Int. J. Pharm. Investigation, 2027; 17(1):155-167.
https://www.jpionline.org

Review Article

Phytosome Technology: A Journey from Formulation Development to Industrial and Commercial Translation

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ABSTRACT

Phytosome technology has transformed the delivery of plant-based bioactives by effectively addressing issues such as poor solubility, instability, and limited oral absorption. Unlike traditional lipid carriers, phytosomes form molecular complexes with phospholipids and phytoconstituents, thereby enhancing their interaction with cell membranes and enhancing systemic exposure. This review highlights the growing importance of phytosomes as advanced delivery systems and explores future opportunities to translate natural bioactives into proven medical solutions by connecting core formulation principles with emerging industrial and commercial trends. A comprehensive literature review was conducted, encompassing advances in phospholipid engineering, hybrid delivery systems, patented technologies, and commercially available phytosome products across pharmaceuticals, nutraceuticals, and cosmeceuticals. Over time, phytosome technology has evolved from merely improving bioavailability to a versatile platform with expanding uses in pharmaceuticals, nutraceuticals, and cosmeceuticals. Advances in phospholipid engineering and hybrid delivery systems have further broadened its therapeutic and industrial applications. The transition of phytosomes from research samples to patented technologies and commercially available products highlights their practical significance. Despite these advances, manufacturing and regulatory challenges, as well as clinical validation challenges, still affect their future growth. Phytosomes hold considerable promise as advanced delivery systems for translating natural bioactives into proven medical solutions.

Keywords: Commercial translation, Nutraceuticals, Phytosome, Patent Landscape, Regulatory challenges.

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Received: 03-07-2026;
Revised: 19-08-2026;
Accepted: 24-10-2026.

INTRODUCTION

Phytosome technology has become a versatile platform for improving the delivery of plant-derived bioactives with poor biopharmaceutical properties. Phytosomes are molecular complexes formed by specific interactions between phospholipids and phytoconstituents, which lead to greater lipid compatibility and increased membrane permeability (Barani *et al.*, 2021a; Koppula *et al.*, 2025). Indena has used phytosome technology since the late 1980s. The products developed, such as Siliphos®, Meriva®, and Greenselect® Phytosome®, have proven to be superior in absorption and therapeutic efficacy compared with traditional herbal extracts (Dwivedi *et al.*, 2023). Many phytochemicals have inherent properties such as low aqueous solubility, low permeability, chemical instability, rapid metabolism, and extensive first-pass elimination, which affect their oral bioavailability and therapeutic efficacy, contributing to the growing interest in phytosomal systems (Drescher & van Hoogevest, 2020). To overcome these problems, various lipid-based delivery systems have been developed, including liposomes, transferosomes, ethosomes, niosomes, solid lipid nanoparticles, nanostructured lipid carriers, and micelles (Singh *et al.*, 2017). Phytosomes are a unique way, as the phytoconstituent does not just get entrapped in a carrier but forms a molecular complex with phospholipids. This unique structural configuration leads to better absorption, greater stability and favourable pharmacokinetic behaviour (Kavatagimath *et al.*, 2026). In recent investigations, new sources of phospholipids, multifunctional hybrid systems, and surface-modified systems have been developed, extending the scope of phytosome technology in terms of stability, targeting, and therapeutic performance (Karpe *et al.*, 2025). Most of the available reviews, however, focus on formulation strategies, individual phytochemicals, or specific therapeutic applications. By contrast, a thorough description of the formulation principles and recent advances in translating the concepts is still lacking. Hence, the present review offers an updated and comprehensive overview of phytosome technology by connecting formulation science with translational and industrial aspects, thus outlining

DOI: 10.5530/ijpi.20270226

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the current advancements and future potential for designing next-generation phytopharmaceutical and nutraceutical delivery systems.

DISTINGUISHING FEATURES OF PHYTOSOMES

Phytosomes have several unique characteristics that set them apart from traditional lipid-based delivery systems. The difference between liposomes, transferosomes, ethosomes and niosomes, where the active compound is physically entrapped in the vesicles, and phytosomes is that the bioactive is an integral part of the carrier system and is formed by molecular association of phytoconstituents with phospholipids, mainly phosphatidylcholine (Dwivedi *et al.*, 2023). The significant structural and functional difference between phytosomes and other lipid-based carriers is highlighted in Figure 1 and summarised in Table 1. Conventional vesicular systems rely on vesicle integrity and drug retention. However, they are prone to drug leakage, fusion, aggregation, and storage instability (Almuqbil & Aldhubiab, 2025; Lee, 2020).

In the same way, solid lipid nanoparticles, nanostructured lipid carriers, and micelles improve bioavailability by physically entrapping the drug in lipid matrices or surfactant assemblies, where drug release depends on matrix properties and partitioning behaviour (Mohammed *et al.*, 2023; Nayak *et al.*, 2025; Perumal *et al.*, 2022). However, phytosomes increase stability and bioavailability through phospholipid complexation, providing better membrane affinity and gastrointestinal absorption (Gaikwad *et al.*, 2021). This particular molecular organisation provides insight into the individual components involved in the formation of phytosomes and their role in formulation performance.

Components Used In Phytosome Formulation

Phospholipids

Phospholipids, which are amphiphilic biomolecules, consist of a glycerol backbone, two hydrophobic fatty acid chains, and a phospholipid head group, forming the basic structural components of biological membranes. In phytosomes, phospholipids, mainly Phosphatidylcholine (PC), form hydrogen-bond mediated complexes with phytoconstituents, which enhance the lipid compatibility, membrane permeation, gastrointestinal absorption and oral bioavailability of poorly soluble herbal bioactives (Figure 2) (Lu *et al.*, 2019). Moreover, phospholipids provide excellent emulsifying properties, biocompatibility, and stability, which in turn lead to better therapeutic efficacy of phytosomal formulations (Gnananath *et al.*, 2017). The most commonly used phospholipids are Soybean Phosphatidylcholine (SPC, ≥90-95% purity), Hydrogenated Soybean Phosphatidylcholine (HSPC, ≥95% purity), Egg Phosphatidylcholine (EPC, ≥90-99% purity) and Phosphatidylserine (PS, ≥98% purity) (Le *et al.*, 2019). According to their sources, phospholipids used in phytosome formulations can be classified as plant-derived, animal-derived, microbial, or synthetic or semi-synthetic, each with distinct compositional and functional properties. Plant-derived phospholipids derived from soybean, sunflower and rapeseed are the most used because of their biocompatibility, cost-effectiveness and their capacity to form stable complexes with phytoconstituents and phospholipids. Nevertheless, with their high level of unsaturation, they are prone to oxidative degradation (Gnananath *et al.*, 2017). Animal phospholipids, such as egg phosphatidylcholine and marine phospholipids with high omega-3 fatty acid content, offer superior membrane compatibility and emulsifying properties but are more expensive and less stable against oxidation (Ahmmed *et al.*, 2020). Microbial phospholipids from yeast, fungi, algae and bacteria have become an attractive alternative that can be sustainably produced and tailored to lipid composition. However, there are still problems with large-scale production and purification (Silva *et al.*, 2023). On the other hand, synthetic and semi-synthetic phospholipids, such as DOPC, DPPC, DSPE and HSPC, are relatively expensive but offer better purity, reproducibility and oxidative stability, which make them attractive for more advanced phytosomal systems (van Hoogevest & Wendel, 2014).

Active Phytoconstituents and Solvent

In addition to phospholipids, phytoconstituents and solvents are the other major factors influencing the formation of phytosomes. Among the most widely studied phytoconstituents are polyphenolic compounds, including flavonoids, tannins, and phenolic acids, because of their structural compatibility and strong affinity for phospholipid complexation (Gaikwad *et al.*, 2021). Therefore, bioactive compounds such as curcumin, quercetin, rutin, and silymarin have been extensively used for incorporation into phytosomal systems because of their outstanding therapeutic activity and ability to form stable phyto-phospholipid complexes (Shriram *et al.*, 2022). The ratio of phytoconstituent to phospholipid has a major effect on the efficiency of complex formation, and ratios of 1:1-1:2 are most frequently used to achieve optimal drug loading and complexation efficiency (Karpe *et al.*, 2025; Pereira *et al.*, 2016). Many studies have shown that as phospholipid content increases, entrapment and stability increase up to an optimum value. The entrapment efficiency of *Tinospora cordifolia* phytosomes, for example, increased from 72.34% to 95.91% as the ratio increased from 1:1 to 1:2 (Peeriga *et al.*, 2025). Likewise, the optimised quercetin, *Pongamia pinnata* and curcumin phytosomes exhibited particle sizes less than 205 nm, entrapment efficiency of more than 73-94% and improved zeta potential, emphasising the importance of the ratio of components in the formulation performance (Kamireddy *et al.*, 2025; Karpe *et al.*, 2025; Mankan *et al.*, 2025).

After selecting appropriate phytoconstituents and phospholipids, the choice of solvent plays an important role, as it facilitates molecular interactions and promotes stable complex formation.

The solvent system directly affects the efficiency of complexation, particle size, entrapment efficiency, and formulation stability (Gnananath *et al.*, 2017; Krishnaswami *et al.*, 2025). Conventional solvents such as dichloromethane, acetone, and ethyl acetate have been used, but due to their toxicity and residual solvent issues, there is a growing shift toward green solvents, notably ethanol and ethanol-water mixtures (Raghav *et al.*, 2024). Due to its good solubilising property, regulatory approval and safety, ethanol is used as a solvent for preparing phytosomes (Shriram *et al.*, 2022). Solvent systems can be used to achieve homogeneous mixing and controlled complex precipitation, thereby enhancing drug incorporation and physicochemical properties. Efficient solvent removal methods, on the other hand, can guarantee product quality and scalability.

METHODOLOGY

Solvent Evaporation Technique

One of the most widely known and practised techniques for preparing phytosomes is solvent evaporation. It has underpinned several subsequent process changes (Lombardo & Kiselev, 2022). In this method, the phytoconstituent and phospholipid are dissolved in a common organic solvent, and the solvent is then removed stepwise to form a phyto-phospholipid complex. However, because relatively large particles are often obtained, the method is often combined with downstream size-reduction methods. For example, a pyrazoloquinolinone ligand-phospholipid complex was prepared by solvent evaporation, followed by high-pressure homogenisation, resulting in nanoparticles with sizes of 145-165 nm and entrapment efficiencies of > 96% (Stanković *et al.*, 2025). In the same way, the use of homogenisation and ultrasonication in the preparation of *Hydnora abyssinica* phytosomes resulted in a particle size of 72.56±9 nm and an entrapment efficiency of 95.45±3.20% (Daba *et al.*, 2024). These studies show the adaptability of solvent evaporation and that it can be performed using typical pharmaceutical equipment, making it suitable for scale-up and forming the basis for several advanced phytosome manufacturing strategies.

Rotary Evaporation / Thin-Film Formation Technique

Rotary evaporation is an improvised version of the solvent evaporation method in which continuous rotation under reduced pressure forms a uniform, thin lipid film. It reduces thermal degradation of heat-sensitive phytoconstituents (Prema *et al.*, 2024). This technique is a further development of the solvent evaporation method, yielding a more homogeneous distribution of phytoconstituents and phospholipids, thereby increasing the reproducibility of complex formation. For instance, the quercetin phytosomes produced by rotary evaporation had a particle size of ~204.6 nm, entrapment efficiency of 84.48-88.59%, and a zeta potential of -28.6 mV (Kamireddy *et al.*, 2025). In a similar way, the polyherbal formulation of milk thistle, curcumin and *Ginkgo biloba* extracts formed stable complexes with a zeta potential of -29.6 mV (Prema *et al.*, 2024). The results show that rotary evaporation is one of the most commonly used methods for developing phytosomal systems that provide reproducible, controlled physicochemical properties.

Thin-Film Hydration Method

The thin-film hydration is an extension of the thin-film formation method, in which the dry lipid film is converted into vesicular phytosomal dispersions by adding a hydration step (Raouf *et al.*, 2024). When the film is hydrated in an aqueous medium, multilamellar vesicles form, which can be reduced in size by homogenisation or sonication. For instance, the particle size of tetrahydrocurcumin phytosomes prepared in this manner was 317.35±5.48 nm, and the zeta potential was -29.88±0.35 mV, which

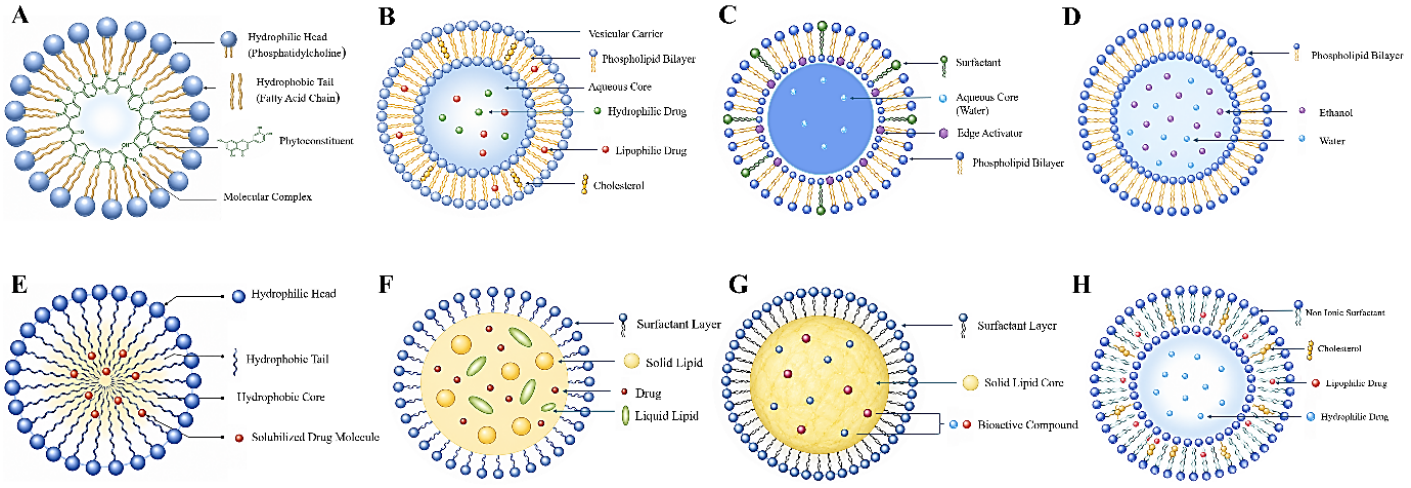


Figure 1: Schematic comparison of lipid-based delivery systems. (A) Phytosome: phospholipid-phytoconstituent molecular complex; (B) Liposome: phospholipid bilayer vesicle with an aqueous core; (C) Transferosome: ultra-deformable vesicle containing edge activators; (D) Ethosome: ethanol-rich phospholipid vesicle; (E) Micelle: self-assembled surfactant aggregate with a hydrophobic core; (F) Nanostructured Lipid Carrier (NLC): mixed solid-liquid lipid matrix; (G) Solid Lipid Nanoparticle (SLN): solid lipid matrix-based carrier; (H) Niosome: non-ionic surfactant vesicle containing cholesterol.

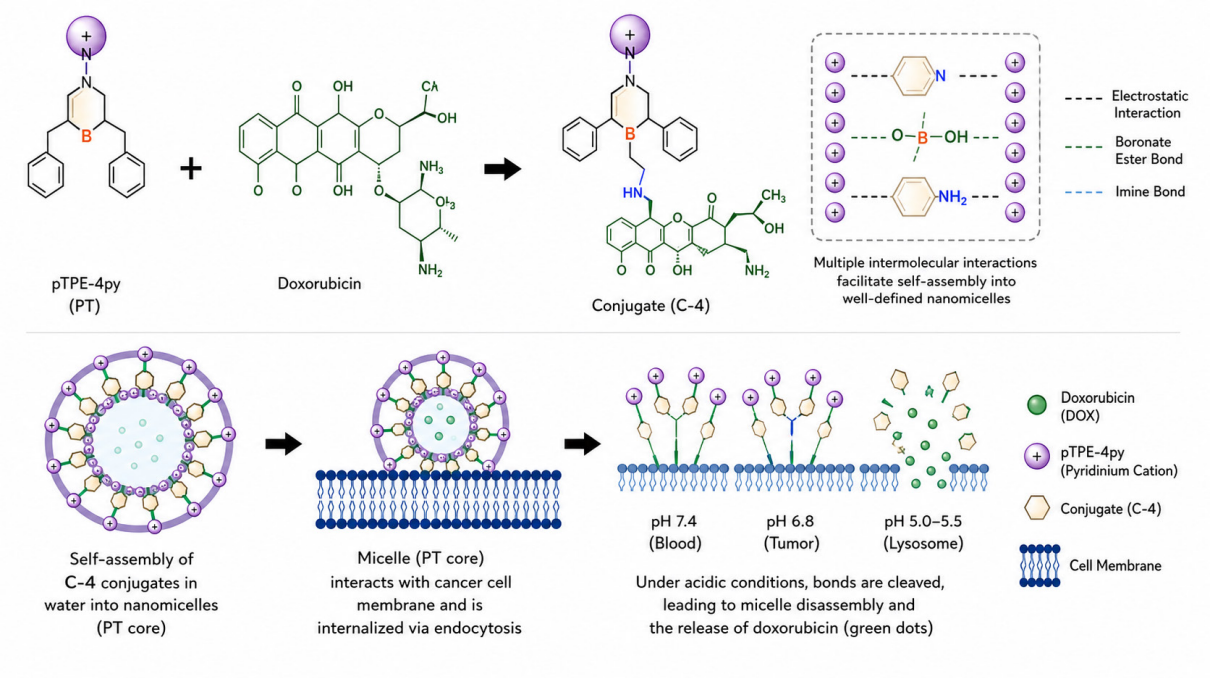


Figure 2: Schematic illustration of phytosome formation and its functional advantages. Non-covalent interactions between phosphatidylcholine and polyphenolic phytoconstituents form stable molecular complexes that spontaneously self-assemble into vesicular phytosomes. This unique architecture enhances membrane affinity and gastrointestinal absorption while providing protection against degradation, thereby improving stability and bioavailability.

confirmed the successful formation of vesicles (Raouf *et al.*, 2024). Moreover, the particle size of hinokitiol-loaded phytosomes was reduced to 138.4 nm, and the entrapment efficiency was increased to 92.77% by the process of homogenisation (Ahmed *et al.*, 2024). The results indicate the versatility of thin-film hydration as a method for preparing stable phytosomal vesicles.

Anti-Solvent Precipitation Method

In anti-solvent precipitation, a non-film-based method, the formation of phyto-phospholipid complexes is promoted by controlled precipitation from solution (Direito *et al.*, 2025). The process is relatively simple and does not require the formation of a thin film, and can be processed efficiently. For example, the entrapment efficiency of *Tinospora cordifolia* phytosomes prepared by the anti-solvent precipitation method was 95.91%, and the formulation yield was approximately 80% (Peeriga *et al.*, 2025). Similarly, polyherbal phytosomes containing extracts of *Acalypha indica, Pergularia daemia*, and *Coleus amboinicus* produced 158-nm nanoparticles with an entrapment efficiency of 86.94% (Vijayakumar *et al.*, 2025). The results show the applicability of the anti-solvent precipitation method for obtaining highly entrapped phytosomal systems.

Co-Solvency Technique

The co-solvency technique was developed to overcome differences in the solubility of phytoconstituents and phospholipids by employing mixed-solvent systems that facilitate efficient molecular interactions prior to drying (Mankan *et al.*, 2025). This approach is particularly useful for complex herbal extracts and thermolabile bioactives. For example, curcumin-lecithin complexes prepared using an ethanol-water co-solvent system followed by spray drying achieved entrapment efficiencies of 86.50-93.97% (Mankan *et al.*, 2025). Similarly, α-mangostin-Phospholipon® 90G phytosomes, prepared using a chloroform-methanol system followed by lyophilisation, yielded nanoparticles of 138.9 nm with an entrapment efficiency of 95.10% and a zeta potential of -44.5 mV (Alamoudi *et al.*, 2024). Collectively, these findings underscore the versatility of the co-solvency approach for producing phytosomal formulations with high entrapment efficiency and favourable physicochemical characteristics.

Mechanical Dispersion and Emulsification Approach

Mechanical dispersion and emulsification are particularly suitable for phytoconstituents with limited lipophilicity, in which phospholipids dissolved in an organic phase are brought into contact with an aqueous phase containing the phytoconstituent via agitation, emulsification, or ultrasonication to facilitate complex formation. Using this approach, *Pentaclethra macrophylla* seed extract phytosomes achieved entrapment efficiencies of up to 93% (Ugwu *et al.*, 2025). Similarly, *Callistemon citrinus* extract phytosomes prepared by emulsification followed by ultrasonication produced nanoparticles of approximately 130 nm with entrapment efficiencies exceeding 80% (Magaña-Rodríguez *et al.*, 2025). These results demonstrate the potential of mechanical dispersion to incorporate relatively hydrophilic phytoconstituents into formulations with desirable characteristics.

Comparative Overview of Preparation Methods

These preparation methods collectively offer adaptable strategies for customising phytosomal systems to specific phytoconstituents and applications, each with unique benefits related to particle size, entrapment efficiency, stability, and manufacturability. Among them, solvent evaporation, including rotary evaporation, and anti-solvent precipitation are particularly suitable for industrial-scale production due to their straightforward process, reproducibility, and compatibility with standard pharmaceutical equipment. The typical workflows for these methods are shown in Figure 3. Therefore, choosing the right preparation method should depend on the physicochemical properties of the phytoconstituent, desired formulation characteristics, scalability, and process requirements to ensure optimal phytosomal performance.

CHARACTERISATION

Particle Size, Polydispersity Index and Zeta Potential

The particle size, Polydispersity Index (PDI), and zeta potential are the key quality attributes which affect the stability, uniformity, and biological activity of phytosomal systems. Dynamic Light Scattering (DLS) and Electrophoretic Light Scattering (ELS) are widely used methods for determining these parameters (Maguire *et al.*, 2018). These are greatly influenced by the phytoconstituent, phospholipid composition and the conditions of preparation. For instance, the particle size of Verbascoside phytosomes was 136.2 nm, with a PDI of 0.13, indicating high homogeneity (Cardullo *et al.*, 2025). In the same manner, the phytosomes of Adiantum capillus-veneris exhibited a particle size of 187 nm, PDI of 0.2421 and a zeta potential of -17.22 mV. By contrast, the Aprepitant phytosomal emulsions exhibited a smaller particle size and a lower zeta potential (-59.0±2.54 mV), indicating better colloidal stability (Jagtap *et al.*, 2023). All the above parameters provide significant evidence of the formation of stable, uniformly dispersed phytosomal systems (Németh *et al.*, 2022).

Entrapment Efficiency

One important parameter indicating the formation of phytosomes is Entrapment Efficiency (EE). It indicates the degree of incorporation of the phytoconstituents into the phospholipid matrix. It is usually calculated by isolating the free drug from the phytosomal fraction and then quantitatively analysing it (Suwanpitak *et al.*, 2024). Phytosomes have high EE values due to high intermolecular interactions. For instance, Vitexin phytosomes were prepared using soybean and egg phosphatidylcholine, which resulted in entrapment efficiencies of more than 98% (Peanparkdee & Yooying, 2023). Adiantum capillus-veneris, Sonneratia alba, and Bergamot essential oil phytosomes, on the contrary, showed EE values of 97-98.4%, 82.40%, and 87.89±4.14%, respectively (Albash *et al.*, 2023; Dewi *et al.*, 2024; Jagtap *et al.*, 2023). The results show efficient phytoconstituent-phospholipid complexation.

Morphological and Structural Characterisation

Morphological and structural characterisation gives direct evidence of the formation of phytosomes. It differentiates between the real phytosome, the phyto-phospholipid complex, and a simple physical mixture. Most phytosomal formulations have a spherical, uniformly dispersed vesicular organisation.

Table 1: Comparative characteristics of phytosomes and other lipid-based drug delivery systems.

Parameter	Phytosome	Liposome	Transferosomes	Ethosomes	Niosomes	SLNs	NLCs	Micelles
Structure	Drug-phospholipid complex	Bilayer vesicle	Ultra-deformable vesicle	Ethanol-rich vesicle	Surfactant bilayer vesicle	Solid lipid matrix	Solid + liquid lipid matrix	Core-shell aggregate
Components	Phospholipid+ phytoconstituent	Phospholipid + cholesterol	Phospholipid + edge activator	Phospholipid + ethanol	Surfactant + cholesterol	Solid lipids	Solid + liquid lipids	Amphiphilic surfactants
Drug Loading Mechanism	Complexation	Encapsulation	Encapsulation	Encapsulation	Encapsulation	Matrix entrapment	Matrix entrapment	Core solubilisation
Physical Stability	High	Moderate	Moderate	Good	Good	Moderate	High	Moderate
Drug Leakage	Low	High	Moderate-High	Moderate	Low	Moderate	Low	Moderate
Drug Loading Capacity	High	Moderate	Moderate-High	Moderate-High	High	Moderate	High	Moderate-High
Scalability	Moderate	Moderate	Moderate	Moderate	High	High	High	High
Advantage	Enhances phytoconstituent bioavailability	Suitable for hydrophilic & lipophilic drugs	Superior skin penetration	Enhanced transdermal delivery	Good stability	Improves oral delivery	High loading & stability	Excellent solubilisation
Limitation	Limited commercialisation	Leakage & instability	Storage instability	Ethanol-related instability	Limited hydrophilic loading	Drug expulsion on storage	Complex formulation	Dissociation below CMC

Abbreviations: SLN, solid lipid nanoparticle; NLC, nanostructured lipid carrier; CMC, critical micelle concentration.

Table 2: Commercially available phytosomal products and their therapeutic applications.

Sl. No.	Product (Company)	Active Phytoconstituent	Therapeutic Application	Dose(mg/day)	Major Marketed Regions
1.	Siliphos® (Indena, Italy)	Silybin ≥29.7-36.3%	Hepatoprotection and antioxidant support	160-480	USA, Canada, EU, Australia
2.	Greenselect® Phytosome® (Indena, Italy)	Catechins ≥19-25%, EGCG ≥13%	Weight management and metabolic support	300	Italy, EU, USA, Canada, Australia, Japan
3.	Leucoselect® Phytosome® (Indena, Italy)	OPCs >25-30%	Cardiovascular and vascular health	300	USA, Canada, EU, Australia
4.	Ginkgoselect® Phytosome® (Indena, Italy)	Ginkgoflavonglucosides ≥7% + terpene lactones ≥2%	Cognitive and circulatory support	120-360	USA, Canada, EU, Australia, Japan
5.	Meriva® (Indena, Italy)	Curcuminoids ≥18-22%	Anti-inflammatory, joint and metabolic health	500-2000	USA, Canada, EU, Australia, India, Japan
6.	Quercefit® (Indena, Italy)	Quercetin ≥34-42%	Immune and respiratory support	250-500	USA, Canada, EU, Australia
7.	Berbevis® (Indena, Italy)	Berberine ≥28-34%	Blood glucose and lipid management	300-500	USA, EU
8.	Ubiqsome® (Indena, Italy)	Coenzyme Q10 ≥18-22%	Healthy ageing and cardiovascular support	100-200	USA, Canada, EU, Australia
9.	Vazguard® (Indena, Italy)	Bergamot flavanols ≥14-18%	Lipid management and cardiovascular health	500-1000	USA, EU
10.	Relissa™ (Indena, Italy)	Rosmarinic acid ≥17-23%	Sleep quality and mood support	200-400	USA, EU
11.	Cronilief™ (Indena, Italy)	Palmitoylethanolamide	Inflammatory response support	300-600	USA, EU
12.	Green Coffee Phytosome® (Indena, Italy)	Chlorogenic acids	Weight management and metabolic syndrome	400	USA, EU
13.	Saw Palmetto Phytosome® (Indena, Italy)	Fatty acids ≥85% + β-sitosterol	Prostate health	320	USA, Canada, EU
14.	Rhodiola Phytosome® (Indena, Italy)	Rosavins ≥3% + salidroside ≥1%	Adaptogen and stress reduction	200-400	EU, USA, Canada, Japan
15.	Ginselect® (Indena, Italy)	Ginsenosides	Energy and immune support	200-400	EU, USA, Canada, Korea, Japan
16.	AprésFlex® (Laila Nutraceuticals, India)	*Boswellia serrata* extract (20% AKBA)	Joint health and osteoarthritis	100	USA, Canada, EU, India
17.	BioPerPhytosome® (Bioreal Technologies, India)	Curcuminoids	Anti-inflammatory and joint health	500-1000	India, EU, USA
18.	Terminalia arjuna Phytosome® (Arjuna Natural, India)	Arjunolic acid + tannins	Cardiovascular support	250-500	India, EU, USA
19.	Ashwagandha Phytosome® (Arjuna Natural, India)	Withanolides ≥5%	Adaptogen and cognitive support	300-600	India, USA, EU

Dosage ranges represent commonly marketed or clinically investigated daily doses. They may vary according to product formulation and regional regulatory recommendations. Percentages indicate the standardised content of the principal active phytoconstituents. Proprietary products are identified by their respective manufacturers. In contrast, products without a specified company represent generic phytosomal formulations marketed by multiple nutraceutical brands. Abbreviations: EGCG, epigallocatechin gallate; OPCs, oligomeric proanthocyanidins; AKBA, acetyl-11-keto-β-boswellic acid; EU, European Union.

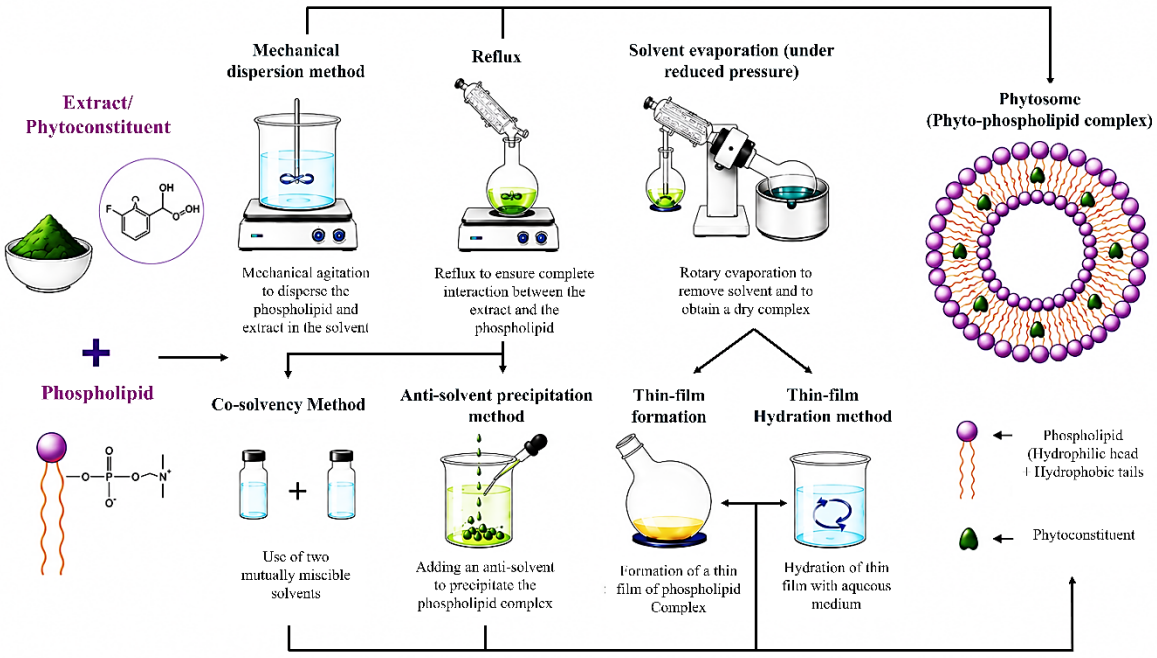


Figure 3: Schematic overview of the major phytosome preparation methods, including solvent evaporation, rotary evaporation/thin-film formation, thin-film hydration, anti-solvent precipitation, co-solvency, and mechanical dispersion/emulsification techniques used for phytoconstituent-phospholipid complex formation.

They are evaluated using microscopic methods such as SEM, TEM, FESEM, and AFM (Aziz *et al.*, 2025). For example, the phytosomes of *Pongamia pinnata* exhibited spherical particles with good dispersion (Kapse *et al.*, 2025), and the spray-dried curcumin phytosomes exhibited characteristic core-shell morphology (Mankan *et al.*, 2025). FTIR, DSC, XRD and NMR analyses are also used to confirm the structural integrity. FTIR studies of aprepitant phytosomes showed hydrogen-bond interactions that were not chemically modified (Li *et al.*, 2023). However, DSC and XRD analysis showed that the crystallinity of carvacrol and quercetin phytosomes was decreased, respectively (Kamireddy *et al.*, 2025; Tafish *et al.*, 2023). All these results collectively support the formation of stable supramolecular complexes with organised nanostructures rather than a simple physical mixture of phytosomal complexes.

Stability

Stability assessment is important to ensure that the physicochemical properties and therapeutic activity are maintained throughout the storage period. Parameters monitored under ICH-recommended conditions are particle size, zeta potential, entrapment efficiency, and visual appearance. For instance, the zeta potentials of Cyclopia subternata phytosomes ranged from -55.0 to -38.9 mV. They offered enhanced protection to the phenolic constituents(Human *et al.*, 2023). Similarly, the stability of Verbascoside phytosomes and Sonneratia alba phytosomes was found to be superior to a regular formulation (Cardullo *et al.*, 2025) (Dewi *et al.*, 2024). Spray-dried curcumin phytosomes, on the other hand, showed better thermal and digestive stability (Mankan *et al.*, 2025). All of these results collectively suggest that phospholipid complexation helps prevent phytoconstituent degradation and maintains the stability of the formulation.

BIOPHARMACEUTICAL ADVANTAGES

After physicochemical characterisation, the importance of phytosomal systems lies in enhancing the *in vivo* performance of phytoconstituents. Phytosomes can be formulated as lipid-compatible molecular complexes, thereby improving membrane affinity and enhancing intestinal absorption, increasing systemic exposure and partly bypassing first-pass metabolism (Thakur *et al.*, 2021). Besides, phospholipid complexation helps prevent chemical and enzymatic degradation of labile phytoconstituents, thereby enhancing bioavailability and circulation time (Lu *et al.*, 2019). Several studies have demonstrated such advantages; for instance, Apigenin phytosomes exhibited enhanced oral bioavailability and antioxidant activity compared with free Apigenin (Telange *et al.*, 2017). Silymarin phytosomes, on the other hand, demonstrated higher systemic exposure and better hepatoprotective efficacy compared with the conventional formulation (Shriram *et al.*, 2022). Similarly, human pharmacokinetic evaluation of Quercetin Phytosome® showed significant increases in C_{max} and AUC compared with unformulated quercetin, suggesting improved absorption and systemic availability (Riva *et al.*, 2018). These pharmacokinetic parameters and bioavailability collectively explain the biopharmaceutical benefits of phytosome technology and form a solid foundation for the successful translation of the technology

into clinically and commercially relevant phytopharmaceutical products.

Manufacturing And Regulatory Challenges

Although the biopharmaceutical benefits of Phytosome systems are impressive, translating these systems from the lab to commercial products is difficult. When scaling up to large-scale manufacturing, batch-to-batch consistency must be maintained, as botanical extract, phospholipid quality, and processing conditions can significantly impact critical quality attributes such as particle size, entrapment efficiency, and stability (Barani *et al.*, 2021). To overcome these problems, the QbD and DoE approaches have been increasingly used to develop robust and reproducible manufacturing processes (Dewi *et al.*, 2024). Furthermore, issues related to solvent use, residual toxicity, and ecological impact have prompted the adoption of more environmentally friendly solvents, such as ethanol, in large-scale production for sustainability (Kapse & Mulla, 2024).

In addition to manufacturing issues, other factors, such as regulatory restrictions, make the commercialisation of phytosomal formulations difficult. However, product approval and access to the global market are complicated by the lack of harmonised regulatory frameworks, variability in botanical materials, and the need for extensive quality, stability, toxicological, and pharmacokinetic evaluations (Kumbhar *et al.*, 2025; Poudyal *et al.*, 2022a). In addition, there is still a lack of large-scale clinical evidence to support regulatory acceptance and widespread clinical adoption (Sakure *et al.*, 2024).

However, manufacturing complexities and regulatory uncertainty are major translation barriers (Figure 4) that impede the successful commercialisation of many Phytosome products, despite their therapeutic potential.

Commercially Available Products

While the challenges of manufacturing and regulation remain, the success of several products shows that phytosomal formulations can help to close the gap between laboratory research and commercial application. Since Indena's advent of phytosome technology in 1989, many formulations have been developed for the treatment of hepatic, cardiovascular, metabolic, cognitive, and immune disorders. An overview of these products is presented in Table 2. The first success was with Siliphos®, a silybin-phosphatidylcholine complex, which proved to be more readily absorbed than conventional silymarin preparations (Sachdeva *et al.*, 2024). This was followed by the introduction of Meriva®, Greenselect® Phytosome, Ginkgoselect® Phytosome, and Leucoselect® Phytosome, which further expanded the therapeutic applications of phytosome technology and generated growing clinical evidence of its efficacy (Chettupalli *et al.*, 2025). In more recent times, phytosomal formulations have been used in sports nutrition, in healthy ageing and cosmeceuticals (Poudyal *et al.*, 2022). As these products have become more commercially successful, significant innovation has occurred, with many patents filed for novel formulations and methods for producing phytosols.

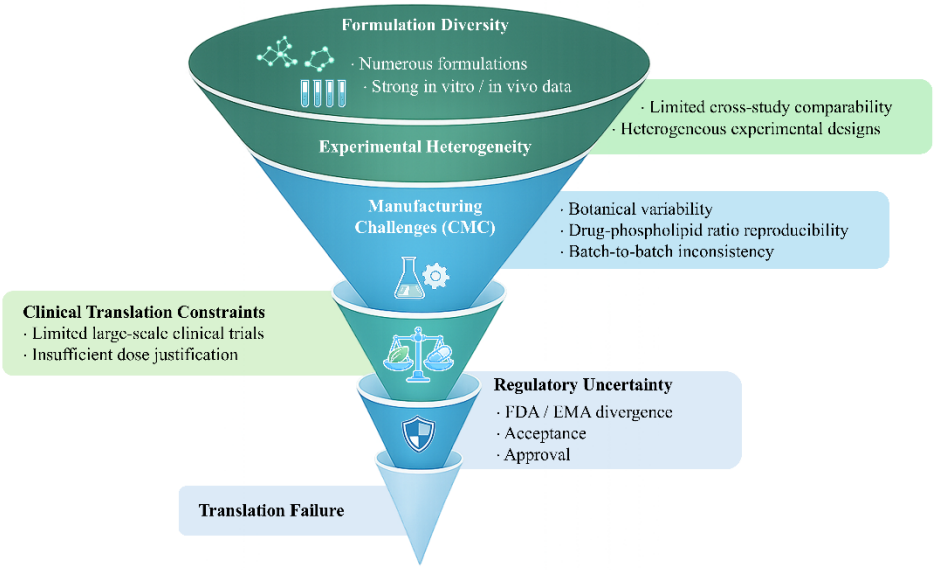


Figure 4: Regulatory and manufacturing bottlenecks in translating phytosome technology.

Table 3: Summary of representative patents (2023-2025) related to phytosome and phospholipid-based drug delivery technologies.

Sl. No.	Patent ID	Year	Title	Novelty	Country	Patent Status	Reference
1.	WO-2023173104-A1	2023	Phospholipid-containing discs and methods of manufacture	Dissolvable phospholipid-containing sheets/discs made by a specific high-viscosity casting and low-moisture drying process, enabling stable, high-load delivery of active ingredients.	International	PCT International Application	(Phipps *et al.*, 2023)
2.	DE-202023102351-U1	2023	Phospholipid-based nanovesicles for improved delivery of boswellic acids	Phytosomal composition of Boswellia acids and phospholipids at a weight ratio of 1:1 to 1:4 (preferably 1:3.5), forming nano-vesicles that improve solubility and bioavailability for treating inflammatory conditions like arthritis.	Germany	Utility Model	(Bhole *et al.*, 2023)
3.	CN-116271082-A	2023	Polysaccharide-modified phospholipid complex and preparation method thereof	Polysaccharide-modified medicinal phospholipid complex in which a phospholipid-drug-drug-drug complex is further coated or conjugated with polysaccharide to enhance tumour targeting, aggregation in tumour cells, and antitumor therapeutic efficacy via synergistic and active-targeting effects.	China	Patent Application	(Chen, 2023)
4.	RO-137953-A2	2024	Phytosomes with biologically active compounds from ginger rhizomes and rosehips	Phytosomes formed from ginger and rosehip hydroalcoholic extracts with phosphatidylcholine at controlled mass ratios, using a defined reflux-sonication process to yield nanoemulsions with high loading efficiency and enhanced bioavailability.	Romania	Patent Application	(Deleanu *et al.*, 2024)
5.	CN-118903230-A	2024	Methyl jasmonate-induced phospholipid nanomaterial of *Phellodendron amurense* extract	Methyl jasmonate-induced*Phellodendron amurense* adventitious root extract bonded with phospholipids to form a nanomaterial, enhancing stability, solubility, bioavailability, anti-inflammatory, and antitumor effects.	China	Patent Application	(Xu & Wang, 2024)
6.	IT-202200020370-A1	2024	Composition useful as an adjuvant in the treatment of acute and chronic pain	Composition combining*Boswellia serrata* extract and coenzyme Q10 (optionally in phytosomal form) for use as an adjuvant in treating acute/chronic pain, especially musculoskeletal inflammation/ trauma in athletes, showing synergistic anti-inflammatory and recovery effects without bleeding risk.	Italy	Patent Application	(Davolio, 2024)
7.	CN-117503946-A	2024	Preparation method of lignum naucleae extract phospholipid complex	Phospholipid complex of*Zanthoxylum avicennae* extract and phospholipids at mass ratio 1:1 to 1:5, prepared by solvent dissolution, stirring, and evaporation to boost oral bioavailability and mask bitterness for respiratory/inflammatory treatments.	China	Patent Application	(Chen *et al.*, 2024)

Sl. No.	Patent ID	Year	Title	Novelty	Country	Patent Status	Reference
8.	CN-118697762-A	2024	Pharmaceutical composition of naringenin and polyethene glycol	Drug composition in which naringenin is present as a phospholipid complex (phospholipid: naringenin weight ratio 2-10:1) combined with 20-30% compound polyethene glycol and excipients, to enhance solubility, stability, and overall bioavailability of naringenin.	China	Patent Application	(Wang *et al.*, 2024)
9.	US-12472188-B1	2025	Method and composition for an improved bioavailability delivery system	A multi-bioavailability delivery system in which a DHEA-derivative supplement is combined with multiple actives and processed as an encapsulated micronised phytosomal formulation	United States	Granted Patent	(Beri, 2025)
10.	EP-4661696-A1	2025	Nutraceutical composition based on *Boswellia serrata* gum resin	Nutraceutical composition of *Boswellia serrata* gum resin dry extract (50-90 wt%), stearic acid (4-45 wt%), and phosphatidylcholine source (1-5 wt%) to enhance bioavailability, with a defined preparation process.	Europe	EPO Patent Application	(Rossano *et al.*, 2025)
11.	KR-102881749-B1	2025	Cosmetic composition with vesicles containing poorly soluble polyphenols and water-soluble extracts	Cosmetic composition containing niosomal / phytosomal vesicles that co-encapsulate water-insoluble polyphenols and water-soluble extracts from*Magnolia sieboldii*, improving simultaneous delivery and stability of both hydrophobic and hydrophilic magnolia actives for skin applications.	Republic of Korea	Granted Patent	(Kim *et al.*, 2025)
12.	KR-102881748-B1	2025	Method for manufacturing niosome-based phytosomal vesicles	Method for preparing niosomal, phytosome-like vesicles that efficiently encapsulate both poorly soluble polyphenols and water-soluble actives, enabling stable co-delivery of hydrophobic and hydrophilic ingredients in cosmetic compositions.	Republic of Korea	Granted Patent	(Kim *et al.*, 2025)
13.	KR-20250006756-A	2025	Powder composition containing *Centella asiatica* extract	Powder composition containing titrated extract of *Centella asiatica* formulated with specific carriers into a stable powder form, improving handling and enabling convenient incorporation into dermatological or cosmetic products for skin benefits.	Republic of Korea	Patent Application	(Jin *et al.*, 2025)
14.	WO-2025109630-A1	2025	Water-soluble micellar formulation comprising curcumin and piperine	Water-soluble micellar formulation containing curcumin and piperine (weight ratio 20:1-50:1) with 77-82% non-ionic water-soluble surfactant and 13-18% cosurfactant, designed to markedly enhance solubility and bioavailability, and usable via multiple administration routes.	International	PCT International Application	(Waghode *et al.*, 2025)

Patent status refers to the state or jurisdiction of intellectual property protection. It includes national patent applications, granted patents, utility models, European Patent Office (EPO) applications, and Patent Cooperation Treaty (PCT) international applications. The novelty column summarises the principal technological innovations introduced by each patent. Abbreviations: PEG, polyethylene glycol; CoQ10, coenzyme Q10; SMEDDS, self-microemulsifying drug delivery system; PCT, Patent Cooperation Treaty; EPO, European Patent Office.

Patent Landscape

The growing market interest in phytosome technology has been accompanied by substantial intellectual property development, reflecting ongoing efforts to refine formulation design and broaden therapeutic applications. A summary of representative patents published from 2023 to 2025 is presented in Table 3. Recent innovations reveal a shift from conventional phytosome complexes toward more sophisticated phospholipid-based architectures, including nanovesicles, micelles, SMEDDS, and multifunctional hybrid systems to improve the solubility, stability, and bioavailability of poorly absorbed bioactives. Considerable attention has also been directed toward scalable manufacturing strategies and the development of solid phospholipid-based systems with enhanced stability and dissolution characteristics. Furthermore, emerging patents demonstrate the extension of phytosome technology beyond oral delivery to nutraceutical, dermatological, and cosmeceutical applications. Overall, current patent trends highlight the growing versatility of phospholipids as multifunctional components of advanced delivery platforms. However, limited *in vivo* and clinical validation remains a major challenge for the successful translation of next-generation phytosomal technologies.

CONCLUSION

Phytosome technology has come a long way from its original concept of enhancing oral bioavailability to its present state as a commercially proven, versatile drug delivery technology with a wide range of therapeutic applications. The phosphatidylcholine-phytoconstituent complex improves membrane permeability and lymphatic uptake, provides structural stability, reduces first-pass metabolism, and improves patient compliance, all of which help connect the dots between promising botanical pharmacology and clinically relevant results.

The commercial landscape remains highly consolidated, with Indena S.p.A.'s Phytosome® platform covering hepatoprotective (Siliphos®), anti-inflammatory (Meriva®), and cognitive (Ginkgoselect® Phytosome®) indications, implying that new market players will need botanicals or therapeutic areas. At the same time, the patent landscape shows a definite geographic shift, with Chinese and Korean filings joining established US and WO applications, and the list of actives being developed as phytosomal growing from classical flavonoids to oncology agents and cannabidiol and melatonin, pointing to a wider therapeutic spectrum that will lead the next generation of clinical and regulatory activity.

Although there is strong commercial precedent and a growing global patent estate, the lack of a standardised *in vitro-in vivo* correlation model and regulatory guidance for phytosomes is the major translational obstacle. There is a gap to be filled, and the ongoing integration of Quality by Design into manufacturing is a challenge for academia and industry to work together. Overall, phytosome technology is a fascinating blend of ancient and contemporary science, with the potential to shape the future of botanical medicine and pharmaceuticals.

ACKNOWLEDGEMENT

We acknowledge the support from the NGSM Institute of Pharmaceutical Sciences, Nitte (Deemed to be University), Mangalore, Karnataka, for providing library access, infrastructure and other necessary resources to complete this work.

ABBREVIATIONS

DOPC: 1,2-Dioleoyl-sn-Glycero-3-Phosphocholine; **DPPC:** 1,2-Dipalmitoyl-Sn-Glycero-3-Phosphocholine; **DSPE:** 1,2-Distearoyl-sn-Glycero-3-Phosphoethanolamine; **HSPC:** hydrogenated soy phosphatidylcholine; **SEM:** Scanning Electron Microscopy; **TEM:** Transmission Electron Microscopy; **FESEM:** Field Emission Scanning Electron Microscopy; **AFM:** Atomic Force Microscopy; **FTIR:** Fourier Transform Infrared Spectroscopy; **DSC:** Differential Scanning Calorimetry; **XRD:** X-ray Diffraction; **NMR:** Nuclear Magnetic Resonance; **ICH:** International Council for Harmonisation; **C_{max}:** Maximum Plasma Concentration; **AUC:** Area Under the Concentration-Time Curve; **QbD:** Quality by Design; **DoE:** Design of Experiments.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

DECLARATION OF AI-ASSISTED TECHNOLOGY

Grammarly was used to enhance the manuscript's clarity, readability, and grammatical quality. The authors bear full responsibility for the accuracy, integrity, originality, and scientific content of the manuscript.

AUTHORS CONTRIBUTION

Mohammed Arfath (M.A): Research concept and design, Data analysis and interpretation, writing the article. **Lokesh PG (L.P.G):** Data analysis and interpretation, writing the article. **Muhammed Nufaiz Khalid (M.N.K):** Collection and/or assembly of data, Data analysis and interpretation. **Akhilesh Dubey (AD):** Critical revision of the article, Final approval of the article. **Manohar Mahadev (M.M):** Research concept and design, Critical revision of the article, Final approval of the article.

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Cite this article: Ismail MAM, Lokesh PG, Khalid MN, Dubey A, Mahadev M. Phytosome Technology: A Journey from Formulation Development to Industrial and Commercial Translation. Int. J. Pharm. Investigation. 2027;17(1):155-67.