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Phytosomes: Bridging Nature And Nanotechnology For Enhanced Drug Delivery

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Abstract

The development of phytosomal drug delivery systems represents a significant advancement in natural medicine, addressing longstanding challenges associated with botanical compounds, including poor absorption and permeation rates, as well as limited bioavailability. The molecular interaction between phytoconstituents and phospholipids, particularly phosphatidylcholine, results in the formation of phytosomes, which substantially improve the lipophilicity and absorption characteristics of hydrophilic extracts. This phytosomal system provides two primary advantages through its pharmaco-absorptive properties: it enhances the drug's potency while concurrently preventing the enzymatic degradation of bioactive substances. The bioavailability of key compounds, such as curcumin, silybin, and quercetin, is significantly improved when utilizing phytosomal formulations rather than traditional extract preparations. Advances in nanotechnology have facilitated the development of nano-phytosomes and surface-modified stealth phytosomes, which extend clinical applicability by enabling controlled drug release, minimizing systemic toxicity, and enhancing targeted delivery. Several phytosome-based products, including Siliphos®, Meriva®, and Greenselect®, have received regulatory approval and achieved market success in clinical applications. Research into formulation methodologies, such as spray drying and novel biopolymer encapsulation techniques, has improved the stability and shelf life of phytosome products. The increasing demand for safer natural therapeutic alternatives positions phytosomal delivery systems at the forefront of integrating traditional medicine with contemporary pharmaceutical technologies. Future research efforts will focus on the development of intelligent, stimuli-responsive phytosomes and the creation of personalised therapeutic strategies tailored to individual patient needs within the framework of precision herbal medicine. This review examines phytosomal systems, focusing on their design principles, current applications, and future potential for enhancing the efficacy of botanical drugs.

Keywords: *Phytosomes, Phospholipids, Bioavailability, Liposomes, Flavonoids, Herbosomes, Phytoconstituents, Phosphatidylcholine*

1. Introduction

Phytosomes, an innovative herbal medication delivery system, were developed in the late 1980s by the Italian company Indena S.P.A. to enhance the bioavailability of plant-derived substances by encapsulating them within phospholipids [1]. Also called the Phytolipid delivery system, it acts as a bridge between traditional and innovative delivery systems.

The word "phytosome" comprises the terms "phyto" meaning plant, and "some" meaning cell-like structure. The purpose of this method was to formulate many herbal extracts with poor absorption to high solubility that potentially can increase therapeutic efficacy [2]. Although the Vedas, the ancient Indian scriptures, do not explicitly mention phytosomes, they describe extensively the use of medicinal plants, herbal formulations, and lipid-based preparations to improve bioavailability. The field of phytosome technology is based on the

fundamentals of phytomedicine, which refers to Ayurvedic texts such as the Charaka Samhita and Sushruta Samhita, which provide a practice of administering herbs along with oils, ghee, and other substances. Thus, phytosomes are a modern innovation, while the root principles of phytosomes are rooted in ancient Ayurvedic wisdom, which gave birth to herbal medicine. It is sometimes referred to as herbosomes [3].

This technology utilizes microscopic cells as scaffolds to protect valuable plant extracts from the effects of digestive enzymes and the bacteria found in the gut. Primary function of phytosomes is to assist in the transition of hydrophilic herbal constituents into a lipid-rich environment of the enterocyte cell membrane, making it more stable, soluble, and permeable to bioactive compounds across biological membranes [4]. Due to its marked pharmacological benefits when extracted traditionally, these herbal extracts exhibit low bioavailability is caused by their rapid removal from the body and poor water solubility. However, these challenges are overcome by phytosome technology, which enables the transfer of a greater concentration of the active ingredient to the bloodstream and its therapeutic effects [5].

Phytosome formulations utilize phospholipids, such as phosphatidylcholine, phosphatidylserine, phosphatidylethanolamine, and phosphatidylinositol. Phosphatidylcholine is most frequently utilized because of its therapeutic advantages. Phosphatidylcholine plays more than a carrier function for bioactive flavonoids. It has been shown clinically to have efficacy in liver disorders such as hepatitis, alcoholic hepatic steatosis, and drug-induced liver injury [6].

It is also known that phytosomes activate several biochemical pathways, such as:

1. Enhancing antioxidant defense systems.

2. Stimulating alpha-adrenergic-induced glucose transport.

3. Regulating the production of pro-inflammatory cytokines.

Water-soluble herbs contain many biologically active constituents such as flavonoids, tannins, and terpenoids, for which a lack of bioavailability is due to large molecular size and low lipid solubility. These properties prevent their passive diffusion across lipid-based cell membranes. However, phytosome technology enhances the pharmacokinetics and pharmacological potential of such compounds, rendering them a valuable tool for anti-inflammatory endeavours and in pharmaceutical and aesthetic applications. Multiple approaches are currently explored to enhance oral bioavailability, including solubility and bioavailability enhancers, structural modifications, and the use of lipophilic carriers [7].

Advances in phytosome technology have facilitated the creation of innovative formulations, including nano-phytosomes, which utilize lipophilic carriers to enhance drug delivery by reducing particle size and improving cellular uptake [8]. With advancements in the natural sciences, phytosomes have gained widespread use in pharmaceuticals, cosmeceuticals, and nutraceuticals, being incorporated into various products, including solutions, emulsions, creams, lotions, and gels. Multiple organizations, such as Indena, Jamieson Natural Resources, Thorne Research, Natural Factors, and Nature's Herb, are actively developing and commercializing phytosomal products [9].

1.1. Advantages of Phytosomes: [10,11,12]

- Phytosomes enhance the absorption of plant-based compounds by improving their solubility and ability to cross cell membranes, making the active ingredients more effective than traditional herbal extracts.
- The phospholipid structure of phytosomes protects sensitive plant compounds from degradation due to heat, light, or oxidation, which improves shelf life.

- Their compatibility with biological membranes enables them to deliver active ingredients more efficiently to specific tissues or organs.
- Enhanced absorption and effectiveness enable lower doses of phytosome-formulated products to achieve the desired therapeutic effects, thereby reducing the risk of side effects.
- Phytosomes are composed of phospholipids that naturally occur in the body, thereby contributing to improved biocompatibility and reduced toxicity.
- Enhance the bioavailability of poorly absorbed phytochemicals, such as curcumin, quercetin, and silybin, thereby improving their therapeutic potential.
- They offer a more stable formulation than conventional extracts, reducing the need for preservatives or stabilizers.
- This technology can enhance the controlled and sustained release of active compounds, leading to prolonged therapeutic effects.
- These formulations often exhibit improved patient compliance due to better efficacy, lower dosing frequency, and reduced gastrointestinal irritation.
- Phytosomes are versatile and capable to be incorporated into numerous delivery systems, like capsules, tablets, creams, and gels, thereby expanding their applications in both pharmaceuticals and cosmetics.

1.2. Disadvantages of Phytosomes: [10,13]

- The production of phytosomes is costly due to the need for advanced techniques, specialized equipment, and high-purity phospholipids.
- Some phytosomes still face solubility challenges in highly aqueous environments, limiting their use in certain water-based formulations.
- Phospholipids in phytosomes are prone to oxidation, which can shorten shelf life and require careful storage conditions.
- Developing effective phytosome formulations is a complex process, requiring extensive research and customisation for various plant extracts.
- Phytosome technology is still emerging and may face regulatory hurdles due to variability in plant sources and the lack of standardized guidelines.

2. Structure of phytosomes

The polar head (choline moiety) and active phytoconstituents mix chemically and physically to form phytosomes and Guggulosomes, which are complexes of phyto-phospholipids as shown in Fig.1. Phospholipid head groups must be anchored in these complexes [14]. A fatty acid chain encapsulates the polar component in complexes that produce a lipophilic surface. The active component of a liposome can be found in a cavity between the many layers of the membrane. The membrane itself contains the material that gives phytosomes their activity [15].

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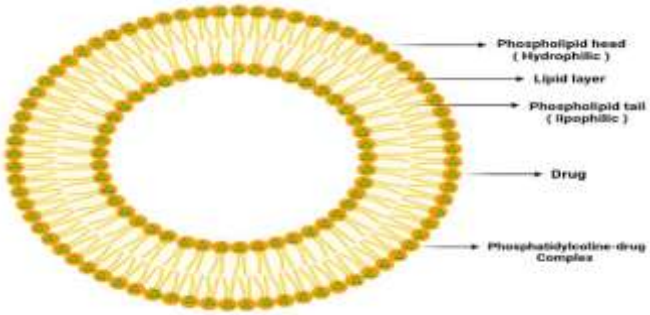

Fig 1. Structure of phytosome

3. Components of phytosomes

Four essential elements are required to synthesis of phyto-phospholipid complexes mentioned in present literature are phytoconstituents, the function of phospholipids, the stoichiometric ratio, and solvents. Apart from polyphenols, other substances, including siramesine, evodiamine, and 20(R)-25-methoxyl-dammara-3,12,20-triol (25-OCH3-PPD) can serve as active agents in phytosomal formulations. Subsequently, complexes derived from phytosomes might theoretically be combined with any active moiety because they are not just polyphenols [16].

3.1. Plant-based ingredients

Selected by the researcher, the pharmacological impact of phytoactive components isolated from plants is assessed in vitro rather than in vivo. These substances are mostly polyphenols, some of which are found in polyphenolic components, favour the aqueous phase, and cannot cross living things' membranes [17]. On the other hand, some, like rutin and curcumin, have lipophilic properties that make them insoluble in the aqueous stomach content.

Both the permeability of cell membranes with hydrophilic polyphenols due to the water phase and the solubilization of lipophilic polyphenols due to the water phase are enhanced by phyto-phospholipid complexes. Furthermore, polyphenols may be protected from photolysis, oxidation, and hydrolysis by complex formation [18].

3.2. Phospholipids

Phospholipids, notably sphingomyelins and glycerophospholipids, are found in large quantities within plants and the yolk of eggs. They are categorized according to their backbones. Phosphorylcholine, phosphorylethanolamine, phosphorylglycerol, phosphorylserine, phosphorylinositol, and phosphoric acid (PI) are the main constituents of glycerophospholipids. Phospholipids that are manufactured commercially are currently available for purchase. PS, PE, and PC are the principal phospholipids that participate in the assembly of complexes characterized by a hydrophilic head group and two hydrophobic hydrocarbon chains. PC is the most favoured phospholipid among them. It is used in the phospholipid complex building process because of its amphipathic character, which permits mild solubilization in lipid solution and in aqueous environments. PC is also a crucial part of cell membranes, which helps to explain why it doesn't damage or interfere with living organisms [19].

3.3. Phyto-Active Constituents and Phospholipids in a Stoichiometric Ratio

Typically, phytoconstituents are combined with high amounts of either synthetic or natural phospholipids at a wide range of molar ratios i.e., 0.5:1 to 2:1, to create phytosomes. The 1:1 molar ratio is the most preferred

ratio for phylipid complexation in many cases [20]. Thus, quercetin-slash-phospholipid complex is also referred to when Lipoid S 100 and quercetin collide in equal parts (1:1). In a similar vein, a 1:1 proportion of SPC Lipoid® S100 and curcumin becomes the source of a curcumin phytosomal soft gel and the respective phytosome in one process. Such studies also reveal that these formulations are very effective not to mention that they become more stable also [21]. In another investigation, the researchers found that diosgenin phytosomes produced at a 1:1 molar ratio effectively combat lung cancer cells. The results showed enhanced diosgenin water solubility and more cytotoxic effects against human cancer cells. Nonetheless, research has employed a variety of phospholipids and active ingredients in stoichiometric ratios. Silymarin phytosomes were synthesized in a variety of stoichiometric ratios, including 1:5, 1:10, and 1:15. According to the scientists ' findings, phytosomes with the highest drug loading and the finest physical properties are produced at a stoichiometric ratio of 1:5. Conduct a comparative analysis by synthesizing phytosomes with the following stoichiometric ratios: 1:1, 1.4:1, 2:1, 2.6:1, and 3:1. The results showed that the most efficient stoichiometric ratio was 3:1. Furthermore, chrysin-loaded phytosomes were developed to improve the absorption of glucose by muscle cells. The authors found that adopting a 1:3 molar ratio achieved the determined stable ratio. As an outcome, a 1 to 1 molar ratio is not necessary to target the phospholipid synthesis interactions. The phospholipid/active transporter stoichiometry components would be altered for different types of medications to accomplish particular objectives, such as high drug loading [22].

3.4. Solvents

Scientists have already employed a variety of them to create phospholipid phytocomplexes. Most often, complexes of phytophospholipids have been synthesized using aprotic solvents such as methylene chloride, cyclic ethers, ethyl acetate, hydrocarbons, and halogen derivatives. However, protic solvents like ethanol and methanol have replaced them due to their success rate. Methanol, rutin, and phospholipids are combined in studies to treat inflammatory diseases. To improve the duration of medicine retention on the skin, the scientists created a polymeric matrix patch [23]. When compared to regular diclofenac gel, the results showed that the enhanced preparation had 31.32 and 26.56% skin penetration. The anti-inflammatory effect of the patch was also shown to be effective in a rat-paw oedema model. Phytosomes containing chrysin were formulated to boost glucose absorption in muscle cells. Chrysin-loaded phytosomes produced using the solvent evaporation method. Phospholipids from eggs or soy PC were integrated to generate phytosomes [24].

4. Properties of Phytosomes

4.1. Chemical Properties

Phytosomes use phospholipid complexation to increase the bioavailability of chemicals produced by plants. Phospholipids like phosphatidylcholine are bound by phytochemicals like flavonoids and polyphenols through hydrophobic and hydrogen bonding interactions [25]. Phytosomes are more effective than traditional plant extracts because of this complexation, which increases solubility and absorption. They may interact with both lipid and water environments since they are amphiphilic. Better gastrointestinal absorption and effective distribution of bioactive chemicals are made possible by the hydrophilic part's interaction with body fluids and the lipophilic part's integration with cell membranes. Additionally, phytosomes have increased lipophilicity, which enhances pharmacokinetics. When complexed with phospholipids, poorly soluble substances such as curcumin and quercetin become more lipophilic, thereby enhancing membrane integration and systemic circulation and improving therapeutic efficacy. Effectiveness of pharmaceutical and nutraceutical formulations. Their steadiness is yet another vital benefit [26]. Phytosomes shield sensitive bioactive substances from oxidation, heat, light, and enzyme destruction. In pharmaceutical and nutraceutical formulations, this prolongs shelf life and preserves medicinal efficacy. Phytosomes entail the direct molecular bonding of phytochemicals with phospholipids, in contrast to liposomes, which encapsulate active

compounds. Because of this special interaction, a more stable and effective complex is produced, guaranteeing greater absorption and controlled release of bioactive chemicals [27].

4.2. Physical Properties

The structure of phytosomes is nanoscale, with particle sizes usually falling between 50 and 500 nanometers. More effective drug administration is made possible by their compact size, which improves their permeability and absorption in the gastrointestinal tract [28]. Phytosomes are an efficient way to deliver bioactive plant components to specific locations in the body because of their smaller particle size, which also makes it easier for them to distribute throughout various tissues. The enhanced solubility of phytosomes in lipid and aqueous environments is another significant physicochemical characteristic. The phospholipid complexation enhances the dispersibility and absorption of hydrophobic phytochemicals by increasing their solubility in body fluids. This enhanced solubility is especially advantageous for plant extracts that have low water solubility, such as resveratrol and curcumin, which would ordinarily have few therapeutic benefits because of inadequate absorption [1]. Additionally, phytosomes have a high entrapment efficiency, which indicates that a significant amount of the active ingredient is effectively integrated into the phospholipid complex. Due to its high efficiency, the phytochemical is guaranteed to remain stable and bioavailable during formulation and storage. Phytosomes ensure that a greater proportion of the bioactive ingredient enters the systemic circulation, thereby enhancing the therapeutic efficacy of traditional plant extracts, which can lose their potency due to inadequate absorption or breakdown [29]. Furthermore, the controlled release characteristics of phytosomes aid in the gradual release of bioactive substances. By controlling the release of the active ingredient, the phospholipid complex ensures a longer duration of action and reduces the need for frequent dosing. Maintaining steady therapeutic levels of phytochemicals in the body, enhancing patient compliance, and enhancing therapy results are all made possible by this sustained-release method [30].

4.3. Pharmacokinetic Properties

Phytosomes demonstrate superior pharmacokinetic properties compared to conventional plant extracts. Their ability to effectively integrate into biological membranes due to their phospholipid-based nature makes improved absorption one of their most significant benefits. The therapeutic potential of phytosomes is increased due to their enhanced permeability, which raises the plasma concentrations of bioactive substances [31]. According to studies, substances like silymarin and curcumin that are formed into phytosomes have much better absorption than those that are not. The enhanced tissue dispersion of phytosomes is another important pharmacokinetic characteristic. Phytosomes can readily pass cellular membranes and disperse throughout the body's tissues due to their lipophilic nature. This feature is beneficial for targeting organs that traditional plant extracts may not reach as well, such as the liver, brain, and skin. The efficacy of phytosome-based formulations in treating a range of illnesses and ailments is increased by improved tissue dispersion [32]. Additionally, phytosomes have a longer circulation time, which contributes to the long-term maintenance of therapeutic concentrations of bioactive substances in the bloodstream. Because the phospholipid complex shields the phytochemicals from quick digestion and excretion, their effects last longer. When long-term medication action is needed for chronic illnesses, this feature is invaluable. Phytosomes enhance patient adherence to treatment plans by prolonging the circulation duration of bioactive compounds, thereby reducing the frequency of administration [33]. Additionally, when compared to traditional plant extracts, phytosomes show less toxicity and adverse consequences. Phytosome-based formulations require lower doses to provide therapeutic benefits because they improve absorption and bioavailability. Because of this decreased risk of toxicity and negative reactions, phytosomes are a safer option for long-term use. They are appropriate for a range of pharmaceutical and nutraceutical applications due to their non-toxic nature and biocompatibility [34].

5. Comparison between Phytosome and Liposome:

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Phytosomes are not liposomes. They are structurally different, as shown in Fig. 2. While liposomes develop when phosphatidylcholine is combined with a substance that dissolves in water, phytosomes are formed by stirring 1:1 phosphatidylcholine into the extract. The phosphatidylcholine molecules enclose the water-dissolvable material. However, there is no formation of a chemical bond; instead, numerous phosphatidylcholine molecules physically encapsulate the water-based compound [35]. On the other hand, if producing the phytosome, the phosphatidylcholine and the individual plant components are complexing at 1:1 or 2:1 based on substance. Water or buffer solution is used as a medium to form a liposomal drug complex, while the phytosome acts with the solvent of a lower dielectric constant. This has an effect as the phytosomes are a few molecules, and this makes a difference, so there is better absorption of the phytosomes than that of the liposomes [36].

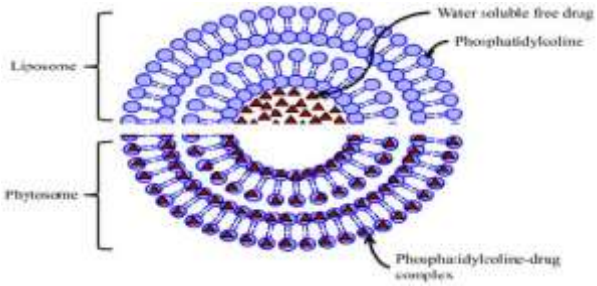

Fig 2. Comparison between phytosomes and liposomes

Phytosomes are considered better than liposomes for skin care. Because of multiple phospholipids, liposomes are capable of encasing phytoactive molecules without forming particular links to them [37]. These products are called delivery vehicles, but these claims have not been true for dietary supplements. In phytosome preparations, scientists have found that the compounds contained are more effectively absorbed and have more positive clinical results. Many firms have used this technology in their standardized flavonoid preparations [38].

6. Commercial Products of Phytosomes:

Numerous commercially available phytosome-based products are more therapeutic than traditional dosage forms; their details are shown in Table 1 which includes their name, leading substances, source, dosage per serving and intended purpose.

Table 1: Commercially available phytosomal product

S no.	Trade name	Chief constituents	Source	Use	Ref.
1	Meriva®	Curcumin	*Curcuma longa* (Turmeric)	Anti-inflammatory, antioxidant, joint health	39
2	Siliphos®	Silybin (Silibinin)	*Silybum marianum* (Milk Thistle)	Liver protection, antioxidant	40
3	Greenselect® Phytosome	Epigallocatechin gallate (EGCG)	*Camellia sinensis* (Green Tea)	Weight management, antioxidants, cardiovascular support	41
4	Ginkgoselect® Phytosome	Ginkgo flavone glycosides	*Ginkgo biloba* leaves	Cognitive enhancement, memory	42

				support, circulation improvement	
5	Leucoselect® Phytosome	Procyanidins	*Vitis vinifera* (Grape Seed)	Antioxidant, cardiovascular health, anti-aging	43
6	Centellase® Phytosome	Triterpenes (asiaticoside, madecassoside)	*Centella asiatica*	Wound healing, skin repair, cognitive function	44
7	MenoPause®	Soy isoflavones	*Glycine max (Soybean)*	Menopausal symptom relief	45
8	Phytosome® Boswellia	Boswellic acids	*Boswellia serrata*	Anti-inflammatory, joint and respiratory health	46
9	Ecosyn® Phytosome	Quercetin	*Various plant sources (e.g., onion, apple)*	Antioxidant, anti-inflammatory, and cardiovascular protection	47
10	Vitaphospholip®	Various polyphenols or herbal extracts	*Various herbal sources*	Enhancing the bioavailability of herbal actives	48
11	PA2 phytosomes	Proanthocynidin	*Horse chestnut bark*	Antiwrinkles, UV protectant	49
12	Sericoside phytosome	Sericosides	*Terminalia sericea*	Skin improver	50
13	Rexatrol	Resveratrol	*Polygonum cuspidatum*	Antioxidant, anti-aging	51
14	Lymphaselect phytosomes	Triterpenes	*Melilotus officinalis*	Indicated in insomnia	52
15	Echinacea phytosome	Echinacosides	*Echinacea angustifolia*	Immunomodulators, nutraceuticals	53

The ® symbol stands for "Registered Trademark.

7. Mechanism of Phytosome Technology:

The reduced absorption and bioavailability of polyphenolic components can be attributed to two main factors. A range of ringed molecules that aren't too small to be absorbed by diffusion are among these primary constituents. The second problem is that flavonoid molecules, which make up the majority of polyphenols, are poorly soluble in lipids [54]. Because of these limitations, they are unable to cross biological membranes, as shown in Fig 3. When polyphenols and phospholipids are complexed in a 1:1 or 1:2 ratio, the main result of phytosome technology is the formation of a phytosomal complex with a lipid covering encircling the contents [55].

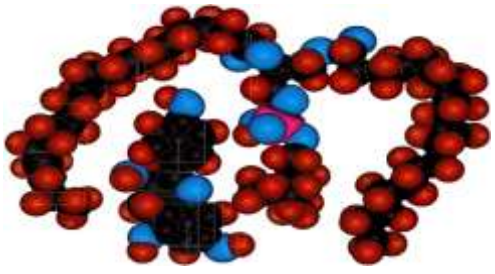

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Fig 3. Schematic of the phytosomes molecular complex

8. Preparation of Phytosomes:

8.1. Solvent Evaporation Method

Phytosome formulation is considered a method for solvent evaporation. Below you will find a quick explanation of the basic process.

It is possible to select any appropriate phospholipid which form a complex with the phytoconstituents in the medicinal plant extract, ideally phosphatidylcholine. Both the phyto-ingredients and the phospholipids are dissolved using the proper solvent. Dependent on the components' solubility and required properties of the finished product, common solvents include methanol, ethanol, chloroform, and combinations of these solvents [56]. Beneficial phytoconstituents are extracted from medicinal plants using a technique like maceration, Soxhlet extraction, or supercritical fluid extraction. If required, these phytoconstituents are concentrated to reach the required concentration of active compounds. The selected solvent is used to disperse the phospholipid until a clear solution is formed.

Furthermore, stronger plant extracts are dissolved in same solvent or a different one. In extracts from therapeutic plants, the right phospholipid—typically phosphatidylcholine—is selected to interact with compounds like phytoconstituents. Both lipid and plant-based molecules should dissolve in the perfect solvent. The solubility of the components and the required properties of the final product determine which solvents are most commonly used: ethanol, methanol, chloroform, or combinations of these [57]. Using a suitable extraction technique, such as maceration, Soxhlet extraction, or supercritical fluid extraction, the relevant phytochemicals are extracted from the medicinal plant and, if required, concentrated to reach the requisite concentration of active components. The chosen solvents are used to dissolve the phospholipids until a clear solution is formed [58].

Additionally, the same or different solvents are used to dissolve concentrated plant extracts. While stirring, the plant extract is added to the phospholipid solution. Together, these elements create phytosome complexes (Fig 4). The solvent is extracted from the complexes using methods such as rotary evaporation (Fig 7) at a regulated temperature and low pressure. Techniques like spray drying are used to create a fine powder after additional drying to remove contaminants. Properties, including particle size, stability, and purity, are assessed by testing. The consistency and purity of the product must be guaranteed. To ensure stability and efficacy, the product must be stored in appropriate containers that protect against oxidation, light, and moisture [59].

Fig 4. Solvent evaporation method

Increasing the number of phytosomes with improved stability and usability is made possible by solvent drying. This method is effective for producing herbal products. Solvent evaporation techniques have been used to create Bombax ceiba phytosomes. Due to its hepatoprotective properties, Bombax ceiba is utilized. Soy lecithin has been complexed with extracts to increase their bioavailability [60].

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8.2. Anti-Solvent Precipitation Process

A specified quantity of phospholipids and herbal extract is refluxed with 20 milliliters of organic solvents, like acetone, under particular experimental circumstances for two to three hours below 50°C. After concentrating the reaction mixture to a minimum volume of 10 milliliters, a low-polarity solvent, like n-hexane, is added during stirring, resulting in the formation of precipitates [61]. Desiccators are used to store and preserve filtered precipitates. The dried precipitates are ground into a fine powder, and the resulting mixture is stored at room temperature in a glass bottle with a dark amber hue [62].

8.3. Solvent Ether-injection Process

This method involves combining lipids dissolved in a chemical solvent with the aqueous portion of plant extracts [63]. Drop by drop, phospholipids that dissolve in diethyl ether are gradually added to the aqueous portion, as shown in Fig 6. The components that need to be encapsulated in this solution are plant-based. Tiny sacs that resemble cells are created after the solvent is removed. For this reason, a complex is formed by the plant ingredients. The amount present determines the structure. Single-layered structures develop at lower levels. Nevertheless, different morphologies, such as spheres, cylinders, discs, cubes, or hexagonal sacs, appear at increasing concentrations [64].

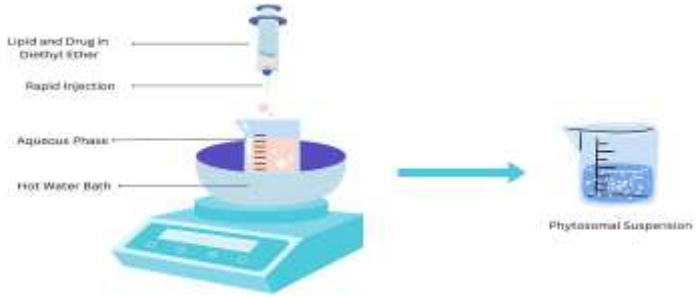

Fig 6. Solvent ether-injection process

8.4. Rotary Evaporation Method

A mixture of the proper amount of plant material and phospholipid in thirty milliliters of tetrahydrofuran was prepared in a flask with a spinning circular bottom. The mixture was then stirred for three hours over low heat which kept the temperature in the mixture below forty degrees Celsius [59]. The thin-film sample was put together, n-hexane was added, and a magnetic stirrer was used to spin the mixture, as shown in Fig 7 continuously. The precipitate was removed and allowed to settle at room temperature in an amber-colored glass container [65].

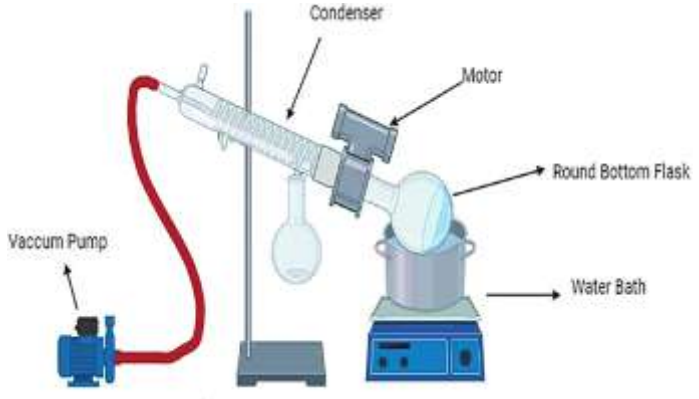

Fig 5. Rotary evaporation

8.5. Lyophilization Process

After melting both natural and synthetic phospholipids and phytoconstituents in different solvents, a phospholipid-containing combination was added to another solution containing phytoconstituents, and the mixture was agitated until a complex formed [66]. Lyophilization is used to separate the formed complex. The phospholipids used in the phytosome process have an acyl group that can be either phosphorylcholine or phosphatidylserine, and phosphatidylethanolamine is made chiefly from stearic, oleic, palmitic, and linoleic acids. Phytosomes' active principle turns into a structural element [67].

9. Characterization and Evaluation of Phytosomes:

Phytosome behaviour in physical and biological contexts are characterized by several factors, including the size of the phytosomes, membrane permeability, the quantity and proportion of entrapped solutes, the chemical makeup, and the purity of the beginning products [68]. Therefore, a physical description of phytosomes must be created, taking into account the nanoparticles' size, shape, distribution, and sporadic aggregation. These consist of the chemical components, the entrapped volume, the percentage released, and the percentage of drug that was captured in the gel [69].

9.1. Differential Scanning Calorimetry

An aluminium cell was used to heat the drug polyphenolic extract, phosphatidylcholine, a physical blending of the drug extract and phosphatidylcholine, and the drug-phospholipid complex at a rate of 50–250°C/minute in a nitrogen atmosphere between 0 and 400°C [70].

9.2. Scanning Electron Microscopy (SEM)

The amount of powder the sample contained and its general condition were also determined using it. In an electron microscope, the dried sample was so affixed on a brass stub coated in gold [71]. The complex is randomly scanned at 100.

9.3. Transition Electron Microscopy (TEM)

The size of phytosomal vesicles was assessed using TEM at 1000 magnification [54].

9.4. Drug Entrapment and Loading Capacity

To separate the phytosome from the remainder of the medication, the drug phytosomal complex was centrifuged for 90 minutes at 4°C at 10,000 rpm. The concentration of the free drug—that is, the drug that is in solution and not bonded to the polymer chains—can be ascertained from the sample's UV [72]. The following calculation can be used to calculate the percentage of drug entrapment using the Ford method mentioned above:

$$\text{Entrapment efficiency \%} = \frac{\text{Weight of total drug – weight of free drug}}{\text{weight of total drug}} \times 100$$

9.5. Fourier Transform Infrared Spectroscopy (FTIR)

FTIR spectroscopy will be purchased to ascertain the drug's phospholipids' structure, outlook, and chemical stability. Potassium bromide and the phytosomal medication will be coated to create pellets at a pressure of 600 kPa. Between 4000 and 400 cm−1, the scanning will be carried out [73].

9.6. Size Analysis and Zeta Potential

Malvern Zetasizer is used to measure the zeta potential and particle size of the phytosomal complex. The Argon laser is employed in this characterization of particle size and zeta potential [74].

9.7. In Vivo and In Vitro Evaluations

The characteristics of the medicine, its primary phytoconstituents enclosed by the phospholipid layer, and the animal model selected for evaluation will all influence in vitro and in vivo research [75].

10. Applications of phytosomes

Phytosomes have become a major breakthrough in the administration of herbal drugs, offering a range of therapeutic benefits by enhancing the efficacy and bioavailability of plant-based substances [76]. Improving the absorption of poorly soluble phytoconstituents, like resveratrol, curcumin, quercetin, and silybin, which have historically had limited therapeutic efficacy because of low gastrointestinal absorption, is one of their main applications. Phytosomes such as Silybin Phytosome (Siliphos®) are used extensively in liver health to assist liver regeneration and detoxification while treating diseases like fatty liver disease, hepatitis, and liver cirrhosis. Quercetin and resveratrol-containing phytosomes are used in cardiovascular care to lower blood pressure, increase vascular flexibility, and protect heart tissues from free radical damage [77].

Additionally, phytosomes exhibit significant anti-inflammatory and analgesic potential; formulations based on boswellic acid are effective in treating inflammatory bowel disease, arthritis, and joint pain [78]. Phytosomal forms of curcumin, genistein, and berberine have shown promising anticancer potential in oncology and are often used as adjuvants to enhance the effectiveness of chemotherapy. Ginkgo biloba and Bacopa monnieri (brahmi) phytosomes are utilized for neuroprotection, supporting memory, focus, and brain function, especially in dementia and age-related cognitive decline [79].

Proanthocyanidins, sericosides, and green tea extract phytosomes offer anti-ageing properties, UV protection, and enhanced skin hydration in the dermatology and cosmetics fields. Notable uses include hormonal balancing and menopausal support, where soy isoflavone phytosomes, such as MenoPause®, assist in reducing symptoms, including night sweats and hot flashes [80]. Additionally, phytosomes that strengthen the immune system, especially those derived from Echinacea, are used to increase resistance to illnesses like the flu and colds. Ultimately, by promoting glucose management and improving lipid profiles, berberine phytosomes show promise in enhancing metabolic health and may be beneficial in the treatment of conditions such as type 2 diabetes and metabolic syndrome. Phytosome technology marks a substantial advancement in the bioavailability, stability, and clinical utility of plant-based medicines for a wide range of medical disorders [81].

11. Future Prospects and Innovations in Phytosome Technology:

Phytosome technology has a promising future ahead, with breakthroughs anticipated in both research and commercial applications. Phytosomes are poised to play a key role in enhancing the bioavailability and efficacy of herbal substances as the market for natural and plant-based medicines expands [82]. Phytosomes were initially developed to improve the absorption of poorly soluble plant extracts. Still, they are now being investigated for a broader range of clinical applications, including cancer treatment, neuroprotection, cardiovascular health, and metabolic disorders [83]. Enhancing phytosome efficiency and enabling targeted, prolonged, and controlled drug release are anticipated outcomes of advancements in formulation science, namely the incorporation of nanotechnology, smart delivery systems, and stimuli-responsive carriers [84].

Phytosomes are likely to become increasingly compatible with personalised treatment strategies in the years to come. Supplements based on phytosomes can be customized to an individual's genetic composition, microbiome composition, and specific medical issues using artificial intelligence and genomics [85]. Furthermore, to create more ecologically conscious phytosome products, the pharmaceutical industry is concentrating on green and sustainable production techniques, employing biodegradable excipients, eco-friendly solvents, and circular economy models [86].

Additionally, efforts are being made to establish uniform regulatory frameworks to ensure the quality, safety, and effectiveness of formulations based on phytosomes [87]. It is anticipated that the growing fusion of contemporary phytosomal technology with traditional medical systems, such as Ayurveda and Traditional Chinese Medicine (TCM), will encourage the creation of innovative treatment alternatives that combine traditional knowledge with cutting-edge science [88]. To provide customers with safer, more efficient, and bioavailable plant-based treatments, phytosomes are, therefore, expected to have a revolutionary impact on the future of nutraceuticals, cosmeceuticals, and evidence-based herbal medicine [89].

12. Some Patented Technology of Phytosome:

In the realm of phytosomes, several academic scientists and industry laboratories have conducted a variety of novel procedures and formulation research investigations. Table 3 lists a few patents for phytosomes and related technologies, along with some of their inventions and uses.

Table 3: Innovation in Phytosome with Patent number and Patent title

Patent No.	Title of patent	Year	Innovation	Ref.
WO2019/016146	Quercetin Phytosome® Formulation (QUERCEFIT®)	2019	Enhanced bioavailability of quercetin using Indena's Phytosome® technology.	90
WO2019/102346	Phytosome Formulations for Enhanced Bioavailability of Silybin	2019	Improved absorption of silybin for liver health applications.	91
US10550632B2	Phytosome Encapsulation of Curcumin for Cancer Therapy	2020	Curcumin-phospholipid complex aimed at enhancing anticancer efficacy.	92
EP3090223B1	Novel Phytosome Compositions for Hepatic Tumors	2020	Phytosome-based delivery systems targeting liver tumours.	93
US10782345B2	Method of Preparing Phytosomal Formulations for Cancer	2020	Techniques for creating phytosome formulations to improve cancer treatment outcomes.	94
US11065456B2	Use of Phytosomal Curcumin in Liver Cancer Treatment	2021	Application of curcumin phytosomes specifically for hepatocellular carcinoma therapy.	95
WO2022135652A1	Genistein-Loaded Phytosomes for Liver Cancer Treatment	2021	Oral phytosome formulations of genistein to enhance solubility and bioavailability in liver cancer.	96
US11207388B2	Phytosomal Formulation Using Allium sativum and Murraya koenigii for Breast Cancer	2023	A sustained-release phytosome system combining garlic and curry leaf extracts for breast cancer therapy.	97
IN202341042728	Phytosome Loaded with Biosynthesized Ag Nanoparticles for Bone Cancer Treatment	2023	Second-order targeting phytosome system incorporating silver nanoparticles for bone cancer treatment.	98

US11787761B2	Process for the synthesis of Melphalan	2023	A novel process for preparing Melphalan, an anticancer drug, involving specific chemical conversions.	99
US11786513B2	Compositions comprising berberine	2023	Development of berberine compositions combined with pea proteins and surfactants to enhance bioavailability.	100

13. Conclusion

Researchers have developed phytosomal drug delivery systems, that may help boost the healing benefits of plant-based bioactive compounds. To improve the solubility, absorption, and bioavailability of natural compounds that often exhibit subpar pharmacokinetics, phytosomes form molecular complexes with phospholipids. Nanotechnology-enhanced phytosomes now provide targeted delivery methods, reduced systemic responses, and regulated drug delivery capabilities. Clinical studies using silybin, curcumin, and green tea catechin formulations have revealed encouraging results, as this technique holds promise for use in pharmaceutical and nutraceutical applications. The stability and commercial readiness of phytosome products have improved due to the development of new formulation approaches. Future health systems may depend on phytosomal medication delivery as a result of scientific research into smart phytosomes and customized phytomedicines. Phytosomal technology is a groundbreaking platform that successfully combines cutting-edge nanotechnology-based medication research techniques with traditional herbal therapeutic procedures.

14. References

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