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# Current approaches of phytosomes: A novel drug delivery system

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**Abstract**

Any pharmacotherapeutic approach's main goal is to effectively administer the right medicine at the right concentration at the right place through the use of a rationally designed delivery mechanism. Even though their therapeutic validity is questioned because to their limitations, such as limited lipid solubility, poor stability, big size moiety, and unnecessary gastrointestinal metabolism, phytopharmaceuticals have been used to treat illnesses for millions and billions of years. Using phyto-phospholipid complexes, which combine active ingredients with label-friendly phospholipids, are a potential way to improve the oral bioavailability of components. Phospholipid complexes are a crucial component and are made possible by hydrogen bond interactions between active components and phospholipids. Phyto denotes a plant, and some implies like a cell. A cutting-edge technology called a phytosome is used to make phytopharmaceuticals, which are made of herbal extracts that are surrounded and bound by lipid. The majority of phytomedicine's bioactive components are water soluble substances like flavonoids. Due to their water solubility and lipophilic outer layer, phytosomes exhibit better absorption than conventional herbal extracts. These results in better bioavailability, a decrease in clearance rate, higher dissolution, and an amplified solubility of a variety of natural products by several folds. Due to increased pharmacological and pharmacokinetic properties, phytosomes can be utilised therapeutically as dietary supplements and to treat both acute and chronic liver failure. There are numerous products on the market that use the phytosome technology, including herbal extracts and phytochemicals like curcumin, ginkgo biloba, grape seed, silymarin, and many others that have significant medicinal promise. The current review highlights the preparation process, properties, benefits, characterization, applications, and key findings of recent research on phytosomes

from our own perspectives, which can provide new directions and advancements for herbal dosage forms as well as the technical aspects of phyto-phospholipid formulations to meet future challenges.

**Keywords:** Phytosome, Phyto-phospholipid complexes, Active constituents, Herbal drug delivery, Bioavailability

## Introduction

The ability of the dosage form to carry the medication to its site of action at a rate and amount sufficient to elicit the intended pharmacological response is a requirement for the therapeutic effectiveness of any drug produced from plants, animals, or synthetic materials [1]. The goal of a novel drug delivery system is to distribute the medicine at a pace determined by the body's requirements over the course of treatment and guide the active ingredient to the site of action. In order to accomplish controlled and targeted medication delivery by encapsulating the drug in systemic circulation, which lessens the tonicity and selective reception of the drug, a number of innovative drug delivery systems have been developed. As a result, several vesicular drug delivery systems were created, including liposomes, niosomes, transferosomes, and pharmacosomes. Since then, vesicular drug delivery has advanced, enabling the creation of devices that enable drug targeting and the sustained or regulated release of conventional medications [2, 3]. Since ancient times, active components derived from plants have been employed to treat a variety of ailments [4, 5]. Since 2000 years ago, silybin, which is derived from milk thistle fruit, has been utilised to strengthen the liver [6]. According to reports, turmeric's curcumins have antioxidant and anticancer effects [7, 8]. Additionally, polyphenols including flavonoids, terpenoids, and phenolics are some of the most extensively researched active ingredients [9, 10]. However, many active plant components that are extracted have low oral absorption, which restricts their broad use [11, 12]. These chemicals' low absorption is caused by two characteristics. First, passive diffusion or non-active absorption cannot sufficiently absorb polyphenols because of their massive multi-ring structures. Second, these chemicals are unable to traverse the outer membrane of gastrointestinal cells due to their weak water or lipid solubility [13, 14]. Natural plant extracts that are active have been proven to have strong pharmacological effects in vitro but limited in vivo absorption. Poor absorption has been addressed in a number of ways, including the creation of emulsions [16], liposomes [17], and nanoparticles [18], the modification of chemical structures [19], and the administration of prodrugs [20]. Among the possible tactics, phyto-phospholipid complexes, also referred to as phytosomes,

have shown promise for increasing the bioavailability of active ingredients [14]. Active components are complexed with phospholipids at specific molar ratios to create phytosomes under specific circumstances [21]. In order for active components to get past the outer membrane of gastrointestinal cells and finally reach the blood, amphipathic phospholipids primarily serve as their "ushers" [14]. Constituents' oil-water partition coefficient and membrane permeability are significantly increased after forming phospholipid complexes. In contrast to free active components, phytosomes are thus more easily absorbed and produce better bioavailability [22, 23]. Positively, the approach of phospholipid complexes has gotten over the problem of many active components having poor bioavailability [24, 25]. As a result, recent years have seen a rise in interest in phytosome preparation [23]. We cover many elements of phytophospholipid complexes, including their synthesis process, benefits, characterisation, and applications. We also highlight new developments in the kinds of active ingredients, including phospholipids, solvents, and stoichiometric ratios. All of these reviews are based on the literature.

**Phytosomes**

Indeed, the phospholipid complexation process was created in 1989 by the Italian pharmaceutical and nutraceutical company Indena by chemically interacting polyphenolic plant actives with phospholipids comprising phosphatidylcholine (PC) and later patenting the concept under the name Phytosome [26]. By adding phospholipids to standardised plant extracts, phytosome technology has increased absorption, resulting in greater bioavailability and improved pharmacological and pharmacokinetic qualities than ordinary herbal extracts [27]. when standardised extract and phosphatidylcholine in a nonpolar solvent reacted in a stoichiometric amount [28]. Phytosomes, also known as phytolipid delivery systems, serve as a link between traditional and cutting-edge delivery methods. The terms "some" and "phyto" both refer to plant-like entities [29]. Lipid (one phyto-constituent molecule coupled with at least one phospholipid molecule) surrounds and binds phytoconstituents of herb extract in a vesicular drug delivery system known as a phytosome. Because phytosomes shield important herbal extract components from gut microbes and digestive secretions, they exhibit improved absorption. The hydrophilic character of the choline moiety and the lipophillic nature of the phosphatidyl moiety make phosphatidylcholine a bifunctional molecule. The phosphatidylcholine molecule's choline head binds to the phytoactive component in the phyto-phospholipid complex, and the lipid-soluble section envelops the choline bound substance. It therefore generates phytophospholipid complex. It has been

determined by spectroscopic methods that molecules are chemically bound to the phosphatidylcholine's choline head [27, 30]. The distribution of phytosomes to tissues with increased therapeutic effect has proven helpful in increasing bioavailability.

**Structure of phytosome**

Active components and the polar head of phospholipids interact to generate phytosomes [31]. Phospholipid complexes, in which the phospholipids head group is anchored, can develop by interactions between active ingredients and phospholipids, but the two long fatty acid chains are not involved in the complex formation process. To create a lipophilic surface, the two long fatty acid chains can migrate and enclose the polar component of complexes. When diluted in water, phytosomes form agglomerates that resemble tiny cells and bear some resemblance to liposomes; Figure 1 [32] illustrates the differences between complexes and liposomes. The main distinction between liposomes and phytosomes can be seen in Figure 1. In liposomes, the active ingredient is dispersed in the medium within the cavity or in the layers of the membrane, whereas in phytosomes, it is the molecules stabilised through hydrogen bonds to the polar head of the phospholipids, which are an integral part of the membrane. In contrast to open vesicles, liposomes are closed vesicles made of lipid bilayers that can enclose substances in an aqueous compartment or several lipid bilayers [28].

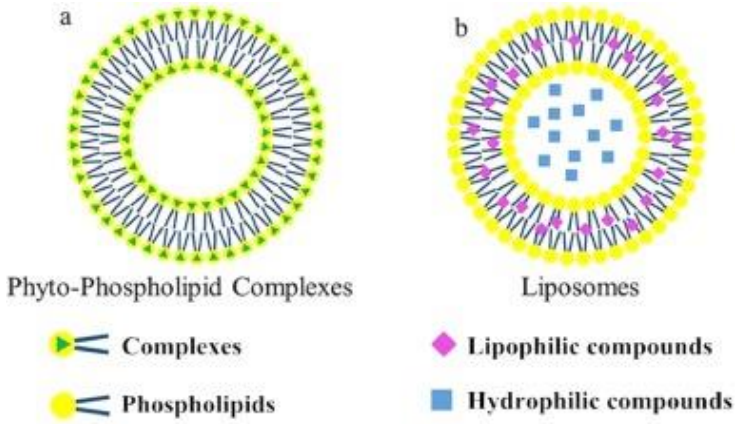


**Figure 1 Structure of phyto-phospholipid complexes and liposomes**

**Phytosome components**

According to Bombardelli's theory [33], phyto-phospholipid complexes can be produced by phospholipids reacting in a stoichiometric ratio with active components that are isolated from plants. This early description of phyto-phospholipid complexes has been refuted by subsequent research. Our updated list of the four crucial ingredients phospholipids,

phytoactive substances, solvents, and the stoichiometric ratio required for the formation of phyto-phospholipid complexes is based on the literature [32].

***Phospholipids***

The amphiphilic and zwitterionic phospholipids are thought to constitute a crucial part of the cell plasma membrane [34]. Due to the existence of a hydrophilic (head region) region made up of negatively charged phosphate groups and a hydrophobic (tail region) region made up of long chain fatty acids, it acquires an amphiphilic character. In biological systems, these head and tail sections are linked by a glycerol or alcohol group, forming a lipid bilayer. According to the amount of alcohol they contain, phospholipids can be broadly divided into two types: glycerophospholipids and sphingophospholipids. Glycerol is present in the neck area of glycerophospholipids, whereas sphingomyelins have sphingosine as their alcoholic moiety [35]. The phospholipid content of plant seeds and egg yolk is high. Phospholipids are currently synthesised industrially [31]. Phosphatidylcholine (PC), phosphatidylethanolamine (PE), phosphatidylserine (PS), phosphatidic acid (PA), phosphatidylinositol (PI), and phosphatidylglycerol (PG) are further glycerophospholipids [36]. The three main phospholipids utilised to create complexes with a hydrophilic head group and two hydrophobic hydrocarbon chains are PC, PE, and PS [37]. The most used phospholipid among these to prepare phospholipid complexes is PC. The amphipathic characteristics of PC, which give it a moderate solubility in lipid and aqueous environments, are among its advantages. Furthermore, PC demonstrates strong biocompatibility and minimal toxicity due to its crucial role in cell membranes. In the treatment of liver illnesses such hepatitis, fatty liver, and hepatocirrhosis, PC molecules have been shown to have therapeutic effects due to their hepatoprotective properties [38]. High-affinity siramesine and PA small molecule phospholipid complexes were created by Patel et al. [28]. The creation of phospholipid complexes using PG and PI has not yet been documented.

***Phyto-active constituents***

Basically, for the formulation of phospholipid complexes, either active components or standardised extract were chosen. Whole plant extracts are preferred in these situations since natural products may lose some or all of their particular biological activity during isolation and purification. As opposed to molar ratios for active constituents, phospholipid complex formulations are typically manufactured on a weight basis for standardised extract. The choice of plant extract is based on its phytochemical and pharmacokinetic profile, including its polyphenols, triterpenoids, tannins, alkaloids, and saponins. They frequently contain

several ring molecules that are too big to be absorbed through simple diffusion and have low permeability across the cellular walls of the intestine. A medication that can create a hydrogen bond with N-(CH3) of PC molecules because it contains an active hydrogen atom, such as -COOH, -OH, -NH2, -NH, etc. Any medication with an electron can be made into a variety of complexes with phospholipid molecules. Actives that are both lipophilic and hydrophilic can be complexed to increase bioavailability [39–42].

***Solvents***

The choice of solvent in phospholipid complexation process depends on the solubility of both the medication and the phospholipids. Different researchers have used various solvents as the reaction medium for creating phytosomes. Protic solvents like ethanol have essentially replaced aprotic solvents used in the past to create phytosomes, such as aromatic hydrocarbons, halogen derivatives, methylene chloride, ethyl acetate, or cyclic ethers [29, 43]. Indeed, more recently, phospholipid compounds have been effectively prepared using protonic solvents like ethanol and methanol. In order to create silybin-phospholipid complexes, for instance, Xiao used ethanol as a protonic solvent, which was then removed under pressure at 40°C [25]. Solvents of various kinds have been successfully researched. Ethanol is a helpful and well-liked solvent that leaves fewer residues behind and does no harm when the production of phospholipid complexes is high enough. When there is water or buffer solution present, certain liposomal drug complexes function because the phytosomes interact with a solvent that has a lower dielectric constant [28]. Recent investigations have used the supercritical fluid (SCF) technique to regulate the material of interest's size, shape, and morphology. One of the SCF technologies that is emerging as a promising method to manufacture micronic and submicronic particles with regulated size and size distribution is the supercritical anti solvent process (SAS) [44]. In order to decrease the solute's solubility in the solvent, a supercritical fluid (often CO2) will be used in this procedure as an anti-solvent.

***Stoichiometric ratio of active constituents and phospholipids***

The active ingredients are typically reacted with a synthetic or natural phospholipid in a molar ratio between 0.5 and 2.0 to create phytosomes [45]. The most effective stoichiometric ratio for creating phospholipid complexes is thought to be 1:1 [46]. For instance, lipoid S 100 and quercetin were combined in a 1:1 molar ratio to create quercetin-phospholipid complexes [47]. Different stoichiometric ratios between the active ingredients and the phospholipids have, however, been employed. The silymarin-phospholipid complexes made by Maryana et al. had stoichiometric ratios of 1:5, 1:10, and 1:15, and they discovered that these complexes

had the greatest physical characteristics and the largest loading capacity of 12.18% 0.30% [48]. In a comparison research by Yue et al. employing the stoichiometric ratios of 1:1, 1.4:1, 2:1, 2.6:1, and 3:1 to produce oxymatrine-phospholipid complexes, they found that the ratio of 3:1 produced the most amounts. Therefore, it is not always best to build phospholipid compounds at a 1:1 stoichiometric ratio. To achieve certain goals, such as the maximum drug loading, we need experimentally modify the stoichiometric ratio of active components and phospholipids for various types of pharmaceuticals.

**Properties of phytosomes**

Following are some of the important properties of phytosomes

***Physico-chemical properties***

- The standardized plant extracts used as the substrate are combined with a stoichiometric amount of phospholipid to create phytosomes. The spectroscopic data shows that the hydrogen bond formed between the polar head of the substrate (the phosphate and ammonium group) and the polar functionality is what causes the phospholipid substrate contact. [49].
- The size of phytosome varies from 50 nm to a few hundred μm [50].
- When exposed to water, phytosomes take on a micellar shape resembling liposomes, and photon correlation spectroscopy (PCS) confirms that phytosomes have acquired these liposomal structures[51].
- The H1 NMR and C13 NMR data calculated that the fatty chain yields unchanged signals both in free phospholipid and in the complex, indicating that long aliphatic chains are wrapped around the active principle to produce a lipophilic envelope [52].
- The complexes are frequently insoluble in water, moderately soluble in lipids, easily soluble in aprotic solvents, and relatively unstable in alcohol. However, upon complexation with phospholipid, the phytosomes of some lipophilic phytoconstituents, such as curcumin, have demonstrated an increase in water solubility[53].

***Biological properties***

In comparison to traditional herbal extracts or non-complex extracts, phytosomes are novel complexes that are better absorbed and utilised, producing greater bioavailability and better results as shown by pharmacokinetic studies or pharmacodynamic tests in experimental animals and human subjects [53, 54].

**Methods for the preparation of phytosome**

Phytosome complexes can be made using three main techniques: solvent evaporation, freeze-drying, and anti-solvent precipitation. Figure 2 depicts the typical steps in phytosome production.

***Solvent evaporation method***

Solvent evaporation is a common technique for making pharmacological phospholipid complexes. This procedure involves dissolving the target compound and the phospholipid in a solvent or mixture of solvents, which is then refluxed for a predetermined amount of time and subsequently evaporated using a rota evaporator [55]. The rota evaporator's solvent evaporation method is based on the idea that the boiling point of a solution can be lowered by applying vacuum, which is then followed by rotating to increase the solution's heating surface area. Rota evaporators are a perfect way to produce complicated formation because of their speed and capacity to handle enormous volumes of solvents. But in order to achieve the correct boiling point depression when evaporating high boiling point solvents like DMSO and DMF, etc., a high pressure vacuum system is needed.

***Co-grinding***

The primary external mechanical force used in this procedure is to knead the medication and phospholipid into a complex. Probucol phospholipid complex, which was made using the co-grinding approach and contrasted with the solvent evaporation method, provides an explanation for this. When compared to co-grinding, it was shown that solvent evaporation produced a high degree of drug complexation. However, this approach was shown to be acceptable for production on a larger scale [56].

***Mechanical dispersion method***

The phospholipid is dissolved in a solvent and exposed to sonication for a few to several minutes when using the mechanical dispersion method. The medication solution is then repeatedly added while the mixture is being sonicated, drop by drop. In a study conducted by Sikarwar et al. [57], the example demonstrating the utilisation of mechanical dispersion to create drug-phosphoipid is well illustrated. The authors used mechanical dispersion to create a marsupin phospholipid complex that increased bioavailability and proved to be stable.

***Super critical fluid process***

Because they may be utilised to create particles with precise control over size and distribution, SCF technologies are a potential method. Mild pressure and temperature levels are suitable for this process. In addition, it is more environmentally friendly than the procedure using organic solvents. Because of its critical temperature of 31°C and critical

pressure of 74 bar, which enable use in mild temperature conditions (40–60°C), carbon dioxide is the most commonly utilised supercritical fluid. However, there are several drawbacks to this approach, such as the insufficient solubility of polar molecules in supercritical CO2. This process was published by Li et al. [58] who also compared it to more traditional techniques such solvent evaporation, freeze drying, and gas anti-solvent crystallisation. Due to their greater capacity to cause the drug to amorphize, they stated that the phospholipid complex produced by supercritical fluid technology demonstrated more dissolving efficiency than that produced by the other three techniques.

***Co-solvent lyophilization***

The lyophilization process relies on the sublimation (removal of water from the frozen state without liquid phase) principle. Ice can be sublimated through lyophilization, which is accomplished at temperatures and pressures below triple point. The freezing stage, primary drying, and secondary drying are the three stages that make up the lyophilization process. In a work by Cui et al. [59], an illustration of the utilisation of co-solvent lyophilization to create drug-phospholipid complexes is provided. Authors created an insulin phospholipid complex during their experiment, which was afterwards examined using X-ray diffraction, IR, and solubilization. The characterization studies previously stated collectively contributed to the confirmation of the drug-phospholipid complex formation.

***Anti-solvent precipitation***

In the anti-solvent approach, the drug and the phospholipid are dissolved in a solvent and refluxed for a predetermined amount of time. The complex is then precipitated using an anti-solvent, which has a restricted solubility. Without utilising expensive equipment, the anti-solvent precipitation method can be carried out at room temperature and pressure. In a research published by Murugan et al. [60], this process is extensively described. By employing n-hexane as an anti-solvent and DCM as a solvent, the scientists were able to precipitate a ellagic acid phospholipid complex. Collectively, DSC and TEM studies supported the development of the drug-phospholipid complex.

***Solvent ether-injection process***

In this method, herbal extracts in an aqueous phase react with lipids that have been dissolved in an organic solvent. The phytoconstituents that are to be encapsulated are progressively injected drop by drop with phospholipids solubilized in diethyl ether. On subsequent solvent removal, it causes the creation of cellular vesicles, which results in complex formation [31]. When the concentration is low, amphiphiles are created in mono state, but as the

concentration rises, a range of structures with various forms, such as spheres, cylinders, discs, and cubic or hexagonal vesicles, may emerge.

**The factors influencing the phytosome formation**

Solvent, stoichiometric ratio of active ingredients, reaction temperature, and reaction duration are the primary variables that affect the formation of phytophospholipid complexes. Numerous process variables are available, and they can be chosen based on the desired aim. Saoji et al. investigated the effects of process variables such the phospholipid-to-drug ratio, the reaction temperature, and the reaction duration in order to obtain the best formulation for highest yield [61]. They employed a central composite design. Different stoichiometric ratios of a rutin phytosome were developed by Das and Kalita for the greatest solubility and skin penetration [62]. Telange and his colleagues produce the best yield apigenin-phospholipid complexes, according to a recent publication [63], by adjusting stoichiometric ratios and reaction temperature.

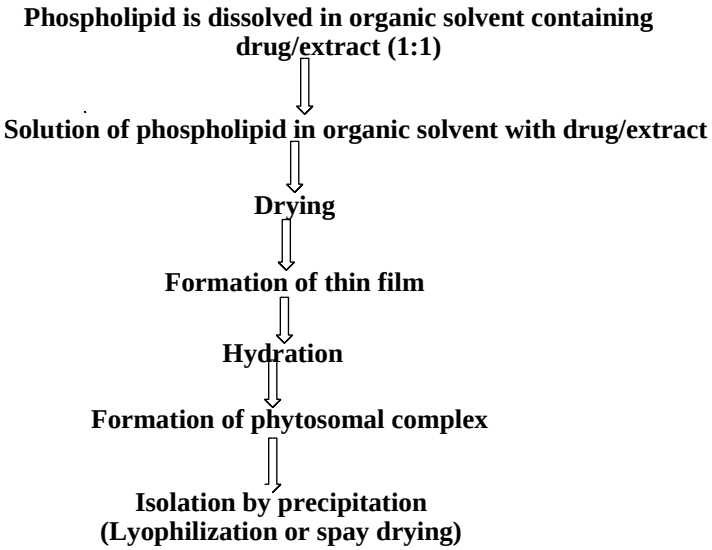


**Figure 2 Common stages for preparation of phytosomes [28]**

**Characterization of phytosomes**

***Solubility and partition coefficient***

To identify active ingredients, active constituent phytophospholipid complexes, and physical mixes, it is important to determine solubility in either water or organic solvents and the n-octanol/water partition coefficient (P). Generally speaking, phyto-phospholipid complexes exhibit improved lipophilicity and hydrophilicity compared to active components [32]. Embelin in complex is more soluble in n-octanol and water than it is in the corresponding physical combinations, according to Rahila [64].

***Particle size and zeta potential***

Particle size and zeta potential are important properties of complexes that are related to stability and reproducibility. In general, the average phospholipid complexes particle size ranged from 50 nm to 100 μm. *Mazumder* prepared sinigrin phytosome complexes, and the average particle size and zeta potential of the complex were 153 ± 39 nm and 10.09 ± 0.98 mV, respectively [65].

***Scanning electron microscopy (SEM) and transmission electron microscopy (TEM)***

SEM has provided crucial new insights into the surface appearance and solid state characteristics of complexes. When examining the crystallisation and dispersion of nanomaterials and determining the particle size of nanoparticles, TEM is frequently used. Active compounds can be seen under a scanning electron microscope (SEM) in a highly crystalline state, however the structured crystals vanished upon complexation. TEM demonstrated that phyto-phospholipid complexes display vesicle-like structures when diluted in distilled water with minimal shaking [65].

**Spectroscopic evaluation**

The following spectroscopic techniques are employed to verify the development of a complex or investigate the reciprocal interaction between the phytoconstituents and the phospholipid.

***Ultraviolet spectra (UV-spectra)***

Samples that exhibit various UV wavelength absorption can be utilised to characterise their own structural characteristics. The majority of research has found no variations between components' UV absorption properties before and after complexation. The distinctive peaks of luteolin were still present in the luteolin-phospholipid complexes made by Xu et al. [66]. As a result, we draw the conclusion that complexing with phospholipids has no effect on the chromophores of substances.

***Differential scanning calorimetry (DSC)***

In DSC, interactions can be seen by contrasting transition temperatures, new peaks appearing and disappearing, melting points, and changes in the relative peak area [67]. When compared to a physical combination, phyto-phospholipid complexes typically show radically distinct characteristic peaks. It is believed that strong interactions take place between the active substances and the two phospholipid fatty chains, and that the polar portion of phospholipids also prevents free rotation. Rutin-containing phyto-phospholipid complexes were created by Das and Kalita, and the rutin and PC peaks vanished from the DSC thermogram that resulted

[62]. These two characteristic peaks were lower than those of the physical combination.

***Fourier transforms infrared spectroscopy (FTIR)***

The FTIR technique is an effective tool for structural investigation since it produces several functional groups with unique properties in terms of band number, position, shape, and intensity. By contrasting the phospholipid complexes' spectroscopy with that of physical mixtures, it is possible to confirm the development of phyto-phospholipid complexes. Different studies might produce different findings. In fact, rutin-based phyto-phospholipid complexes were made by Das and Kalita. It was possible to compare the FTIR of pure tutin with that of a physical mixture of rutin and phyto-phospholipid complexes [62]. The FTIR of the sinigrin-phytosome complex produced by Mazumder et al. [65] showed distinct peaks from those of sinigrin, phospholipids, and their mechanical mixes.

***X-ray diffraction***

The microstructure of various amorphous materials as well as crystal materials can currently be examined using X-ray diffraction. X-ray diffraction is typically carried out on PCs, PC phytophospholipid complexes, active components, and their physical combinations. An active component and physical mixture's X-ray diffraction reveals strong crystalline peaks that point to a high crystal form. The absence of a crystalline peak in active component phyto-phospholipid complexes, however, shows that the constituents in these complexes have a molecular or amorphous structure. The finding that phyto-phospholipid complexes had better lipophilicity and hydrophilicity than active components [32] may be explained by this.

***Nuclear magnetic resonance (NMR)***

The identification of the complexes' structural details relies heavily on the 1H and 13C NMR methods. As mentioned above, hydrogen bonds rather than chemical bonds are responsible for the interactions between polyphenols and phospholipids. Based on NMR data, Angelico et al. determined that silybin A's polar phenolic functional groups and phospholipids can form hydrogen bonds [68]. According to the spectra of many phyto-phospholipid complexes, lipids' hydrophobic side may operate as an envelope to protect the core, choline-bioactive portions of these complexes.

**Oral Bioavailability Enhancement Using a Phospholipid Complex: A Mechanistic Outlook**

Drugs with poor permeability (BCS classes III and IV) or poor solubility (BCS class II) typically have relatively low bioavailability when administered orally [69]. Other sources of reduced bioavailability include the presence of metabolising enzymes, the environment's pH-

mediated degradation, and the P-gp pump, which results in the efflux of naked medicines [70]. Drugs must therefore be transported in order to reach the desired amount in the systemic circulation [71]. Phospholipid-drug complexes, whose absorption mechanism is comparable to that of triglycerides and essential phospholipids, might be utilised for the same purpose. The endogenous absorption of phospholipids by enterocytes is comparable to how the phospholipid-drug combination is absorbed [72]. The phospholipid is composed structurally of two fatty acid chains joined to the diacylglycerol moiety, which is hydrolyzed to liberate fatty acid, which causes its absorption. The drug-diacyl glycerol combination also experiences hydrolysis when given orally. At a pH of 1.5, minor hydrolysis takes place in the stomach, and the majority of it begins in the duodenum, where juice-like secretions from the pancreas, bile bladder, and liver are produced [73,74]. Due to the presence of phospholipases, particularly phospholipase A2, drug-diacyl glycerol hydrolyzes in the intestine, releasing fatty acids and forming drug-monoacyl glycerol. Micellar vehicles are then created from the previously mentioned substance, monoacyl glycerol, and bile salts. The secretion of the hormone cholecystokinin (CCK), which is released when a larger concentration of fatty acids are created by the hydrolysis of diacyl-glycerophospholipids and triglycerides, is essential for the formation of these micelles in the duodenum [73, 75]. However, the stomach's small hydrolysis tends to release the fatty acid that originally causes the release of CCK, which in turn further controls the release of bile acids and salts. Following hydrolysis, enterocytes passively diffuse the drug-monoacyl phospholipid vesicles into their cells. Drug-monoacyl phospholipids and endogenous diglycerides are converted to diacyl phospholipids and triglycerides, respectively, by enzymes in the smooth endoplasmic reticulum of enterocytes. Additionally, apoportein B-48 is integrated into the phospholipid vesicle in the golgi apparatus to create nascent chylomicron [76]. Bypassing the first pass metabolism, the chylomicron enters lacteal (lymph capillary), departs the enterocyte via exocytosis through the basal membrane, and travels outside the intestine. At the thoracic duct junction with the left subclavian vein, the chylomicrons transfer the drug complex into systemic circulation [77]. When nascent chylomicron reaches the systemic circulation, high density lipoprotein distributes apolipoprotein C-II and apolipoprotien E to the nascent one, converting it to mature chylomicron. The matured chylomicron returns the apolipoprotein C-II after storing the triglycerides, and at that point, they are known as chylomicron remnants, which are often found in the liver for endocytosis and disintegration [78]. As a result, the medication phospholipid complex reaches the systemic circulation via the chylomicron and skips the first

pass metabolism. The drug phospholipid complex's mechanism enables the absorption of medications that are either not soluble or have exhibited substantial first pass metabolism. Figure 3 shows a schematic representation of the same.

**Potential of Phytosomes as a Novel Drug Delivery System: Applications**

Phytosomes are used to treat a number of illnesses, including heart disease and liver disease. Phytosomes are also used as an anti-inflammatory, lipolytic, vasokinetic, and anti-edema agent, among many other things. Additionally, it functions as an antioxidant, immunomodulator, nutraceutical, etc. Yanyu et al. [80] showed that oral administration of the produced silybinphospholipid complex significantly enhanced the bioavailability of silybin in rats. Similar to this, Tedesco et al. [81] shown that silymarin phytosomes have stronger antihepatotoxic activity than silymarin alone in protecting against the toxic effect of aflatoxin B. In rat liver injury caused by carbon tetrachloride, quercetin phospholipids complex exerted stronger therapeutic activity than the molecule [82]. Following are some of the many benefits and uses of phytosomes:

1. Phytosome permeates the nonlipophillic botanical extract, making botanical extracts better bioavailable
2. Phytosome works in small quantity to give desired results and is widely used in cosmetics due to their better skin penetration.
3. Phytosome finds applications in giving liver-protectant flavonoids due to their easy bioavailability.
4. The phytosome process gives rise to little cells whereby the costly components of the herbal extract are protected from damage by digestive secretions and gut bacteria.
5. Phytosomes are used in anti-inflammatory formulations, pharmaceuticals, and cosmetic formulations. Phytosomes are also used to treat acute and chronic liver disease.
6. Phytosomes are also used as cancer chemopreventive agent, antioxidant, brain stimulant, immunomodulator, skin-improving agent, anti-wrinkle and antiaging supplement, antihypertensive agents, etc [83]. Phyto-phospholipid complexes on the market are shown in Table 1.

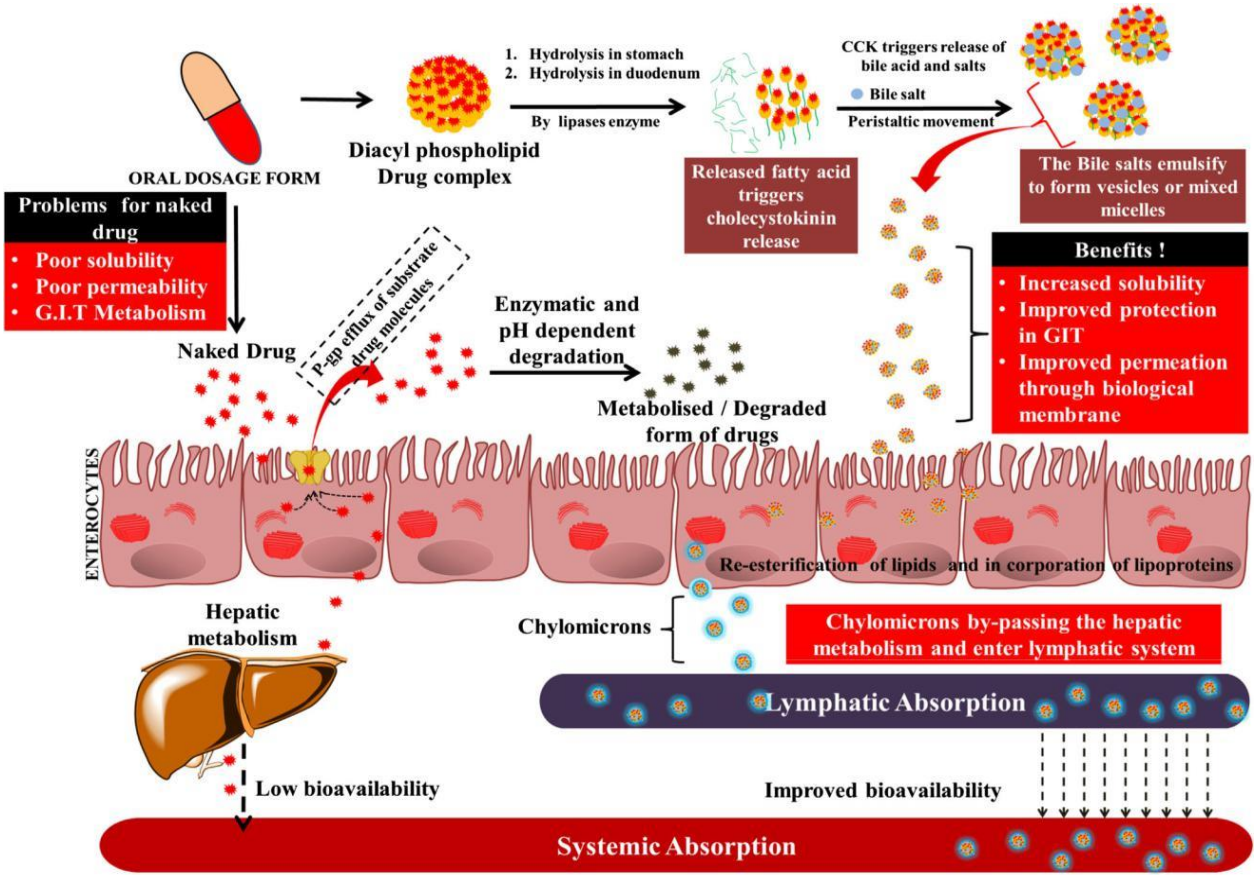


**Figure 3 The general mechanism of drug phospholipid complex to enhance bioavailability [79].**

## Conclusion

Since ancient times, herbal medicines have enjoyed widespread acceptance around the world due to their superior medicinal effectiveness and significantly fewer side effects when compared to contemporary allopathic medications. Biological standardisation, pharmacological and toxicological evaluation, exploration of sites of action/absorption, safety, toxicity, legal and regulatory issues of herbal treatments, etc. are just a few of the challenges that come with using herbal medications. Additionally, in order to boost the efficacy of Ayurvedic medications/phytotherapeutics, a proper delivery method for the active ingredients to the target location is required, with new drug delivery systems being the preferred option. By lowering toxicity and raising bioavailability, novel drug delivery methods like phytosomes serve to boost therapeutic value while also minimising the need for recurrent drug administration. The traditional drug delivery system and the cutting-edge drug delivery method are connected by phytosomes. Phytosomes are utilised as medicines and have a wide range of applications in the medical sciences. Many more areas of phytosome applications will be made public in the future with an eye towards pharmaceutical use.

**Table 1 Therapeutic application of different phyto-phospholipid complexes on the market [84].**

| S. no. | Trade name | Phytoconstituents complex | Indication |
|---|---|---|---|
| 1 | Greenselct® phytosome | Epigallocatechin 3-O-gallate from cameliasinensis (green tea) | Systemic antioxidant. Protect against cancer and damage to cholesterol. |
| 2 | Ginkgoselect® phytosome | Ginkgo flavono glycosides from Ginkgo biloba | Protects brain and vascular lining |
| 3 | Silybin phytosome | Silybin from silymarin | Provides antioxidant protection for the liver and skin. |
| 4 | Glycyrrhiza phytosome | 18-beta glycyrrhetinic acid Anti | inflammatory activity |
| 5 | Grape seed (Leucoselect) phytosome | Procyanidins from vitis Vinifera | Anti oxidant, anticancer |
| 6 | Curcumin (Merinoselect) phytosomes | Polyphenol from Curcuma Longa | Cancer chemopreventive agent improving the oral bioavailability of curcuminoids, and the plasma. |
| 7 | OleaselectTM phytosome | Polyphenols from olive oil | Inhibit harmful oxidation of LDL cholesterol, and provides an anti-inflammatory effect. |
| 8 | Sabalselect® phytosome | An extract of saw palmet to berries through supercritical CO2 (carbondioxide) extraction | It is beneficial to the normal functioning of the prostate |
| 9 | PA2 phytosome | Proanthocyanidin A2 from horse Chestnut bark | Anti-wrinkles, UV protectant |
| 10 | Zanthalene phytosome | Zanthalene from zanthoxylum bungeanum | Soothing, anti irritant, anti itching |
| 11 | Centella phytosome | Terpenes | Vein and skin disorders |
| 12 | Hawthorn phytosomeTM | Flavonoids from Crataegus sp. | Nutraceutical, cardio-protective and antihypertensive |

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