

Phytosomes, A Versatile Phyto-Phospholipid Nanocarriers: A Review

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Phytosomes are lipid based vesicular nanocarriers that encapsulate phytoconstituents within phospholipid layers, designed to overcome the limitations of herbal extracts such as inadequate lipid solubility, restricted permeability, low bioavailability, and chemical instability, while improving the absorption, stability, and therapeutic efficacy of phytoconstituents or herbal extracts in pharmaceutical, nutraceutical, and cosmetic formulations. The review aims to provide an overview of phytosomes, including their complexation mechanism structural features, formulation methodologies, and characterization techniques for evaluation of this phyto-phospholipid complex. The review briefly summarizes phytosomes technology, including structural, molecular interaction between active agent and lipids, formulation techniques, storage conditions, stability considerations, and therapeutic applications, commercially available phytosome-based formulations. Challenges faced by technology emphasizing the role and importance of phytosomes as a promising platform for turning herbal active agents into effective and standardized dosage forms.

Keywords: Absorption; Bioavailability; Encapsulation; Nanocarriers; Phytosomes; Phospholipid.

Medicinal plants have been serving as an integral part of the traditional medication system in different cultures as a source of therapeutic agents for treatment, mitigation of numerous diseases, disorders, or dermatological conditions.¹ Herbal extracts offers a reservoir of bioactive phytoconstituents such as minerals, vitamins, flavonoids, terpenoids, tannins, glycosides, alkaloids, phenols, polyphenols, essential oils, etc. offering a diverse pharmacological effects, including antioxidant, anti-inflammatory, and anticancer properties. Most of the phytoconstituents are usually well-tolerated with potentially lesser side effects than synthetic compounds.²⁻⁴ However,

the clinical utility of these compounds often hampered due to higher molecular weight and complex chemical structures giving rise to physicochemical barriers such as low lipid solubility, poor permeability across biological barriers, rapid metabolism, and restricted absorption, resulting in constrained systemic bioavailability upon oral and topical application.⁵⁻⁶

To combat these drawbacks associated, several nanotechnology based drug delivery system has been explored till date.⁴⁻⁵ One such technology named, phytosomes alternatively referred as herbosomes or phyto-phospholipid complex. Phytosomes are self- assembled phyto-

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phospholipid complex, recently emerging as a promising lipid-based vesicular drug delivery method to eliminate the shortcomings associated with conventional drug delivery approaches used for herbal actives agents. This food-grade biocompatible nanovesicles was pioneered and patented by Indena S.P.A, Italian Pharmaceutical and nutraceutical organisation to improve the solubility, permeability and bioavailability and pharmacokinetic characteristics of poorly absorbed herbal phytoconstituents.⁵⁻⁷

Structural component and molecular arrangement of phytosomes vesicles

Phytosomes developed by complexation of phospholipids and phytoconstituents in suitable solvent system, typically in stoichiometric ratio of 1:1 to 1:2. Upon hydration, these complexes self-assemble into nano-vesicular or micellar structures size ranging from 50 to 300 nm⁽⁸⁻⁹⁾. The prerequisites for the development of phytosome molecular assemblies are phytoconstituents preferably hydrophilic agent (containing hydrogen-bonding groups –OH, –COOH, –NH₂, etc.),⁶⁻⁹ a phospholipid molecule (phosphatidylcholine, phosphatidylethanolamine, phosphatidylserine, etc), and suitable solvent system.¹⁰⁻¹² Sometimes cholesterol is incorporated additionally as a supportive film forming agent to improve membrane rigidity and to stabilize the phytosomal system.¹³ Additionally, buffered system such as saline phosphate buffer (pH 6.5-7.4), ethanol tris buffer (pH 6.5), distilled water, etc. used as a hydrating medium to form stable colloidal dispersions of phytosomes.¹⁵

The fundamental unit of phytosomes vesicles is phospholipid molecule, predominantly Phosphatidylcholine (PC). PC being amphiphilic in nature consists of hydrophilic polar head (phosphate moiety) and hydrophobic fatty acid non-polar tails (choline).^{10, 13-15} The polar head of PC binds non-covalently with water-soluble phytoconstituents via hydrogen bonding. While the lipophilic tails, forms protective envelope around the phytoconstituents, resulting in amphiphilic molecule (phytosomes vesicle) which can drastically enhances both, lipid solubility and membrane permeability of phytoconstituents as compared to its free form. This also helps to prevent degradation of phytoconstituents by the gastric environment.⁹⁻¹⁰ The schematic representation phytosomes

vesicle encapsulating phytoconstituents within phospholipid, demonstrated in figure 1.

Methods for development of phytosomes vesicles

Phytosomes formulated by promoting a controlled molecular interaction between active phytoconstituents and PC under specific solvent system and processing conditions. Several methods used for development of phytosomes, including solvent evaporation, solvent injection, co-solvent lyophilisation, and thin-film hydration, anti-solvent precipitation, salting out techniques etc. The selection of appropriate method is generally based on the nature of phytoconstituent, desired vesicle size, polydispersity, stability, scalability requirements, dosage form and route of administration. A few of them as discussed below.¹⁵⁻¹⁷

Solvent Evaporation Method

Among all methods, this is most prevalent methods to develop lipid-based nano-carriers. The active ingredient and phospholipid solubilized into a suitable organic solvent and refluxed for 2–3 hours. Further rotary evaporator used to evaporate the solvent under pressure and film subsequently hydrated with phosphate buffer saline solution (pH 6.5 to 7.4) at temperature of 40 to 60°C. This method offers an excellent complexation efficiency.^{5-6, 19}

Thin-Film Hydration Method

It is one of the most consistent and reliable methods. Here, PC and herbal concentrate blended in the preferred solvent system (based on the nature of active constituent and PC). This suspension subjected to continuous rotation in a rotary evaporator for a couple of hours. Subsequently, the solvent is evaporated under pressure, generating a delicate film of phytoconstituent-phospholipid complex inside the edges of a round-bottom flask. The film is further hydrated with a buffered system to produce multi-lamellar vesicles, whose sizes are subsequently reduced by sonication or membrane extrusion techniques.¹⁶⁻¹⁸

Solvent Injection Technique

Excellent method for complexation of heat-labile active constituents. The phyto-phospholipid complex is dispersed in alcohols such as ethanol or diethyl ether and is immediately introduced into an agitated aqueous phase (pH 6.5-7.0) by means of injection. This leads to the diffusion of solvent into the phyto-phospholipid

complex, resulting in spontaneous phytosomes vesicle formation. While the residual solvent is extracted via vacuum evaporation. This strategy generates comparatively small unilamellar vesicles (80-150 nm) with minimal polydispersity, which is beneficial for thermolabile chemicals.¹⁹⁻²⁰

Co-solvent Lyophilisation Method

The most efficient approach to retaining stability of phytosome vesicles over an extended period. A water-miscible co-solvent system such as ethanol-water or t-butanol-water, used to generate the phyto-phospholipid complex, which is subsequently mixed with 5-10% cryoprotectant agents like mannitol or trehalose and frozen at -80°C and lyophilize the resulting mixture to generate a free-flowing powder required to reconstitute before use. Due to micronized powder form, the phytosomes developed by this method exhibits exceptional stability (>24 months) along with significantly high drug loading capacity.¹⁹⁻²¹

Anti-solvent precipitation method

This is a fast and sustainable method for manufacturing phytosomes, especially for heat-sensitive phytoconstituents. In this manner, the phytoconstituent and phospholipid dispersed in the smallest possible amount of water-miscible organic solvent (ethanol or acetone). The resultant transparent mixture injected gradually onto a surplus volume of an anti-solvent solution (distilled water or a pH 6.5-7.4 phosphate buffer saline solution) in moderate stirring at 500-1000 rpm. A rapid fall in solvent strength produces immediate super saturation, resulting in the precipitation of nano-scale phytosomal particles via molecular complexation. The precipitate is gathered via centrifugation, rinsed to remove residual solvent, and dehydrated by means of air-drying or lyophilization to produce a fine powder that can quickly disperse into stable vesicles when hydrated.^{19, 21}

Among all methods, thin film hydration and solvent evaporation are frequently utilised at laboratory as well as industrial level due to simplicity, high yield, and proven scalability in commercial phytosome products.^{19, 21} General method for preparation of phytosomes demonstrated in figure number 2.

Characterization of Phytosomes

The uniformity and stability profile of phytosomes influenced by formulation and

processing variables, including but not limited to: the type of solvent, stoichiometric ratio between active agent and PC, processing method, temperature, drying conditions, rotations per minute (rpm), etc. All mentioned parameters could significantly affect the stability of final product under storage conditions. Thus, these parameters can be studied, optimized and validated through suitable analytical methods to confirm molecular complexation, morphology, and performance metrics of the vesicles.²³⁻²⁴

Morphological analysis

Morphological examination of phytosomes vesicles employs electron microscopy techniques, such as digital microscopy, transmission electron microscopy (TEM), and scanning electron microscopy (SEM), to visualize phytosomes vesicle size, shape, and surface topology. In SEM, rays of three different electrons are projected: primary backscattered electrons, secondary electrons, and Auger electrons, along with X-rays, which strike directly onto the sample. Secondary electrons of SEM disclose the surface topography, backscattered electrons provide atomic number, and X-rays provide the elemental composition, while confirming the spherical or vesicular structures with sizes of 100-300 nm. On the other hand, TEM uses transmitted electrons to analyze the sample and provides high-resolution surface topography, comprehensive interior structure, and crystallography, which confirms lipid bilayer integrity and entrapment with active agents.²⁵⁻²⁶

Particle Size, Polydispersity Index (PDI) and Zeta Potential

The particle size and zeta potential of phytosomes can be analysed by dynamic light scattering technique using a method via photon correlation spectroscopy (PCS), which measures the hydrodynamic diameter in nanometres. The stability of phytosomes increases with the increase in electrostatic repulsion between the particles. Physical stability of the dispersion is predicted by a zeta potential, evaluated by a light scattering method, which helps to quantify surface charges. A value greater than 20 mV ensures electrostatic repulsion and high colloidal stability.^{22, 24-25}

Entrapment Efficiency (%EE)

The amount of drug entrapped into phyto-phospholipid complex is evaluated by ultra-centrifugation technique. Phyto-phospholipid

complex (or phytosomes) - 10 mg of drug are dispersed into a phosphate-buffered solution and subjected to centrifugation for a specific time at the desired speed (generally, the highest speed for the minimum time). Following separation of the supernatant layer via filtration, it is analysed by either HPLC or UV-Vis spectroscopy. Calculate drug entrapment by following formula:²³⁻²⁴

$$\text{Entrapment efficiency (\%)} = \left[\frac{\text{(total amount of drug - amount of free drug)}}{\text{(total amount of drug)}} \right] \times 100$$

Thermal Analysis and Transition Temperature

Thermal analysis techniques like differential scanning calorimetry (DSC) helps to determination of transition temperature of the phyto-phospholipid complex utilised to analyse the phase transition and thermal stability of phytosomes complex by changes appearance of new peaks and vanishing of old peaks, modifications to peak shape, peak temperature, and melting point, peak onset of action, relative peak area, enthalpy, or deletion of endothermic peaks usually associated with melting point of active agents and transition temperature of PC (30–50°C), indicates fluidity of vesicular membrane.^{22, 27-28}

Crystallinity and Polymorphism

The X-ray diffraction (XRD) technique is employed to analyse the crystalline nature and polymorphic behaviour of phytosomes. A sharp crystalline peak of free phytoconstituents (2θ, at 10–30°), generally disappears or reduces due to phytosomes complexation, confirming molecular dispersion of active constituent within the phospholipid matrix.^{23-24, 28}

Solubility and partition coefficient (log P) value

Phyto-phospholipid complexes are developed to alter the solubility of phytoconstituents. The solubility behaviour of the phyto-phospholipid complex typically determined by shake-flask or n-octanol/water systems.²⁷⁻²⁸

Infrared Spectroscopy (IR)/Fourier transform infrared spectroscopy (FTIR)

IR spectroscopy can help to analyse structural and chemical stability of phytosome complex, phospholipids, and plant drugs. The complex formation of phytosomes can be verified by comparing the IR spectrum of phytosome complex with the spectrum of phospholipid,

phytoconstituents/drug, and its physical mixture separately. Complex formation indicated by the shifting or broadening of original characteristic peaks, which indicates typical interactions between drug and phospholipid.²⁹

In-Vitro and In-Vivo Evaluations

The in-vivo and in-vitro models for phytosome evaluation can be selected based on the expected therapeutic action of the active phytoconstituents or medication included in phytosome formulation.

Storage conditions and Stability profile of phytosomes

Storage conditions Phytosomes, being delicate structural aggregates, need to be stored carefully to prevent peroxidation of lipids, hydrolysis, and vesicle aggregation. Thus, to maintain stability and avoid deterioration, dried phytosomes should be stored at temperatures ranging from -20 to 30°C. While phytosomes in solution form should be stored at 4 ± 2°C in amber, airtight containers with silica gel desiccant (<60% relative humidity) protected from light. Light can accelerate the breakdown of phytosomes.²⁴⁻²⁵

Stability studies for phytosomes: Based on study parameters, the nature of phytoconstituent, phospholipid, and solvent used, a stability studies protocol should be developed based on ICH-Q2 (R1) guidelines, which generally includes long-term testing at 25 ± 2 °C/60 ± 5% relative humidity (RH) and accelerated testing at 40 ± 2 °C/75 ± 5% RH for 6–12 months. Stability studies help to investigate the phytochemical changes of phytosomes throughout storage and circulation. Over several months, stability could be determined by measuring mean vesicle size, zeta potential, size distribution, and trap efficiency.²³⁻²⁵

Merits of phytosomes technology

Enhanced solubility and absorption of phytoconstituents: Phytosomes vesicles improves the solubility and bioavailability phyto-active agents by drug-lipid complexation, tends to increase the aqueous solubility of phytoconstituents.³¹⁻³²

Maryana et al. (2016)³¹ developed Silymarin-PC phytosomal complex with stoichiometric ratios of 1:5, 1:10, and 1:15, by adopting a thin-layer hydration technique, resulting in amphiphilic molecular complexes that enhance the restricted aqueous solubility of free silymarin.

Synergistic effect: A predominantly

used phospholipid for phytosomes complexation is PC, an essential part of the cell membrane, PC nourishes skin. Thus when used in skin care preparation provides a synergistic effect⁽³⁴⁻³⁵⁾. PC also has a potential hepatoprotective activity. When complexed with hepatoprotective agents such as silymarin, it shows a synergistic.^{33, 35-36}

Chi et al. (2020)³⁶ developed, Nanosuspensions of silybin–phospholipid phytosome (SPC-NP) and demonstrated that, SPCs-NP exhibits synergistic hepatoprotective efficacy beyond bioavailability enhancement of silybin, when compared to free silybin. The study showed marked increase in Cmax and AUC providing a stronger hepatoprotective activity in CCl₄-induced liver injury models (greater reduction in ALT/AST, MDA, and histological damage) resulting in superior overall liver protection that exceeds the sum of individual components.

The Silymarin phytosomes developed by Maryana et. al. (2016)³¹, aiming to enhance the bioavailability of silymarin also demonstrated the synergistic role of phospholipid.

Topical/dermal application: Phytosomes complex tends to improve the lipophilicity highly water soluble active agents by developing

stable phyto-phospholipid complexes. This leads significant enhancement in penetration ability of such agents via lipid rich skin barrier, indicating that the technique is appropriate for topical and transdermal medication administration, making it a viable approach for cosmetic preparations.^{34, 37-38}

High drug entrapment efficiency: The rate of drug-lipid complexation in the phyto-phospholipid complex is quite remarkable as compared to liposomes.^{5, 38}

Reduced dose and side effects: As targeted drug delivery can be achieved in phyto-phospholipid complexes, the dose required and dosing frequency can be reduced.⁴⁰⁻⁴¹

Maiti et al. (2007)⁹ conducted a study on curcumin phytosomes and revealed that, in comparison to free curcumin, the curcumin-phospholipid complex was beneficial in producing therapeutic outcomes with lesser dosage and fewer adverse effects.

Enhanced stability: Encapsulation of phytoconstituents into phospholipid molecule developed a protective layer/envelop around active constituents, protects from gastric environment, environmental factors etc.

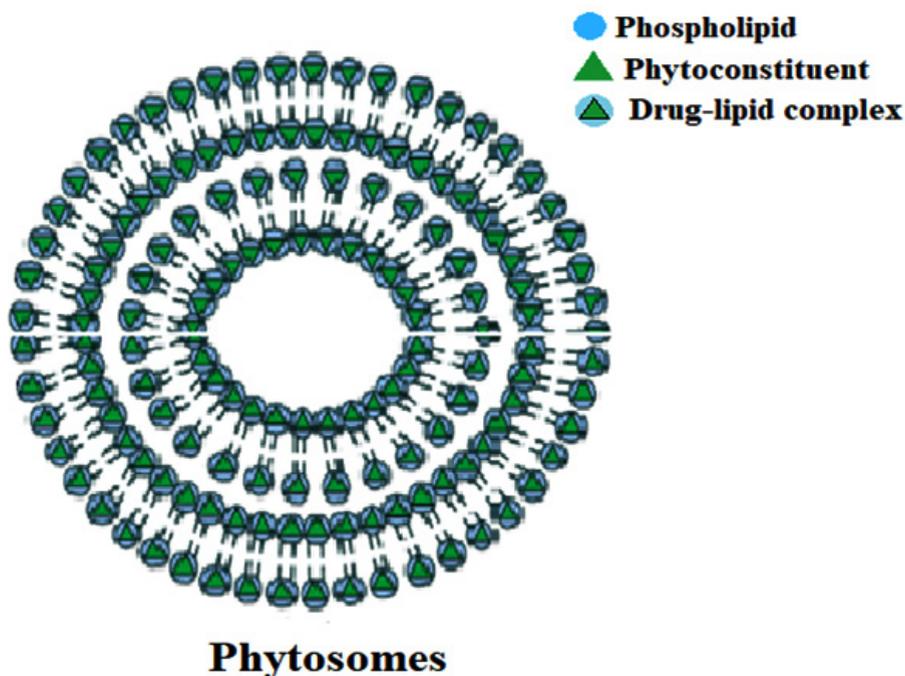


Fig. 1. Schematic representation of a vesicle encapsulating phytoconstituents within phospholipid

Effionora and Nadira (2018)⁴² formulated phytosomes loaded with maltodextrin gun Arabic microsphere for enhancing absorption and stability of *Camellia sinensis* extract (green tea extract).

Targeted drug delivery: Phytoconstituents complexed in phospholipids can help in achieving targeted drug delivery.

Nandayasa et al. (2023)⁴³ demonstrated that phytosomes technology could be used as targeted drug delivery for diseases like cancer.

Zhao and Liu (2016)⁴⁴, developed on Ginkgo biloba extract-loaded phytosomes showed targeted drug delivery to the brain, strengthening

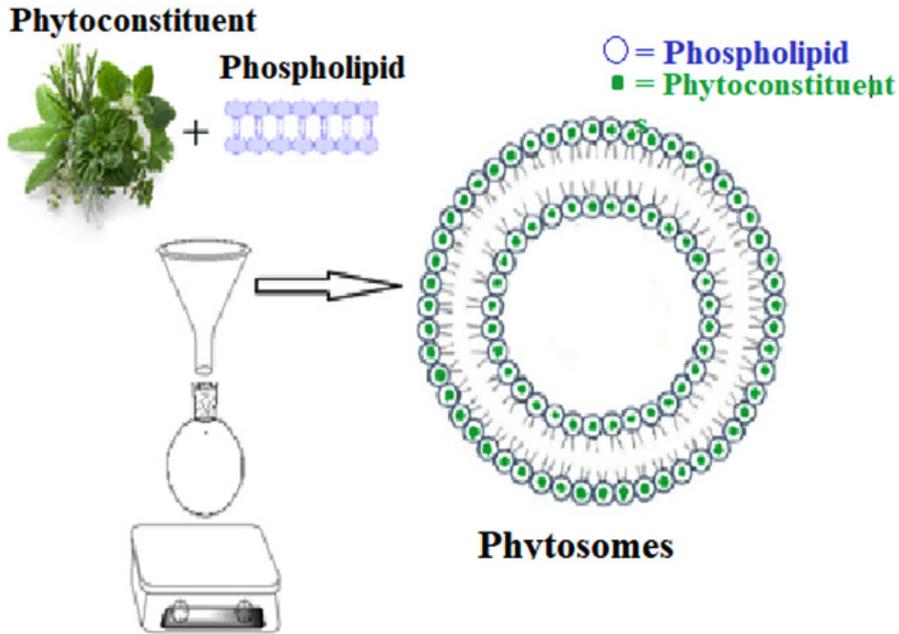


Fig. 2. General method for preparation of phytosomes

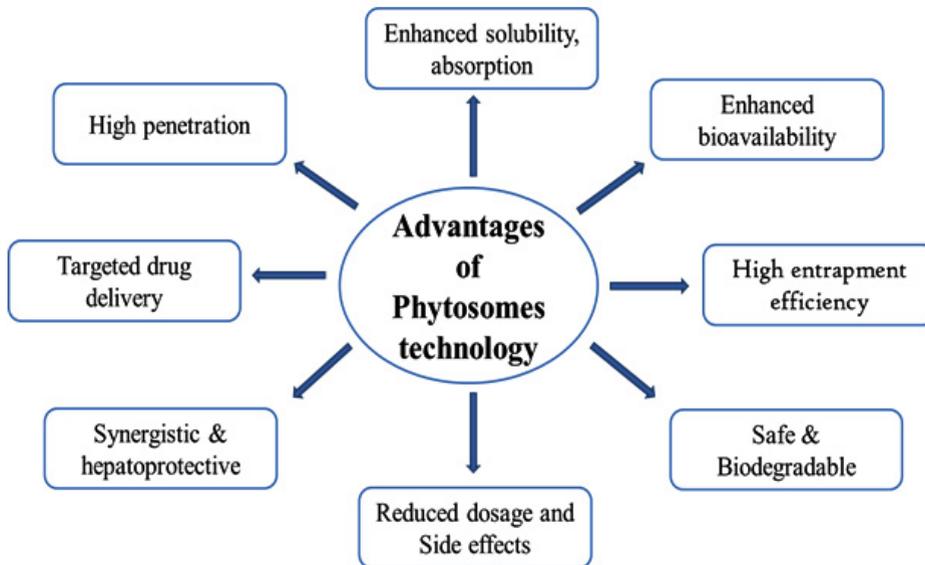


Fig. 3. Advantages of Phytosomes

the therapeutic efficacy in neurodegenerative disorders.

Typical advantages of phytosomes are highlighting figure number 3.

Therapeutic applications of phytosomes technology

Wound healing: Tafish et al., (2023)³⁰ developed CAR (carvacrol) loaded phytosomal formulation thin-film hydration, salting out and co-solvency method by using phospholipon 90 H and Lipoid S 100. Further study results demonstrated that its effective wound-healing ability has been increased after complexation with lipids compared to its free form of CAR.

Cancer treatment: the applicability of various herbal agents has been increased by applying phytosomes technology to enhance multiple factors such as solubility, absorption, targeted delivery, etc. Various phytosomes formulation developed as an anti-cancer targets are extensively discussed by Gaikwad SS, et al., (2023).²⁰

Breast cancer: Alhakamy et al., (2022)⁴⁶ paired quercetin (QRT) and scorpion venom peptides (SV) into phytosomes as an anticancer medicine. This phytosomes to aid in cellular intake and antiproliferative action against lung cancer cell line-derived human breast cancer cell (MCF-7). The results of the study indicated that a QRT

Table 1. Commercially available phytosomes⁴⁸⁻⁴

Product Name	Active Ingredient	Category	Therapeutic Uses
Siliphos®	Silybin, present in Silybum marianum or milk thistle	Antioxidant, Hepatoprotective	support and improves liver health, detoxification, hepatoprotection
Greenselect® Phytosome	Catechin, from green tea	Antioxidant, Anti-inflammatory, Weight loss	For management of weight, support metabolic demands, antioxidant and anti-inflammatory
Meriva®	Curcuminoids, obtained from Curcuma longa	Antioxidant, Anti-inflammatory	Used in management of joint health, inflammatory response, antioxidant support
Casperome®	A mixture of triterpenoid from gum resin and Boswellia serrate	Anti-inflammatory modulation	Manages joint and gut health, healthy inflammatory response
Quercefit®	Quercetin from Sophora japonica L.	Supports nutrition, endothelial function and histamine modulation, Anti-inflammatory, antioxidant,	improves seasonal immune health and provides anti-inflammatory effect, anti-oxidant
Vazguard®	Bergamot extract, polyphenolic extract obtained from Citrus bergamia	Enhances lipid-lowering effects	Supports health in metabolic syndrome, lipid profile management and cardiovascular health,
Ubiqsome®	Nonbotanical compounds madeup of Co-enzyme Q10	Antioxidant, energy production, supports electron transport chain	Antioxidant, engaged in energy generation, supports cardiovascular and cellular health
Hawthorn Phytosome	Flavonoids from Crataegus species	Anti-hypertensive and cardioprotective and antioxidant	Support CVS (cardioprotective), antihypertensive
Oleaselect™ Phytosome	Polyphenols from Olea Europaea or olive leaf	Antihyperlipidemic, anti-inflammatory, cardioprotective	Antihyperlipidemic, anti-inflammatory, cardioprotective

formulation might be a possible curative approach to treating breast cancer.

Cosmeceutical applications: Phytosomes have gained attention in the cosmeceutical and nutraceutical industries due to a marked enhancement in solubility, bioavailability, and stability of phytoactive agents^(34, 37-38). Indena, S.P.A., Italy⁴⁸⁻⁴⁹ has developed phytosomes with cosmetics application Meriva®, A potent anti-oxidant agent.

Obesity management: Menshawe et al., (2018) created a nano lipo-vesicle phytosomal thermo gel from soybean and examined it for anti-obesity properties. Author, discovered that the soy phytosomal thermo gel had a local anti-obesity effect on the abdomen of experimental male albino rats and a small systemic influence on lipid profiles⁽⁴⁷⁾. Greenselect® Phytosome, Indena, S.P.A., for weight loss management.⁴⁸⁻⁴⁹

Hepatoprotective effect: The Silybin-Phosphatidylcholine and Vitamin E complex was developed by Loguercio et al. (2019)³⁵ to treat non-alcoholic fatty liver disease and investigated its hepatoprotective activity along with antioxidant activity. Maryana et. al., (2016)³¹, also demonstrated the synergistic role of phospholipid.

Commercially available phytosomes: The fields of cosmetics, nutraceuticals, and pharmaceuticals all make extensive use of phytosome technology. Few of the phytosomes developed and marketed by Indena S.P.A., Italy discussed in table 1.⁴⁸⁻⁴⁹

Future scope: Phytosome technology is constantly improving in terms of stability and formulation diversity. Novel approaches for phyto-phospholipid complexation, drug-lipid ratio optimization, and methods for complex creation to boost stability are among the several developments. Phytosome approaches have also been investigated in terms of different formulations by combining them with nanotechnology and other innovative drug delivery systems. Munot et al. (2022)⁵¹ studied quercetin nanocochleated liposomes and discovered increased bioavailability, antioxidant activity, and anticancer potential.

As phytosome-based innovative formulations continue to be created, regulatory agencies should focus on establishing guidelines for developing and commercializing phytosomes and their products.

Limitations of phytosomes technology

Despite the numerous benefits, phytosomes technology-based products might encounter limitations such as lipid peroxidation, phytoconstituent leaching from the lipid membrane, inconsistency in formulation quality and large-scale formulation standardization. As the drawbacks associated with phytosomes technology is not yet completely documented, clinical evidence for this investigation is minimal.^{8, 16}

CONCLUSION

Phytosomes technology plays a significant role enhancing the applicability of phytoconstituents with poor bioavailability by forming stable phytoconstituents-lipid complexes. This complexation enhances the solubility due to lipid encapsulation, improves absorption and prolongs circulation of phytoconstituents within the systemic circulation. Despite several benefits, challenges remain with large-scale formulation standardization and the limited availability of clinical data compared to conventional drug delivery systems. In order to validate therapeutic claims, future research should focus on developing regulatory guidelines, refining formulation techniques, and conducting well-designed clinical trials. Overall, phytosomes offer an ideal platform for converting phytoconstituents into safe and efficiency dosage forms with a strong potential to bridge a gap between traditional herbal medication and a modern drug delivery technologies.

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This research did not involve human participants, animal subjects, or any material that requires ethical approval.

Informed Consent Statement

This study did not involve human participants, and therefore, informed consent was not required.

Clinical Trial Registration

This research does not involve any clinical trials.

Permission to reproduce material from other sources

Not Applicable

Author Contributions

Sonali Ravindra Patil: Conceptualization, Methodology, Data Collection, literature survey, investigation, formal analysis, Writing – Original Draft, Review & Editing; Santosh Subhash Chhajed: Conceptualization, Visualization, Supervision, critical revision of the manuscript for important intellectual content.

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