver.\(^{[25]}\)
4. Phytosomes present a cost effective means of administering skin protective phytoconstituents in both a normal and stressful environment. Once again, phosphatidylcholine helps care for the skin by providing nourishment.\(^{[2]}\) Phytosomes also help increase the distribution of phytoconstituents made via dermal and transdermal routes.\(^{[26]}\) Zaveri et al., 2011 conducted a study comparing the permeation of curcumin and curcumin phytosome and reported that the curcumin phytosome had a 60% better permeation.\(^{[27]}\)
5. Phytosome technology is passive, non-invasive, provides increased bioavailability and is market-ready.\textsuperscript{[26]}

6. The obstacle of drug entrapment does not arise during the formulation process.\textsuperscript{[19]}

7. Phytosomes present a means of delivering a wide range of therapeutic compounds in addition to being a more stable option due to the chemical bonding between the phospholipid and the therapeutics compounds.\textsuperscript{[9]}

8. As a result of the increased bioavailability and absorption of the phytoconstituent and sustained release pattern of the phytosome, the effective dose could potentially be reduced, i.e. the phytoconstituent could be administered in a smaller quantity but still be able to attain the desire result.\textsuperscript{[23,28]}

9. The synthesis of phytosomes involves a fairly simplistic process and therefore presents no immense technical or monetary investments.\textsuperscript{[9]}

10. Phytosomes can effectively and efficiently pass from a hydrophilic environment to a hydrophobic one (enterocyte membrane) and furthermore to the cell. They can therefore be used for systemic targeting.\textsuperscript{[10]}

\textbf{Disadvantage}

1. It has been reported that phytosomes could rapidly eliminate the phytoconstituents.\textsuperscript{[23]}

\textbf{Applications of Phytosomal Technology}

Recent research and clinical studies have demonstrated a marked increase in the bioavailability and absorption of herbal drugs administered in conjugation with phytosomes, as compared to the conventional therapies and other means. It has also been reported that a majority of phytosomal studies are based on preparations with \textit{Silybum marianum} or the milk thistle, containing a number of potent liver-protecting flavonoids, which if taken as oral or intravenous preparation, is poorly absorbed.\textsuperscript{[4]}

\textit{Hepato-protective activity}

Study conducted by Tedesco et al., 2004, reported the anti-hepatotoxic activity of silymarin (milk thistle) conjugated phytosomes.\textsuperscript{[29]} The study aimed at demonstrating the protective effects of silymarin phytosomes against the highly potent alfatoxin B1 on the broiler chicks’ performance.

In a study of 232 patients suffering from chronic hepatitis (alcohol, drug or viral induced) were subjected to treatment with silybin phytosome, at a fixed dose of 120 mg, twice or thrice
a day, for 120 days. After the successful completion of the treatment, liver functions were found to be returned to normal quicker in silybin phytosome treated patients as compared against two groups of controls, where 117 patients were given placebo or were untreated and 49 patients were given commercially manufactured silybin treatment.\(^{[30]}\)

Similarly, a phytosomal complex of quercetin-phospholipid demonstrated better therapeutic activity in case of carbon tetrachloride induced liver injury in rats.\(^{[31]}\)

**Fetoprotectant activity**

Studies carried out by Busby et al., 2002 and La Grange et al., 1999, demonstrated yet another important therapeutic application of phytosomal technology. Both these studies individually reported the fetoprotectant activities of silymarin phytosome, upon oral administration, against behavioural deficits induced by ethanol, ingested maternally.\(^{[32,33]}\)

**Antioxidant and cardioprotectant activity**

Silymarin conjugated phytosomes have been reported to show a marked decrease in odema, antioxidant, myeloperoxidase inhibition activity as well as scavenging of free radicals property, along with long lasting effects and higher specificity.\(^{[34]}\) Studies have also shown that ginkgo phytosomes, synthesised using standardised extract from the leaves of *Ginkgo biloba*, were able to produce 30-60\% improvement among patients with peripheral vascular diseases, like Raynaud’s disease.\(^{[7]}\)

Consisting of oligomeric polyphenols (proanthocyanidins or procyanidins from the extract of *Vitis vinifera* grape seed), grape seed phytosomes have shown to have an overall increase in the antioxidant capacity along with the stimulation of plasma antioxidant defence, protection against atherosclerosis and ischemia-induced cardiac damages with an overall protection of cardiovascular system.\(^{[35]}\)

In a study of randomised human trials, reported by Facino et al., 1994, grape seed phytosome was given to young healthy human volunteers, once for 5 days and TRAP (Total Radical-trapping Antioxidant Parameter) levels in the blood were measured at various intervals of time on day one and day five. It was recorded that 30 minutes after administration of grape seed phytosome on day 1, TRAP levels in blood were found to be significantly elevated as compared to the control group, who were given the conventional standardised grape seed.\(^{[22]}\)
Anti-carcinogenic activity

Green tea extract, containing epigallocatechin and its derivatives, has been shown to impart many long term beneficial effects, such as being an antioxidant, anticarcinogenic, cardioprotective, antimutagenic, antibacterial, antiatherosclerotic, to name a few. However, despite having a tremendous potential for good health, green tea polyphenols suffer from poor bioavailabilty, when administered orally.

The complex formed from phytosomal phospholipids and green tea polyphenols was designed to overcome this lack of bioavailability. Following this, a study on healthy human volunteers was performed to access the prepared phytosomal absorption orally. Over the period of six hours, a 50% increase in the flavonoid concentration was recorded in blood plasma along with a marked 20% increase in TRAP blood levels\cite{36}, corresponding to greatly reduced chances of cancer.

Phytosomes of curcumin, flavonoid derived from turmeric Curcuma longa, were synthesised by Maiti et al., 2007, which were able to demonstrate a higher level of antioxidant, anti-inflammatory as well as anticancer activity.\cite{37}

Targeted drug delivery

So far, various herbal extract conjugated with phytosomes have been prepared for a number of therapeutic uses, as mentioned in the various other applications of phytosomes. Some of these formulations have been tested in various clinical studies for their increased bioavailability and both, preventive and curative actions. However, to further increase the specificity towards targeted diseased cells, such as in the case of curcumin or grape seed phytosomes, displaying anticancer and cardioprotectant activities, respectively, cell specificity or particularly diseased cells, such as cancer cells, could be targeted for better and faster healing or recovery of the patient. These phytosomes can be converted into vehicles of targeted cell therapy by further incorporation PEG (poly-ethylene glycol derived lipids) into the phytosome preparation and conjugating Fab’ fragments of different desired monoclonal antibodies to the PEG molecules at the distal ends of the surface exposed moieties, similar to what has been performed in case of virosomal therapy.\cite{38}

The monoclonal antibodies could be chosen based on the disease and cell type targets, for example, monoclonal antibodies against transferrin receptors, which have been found to highly up-regulated on a variety of cancer cells.\cite{39} These may be chosen for curcumin
complexed phytosome to target the growing tumour cells in the body, as an adjuvant to chemotherapy or radiotherapy. This could further go on to define a wider range of applications for phytosomal technology in clinical medicine, as illustrated by figure 3.

![Figure 3](image)

**Fig.3-** phytosome tagged with mAbs: for a more cell specific and targeted delivery, phytosomes may be prepared with PEG (polyethylene glycol) surrounding them like a shield, imparting protection against the body’s immune cell, upon intravenous administration. The distal ends of PEG may be tagged with specific monoclonal antibodies in order to achieve targeted delivery of the drug or herbal extract via phytosomes.

**Table 1- Different types of cell-like particles used in the "some" technology**

<table>
<thead>
<tr>
<th>Vesicular System</th>
<th>Description</th>
<th>Benefits and potential uses</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aquasomes</td>
<td>Self-assembled spherical particles ranging between 60-300 nm in size. They consist of a solid phase nanocrystalline core coated by an oligomeric film to which biochemically active compounds are adsorbed.</td>
<td>Preserves the conformation and stability of the bioactive constituents. Insulin, antigen, gene and drug delivery; oxygen carrier; for the oral delivery of an acid labile enzyme</td>
<td>[40,41]</td>
</tr>
<tr>
<td>Archaeosomes</td>
<td>Liposomes made from naturally occurring archaeabacteria membrane lipids.</td>
<td>Stable under varying conditions of temperature, pH, oxidative conditions, pressure etc.</td>
<td>[42]</td>
</tr>
<tr>
<td>Colloidosomes</td>
<td>They are hollow microcapsules comprising of either coagulated or fused particles at the interface of the emulsion droplets. Size ranges between several microns to about 5 nm.</td>
<td>Easily constructed, flexible, controlled permeability, significant mechanical strength.</td>
<td>[43,44]</td>
</tr>
<tr>
<td>Cryptosomes</td>
<td>They are lipid vesicles that have surface coats comprising of phosphatidylcholine and polyoxyethylene derivative of phosphatidylethanolamine.</td>
<td>The modified surface coat serves to reduce macromolecular adsorption on the vesicle surface thereby, increasing the circulation time in</td>
<td>[45]</td>
</tr>
<tr>
<td>Particle Type</td>
<td>Description</td>
<td>Pharmaceutical Properties</td>
<td>References</td>
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<tr>
<td>Cubosomes</td>
<td>Particles formed by the high energy dispersion of bulk cubic phase liquids. These cubic phases consist of two hydrophilic regions divided by a lipid bilayer.</td>
<td>Provide a means of targeted and controlled release of therapeutic compounds. Easily prepared, biodegradable and bioadhesive. Hydrophilic, hydrophobic and amphiphilic drugs can be loaded.</td>
<td>[46,47]</td>
</tr>
<tr>
<td>Discosomes</td>
<td>Niosomes that have been coupled with a non-ionic surfactant, Solulan C24 (a lanolin derivative).</td>
<td>Potential for use as ophthalmic drug carriers.</td>
<td>[48]</td>
</tr>
<tr>
<td>Emulsosomes</td>
<td>They are nanolipid particles that consist of a lipid assembly with an apolar core.</td>
<td>Used for administration of sparingly water soluble drugs via the parenteral route.</td>
<td>[49,50]</td>
</tr>
<tr>
<td>Enzymosomes</td>
<td>They are liposomes with enzymes covalently associated to the surface.</td>
<td>Potential for targeted delivery to tumor cells.</td>
<td>[51]</td>
</tr>
<tr>
<td>Erythrosomes</td>
<td>An erythrocyte cytoskeleton coated with a lipid bilayer.</td>
<td>Potential encapsulation systems for macromolecular drugs</td>
<td>[52]</td>
</tr>
<tr>
<td>Ethosomes</td>
<td>Soft and malleable vesicles, composed of phospholipids, ethanol and water, ethanol helps increase permeation through skin layers.</td>
<td>Used to enable drugs to reach deep skin tissue and the systemic circulation.</td>
<td>[53]</td>
</tr>
<tr>
<td>Genosomes</td>
<td>Large molecular complexes used for the transfer of genes. Cationic liquids are best suited due to their increased biodegradability and stability in the blood.</td>
<td>Non-viral transfer of genes to specific cells.</td>
<td>[54]</td>
</tr>
<tr>
<td>Hemosomes</td>
<td>These are hemoglobin containing liposomes, prepared by combining hemoglobin with polymer-forming lipids.</td>
<td>Used as a high capacity oxygen carrying system.</td>
<td>[55]</td>
</tr>
<tr>
<td>Layerosomes</td>
<td>Liposomes containing several layers; these layers consist of biocompatible electrolytes in order to increase structure stability.</td>
<td>Potential for oral administration or incorporation in biomaterials.</td>
<td>[56]</td>
</tr>
<tr>
<td>Niosomes</td>
<td>Non-ionic surfactants vesicles (either unilamellar or multilamellar) produced by addition of non-ionic surfactant to cholesterol.</td>
<td>More stable, easier handling, flexible design in comparison to liposomes. Osmotically active, increase bioavailability and can entrap drugs with a wide range of solubility. Niosome loading of voriconazole, acyclovir etc. have been investigated.</td>
<td>[57–59]</td>
</tr>
<tr>
<td>Photosomes</td>
<td>Liposomes encapsulated with photolyase. Photolyase DNA repair enzyme obtained from bacteria.</td>
<td>Capable of repairing ultraviolet B induced pyrimidine dimers in eukaryotic cells. Could be used in sunscreens.</td>
<td>[60]</td>
</tr>
<tr>
<td>Sphingosomes</td>
<td>Similar to liposomes, instead are composed of sphingolipids.</td>
<td>More resistant to hydrolysis, reduced toxicity, can be administered via SC, IV, IA, IM, oral and TD routes.</td>
<td>[61]</td>
</tr>
<tr>
<td>Transferosomes</td>
<td>Deformable, stress responsive, complex vesicles consisting of an aqueous core</td>
<td>Increased permeability over niosomes and liposomes.</td>
<td>[62–64]</td>
</tr>
</tbody>
</table>
enveloped by a lipid bilayer. Amphiphilic in nature, entrap both high and low molecular weight drugs, protect drug from enzymatic and metabolic degradation and can penetrate narrow pores of skin. Tranferosome loading of meloxicam, ibuprofen etc. have been investigated.

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</tr>
</thead>
<tbody>
<tr>
<td>Ufasomes</td>
<td>Unsaturated fatty acid vesicles; developed to enhance the penetration of a drug through the stratum corneum layer of skin. Increased stability, better entrapment efficiency and cheaper than liposomes counterparts. [65]</td>
</tr>
<tr>
<td>Vesosomes</td>
<td>Lipid bilayer within a bilayer i.e. nested lipid bilayers, with an aqueous core. The facility of multiple compartments lends improved protection to the internal contents. [66]</td>
</tr>
<tr>
<td>Virosomes</td>
<td>Liposomes prepared using natural or synthetic phospholipids, viral spike proteins and viral envelope proteins. Used as influenza vaccines [67]</td>
</tr>
</tbody>
</table>

**CONCLUSION**

In the recent years, botanicals have proven themselves to be of great therapeutic value in terms of prophylactic, diagnostic, preventive as well as curative. Their delivery, however, the prime cause of reduced bioavailability, has also been overcome by the development of phytosomal technology, allowing their therapeutic action to become more enhanced, prolonged and detectable in the blood serum levels.

Due to various advantages associated with the phytosomal technology, this may be further developed to achieve targeted cell therapy by conjugation of the desired monoclonal antibodies to the phytosomes. Further studies and experiments are needed to test this approach via phytosomes, giving way to yet another tremendous applicative potential of this phytosomal technology, for diseases like cancer, cardiovascular inflections, diabetes and many more.

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