

# EMERGENCE OF PHYTOSOMES IN THE FIELD OF NOVEL DRUG DELIVERY SYSTEM

## Abstract

In the arena of novel drug delivery system, phytosomes have emerged as a ground-breaking carrier system, owing to elimination of side effects, that are generally caused in case of metallic nanocarriers or those having synthetic origin. Phytoconstituents have been stated to have strong *in vitro* pharmacological activity, although possessing poor *in vivo* absorption. In order to increase their bioavailability and absorption, combatting the drawbacks and undesirable effects of traditional herbal extracts, among various novel drug delivery systems. Phytosomes resolves the problem of low bioavailability, apart from target specific conveyance of drug, it also reduces adverse effects, amends absorption, lowers dose and augments therapeutic efficacy. Many researchers have reported the pharmacological potential of phytosomes and established its supremacy, on comparison to the efficacy of traditional drugs as well as conventional liposomes. Phytosomes are well-known biocompatible nanocarriers that can be employed to increase the solubility and permeability of phytopharmaceuticals. This review aims to provide a comprehensive insight about the characteristics, method of fabrication, application in drug delivery and therapeutics, with the challenges faced and the future prospects of phytosomes.

**Keywords:** Phytoconstituents, nanocarriers, phytosomes, biocompatibility, bioavailability.

## Authors

**Shayeri Chatterjee Ganguly**  
Department of Pharmaceutical Technology  
Brainware University  
Kolkata, India.

**Aliviya Das**  
Department of Pharmaceutical Chemistry  
Calcutta Institute of Pharmaceutical  
Technology & Allied Health Sciences  
Howrah, India.

**Sk Sangram**  
Department of Pharmaceutical Chemistry  
Calcutta Institute of Pharmaceutical  
Technology & Allied Health Sciences  
Howrah, India.

**Disha Bhattacharya**  
Department of Pharmaceutics  
Calcutta Institute of Pharmaceutical  
Technology & Allied Health Sciences  
Howrah, India.

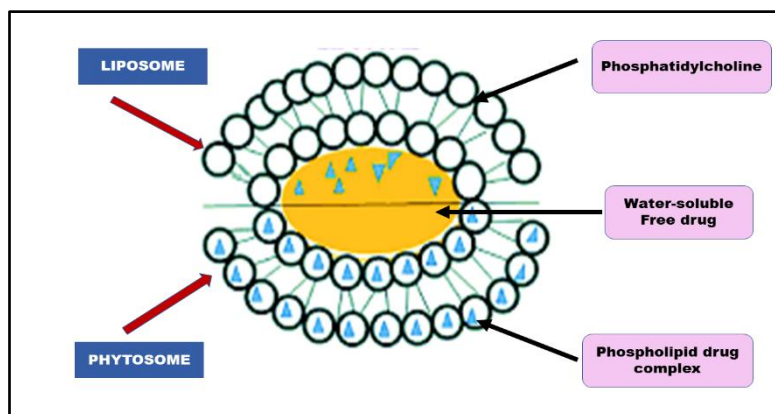
**Sayani Paul**  
Department of Pharmaceutical Chemistry  
Calcutta Institute of Pharmaceutical  
Technology & Allied Health Sciences  
Howrah, India.

## I. INTRODUCTION

Active components present in medicinal plants like tannins, flavonoids, terpenoids and tannins exhibit poor oral absorption, that restrains their pharmacological as well as therapeutic activity. [1]. The reason of poor absorption of phytoconstituents can be due to polyphenols structure, that are too large to be absorbed and limited hydrophilicity or lipophilicity of the phytoactives, that restricts its passage through gastrointestinal membrane [2]. Herbal drugs that can be packed into vesicular cavities and can occur as nanostructures are termed as phytosomes. They form an envelope-like covering over the medicament, averting microbes as well as digestive enzymes from terminating the activities of the phyto extract [3]. This technology is also accountable for amended in-vivo activities of phyto extract, due to its target specificity; its nanoscale size has fixed the hindrance of low permeability of macro sized, water soluble herbal constituents across biological membrane; enhanced dissolution and absorption, along with a better pharmacokinetic profile, delivers improved therapeutic effect at lesser dose; therefore, it can be implemented in therapeutics [4]. Phospholipid complexes, termed as phytosomes, have become a successful method to enhance the bioavailability of active ingredients [5]. In order to improve their bioavailability and absorption and bypass the drawbacks and negative effects of traditional herbal extracts, phytosomes, a unique developing vesicular drug delivery technology, have emerged that includes plant extracts or hydrophilic phytochemicals in phospholipids [6]. The polar head of phospholipids interact with the active components to produce phytosomes [7]. Phytosomes may turn into agglomerates on dilution with water, and that bear a resemblance to tiny cells as well as to liposomes.

In liposomes, the active component is dispersed either within the inner aqueous compartment or within the layers of the membrane. However, in phytosomes, the active molecules are stabilized through hydrogen bonding with the polar heads of phospholipids, which are integral components of the membrane. Unlike open vesicles, liposomes are closed structures, composed of lipid bilayers that can encapsulate substances in an aqueous environment or between multiple lipid bilayers [8-9]. Phosphatidylcholine (or phosphatidylserine) is a compound of dual-function, serving two roles. The choline (or serine) component is hydrophilic, while the phosphatidyl moiety is lipophilic. This dual solubility of phospholipids makes them potent emulsifiers. Consequently, the choline head bonds with the active substances, while the lipophilic portion, comprising the body and tail, surrounds the choline-bound material. This interaction forms the phyto-phospholipid complex, a molecular compound compatible with lipids and phospholipids [10-11].

The phospholipid undergoes docking with the active polar moiety, which serves as an essential part of the membrane, permitting stabilization of molecules via hydrogen bonding. Phytosomes possessing the micelle like cluster of phosphatidylcholine, corresponds to the configuration of the cell membrane [12].



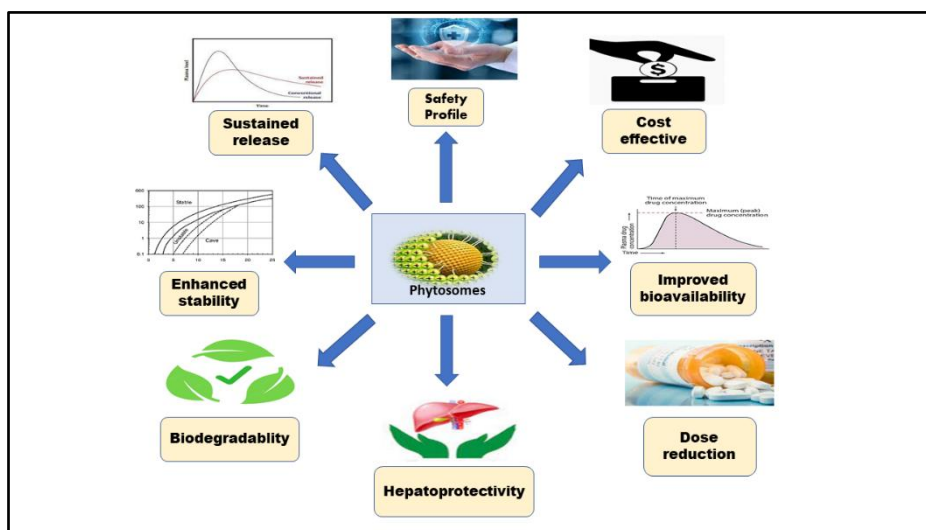
**Figure 1:** Diagram showing the difference between Liposome and Phytosome

## II. PRINCIPLE

Phytosomes, commonly referred to as phytophospholipid delivery systems, act as a bridge between conventional and modern delivery strategies[13-14]. The advent of phytosomes was to improve the bioavailability of the medicines that are to be originated from the plant sources by incorporating phospholipids. The concept of the phytosomes is the production of lipo-compatible complex molecular compounds by combining phospholipids with standardized plant extracts and water soluble phyto-constituents. This dramatically raises bioavailability and absorption through biological barriers[15]. Phosphatidylcholine, phosphatidylserine, phosphatidylethanolamine, and phosphatidylinositol are the phospholipids that are used, but phosphatidylcholine is the one that is most frequently used because it has been shown to have therapeutic value in the treatment of liver diseases like alcoholic steatosis, drug-induced liver damage, and hepatitis [13][15]. Standardized plant extracts with phospholipids added through the use of phytosome technology have higher bioavailability, improved pharmacokinetic properties with enhanced pharmacological effects, than regular phyto extracts due to increased absorption. Phospholipids are also employed as natural digestive aids and as carriers of water- and fat-soluble nutrients. Phytosomes can easily cross the lipophilic route of enterohepatic cell membranes and the stratum corneum layer of the epidermis[16]. Phosphatidylcholine or phosphatidylserine, is a chemical with two distinct roles. The phosphatidyl moiety is a lipophilic molecule, whereas choline (serine) is a hydrophilic substance. The phospholipid is a potent emulsifier due to its twofold solubility. The choline head of the phosphatidylcholine molecule binds to these molecules as a result, and the lipid-soluble phosphatidyl portion, which consists of the body and tail, surrounds the choline-bound substance. As a consequence, the phytoconstituents generate the phyto-phospholipid complex, a molecular structure containing phospholipids that is compatible with lipids. The main factor that imparts better biopharmaceutical properties is the hydrogen bonding or the presence of active hydrogen in the phospholipids moiety.

Phytosomes, a novel and emerging vesicular drug delivery method, include plant extracts or hydrophilic phytochemicals in phospholipids to enhance their bioavailability and absorption and avoid the disadvantages and adverse effects of conventional herbal extracts. These are like micelles created by the interaction of water with phospholipids. Polyphenolic plant extracts are used to improve the connection[17]. Through hydrogen

bonding and polar contact, the polar functional groups of lipophilic substances bind to the charged phosphate head of phospholipids to create micelles. These micelles hold the polyphenolic chemicals in place. In contrast to liposomes, phytosomes contain the bioactive substance either within the vesicle or in the spaces between the layers of shell membrane [18]. The bioactive molecule is a crucial component of this vesicular drug delivery system are phytosome with lipid (a phyto-constituent molecule is associated with a phospholipid molecule) environs and binds phytoconstituents of herbal extract. Phytosomes display enhanced absorption because they protect crucial herbal extract components from gut bacteria and digestive secretions[19]. Phosphatidylcholine is a bi-functional molecule due to the hydrophilic nature of the choline moiety and the lipophilic nature of the phosphatidyl moiety[20]. The phytoactive component of the phyto-phospholipid complex binds to the choline head of the phosphatidylcholine molecule, which is then enveloped by the lipid-soluble portion[16]. Consequently, a phytophospholipid complex is produced. Spectroscopic techniques have revealed that molecules are chemically bonded to the choline head of phosphatidylcholine. Bioavailability has been found to increase with the distribution of phytosomes to tissues with improved therapeutic impact.



**Figure 2:** Image exhibiting significance of Phytosomes

### III. PROPERTIES (CHEMICAL, PHYSICAL, BIOLOGICAL)

Phytosomes are specialized formulations in which active plant components attached to the phospholipids, which produces unique chemical, physical, and biological properties that leads to their better effectiveness and applications[21].

#### 1. Chemical Properties

- **Amphiphilic Nature:** Phospholipids, the primary aspects of phytosomes, possess both hydrophilic (water-attracting) and hydrophobic (lipid-attracting) regions. This amphiphilic nature enables phytosomes to self-assemble into bilayer frameworks, replicating the structure of cell membranes.

- **Molecular Structure:** Phytosomes consists of a primary centre of active plant components surrounded by a phospholipid layer. The active components can be different phytochemicals such as flavonoids, terpenes, polyphenols and depending on the plant extract used[22].
- **Encapsulation Efficiency:** Phytosomes have high encapsulation efficiency means they can effectively encapsulate and maintain a significant number of active compounds, protecting them from degradation and improving stability[23].

## 2. Physical Properties

- **Particle Size:** Phytosomes usually have a nanoscale particle size, ranging from ten to hundreds of nanometers. That small particle size increases their solubility and absorption properties[24].
- **Colloidal System:** Phytosomes form stable colloidal systems in aqueous solutions due to their amphiphilic nature. This colloidal property helps in the dispersion and delivery of active compounds.
- **Transparency:** Phytosomes are generally transparent or translucent when dispersed in water, indicating their colloidal nature and uniformity[25].

## 3. Biological Properties

- **Improved Bioavailability:** Phytosomes significantly enhance the bioavailability of active plant components. The phospholipid coating increases their solubility, allowing for greater absorption through both lipid-based and water-based routes in the body[26].
- **Targeted Delivery:** The phospholipid coating on phytosomes promotes their interaction with cell membranes, supporting targeted delivery of the encapsulated compounds to specific tissue or cells[24].
- **Cellular Uptake:** Phytosomes strengthen the cellular uptake of active substances due to their phospholipid structure, resulting to higher intracellular concentrations and enhanced therapeutic aspects[24].
- **Biocompatibility:** Phospholipids are naturally occurring substances present in cell membranes, causing phytosomes biocompatible and well-tolerated by the body. This property decreases the risk of adverse reactions[22].
- **Synergistic Effects:** Phytosomes can be formulated to contain numerous active compounds from different plant extracts. This allows for coordinated delivery and possible beneficial effects of the combined compounds, increasing therapeutic outcomes[24].

## IV. PREPARATION OF PHYTOSOMES

Phospholipids can be prepared by various conventional techniques, as well as by novel techniques.

1. **Solvent Evaporation Method:** This is accomplished by dissolution of phosphatidylcholine in a non-polar solvent, under continuous stirring using magnetic stirrer. The phytoconstituent to be incorporated, should be first dissolved in another non-

polar solvent before its addition to the phosphatidylcholine solution. The solution needs to be stirred for around 2 hours and must be subjected to drying under vacuum at 60 °C, then transferred to vacuum at 40 °C and finally, it is allowed to dry overnight. The light-yellow colored residue obtained is stored in powdered form, which is a typical complex of phytophospholipid [27].

- 2. Anti-Solvent Precipitation Method:** Here, the bioactive molecule along with the phospholipid are dissolved in an organic solvent. A rotating vacuum evaporator is required for extraction. In the round bottom flask, there would be a formation of thin layer consisting of a conjugated blend of phospholipid and bioactive molecule and the removal of solvents from the thin layer is generally carried out with hexane. This leads to formation of a precipitate that is stored in vacuum desiccators after subsequent filtration and drying. Precipitate is sieved through #100 mesh [28]. The formation of the andrographolide phyto-phospholipid complex by means of dichloromethane as the reaction medium and n-hexane as the final precipitation anti-solvent has been extensively researched on a patented analogous approach [29-30].
- 3. Rotary Evaporation Method:** A predetermined amount of herbal extract and phospholipids must be blended together in a glass round-bottom container, along with some water-miscible organic solvent. The mixture was stirred for two hours using a rotary evaporator. Afterwards, continuous stirring will lead to the formation of a thin coating, which could be further treated with an antisolvent [31-32]. The resulting precipitate need to be stored for future use.

Conventional techniques have abundant downsides, from being a lengthy one to difficult extraction procedure. Supercritical fluid technique changes the shape, and morphology of the concerned component. Apart from having high product purity, control of polymorphism and the capacity to develop thermolabile materials, it is a single-step process, with ecological technology and novel methods of development have also evolved like gas anti-solvents technique, cosolvent lyophilization. [33].

- 4. Gas Anti-Solvents Technique (GAS):** This method involves injection of CO<sub>2</sub> into a closed chamber from below to ensure uniform mixing. When CO<sub>2</sub> dissolves in the solution, it diminishes the organic solvents ability to dissolve solutes, triggering them to precipitate. Subsequently, the precipitated particles are washed with extra antisolvent to eradicate any residual solvent. This step is crucial because insufficient removal of the solvent may cause solubilization again, endangering the product's stability. Compared to the solvent antisolvent technique, the gas antisolvent technique delivers greater outcomes when implemented at industrial scales [34].
- 5. Supercritical Anti-Solvent Technique (SAS):** Lowering the pressure inside the SAS eliminates the solvent from the gaseous phase, leading to the development of submicron-sized particles with a well-controlled size distribution. It requires CO<sub>2</sub> to be in a supercritical state, and both the CO<sub>2</sub> and the solution are introduced into a sealed chamber from the top. Unlike the previous method, this method has been successfully demonstrated on an industrial scale. [35].

- 6. Co-solvent Lyophilization:** This process involves the removal of water from a frozen state through sublimation. This sublimation of ice occurs under specific temperature and pressure conditions below the triple point, consisting of three stages: freezing, primary drying, and secondary drying. In a study, co-solvent lyophilization was implemented to create drug-phospholipid complexes, and its application was illustrated[36].

## V. CHARACTERIZATION OF PHYTOSOMES

- 1. Visualization:** Both transmission electron microscopy (TEM) and scanning electron microscopy (SEM) are used to envision phytosomes. In a particular study, TEM imaging revealed spherical vesicles with rough surfaces and no particle aggregation in a soybean phytosome. This technique detects drug's internal environment and distribution within the phospholipid mesh. The size of these vesicles can be determined using TEM [37]. On the other hand, SEM characterizes the surface morphologies of the samples.
- 2. Size of Particles and Zeta Potential [39]:** The stability and consistency of the complexes are affected by two crucial factors, that is, particle size and zeta potential. Phytosomes typically exhibit particle sizes ranging from 50 nm to 100 µm. The measurement of both the attributes can be accomplished using dynamic light scattering (DLS) and photon correlation spectroscopy (PCS) [38]. When the zeta potential fall within the range of 20-30 mV, the particle system tends to be relatively stable, but if it exceeds 30 mV, its stability is higher. A study on curcumin-phytosomes assessed their particle size, polydispersity index (PDI), and zeta potential, and the results exhibited a highly homogeneous system with a PDI of 0.191 and an average size of 131.8 nm [39].
- 3. Entrapment Efficiency and Drug Content:** Entrapment efficiency is detected by ultracentrifugation and the supernatant collected is extracted, with the corresponding solvent, in which the phytoconstituent is soluble, here phase separation takes place. The phase containing drug is checked for detection of drug content, by UV Vis spectrophotometer or HPLC [40-41].
- 4. Solubility and Partition Coefficient-** In order to calculate the apparent partition coefficients, or the solubility in hydrophilic and lipophilic medium, shake-flask method is used [42]. Water and drug loaded n-octanol are taken in equal volumes and phospholipid complex are added and equilibrated with continuous shaking for 24 hours in different volumetric flasks, and the temperature is maintained at 37°C.
- 5. Drug Release:** This can be ascertained using the dialysis method, where the lyophilized product is reconstituted with water or Phosphate buffer (PBS) and kept in dialysis membrane, tightly sealed. It is submerged in 200ml of PBS, and stirring is continued using a magnetic stirrer. Aliquots of sample are taken periodically and equal volume of buffer is refilled to maintain the sink condition. The withdrawn aliquot is analysed spectrophotometrically for quantification of drug release [43].

## VI. SPECTROSCOPIC TECHNIQUES FOR ANALYSIS

Spectroscopy, a branch of study that evaluates the spectra of electromagnetic radiation as a function of its wavelength or frequency using spectrographic equipment and other methods to learn more about the composition and characteristics of pharmaceuticals. It is the field of study that analyses and evaluates the electromagnetic spectra that emerge from the interaction of electromagnetic radiation with matter as a function of the wavelength or frequency of the radiation[44]. In phytosome based drug delivery, various spectroscopic techniques like Nuclear Magnetic Resonance (NMR), Fourier Transform Infrared spectroscopy (FTIR), X-ray Diffraction (XRD) study etc are employed to verify the complex formation by contrasting the outcomes of the individual component with the complexes or to assess the reciprocal interaction between the phospholipids and the incorporated phytoconstituent [45-46].

**1. Fourier Transform Infrared Spectroscopy (FTIR) Study:** FTIR spectroscopy may be used to validate the complex's formation by contrasting its spectrum with the spectra of its constituent parts and their mechanical mixes. When phytosomes are micro-dispersed in water or included in very basic cosmetic gels, FTIR spectroscopy is a valuable technique for controlling their stability. Practically, the stability may be verified by contrasting the spectra of the complex in phytosomes with the spectra of its microdispersion in water following lyophilization, over different interval of time. When using simple formulations, it is required to compare the complex's residual spectrum after deducting the spectrum of the excipients (blank) from the spectrum of the cosmetic form at various time intervals[47].

Udapurkar and his co-researchers developed diosmin-phospholipid complex (DN-PC) in order to improve its oral absorption and bioavailability. Different parameters like Solubility studies, Drug content, particle size determination, infrared absorption (FTIR), X-ray diffraction (XRD), Differential scanning calorimetry (DSC) entrapment efficiency, Scanning electron microscopy (SEM) etc. was incorporated to evaluate diosmin - phospholipid complex. The development of the phyto-phospholipid complex was verified by FTIR[48].

In another study, to increase the bioavailability of hydrophobic extracts, Tiwari et al. developed herbal extracts loaded phyto-phospholipid complexes (phytosomes) against Polycystic Ovarian Syndrome. Although the strength of the peaks was significantly lowered, FTIR analyses revealed no changes in the descriptive peaks in raw and extracted herbs. Ex vivo research indicated that phytosomes with low phospholipid contents had good permeability patterns [49].

**2. Nuclear Magnetic Resonance (NMR) study:** The  $^1\text{H}$  NMR and  $^{13}\text{C}$  NMR studies have been employed to analyse complex structures related to phytosomes. Investigations related to the chemical shift value, presence and absence of a certain proton's NMR peak can be used to characterize phytosomes. The long tail part of the phospholipid molecule's peak is seen in the  $^1\text{H}$ -NMR spectra of phytosomes made up of different phytoconstituents, indicating that the tail part does not participate in chemical interactions and acts as a sheath to the choline part present in the centre, linked to the phytoconstituent. Besides, to validate the sort of interaction involved in the complexation, the  $^{13}\text{C}$ -NMR is frequently



used[50]. Research has been done on the NMR spectra of (+)-catechin and its stoichiometric distearoylphosphatidylcholine complex by Bombardelli & Spelta. The  $^1\text{H}$ -NMR signal from the atoms involved in the complex's synthesis changes noticeably in nonpolar solvents, with no accumulation of the signal specific to individual molecules. To prevent the proton from being released, the flavonoid protons' signals must be strengthened. All of the signals in phospholipids expand, but the singlet related to the choline  $\text{N}-(\text{CH}_3)_3$  undergoes an upward shift. The sample is heated to  $60^\circ$ , which causes the emergence of certain new wide bands that primarily correlate to the resonance of the flavonoid moiety. In the same study, when recorded in  $\text{C}_6\text{D}_6$  at ambient temperature, all the flavonoid carbons are plainly undetectable in the  $^{13}\text{C}$ -NMR spectra of (+)-catechin and its stoichiometric complex distearoylphosphatidylcholine. While most of the resonances of the fatty acid chains preserve their original shape, the signals corresponding to the glycerol and choline part of the lipid (between 60 and 80 ppm) broadened and some get shifted. All of the flavonoid moieties' signals reappeared after heating to  $60^\circ$ , however they were still quite broad and somewhat overlapped[46].

Another research was performed on phytosome-nanosuspensions for silybin-phospholipid complex (SPCs-NPs) to improve bioavailability and hepatoprotection efficacy of silybin. Utilising the optimised SPCs-NPs formulation, physicochemical characteristics such as interactions between silybin and phospholipid and crystalline variation were confirmed by using  $^1\text{H}$  NMR study. The active protons in silybin and certain phospholipid protons were shown to have broadened widely and became less detectable signals in the  $^1\text{H}$ -NMR spectra of the SPCs complex, and these protons were engaged in the production of the SPCs complex. The  $^1\text{H}$ -NMR data further supported the intermolecular interactions between the silybin hydroxyl and the polar head of phospholipids. The complex's NMR spectra also raised the idea that the development of the complex led to concomitant structural alterations in phospholipids[51].

By combining NMR characterization in aqueous solution with DFT theoretical calculations, it was possible to establish the stoichiometry, the host-guest affinity, and the geometry of inclusion in the interaction of aescin with the oligosaccharide hosts  $\beta$ -Cyclodextrin and  $\gamma$ -Cyclodextrin respectively. According to the findings, it was found out that though the inclusion also happens with  $\beta$ -CD, experimental evidence from aqueous-state NMR measurements and theoretical calculations have shown that aescin is more suited for  $\gamma$ -CD, which is the host that is most appropriate for it. The triterpene segment of aescin is incorporated into the host cavity, defining the shape of the  $\gamma$ -CD aescin complex[52].

- 3. X-ray Diffraction (XRD) Study:** The crystallinity of the phytoconstituents gets tarnished, on complexation of phytoconstituents, which increases the hydrophilicity of hydrophobic phytoconstituents and maintains a balance between their hydrophilicity and lipophilicity. The X-RD Analysis can establish the crystallinity as well as the interaction of phospholipid with phytoconstituent. The melting point of the phytosome is lesser than the pure drug and exhibits a broad peak. The broad peak is a sign of crystallinity degradation. The diffraction angles ( $2\theta$ ) of constituents, phytosomes, along with phospholipids are also collated. Drug interactions and sheath-entrapment are confirmed by the overall XRD study's finding of drug crystalline peak loss[53].

Besides the above techniques, there are various other techniques available for the characterization of phytosome. For example, for determining the size of the vesicle and verifying the vesicular structure following hydration, the Photon Correlation Spectroscopy (PCS) approach is utilised. By using this approach, the polydispersity of vesicles is studied, providing insight into the distribution of diverse vesicular structural sizes. The PCS study demonstrates that upon hydration, phytosomes mostly form unilamellar liposomal structures[54]. Another simple approach for characterising phytosomes is HPTLC. When the phytosomes are eluted with the appropriate solvent system, they exhibit a retention factor value that is distinct from the phytoconstituents and phospholipids, confirming the formation of a new molecular structure[55].

## VII. APPLICATIONS OF PHYTOSOMES

The therapeutic benefits of natural plant components for boosting health and curing disorders has gained more acceptance in recent years. Still, the poor absorption and low bioavailability of several of these substances have severely limited their usefulness. Researchers and scientists developed "phytosomes," which are specialised formulations that improve the delivery and bioavailability of active plant chemicals, as a creative solution to such problems. Since the prehistoric times, ethnobotanical plants have been utilized to manage a variety of disorders. The plant-based components have strong CNS actions as well as anti-tumor, anti-inflammatory, antinociceptive, anti-obesity, and cardioprotective properties. They also have anti-asthmatic, anti-diabetic, anti-oxidant, and anti-asthmatic properties. To transport the medicine to the site of action without it being metabolised, many drug delivery methods including liposomes, niosomes, transferosomes, ethosomes, phytosomes, colloidosomes, etc. are being developed. The bioavailability and effective dose concentration of phytoconstituents with varied chemical natures are the main issues, which might be resolved by using phytosome technology. Phytosomes are phospholipid vesicles that are joined to one or more phytochemicals via a hydrogen bond [23][56].

- 1. Pharmaceutical Applications:** Phytosomes have transformed the field of medications by improving the therapeutic potential of traditional medicines. By enhancing the absorption and bioavailability of active substances, phytosome-based medications can achieve more reliable and consistent outcomes compared to conventional herbal extracts. For example, phytosomal formulations of curcumin have demonstrated promising outcomes in the treatment of various inflammatory diseases such as arthritis [25].
- 2. Nutraceuticals and Dietary Supplements:** The use of phytosomes in nutraceuticals and dietary supplements is increasing popularity due to their capacity to improve the delivery of bioactive substances, resulting in enhanced health benefits. Dietary supplements including phytosomes of green tea catechins, resveratrol, and grape seed extracts have been recognised for their potent antioxidant properties, which may help in reducing oxidative stress and the risk of chronic diseases [57].
- 3. Skin Care Products:** Phytosomes have found significant application in the cosmeceutical industry, especially in skincare products. Their specific ability to penetrate the skin barrier effectively allows for selective absorption of active herbal components, which may stimulate collagen synthesis, reduce wrinkles, and enhance overall skin health.

Products that contained phytosomes of silymarin, derived from milk thistle, are frequently utilized for their anti-aging and protective benefits on the skin [58].

4. **Anti-Inflammatory Agents:** phytosomes have the efectivity in delivering Anti-inflammatory substances to specific target tissues. By encapsulating compounds like boswellic acids from *Boswellia serrata* or quercetin from *Ginkgo biloba*, phytosomes enable targeted administration and enhanced efficacy in treating inflammatory conditions, such as asthma and inflammatory bowel disease[59].
5. **Weight Management:** Phytosome-based medications have been investigated as well in the context of weight management. The formulations that contained green tea catechins and caffeine as phytosomes have shown potential for stimulating thermogenesis and fat metabolism, which may assist in weight loss and weight maintenance[56][59].
6. **Liver Health:** The liver serves an essential function in detoxification processes, and phytosomes have been developed to target the liver for therapeutic reasons. Phytosomal compositions of substances like silymarin from milk thistle have been shown to have hepatoprotective effects and might be helpful in managing liver-related disorders [60].
7. **Cardiovascular Health:** Phytosomes with active compounds obtained in certain plants, such as hawthorn extracts which have demonstrated promising activity in supporting cardiovascular disease. These formulations can help to improve blood flow, decrease blood pressure, and improve overall heart function [22].
8. **Cognitive Function:** Some researchers have explored the use of phytosomes to improve the delivery of medicinal compounds that may support brain health and cognitive function. For example, phytosomal preparations of bacopa extracts have been explored for potential advantages in improvement of memory and neuroprotection [61].

## VIII. CONCLUSION

Phytosomes indicate a revolutionary advancement in the field of natural medication and therapeutic applications. By enhancing the bioavailability of active plant components, phytosomes provide a more efficient and effective means of utilizing the power of nature to promote human health and well-being. The numerous uses of phytosomes, ranging from pharmaceuticals to skin care, indicate their flexibility and potential effect on various aspects of human health. As investigation into this field continues to expand, one can expect to discover further creative uses of phytosomes to cope with complex health challenges and deliver better health benefits for people around the world. However, as with therapeutic approach, further research and clinical trials are needed to fully understand and reduce the benefits of phytosome-based formulations.

The development of phytosomes in the field of novel drug delivery systems serves a major advance that holds an enormous potential for revolutionizing the pharmaceutical and nutraceutical industries. The distinctive composition of phytosomes, achieved through the interaction of active plant compounds to phospholipids, has successfully resolved prevalent challenges connected to the poor bioavailability and limited efficacy of many plant-based compounds. Numerous uses of phytosomes in pharmaceuticals, dietary supplements, skin

care, and other fields demonstrate their versatility and potential to address a wide range of health conditions. Their ability to improve the absorption and targeted delivery of bioactive substances has resulted in more effective therapies and improved patient outcomes. Phytosomes have opened up new possibilities for incorporating herbal medications into prevalent healthcare systems with their greater efficacy and stability, phytosome-based drugs have the potential to be as effective as conventional pharmaceuticals in treating different diseases, while offering safer and more economical alternatives.

Furthermore, the incorporation of phytosomes in nutraceuticals and dietary supplements has revealed the therapeutic value of natural substance, empowering people with more potent and trustworthy health-promoting products. In the cosmeceutical industry, phytosomes have cleared the way for innovative skincare compositions that can break down the skin barrier efficiently, providing people with enhanced anti-aging and protective benefits.

Despite the enormous advances made in the field of phytosomes, additional research and clinical trials are necessary to fully explore their abilities and reduce their applications. Long-term safety evaluations and comparative studies using current drug delivery systems will be extremely important to gain greater acceptance and recognition from the medical community.

Scientists, researchers, and healthcare professionals must work together and share their findings as phytosomes continue to gain popularity. This will hasten the creation of new phytosomal formulations and broaden the range of potential uses for them.

The recent development of phytosomes in the field of novel drug delivery systems offers a glimpse into the future of medicine, where the power of nature can be used and optimized to provide more effective, safer, and personalized healthcare solutions for individuals worldwide.

## **IX. FUTURE PROSPECTS**

Numerous phytochemicals have been successfully manufactured as phytosomes, and it is expected that additional phytochemicals can gain from similar formulations. The use of phytosomes in combination with other phytochemicals or the combination of a medicine and a phytochemical in a nano-vesicle are possible future research topics that could result in synergistic effects. Phytochemicals may be used topically for a variety of medicinal and esthetic purposes. Nanoengineered drug delivery methods are utilized to improve the penetration of bioactive polyphenolic phytocompounds across biological barriers, hence enhancing their bioavailability, due to their limited absorption profile. Phytosome nanocarriers are one of these cutting-edge platforms for drug delivery systems for phyto constituents. In comparison to the extract of phytochemicals alone, phytosomes have a greater ability to permeate epidermal layers due to their lipid content and nano-vesicular structure. When it comes to vesicular structure, stability, and skin penetration, phytosomes are comparable to liposomes. However, in phytosomes, the polar head of the phospholipid and the polar functionality of the bioactive components form an H-bond, which allows the phospholipid to interact with the phytochemicals. In comparison to liposomes, this significantly improves the stability and skin penetration of phytochemicals. Originally used in

cosmetics, phytosomes are now frequently used in the treatment of cancer, heart disease, inflammation, tumors, and other liver-related illnesses. With this newly created formulation tool, phytosomes has reiterated the significance of herbals in modern drug targeting approaches. By binding specific ligands and antigens to the cellular structures, phyto-phospholipid complexes can also be robust candidates for active as well as passive targeting. As a result, more illnesses, such as cancer, osteoarthritis, and rheumatism, can be treated with phyto-phospholipid complexes. Such size-controlled products would be helpful in more precisely targeting various microbiological regions such as inflammation and tumor by virtue of their better penetrating power and increased retaining capacity. By reducing barriers brought on by inadequate lipid solubility and improving the bioavailability of beneficial phytochemicals like silybin, ginkgo, and poly-phenolic compounds found in olive oil, the development of nanotechnology-based phytosomes may have an impact on the administration of medications. Since combining both natural and synthetic anti-cancer medicines into nanophytosomes considerably increases oral bioavailability and inhibits tumor growth, it is anticipated that nano-phytosomal delivery methods for cancer therapy will advance and extend in the near future. The way hydrophilic plant compounds are employed in cancer treatment may be revolutionized by the utilization of phytosome technology in the nano-formulation of nutraceuticals. Future research may find stimulatory effects when phytosomes are used in conjunction with other phytochemicals or when a drug and a phytochemical are combined in a nano-vesicle. In the very near future, theranostics will also be possible for phytosomes and liposomes encapsulating plant extracts for individualized or personalized therapy. The phytosome formulation process is straightforward, repeatable, and easily upgradable to a commercial scale. The phytosome technology has a bright future as far as applications of hydrophilic plant chemicals and formulation technology are concerned. By successfully transporting the active phytoconstituent in the preparation in a controlled release pattern with superior bioavailability and amended bioactivity, the phytosome technology may open a new route towards the study of phytopharmaceuticals.

## REFERENCES

- [1] Teng Z, Yuan C, Zhang F, Huan M, Cao W, Li K, Yang J, Cao D, Zhou S, Mei Q. Intestinal absorption and first-pass metabolism of polyphenol compounds in rat and their transport dynamics in Caco-2 cells. *PLoS One*. 2012 Jan 13;7(1):e29647.
- [2] Bhattacharya S. Phytosomes: the new technology for enhancement of bioavailability of botanicals and nutraceuticals. *International Journal of Health Research*. 2009;2(3):225-32.
- [3] Kumar A, Kumar B, Singh SK, Kaur B, Singh S. A review on phytosomes: novel approach for herbal phytochemicals. *Asian J Pharm Clin Res*. 2017;10(10):41-7.
- [4] Kamel R, Basha M. Preparation and in vitro evaluation of rutin nanostructured liquisolid delivery system. *Bulletin of Faculty of Pharmacy, Cairo University*. 2013 Dec 1;51(2):261-72.
- [5] Lu M, Qiu Q, Luo X, Liu X, Sun J, Wang C, Lin X, Deng Y, Song Y. Phyto-phospholipid complexes (phytosomes): A novel strategy to improve the bioavailability of active constituents. *Asian journal of pharmaceutical sciences*. 2019 May 1;14(3):265-74.
- [6] Karpuz M, Gunay MS, Ozer AY. Liposomes and phytosomes for phytoconstituents. In *Advances and avenues in the development of novel carriers for bioactives and biological agents 2020 Jan 1* (pp. 525-553). Academic Press.
- [7] Patel J, Patel R, Khambholja K, Patel N. An overview of phytosomes as an advanced herbal drug delivery system. *Asian J Pharm Sci*. 2009 Apr;4(6):363-71.
- [8] Khan J, Alexander A, Saraf S, Saraf S. Recent advances and future prospects of phyto-phospholipid complexation technique for improving pharmacokinetic profile of plant actives. *J Control Release* 2013; 168(1):50–60.

- [9] Ghanbarzadeh B, Babazadeh A, Hamishehkar H. Nano-phytosome as a potential food-grade delivery system. *Food Biosci* 2016; 15:126–35.
- [10] Bombardelli E. Phytosome: new cosmetic delivery system. *Bollettino chimico farmaceutico*. 1991 Dec 1;130(11):431-8.
- [11] Shivanand P, Kinjal P. Phytosomes: technical revolution in phytomedicine. *International Journal of PharmTech Research*. 2010;2(1):627-31.
- [12] Hou Z, Wei H, Wang Q, Sun Q, Zhou C, Zhan C, Zhang Q. New method to prepare mitomycin C loaded nanoparticles with high drug entrapment efficiency. *Nanoscale Res. Lett*. 2009;4(7):732-
- [13] Kumar AB, Habbu P, Thimmasetty, Lakshman, Hullatti P, Kumar S R. Phytosomes as novel drug delivery system for herbal medicine - A review. *Syst Rev Pharm*. 2016;8(1):5–7.
- [14] Gaikwad AR, Ahire KD, Gosavi AA, Salunkhe KS, Khalkar A. Gaikwad Abhijeet R. Phytosome as a Novel Drug Delivery System for Bioavailability Enhancement of Phytoconstituents and its Applications: A Review. *J Drug Deliv Ther*. 2021;11(3):138–52.
- [15] Phoke S V, Hatkar AD, Rawat SS, Ambhore NR, Ramteke CR. Review on : application of novel drug delivery system in herbal drugs. 2023;(04):5450–7.
- [16] Chauhan M, Dubey SK, Chauhan M. Current approaches of phytosomes : A novel drug delivery system. 12(6):6846–68.
- [17] Jain N, Gupta BP, Thakur N, Jain R, Banweer J, Jain DK, Jain S. Phytosome: a novel drug delivery system for herbal medicine. *Int J Pharm Sci Drug Res*. 2010 Oct;2(4):224-8.
- [18] Gaikwad SS, Morade YY, Kothule AM, Kshirsagar SJ, Laddha UD, Salunkhe KS. Overview of phytosomes in treating cancer: Advancement, challenges, and future outlook. *Heliyon*. 2023 May 24.
- [19] Sen S, Yadav R, Sawale J, Jain G, Kushwaha S. Section A-Review paper Abstract As dietary supplements for the homeostatic management of inflammation , toxins , malignancies , weight reduction , and other chronic or acute degenerative illnesses , plant-derived products or plant extracts are gaining mor. 2023;12(2):1763–73.
- [20] Sangiovanni E, Angarano M. Phytosomes as Innovative Delivery Systems for Phytochemicals : A Comprehensive Review of Literature. 2021.
- [21] Sadak Vali C, Khan A, Bharathi MP, Prasad SS, Yusuf SM, Khanam A, et al. Phytosomes: novel carriers for delivery of phytoconstituents, Vol. 5, *International Journal of Modern Pharmaceutical Research*. 2015.
- [22] Kumar A, Kumar B, Singh SK, Kaur B, Singh S. A review on phytosomes: novel approach for herbal phytochemicals. *Asian J Pharm Clin Res*. 2017;10(10):41-7.
- [23] Singh RP, Parpani S, Narke R, Chavan R. Phytosome: Recent advance research for novel drug delivery system. *Asian journal of pharmaceutical research and development*. 2014 May 1:15-29.
- [24] Khanzode MB, Kajale AD, Channawar MA, Gawande SR. Review on phytosomes: A novel drug delivery system. *GSC Biological and Pharmaceutical Sciences*. 2020;13(1):203-11.
- [25] Nimbalkar CK, Hatware K. Phytosomes-novel drug delivery system. *Indian Journal of Drugs*. 2017;5(1):16-36.
- [26] Patel J, Patel R, Khambholja K, Patel N. An overview of phytosomes as an advanced herbal drug delivery system. *Asian J Pharm Sci*. 2009 Apr;4(6):363-71.
- [27] Zhao X, Shi C, Zhou X, Lin T, Gong Y, Yin M, Fan L, Wang W, Fang J. Preparation of a nanoscale dihydromyricetin-phospholipid complex to improve the bioavailability: in vitro and in vivo evaluations. *European Journal of Pharmaceutical Sciences*. 2019 Oct 1;138:104994.
- [28] Singh RP, Gangadharappa HV, Mruthunjaya K. Phytosome loaded novel herbal drug delivery system: A review. *Int Res J Pharm*. 2016;7(6):15-21.
- [29] Murugan V, Mukherjee K, Maiti K, Mukherjee PK. Enhanced oral bioavailability and antioxidant profile of ellagic acid by phospholipids. *Journal of agricultural and food chemistry*. 2009 Jun 10;57(11):4559-65.
- [30] Franceschi F, Giori A, inventors; Indena SPA, assignee. Phospholipid complexes of olive fruits or leaves extracts having improved bioavailability. 2007 Oct 25.
- [31] Azeez NA, Deepa VS, Sivapriya V. Phytosomes: emergent promising nano vesicular drug delivery system for targeted tumor therapy. *Advances in Natural Sciences: Nanoscience and Nanotechnology*. 2018 Sep 5;9(3):033001.
- [32] Singh RP, Parpani S, Narke R, Chavan R. Phytosome: Recent advance research for novel drug delivery system. *Asian journal of pharmaceutical research and development*. 2014 May 1:15-29.
- [33] Barani M, Sangiovanni E, Angarano M, Rajizadeh MA, Mehrabani M, Piazza S, Gangadharappa HV, Pardakhty A, Mehrbani M, Dell'Agli M, Nematollahi MH. Phytosomes as innovative delivery systems for phytochemicals: A comprehensive review of literature. *International journal of nanomedicine*. 2021 Oct 15:6983-7022.

- [34] Shah N, Sandhu H, Choi DS, Chokshi H, Malick AW. Amorphous solid dispersions. Theory and Practice; Springer: Berlin, Germany. 2014.
- [35] Semalty A. Cyclodextrin and phospholipid complexation in solubility and dissolution enhancement: a critical and meta-analysis. Expert opinion on drug delivery. 2014 Aug 1;11(8):1255-72.
- [36] Cui F, Shi K, Zhang L, Tao A, Kawashima Y. Biodegradable nanoparticles loaded with insulin-phospholipid complex for oral delivery: preparation, in vitro characterization and in vivo evaluation. Journal of controlled release. 2006 Aug 28;114(2):242-50.
- [37] El-Menshawe SF, Ali AA, Rabeh MA, Khalil NM. Nanosized soy phytosome-based thermogel as topical anti-obesity formulation: an approach for acceptable level of evidence of an effective novel herbal weight loss product. International journal of nanomedicine. 2018 Jan 9:307-18.
- [38] Fry DW, White JC, Goldman ID. Rapid separation of low molecular weight solutes from liposomes without dilution. Analytical biochemistry. 1978 Oct 15;90(2):809-15
- [39] .Tung BT, Hai NT, Son PK. Hepatoprotective effect of Phytosome Curcumin against paracetamol-induced liver toxicity in mice. Brazilian Journal of Pharmaceutical Sciences. 2017 Apr 20;53.
- [40] Patel J, Patel R, Khambholja K, Patel N. An overview of phytosomes as an advanced herbal drug delivery system. Asian J Pharm Sci. 2009 Apr;4(6):363-71.
- [41] Gnananath K, Nataraj KS, Rao BG. Phospholipid complex technique for superior bioavailability of phytoconstituents. Advanced pharmaceutical bulletin. 2017 Apr;7(1):35.
- [42] hanbarzadeh B, Babazadeh A, Hamishehkar H. Nano-phytosome as a potential food-grade delivery system. Food bioscience. 2016 Sep 1;15:126-35.
- [43] Sen S, Yadav R, Sawale J, Jain G, Kushwaha S, Kushwaha M, Shipra JM. Review on phytosomes: A novel drug delivery system. European chemical bulletin. 2023; 12 (2):1763-1773.
- [44] Sutton MA. Sir John Herschel and the development of spectroscopy in Britain. The British journal for the history of science. 1974 Mar;7(1):42-60.
- [45] Patel PM, Modi CM, Patel HB, Patel UD, Ramchandani DM, Patel HR, Paida BV. Phytosome: An Emerging Technique for Improving Herbal Drug Delivery. J. Phytopharm. 2023;12(1):51-8.
- [46] Bombardelli E, Spelta M. Phospholipid-polyphenol complexes: A new concept in skin care ingredients. Cosmetics and toiletries. 1991;106(3):69-76.
- [47] Singh RP, Parpani S, Narke R, Chavan R. Phytosome: Recent advance research for novel drug delivery system. Asian journal of pharmaceutical research and development. 2014 May 1:15-29.
- [48] Udapurkar PP, Bhusnure OG, Kamble SR. Diosmin Phytosomes: development, optimization and physicochemical characterization. Indian J Pharm Educ Res. 2018 Oct 1;52(4):S29-36.
- [49] Tiwari R, Tiwari G, Sharma S, Ramachandran V. An Exploration of herbal extracts loaded phyto-phospholipid complexes (Phytosomes) against polycystic ovarian syndrome: Formulation considerations. Pharmaceutical Nanotechnology. 2023 Feb 1;11(1):44-55.
- [50] Kumar M, Ahuja M, Sharma SK. Hepatoprotective study of curcumin-soya lecithin complex. Scientia pharmaceutica. 2008 Dec;76(4):761-74.
- [51] Chi C, Zhang C, Liu Y, Nie H, Zhou J, Ding Y. Phytosome-nanosuspensions for silybin-phospholipid complex with increased bioavailability and hepatoprotection efficacy. European Journal of Pharmaceutical Sciences. 2020 Mar 1;144:105212.
- [52] Ramos AI, Vaz PD, Braga SS, Silva AM. Association of aescin with  $\beta$ - and  $\gamma$ -cyclodextrins studied by DFT calculations and spectroscopic methods. Beilstein Journal of Nanotechnology. 2017 Feb 3;8(1):348-57.
- [53] Yue PF, Zhang WJ, Yuan HL, Yang M, Zhu WF, Cai PL, Xiao XH. Process optimization, characterization and pharmacokinetic evaluation in rats of ursodeoxycholic acid-phospholipid complex. AAPS PharmSciTech. 2008 Mar;9:322-9.
- [54] Tripathy S, Patel DK, Barob L, Naira SK. A review on phytosomes, their characterization, advancement & potential for transdermal application. Journal of Drug Delivery and Therapeutics. 2013 May 13;3(3):147-52.
- [55] Maiti K, Mukherjee K, Gantait A, Saha BP, Mukherjee PK. Enhanced therapeutic potential of naringenin- phospholipid complex in rats. Journal of pharmacy and pharmacology. 2006 Sep;58(9):1227-33.
- [56] Chivte PS, Pardhi VS, Joshi VA, Rani A. A review on therapeutic applications of phytosomes. Journal of Drug Delivery and Therapeutics. 2017 Sep 13;7(5):17-21.
- [57] Gaikwad SS, Morade YY, Kothule AM, Kshirsagar SJ, Laddha UD, Salunkhe KS. Overview of phytosomes in treating cancer: Advancement, challenges, and future outlook. Heliyon. 2023 May 24.
- [58] Khanzode MB, Kajale AD, Channawar MA, Gawande SR. Review on phytosomes: A novel drug delivery

- system. GSC Biological and Pharmaceutical Sciences. 2020;13(1):203-11.
- [59] Gaurav V, Paliwal S, Singh A, Pandey S, Siddhiqui MA. Phytosomes: Preparation, Evaluation and Application. Vol. 9, International Journal of Research in Engineering and Science (IJRES) ISSN.
- [60] Babazadeh A, Zeinali M, Hamishehkar H. Nano-phytosome: a developing platform for herbal anti-cancer agents in cancer therapy. Current drug targets. 2018 Feb 1;19(2):170-80.
- [61] Patel J, Patel R, Khambholja K, Patel N. An overview of phytosomes as an advanced herbal drug delivery system. Asian J Pharm Sci. 2009 Apr;4(6):363-71.