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Review Article

A Comprehensive Review on Phytosomes: A Novel Drug Delivery System of Phytoconstituents

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Abstract: Phytosomes are referred to as novel compounds containing lipophiliccomplexes of components of different plants which are composed of glycerophospholipids. In the novel drug delivery system, it is a need of the hour to search for such a novel delivery system that can provide more bioavailability and efficacy for any extract containing phytoconstituents or Phyto extracts. The present study data were collected from extensive literature surveys from different esteemed scientific repositories such as Pubmed, Science direct, Research gate, Cochrane, Google scholar, Willey, Core, I Library, etc. Many phytoconstituents that are obtained from nature have high biological activities in many chronic diseases and has the best therapeutic efficacy. The main advantage of using phytoconstituents is that it does not have most adverse side effects. Phytosome is used for phytopharmaceutical formulations, herbal formulations, and in Ayurveda. It improves the bioavailability of medicaments and absorption of drug molecules. It has a better pharmacokinetic and pharmacodynamic profile as compared to the normal traditional medicinal plant extracts. The objective of this comprehensive review work is, to provide a combination of all the scientific aspects regarding the phytosomes (phyto-phospholipids complexes) point of view that were missed by some articles by highlighting the history, technology, characterization, chemical properties, its preparation, formulation, interactions, solvents systems, therapeutic utilization with dosages forms, side effects, latest patented technology, the difference between phytosome and liposome, Phyto-phospholipid complexes, Lamellarity and Stability, Solubility and partition coefficient, SEM & TEM, FTIR spectroscopy, bioavailability, advantages, other lipid-based nano-carriers; similarities and differences, biological or pharmacological properties, interactions between active constituents and phospholipids, vesicular systems for phytosome development, commercial marketed phytosomes products, recent advancements and limitations in this review paper.

Key words: Phytosome, Bioavailability, Phytoconstituents, Phospholipids, Novel Drug Delivery System (NDDS).

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1. INTRODUCTION

In the past few decades, the novel drug delivery system has been studied a lot; also this system is getting more attention for its development. The two key requirements for the system to be referred as novel are: drug should be delivered at a predetermined rate with predetermined time span and the the drug should mostly reach the targeted site at desired concentration.[1] However, the drug delivery system which is being used for administering herbal medicine to the patient is found to be traditional and outdated, due to which there is reduction in efficacy of the drug. Thus to increase the efficacy and reduce the side effects of the herbal compound, the novel drug delivery technology can be useful in herbal medicine. The basic idea is about incorporating a novel method of drug delivery in herbal medicines. Thus, it has become important to apply novel drug delivery system in Indian Ayurvedic medicines to tackle more serious diseases in future.[2] Most of the bioactive constituents of phytomedicines are plant secondary metabolites like glycosides, flavonoids, and terpenoids etc. which are known to retain several pharmacological activities. However, when taken orally or when applied topically, they are absorbed poorly. The two main reasons behind this phenomenon are: that the heavy molecular structure of these phytoconstituents cannot be absorbed by simple diffusion and they cannot pass across the lipid-rich outer membranes of the enterocytes of the small intestine due to their poor lipid solubility. Thus, for any herbal product to take effect, it depends on the delivery of an effective level of the active compounds in the targeted site. The phytosome technology developed by Indena acquires this challenge by enhancing the bioavailability of phytoconstituents.[3] Novel Drug Delivery System (NDDS) can reduce both frequencies of administration and the Peak and valley fluctuations which results in enhanced bioavailability. In Phyto-formulation research, different drug delivery vehicles are used, such as liposomes, solid lipid nanoparticles (SLNs), microemulsion, polymeric nanoparticles, and microspheres, solid lipid nanoparticles (SLNs) where phytoconstituent are solubilized and the drug is released in a sustained manner.[4] Many popular herbal extracts, such as Ginkgo biloba, grape seed, hawthorn, milk thistle (*Silybum marianum*), green tea (*Thea sinensis*), and ginseng, have been subjected to the phytosome process (*Panax ginseng*). The flavonoid and terpenoid components of these plant extracts are ideally suited to direct phosphatidylcholine binding.[5] As a result; the production of phyto-phospholipid complexes has received a lot of attention recently. The objective of this comprehensive review work is to provide a combination of all the scientific aspects regarding the phytosomes (phyto-phospholipids complexes) in a point of view that were missed by some articles by highlighting the history, technology, characterization, chemical properties, its preparation, formulation, interactions, solvents systems, therapeutic utilization with dosages forms, side effects, latest patented technology, difference between phytosome and liposome, Phyto-phospholipid complexes, Lamellarity and Stability, Solubility and partition coefficient, SEM & TEM, FTIR spectroscopy, bioavailability, advantages, other lipid-based nano-carriers: similarities and differences, biological or pharmacological properties, interactions between active constituents and phospholipids, vesicular systems for phytosome development, commercial marketed phytosomes products, recent advancements and limitations in this review.

2. HISTORY OF PHYTOSOME

Firstly, Bombardelli developed phytosome in the year 1991 in Milano. It was named as 'phyto-vesicle', 'phytophospholipid complex' and 'herbosome' in different publications. Phospholipid (phosphotidylcholine, phosphotidylserine etc.) was used to overcome the absorption related problems of mainly flavonoids, tannins, terpinoids and triterpens.[6] Over the past century, both chemical and pharmacologic science developed the compositions, biological activities and healthy benefits of different plant extracts. However, when individual components were separated from the whole extract the activity was no more active and the natural ingredient also became lost. The phytosomes process has been applied to many popular herbal extracts, including Milk thistle, Ginkgo biloba, Grape seed, Green tea, Hawthorn, Ginseng, etc.[7]Thus, to solve this problem, standardization was developed. It was discovered that, complexation along with other clinically useful nutrients significantly improved the bioavailability of such extracts. Such nutrients that wereso helpful for enhancing the absorption of other nutrients was found to be phospholipids. Phospholipids are referred as complex molecules that are used in all known organisms to make cell membranes.[8] The increased bioavailability of the phytosomes over the simple and noncomplex plant extracts was demonstrated via pharmacokinetic (tissue distribution) and activity was studied by conducting experiment in animals as well as in humans. Phytosomes have played an important role in health giving activity of the phospholipids themselves. Phytosomes showed better pharmacokinetic and pharmacodynamic effect than orthodox herbal extracts.[9,10]

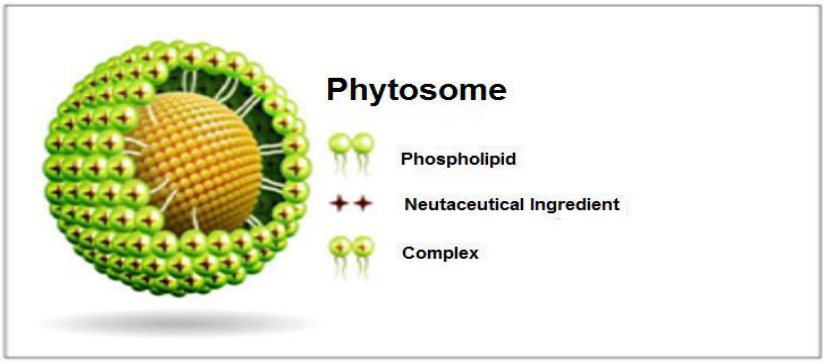


Fig1: Structure of phytosome[11]

Phytosome is a recently known patented technology where phyto molecule forms a complex with phospholipid by making hydrogen bonds. They are capable to transfer from the water phase external to the enterocyte lipid layer and then into the cell from where it finally reaches into the blood to show its action.[12] This complex is formed via reaction of stoichiometric amounts of phospholipid with the selected polyphenolic phytoconstituent in a nonpolar solvent.[13] On the basis of their physicochemical and spectroscopic knowledge, it has been proved that, the main phospholipid substrate interaction is as a result of formation of hydrogen bonds between the polar head of phospholipids (i.e. phosphate and ammonium groups) and the polar functional groups of the substrate. Example: formation of H-bonds between the phosphate ion on the phosphatidylcholine moiety in catechin-phosphatidylcholine complex supported by 1 H-NMR and 13C-NMR spectra of the complex with those of the pure phyto molecule and phenolic hydroxyl end of the flavone moiety.[14] The main phospholipid used in the preparation of phytosomes is phosphatidylcholine which is the principle molecular building block of cell membranes, and is miscible both in oil and in water environments, and absorbs very well when administered orally. Chemical analysis shows that phytosomes is usually a phytoconstituents molecule linked with at least one PC molecule. The phosphatidylcholine moiety consists of gastroprotective properties that protect the drug from the degradation by gastric enzymes and secretions.[15] Phytosome is more bioavailable and its capacity of solubilization is high. Thus it can cross the lipid bilayer membrane, and can reach the systemic circulation to provide desired therapeutic effect. Phosphatidylcholine cannot be referred only as a passive "carrier" for the bioactive flavonoids of the phytosomes, it itself is a bioactive nutrient having clinical evidence of hepatoprotective activity.[16]

3. PROPERTIES OF PHYTOSOME

3.1 Physicochemical Properties

- Phytosomes are a complex between natural phospholipids (such as soy phospholipids) and natural products. The complex is formed as a result of reaction between standardized herb essence as substrate and stoichiometric amounts of phospholipid in an appropriate solvent.
- The spectroscopic information reveals that the phospholipid substrate interplay is due to the generation of hydrogen bonds in between the polar head (i.e., phosphate and ammonium group) and the polar functionalities of the substrate.
- The magnitude of Phytosome changes from 50 nm to a few hundred µm.[17]
- When exposed to water, phytosomes convert into a micellar shape forming liposomal-like structures.
- The active principle in phytosomes is anchored to the polar head of phospholipids, which becomes an integral part of the membrane. Example in catechin distearoyl phosphatidylcholine complex, there is a formation of H-bonds between the phenolic hydroxyls of flavone moiety and the phosphate ion on the side of phosphatidylcholine.
- Phytosome complexes are mostly freely soluble in aprotic solvents, moderately soluble in fats and insoluble in water. Also it is seen that, they are comparatively unstable in alcohol. However, some exceptions include lipophilic phytoconstituents like curcumin which have maximum water solubility upon complexation with phospholipid.

3.2 Biological/Pharmacological properties

3.2.1 In Cardiovascular Protection:

Histopathological tests indicated that ginkgo biloba phytosome (200 mg/kg) significantly reduced ISO-induced myocardial necrosis. Furthermore, myocardial necrosis was reduced, and endogenous antioxidants were enhanced, indicating a cardioprotective effect. The same researchers looked into whether a combination of Ginkgo biloba phytosome (100 mg/kg) and Ocimum sanctum extract (OS) (50 and 75 mg/kg) could protect rats from isoproterenol (ISO) (85 mg/kg)-induced cardiac necrosis. Both serum marker enzymes and the lipid peroxidation marker malondialdehyde (MDA), both produced by ISO, were suppressed by the therapy. However, none of the combined therapies outperformed the single Ginkgo biloba phytosome or OS therapy in terms of cardioprotective or antioxidantefficacy[18].

3.2.2 In Cognitive Impairment and Neuronal Damage

The study looked into phytosome formulations using Annona muricata water extract, with the goal of enhancing permeability across the blood–brain barrier (BBB) and thereby improving antidepressant like activity by inhibiting monoamine oxidase B. (MAO-B). The phytosome formulation showed the best performance as a radical scavenger and MAO inhibitor in an in vitro transwell model of BBB, making it a valuable model for improving the extract's antidepressant-likeeffect[19].

3.2.2 In Neurodegenerative Diseases

Langasco et al investigated brain delivery of the isoflavone genistein using a variety of nanotechnological techniques; treatment with phytosomes reduced oxidative stress in PC12 cells (a neuron cell line), and the impact was superior to that of unformulated genistein. Following repeated oral administration of the formulation for five days (134 mg/kg/die as curcuminoids equivalent) in rats, curcumin bioavailability in the hippocampus and frontal lobe was observed to be increased. Curcumin showed 30 minutes after treatment in the frontal lobe, peaked at 1 hour, and then returned to normal after 3 hours, suggesting that curcumin phytosome can reach the brain inrats.[20-21]

3.2.3 In Cerebral Ischemia

In an animal model of cerebral ischemia, rutin, a glycoside of the flavonoid quercetin, was placed in a phospholipid framework and examined for bioavailability. Rutin, given at 100 mg/kg to Sprague Dawley rats, reached the brain at quantities ranging from 20 to 50 ng/g, according to LC-MS/MS analyses. In a stroke animal model, a rutin-rich formulation significantly improved functional outcomes. In the second experiment, rats were given an oral phytosomal complex containing an ethanolic extract of Ashwagandha (Withania somnifera) roots (85 mg/kg) one hour before ischemia and six hours after reperfusion. Treatment resulted in a significant reduction in cerebral infarction (82.7%), as well as improved protection on all neurological impairmentmarkers.[22-23]

3.3.4 In Migraine

The efficacy of Ginkgo biloba terpenes phytosome (60 mg), vitamin B2 (8.7 mg), and coenzyme Q10 (11 mg) as components, provided twice daily, was evaluated in fifty migraine plus aura patients in two investigations by the same research group. Within four months of treatment, positive effects in lowering migraine with aura, both frequency and duration, were seen. The presence of ginkgolide B, the most abundant terpene found in Ginkgo biloba leaf extract, was most likely responsible for theseeffects[24].

3.3.5 In Pancreatic Cancer

In a prospective Phase II experiment, the potential synergistic effects of gemcitabine and the curcumin phytosome in advanced pancreatic cancer were assessed. A total of 44 patients with locally advanced or metastatic pancreatic cancer were included in the study, and they were given 2000 mg/die daily (4 capsules, each 500 mg) as well as gemcitabine (10 mg/m2 /min, infusion over 100 minutes on days 1, 8, 15, and 28 days). The primary aim of this trial was the response rate; supplementary endpoints were progression-free survival, overall survival, quality of life, and tolerability. The findings of the study show that curcumin phytosome could be utilized in conjunction with gemcitabine in the treatment of pancreaticcancer.[25-26]

3.3.6 In Breast cancer

In the first research, twelve early breast cancer patients were given a daily dose of 300 mg (equivalent to 44.9 mg of epigallocatechin-3-gallate or EGCG) of a commercial lecithin formulation containing catechins from green tea for four weeks before surgery. The active principles were identified at concentrations of up to 8 ng/g of EGCG in the entire tumor tissues tested, demonstrating their potential to reach human breast tissue. Ki-67, a proliferation biomarker, was found to have a substantial inverse relationship with EGCG plasma levels in eachpatient.[27]

3.3.7 Phytosomes in Female Reproductive System Conditions

The efficacy of curcumin phytosome on 6 patients with endometrial cancer was studied in a clinical experiment. The supplement was given to the patients for two weeks at a dose of 2 g (4 500 mg per day) without any concurrent oncological therapy. Supplementation reduced MHC expression on leukocytes, monocyte numbers, and CD8 +T cell ICOS protein levels. Other inflammatory markers, such as the number of distinct immune cell types, T cell activation, and cyclooxygenase-2 protein levels, showed no significant alterations (COX-2).[28-30] In a second trial, 48 rats who had their ovaries removed were given a quercetin phytosome (10 or 50 mg/kg, each os). When compared to similar amounts of free quercetin, treatment with phytosome resulted in significant increases in calcium, inorganic phosphorus, and glutathione in serum. The phytosome dramatically reduced serum alkaline phosphatase, TNF-, acid phosphatase, MDA, and glucose levels and improved the lipid profile as compared toquercetin[31].In addition, an icariin-containing phytosome was tested in OVCAR-3 ovarian cancer cells. In comparison to pure icariin, phytosomes had higher cytotoxicity against ovarian cancer cells (6.31 vs 13.1 M), and the number of cells in the G2-M phase, caspase-3 concentration, and intracellular ROS were all increased after incubation withphytosomes[32].

3.3.8 In Urinary Tract Dysfunctions

The biological effects of phytosomes in the urinary system were studied in two clinical trials. Cranberry was tested in 13 healthy volunteers in the first study to determine the Candida albicans antiadhesive effects of urine after intake of cranberry extract phytosome or the comparable standardized extract. For a week, the individuals took two capsules of cranberry phytosome or cranberry extract each day, and urine samples were taken at various periods. The fractions retrieved after 12 hours of extract or phaosomal form treatment reduced C. Albicans adhesion considerably and comparably, while phytosome only contained 33% of the cranberry extract (phytosome:12mg proanthocyanidins / capsule; extract:36mg proanthocyanidins/capsule)[33].

3.3.9 Effect in Wound Healing

In diabetic foot ulcer patients, a combination of Ginkgo biloba, -lipoic acid, and grape seed phytosome, along with advanced drugs, was effective in the treatment of persistent diabetic ulcers. Moringa oleifera aqueous leaf extract-containing phytosomes were shown to be non-toxic in NHDF cells up to 3.0 mg/mL. When compared to the extract at the same dose, the formulation at 1 mg/mL offered the quickest gap closing (94.8 percent at 24 h). Higher doses (1.25 and 1.50 mg/mL), as well as lesser doses, did not provide statistically significant outcomes.[34,35]

3.3.10 In Musculoskeletal System

A pilot study made on the therapy of osteopenia patients. Curcumin phytosome, a curcumin-based supplement, was given to subjects with reduced bone density but no symptoms for 24 weeks. At 4, 12, and 24 weeks, the bone density of the heel, small finger, and upper jaw were measured. The group given 1 tablet per day containing 1000 mg of curcumin phytosome showed a general improvement in bone density, whereas the control group showed no significant improvements. The same formulation, evaluated at the same dose either alone or in combination with other nutritional supplements and exercise, produced positive benefits in senior adults (>65 years) with weakness, contributing to improved strength and physicalperformance.[36,37]

3.3.11 Role in the Respiratory System Diseases

About 32 asthmatic people were enrolled in a multicenter research and were given a combination of corticosteroids and beta-agonists, which is the typical treatment for patients with mild or severe chronic asthma. For four weeks, the individuals were given either 500 mg of Boswellia serrata phytosome or no extra treatment. In comparison to patients who only received standard medication, patients in the phytosome group required fewer inhalations. The phytosome treatment was well received, with only minor to moderate side effects such as sleeplessness and nauseareported[38]. The research created a new phytosome to increase naringenin bioavailability in thelungs[39]. Dipalmitoylphosphatidylcholine (DPPC), one of the primary lipids found in pulmonary surfactant, was successfully employed to administer naringenin. In rats with acute lung injury, the

pharmacodynamics of naringenin-loaded DPPC phytosomes for dry powder inhalation (NPDPIs – 10 mg/rat, containing roughly 3 mg naringenin) were investigated, as well as their related mechanisms of action. When injected directly into the lungs, these phytosomes have shown to protect rats from lung injury. NPDPIs reduced pulmonary edemas by reducing fluid exudation and dramatically lowering the expression of cytokines like COX-2 and ICAM-1, according to the findings. Furthermore, naringenin and DPPC reduced oxidative stress in rats by increasing SOD activity, and the use of NPDPIs increasedthis.[40]

4. Characterization Of Phytosomes

There are various factors, such as the physical size, membrane permeability, chemical composition of the preparing materials, percentage of entrapped solutes which can dramatically influence the performance of phytosomes in physical and biological systems. Following are the factors under which phytosomes arecharacterized.[41]

4.1 Visualization

Visualization of phytosomes is done by the use of Scanning Electron Microscopy (SEM) shown in and by Transmission Electron.[42]

4.2 Solubility and partition coefficient

Characterizing active ingredients, active constituent phyto-phospholipid complexes, and physical mixes requires determining solubility in either water or organic solvents, as well as the n-octanol/water partition coefficient (P). Phyto-phospholipid complexes, in general, have higher lipophilicity and hydrophilicity than active ingredients, and often have better lipophilicity. According to Rahila, embelin in complexes is more soluble in n-octanol and water than embelin and its physical combinations[43,44].

4.3 Particle size and zeta potential

Particle size and zeta potential are two crucial features of complexes that are linked to their stability and repeatability. The typical particle size of phospholipid complexes ranged from 50 nm to 100 m. Anisha Mazumder created sinigrin phytosome complexes with an average particle size of 153 39 nm and a zeta potential of 10.09 0.98 mV, respectively.[45]

4.4 Surface tension activity measurement

Du Nouy ring tensiometer drug is used for determining the surface activity of the solution.[46]

4.5 Entrapment efficiency

Phytosomal preparation is exposed to ultracentrifugation method and the entrapment efficiency is determined.[47]

4.6 Transition temperature

Differential scanning calorimetry is used for settling the transition temperature of the vesicular lipid system.[48]

4.7 Vesicle size and zeta potential

Dynamic light scattering confirms the particle size and zeta potential of phytosomes were accomplished by using a computerized examination system and photon correlation spectroscopy.

4.8 Vesicle stability

Vesicle stability is measured by calculating the size and structure of the vesicles over a period of time. DLS calculates the mean size and structural changes are monitored by TEM.[49]

4.9 H1NMR

The NMR spectra are used for assessing the complex development among the active phytoconstituents and the phosphatidylcholine molecule. In nonpolar solvents, there is a visible change in 1H NMR signal starting from atoms tangled in the construction of complexes, without any outline of the signal peculiar to individual molecules. The signs from protons have their place into the phytoconstituents are magnified. In phospholipids, there is a magnification of signals while the singlet corresponding to the N-(CH3)3of choline undergoes an up field shift.[50]

4.10 Spectroscopic evaluation

The spectroscopic estimations are broadly used in order to establish a complex between phytoconstituents and the phospholipid moiety to study the equivalent reaction among the two.

4.11 In vitro evaluations

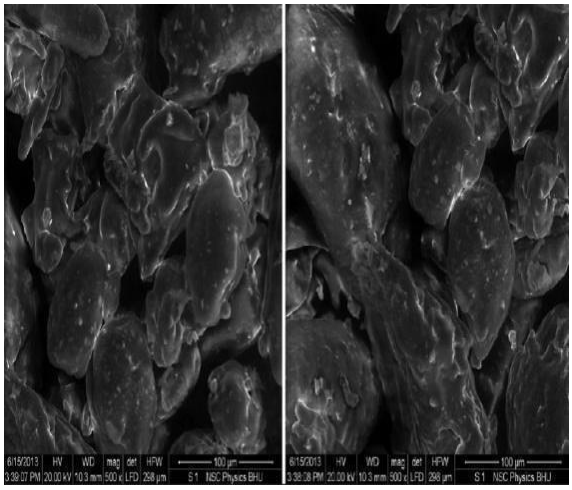
They are designed based on their therapeutic actions which are predictable within the biologically energetic phytoconstituents existing in the phytosomes. Example in vitro anti hepatotoxic activity can be estimated by the antioxidant and scavenging of free radical action of the phytosomes.[51]

4.12 In vivo evaluations

They are also designed based on their therapeutic actions which are predictable within the biologically energetic phytoconstituents existing in the phytosomes. For calculating anti hepatotoxic activity, invivo results of organized phytosomes of animals in contrast to paracetamol, thioacetamide or alcohol- induced hepatotoxicity are evaluated.[52]

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

The surface appearance and solid state characteristics of complexes have been studied using SEM previously shown in Fig 2. The transmission electron microscope (TEM) is frequently used to examine the crystallization and dispersion of nanomaterials, as well as to determine the particle size of nanoparticles. Active chemicals can be seen in a highly crystalline condition using SEM, however the structured crystals vanish after complexation. Fig 3 shows TEM study which has revealed that phyto-phospholipid complexes have vesicle-like structures when diluted in distilled water and shaken gently.[53]



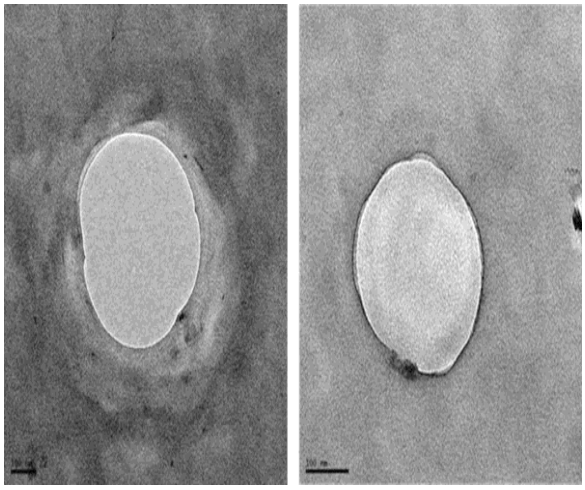


Fig 2: SEM photomicrograph of phytosome [53]Fig3: TEM photograph of phytosome[53]

4.14 C13NMR

In the 13C NMR of the phytoconstituents and the stoichiometric complex with the phosphatidylcholine when stored in C6D6 at room temperature , it was seen that all phytoconstituents carbons were not visible. The signal equivalent to the glycerol and choline portion were magnified and some were shifted, while a maximum of the resonance of the fatty acid chains holds their original sharp line shape.[54]

Table1: Analytical Methods Used For The Characterization Ofphytosome[55]:

Sl.No	Parameters	Techniques
1	Size and Shape	DLS, SEM, TEM, Optical microscopy, Fluorescence microscopy, AFM, Field flow fractionation, Nanoparticle tracking analysis, Scanning ion occlusion sensing, Flow Cytometry, Size-exclusion chromatography, Centrifugal sedimentation, and DSC
2	Surface charge	DLS, free-flow electrophoresis, and laser Doppler velocimetr
3	Chemical composition	FTIR, h1 NMR, GC-MS, LC-MS, DSC, TGA, and Thin-layer chromatography
4	Lamellarity and stability	31P nuclear magnetic resonance, Small-angle X-ray scattering, electron microscopy methods, DSC, TGA, DLS, and UV-Vi
5	Encapsulation efficiency	Mini-column centrifugation, HPLC, UPLC, UV-Vis, dialysis, enzymatic assays, gel electrophoresis, field flow fractionation, sample-and-separate approach, the in-situ method, and the continuous flow
6	Release behavior	Design of Experiment (DoE) with Box–Behnken desig

Abbreviations: DLS, dynamic light scattering; SEM, scanning electron microscope; TEM, transmission electron microscopy; AFM, atomic force microscope; DSC, differential scanning calorimetry; FTIR, Fourier-transform infrared spectroscopy; NMR, nuclear magnetic resonance; GC-MS, gas chromatography-mass spectrometry; LCMS, liquid chromatography-mass spectrometry; TGA, thermal gravimetric analysis; HPLC, high-performance liquid chromatography; UPLC, ultra-performance liquid chromatography.

5. Method Of Preparations Of Phytosomes

While preparing phytosomes, phospholipids are selected from the group consisting dermis or swine brain, phosphatidylcholine, phosphatidylethanolamine, phosphatidyiserine or soy lecithin, through bovine in which acyl group may be same or different and mostly derived from stearic, palmitic, oleic and linoleic acid. The selection of flavonoids are done from a group consisting of quercetin, kaempferol, quercretin3, rhamnoglucoside, quercetin-3-rhamnoside, hyperoside, vitexine, diosmine, (+) catechin, (-) epicatechin, apigenin-7- glucoside, luteolin, 3- rhamnoside, luteolinglucoside, ginkgonetine, isoginkgonetine andbilobetine[56].

5.1 Antisolvent precipitation technique

The precise quantity of drug and soya lecithin were taken into a 100 ml of round bottom flask and then refluxed with 20 ml of dichloromethane at a temperature not surpassing 60°C for 2 h. It is then concentrated upto 5-10 ml and adding 20ml of hexane carefully with constant stirring to get the precipitate which was then filtered and collected and stored in vacuum desiccators overnight. Then the dried precipitate is crushed with the help of mortar and sieved through 100 mesh sieve. The fine powder of phytosomes complex was achieved and placed in an amber colored glass bottle and stored at room temperature.[57-59]

5.2 Rotary evaporation technique

The precise amount of drug and soya lecithin were taken into a rotatory round bottom flask and dissolved 30ml of tetrahydrofuran. It is then followed by vigorous stirring for 3 hours at a temperature not surpassing 40° C. A thin film of the sample was achieved to which n-hexane was added and constantly stirred by using a magnetic stirrer. The precipitate of phytosomes complex was achieved and collected, then placed in an amber colored glass bottle and stored at roomtemperature[60].

5.3 Solvent evaporation method

The precise amount of drug and soya lecithin were kept in a 100 ml round bottom flask and then refluxed in 20 ml of

acetone at a temperature 50 – 60°C for 2 h. That mixture is then concentrated upto 5-10 ml to obtain the precipitate. It was then filtered and collected. The dried precipitate of phytosomes complexes was achieved placed in an amber colored glass bottleand stored at room temperature.[61]

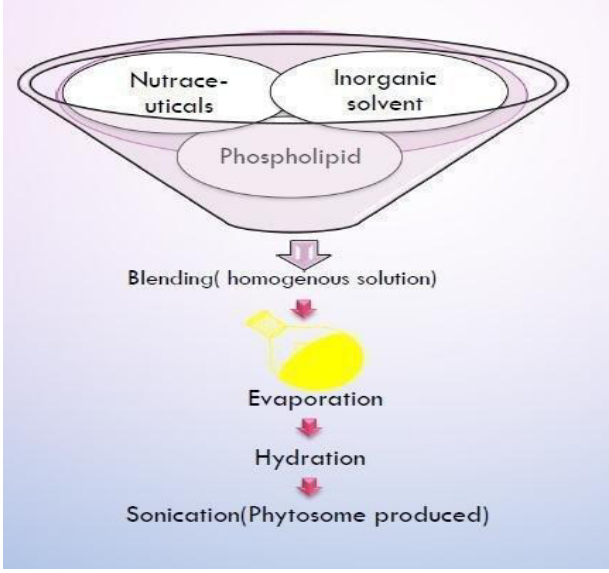


Fig4: Steps of Phytosome Preparation[62]

6. Formulations Of Phytosomes

Phytosomes can be formulated for oral as well as topical administration.

6.1 Soft gelatin capsules

Soft gelatin capsules are referred to as an ideal solution to formulate into phytosome complexes. The phytosome complex is dispersed in oily vehicles to get suspensions to fill in soft gelatin capsules. Vegetable or semi-synthetic oils can be applied to this purpose. Indena suggested a granulometry of 100% <200 µm to perform capsule production optimally. According to Indena experience, not all the phytosome complexes behave in the same way when dispersed in oily vehicles and when the oily suspension is filled inside the soft gelatin capsules; due to this reason preliminary feasibility trials must be performed to select the most suitable vehicle. Example: Ginkgoselect Phytosome.

6.2 Hard gelatin capsules

The Phytosome complex can also be formulated in hard gelatin capsules as well. A direct volumetric filling process (without any precompression) can be used, even if the apparently low density of the phytosome complex is seen as to limit the maximum amount of powder that can be inserted inside the capsule (usually not more than 300 mg for a size 0 capsule). With a piston tamp capsule filling process, however, it is achievable to increase the amount of powder which fills in a capsule, however precompression might affect the disintegration time. Indena® recommends monitoring the related parameters during product/ process development. Example: Ginkgoselect® Phytosome.

6.3 Tablets

Dry granulation is referred to as the ideal manufacturing process to get tablets with high unitary doses, biopharmaceutical properties and suitable technology. However, because of insufficient flow ability, low apparent density and potential stickiness of the phytosome complex, a direct compression process can be applied only for low unitary doses; whenever a direct compression process is applied, the phytosome complex should be diluted with 60-70% of excipients to optimize its technological properties and to obtain tablets with appropriate technological and biopharmaceutical characteristics. On the other hand, wet granulation should be avoided due to the negative effect of water and heat (granulation/ drying) on the stability of the phospholipid complex. Example: Leucoselect® Phytosome.

6.4 Topical dosage forms

The phytosome complex can even be formulated topically. The optimum process to incorporate the phytosome complex in emulsion is by dispersing the phospholipidic complex in a small amount of the lipid phase and adds it to the already created emulsion at low temperatures that is not higher than 40°C. The phytosome complexes are dispersible in the main lipidic solvents used in topical formulations. In case a formulations containing a limited amount of lipids, the phytosome complex may also disperse into the watery phase, and add again to the final formulation at temperature below 40°C. Example: Glycyrrhetinic acid Phytosome® and Escin/ß-Sytosterol Phytosome.[63,64]

7. Chemical properties

1. The principal phospholipid-substrate interaction is due to the creation of hydrogen bonds between the polar head of phospholipids (i.e. phosphate and ammonium groups) and the polar functional groups of the substrate, as according to their physicochemical and spectroscopic data.
2. They are lipophilic compounds with a high melting point that are easily soluble in nonpolar solvents and partially soluble in fats.
3. Phytosomes take on a micellar structure when exposed to water, generating liposomal-like structures.
4. The active ingredient in liposomes is dissolved in an intracellular compartment or floats in the layer

membranes, but the active component in phytosomes is attached to the polar head of phospholipids, becoming an integral part of the membrane.[65-67]

7.1 FTIR Characterization

When phytosomes are micro-dispersed in water or incorporated into extremely simple cosmetic gels, FTIR spectroscopy is a valuable technique for controlling their stability. In practice, the stability of the complex can be verified by comparing the spectrum of the complex in solid form (phytosomes) with the spectrum of its micro-dispersion in water following lyophilization at various intervals. In the case of simple formulations, the spectrum of the excipients (blank) must be subtracted from the spectrum of the cosmetic form at different intervals, and the remaining spectrum of the complex must be compared.[68]

7.2 *Phyto-phospholipid complex*

Bombardelli postulated that, phyto-phospholipid complexes can be made by reacting phospholipids with active ingredients derived from plants in a stoichiometric ratio. This initial description of phyto-phospholipid complexes has been called into question by subsequent research. They offered an updated list of the four fundamental components needed, based on the literature: phospholipids, phyto-active ingredients, solvents, and the stoichiometric ratio involved in the formation of phyto-phospholipid complexes.[69-71]The principal phospholipids utilized to create complexes with a hydrophilic head group and two hydrophobic hydrocarbon chains are PC, PE, and PS.[72] PC's amphipathic characteristics offer it moderate solubility in water and lipid environments, which is one of its advantages. Furthermore, because PC is a necessary component of cell membranes, it has a high biocompatibility and low toxicity. PC molecules have been shown to have hepatoprotective properties and to have clinical effects in the treatment of liver illnesses like hepatitis, fatty liver, and hepatocirrhosis. Mikko J. Parry created siramesine and PA phospholipid complexes with high affinity. To yet, there has been no mention of using PG and PI to make phospholipid complexes.[73-75]

7.3 *Solvents used in phytosomes preparation*

Different studies have used various solvents as the reaction medium for forming phyto-phospholipid complexes. Traditionally, aprotic solvents such as aromatic hydrocarbons, halogen derivatives, methylene chloride, ethyl acetate, or cyclic ethers were employed to prepare phyto-phospholipid complexes, but protic solvents such as ethanol have completely superseded them. More recently, protonic solvents such as ethanol and methanol have been successfully used to produce phospholipid complexes. Yanyu Xiao, for example, used ethanol as a protonic solvent to create silybin-phospholipid complexes, which were then removed under vacuum at 40°C. Solvents of many sorts have been successfully investigated. When the yield of phospholipid complexes is high enough, ethanol can be a useful and popular solvent because it leaves little residue and does not cause damage. Some liposomal drug complexes work in the presence of water or a buffer solution, in which the phytosomes interact with a lower dielectric constant solvent. The supercritical fluid (SCF) technique has recently been employed in a number of researches to regulate the size, shape, and morphology of the material of interest. One of the SCF technologies, the supercritical antisolvent process (SAS), is emerging as a viable technology for producing micronic and submicronic particles with controlled size and size distribution. To lower the solute's solubility in the solvent, a supercritical fluid (typically CO2) will be used as an anti-solvent.[76-81]

7.4 *Interactions between active constituents and phospholipids*

A molecular docking investigation of the interaction of the 20(S)-protopanaxadiol phospholipid complexes revealed that a hydrogen bond developed between one of the –OH groups in 20(S)-protopanaxadiol and the —P=O group in the phospholipids. The spectroscopic data revealed that the phopspholipid-active ingredient interaction is due to the formation of hydrogen bond between the polar head and the polar functionalities of the active ingredient in phyto-phospholipid complexes formed by reaction of stoichiometric amount of phospholipids and the phytoconstituents complex. The 1HNMR and 13CNMR data demonstrate that, the fatty chain signal is unchanged in both free and complex phospholipids, implying that long aliphatic chains are wrapped around the active principle, forming a lipophilic envelope. The similar finding may be drawn from thermal analysis in other research, which has been attributed to the establishment of hydrogen bonds or hydrophobic interactions between the two molecules. In conclusion, most experts agree that hydrogen bonds, rather than chemical or hybrid bonds, provide intermolecular force when active ingredients interact with phospholipids.[82-84]

8. *Advances in phytosome technology over the conventional method.*[85-97]

A growing body of studies showed the value of phytosomal delivery systems over traditional herbal extracts. The following are advancements in phytosomal delivery systems:

- Bacopaside is a well-known main component of the Bacopa monnieri plant, that has antiamnesic properties. The goal of this project is to create a phytosome from bacopaside and test it in vivo on rodents. The therapeutic effectiveness of the chemical produced by phospholipid differs dramatically from that of a simple B. monnieri extract.
- Further study demonstrates that berberine phospholipid complex solid dispersion may be made, which not only improves the compound's solubility but also improves its flowability and dissolving rate for industrial use.
- There is a preparation of sinigrin phytosome, according to another study. The study looked at in vitro wound healing potential, and the results were promising when compared to sinigrin alone.
- According to one study, silymarin phytosomes have stronger antihepatotoxic activity than silymarin alone, and they also play an important role in protecting broiler chicks from B1 aflatoxin.
- The phytosomes from a standardized extract of S. marianum seeds were given orally, and they had a significant effect on the foetus from maternally ingested alcohol.
- Based on one clinical investigation, 232 patients with chronic hepatitis who were treated with silybin phytosome at a dose of 120 mg twice or thrice a day for 120 days had a significant improvement in liver function.

- Grape seed phytosomes play an important role in ischemia-induced cardiac injury, as well as protecting against atherosclerosis. Proanthocyanidins/procyanidins are the major elements responsible for this.
- When compared to uncomplexed green tea extract, Camellia sinensis or the extract of green tea when included in phytosomes has better oral bioavailability. The main active ingredient in green tea is epigallocatechin 3-o-gallate.
- Additional clinical trials revealed that caffeine-free phytosomes from green tea have a substantial anti-obesity and antioxidant impact. It has an effect on low-density lipoproteins as well.
- In rat liver injury caused by carbon tetrachloride, the quercetin phytosomal complex has a better therapeutic effect.

8.1 Vesicular systems for phytosome development

Two important aspects for phytochemical drug carriers are targeted delivery and sustained release rate. Various nano-systems would be employed in disease imaging or therapy, as well as as theranostics. Vesicular drug delivery systems, in which active compounds are encased in a spherical shape, are the most commonly employed nanocarriers for phytochemicals.[98-102]

Table2: Common Used Nanovesicle Encapsulated Herbal Formulations

Nanovesicle	Phytochemicals	Feature/Character	References
Liposome	*Aphanamixis polystachya leaf*	Great improvement in memory function, locomotive behavior, and dementia-induced outpatient quality of mice	103
	Anthocyanins	Increase physiological stability in vitro for 14 days and increase the activity of ROS scavenging and skin absorption.	104
	Curcumin	Fast permeation rate endothelial cell monolayer crossing blood-brain barrier (BBB) and good durability toward digestive enzymes.	105
	Eleusine coracana	Effective antibacterial formulations have a great nutritive value	106
Niosome	*Carum carvi*	Regulate release and decrease of MCF-7 cell migration, high anti-cancer behavior against MCF-7 supported by cytometry flow (G2/M arrest).	107
	Lawsone	Entrapment efficiently of 70%, a sustained release profile, and a significant increase in antitumor activity.	108
	Fumaria officinalis	Rapid degradation, stability in GI conditions simulated, and anti-diabetic and antiinflammatory capacity	109
	Annona squamosa	a Aid with topical drug enhancers to purify the body from harmful impurities and oxidants and can be applied directly to the skin	110
Transfersome	*Mulberry leaves*	Prolonged delivery system, strong safety, and acne vulgaris care via transdermal route	111
	Apigenin	Drug entrapment of 84.24%, strong stability, enhances the permeability of apigenin in the long-term release	112
	Epigallocatechin-3- gallate (EGCG)	Increases cell viability, decreases lipid peroxidation, intracellular ROS, MMP expression in HaCaT cells, and increases skin permeation.	113
	Emodin	High efficiency and stability in encapsulation, reduces body weight, and adipocyte size through ATGL up-regulation, down-regulation of G0S2 expression in adipose tissue, and improved insulin sensitivity	114
Ethosome	*Thymoquinone*	99% efficiency for drug trapping. Cytotoxic activity of 0.95 μg/mL against MCF-7 cell lines is improved.	115
	Capsaicin	Ethosomal hydrogels improve performance and patient compliance with capsaicin treatment.	116
	Terminalia chebula	Effective release comparison with extract in the gel. In vitro anti-arthritic activity demonstrates important anti-arthritic activity as opposed to normal Diclofenac activity	117
	Paeonol	Paeonol-loaded ethosomes showed improved transdermal absorption and skin retention (138.58 μg/cm2 and 52.60 μg/cm2 , respectively)	118-119

Table2: Different forms of vesicular drug delivery systems have been summarized, including liposomes, niosomes, transfersomes, and ethosomes with their phytochemicals and features or characters.

8.2 *Lamellarity and stability of phytosomes*

The number of phytosomal lipid bilayers is referred to as "lamellarity." Electron microscopy, 31P nuclear magnetic resonance, and small-angle X-ray scatter seem to be the most common methods to determine lamellarity. One of the most precise and straightforward ways for determining lamellarity is 31P NMR. The flaw with this approach is that it is sensitive to experimental variables such as reagent concentration, vesicle type, and buffer concentration. Negative staining electron microscopy, freeze-fracture, and cryo-microscopy are some more newly used imaging techniques. Recently used cryogenic transmission electron microscopy and small-angle neutron scattering to assess the structure of the vesicle membrane and provided insights into the impact of the formulationmethod and lipid composition on the development of liposomes with a defined membrane structure. Another crucial issue in the construction of a good carrier is phytosomal stability. Stability studies are carried out to investigate phytochemical changes in phytosomes throughout storage and circulation. The mean vesicle size, zeta potential, size distribution, and trap efficiency can all be

measured over several months to determine stability. Cheng et al investigated the thermal and photochemical stability of rhamnolipids (RL) modified curcumin liposomes, finding that the loaded liposomes were more stable under various pH, ionic, and heatconditions[120-122]

Table3:PATENT TECHNOLOGIES OF PHYTOSOME

Patent Title	Innovation	Patent No.	Reference
An anti-oxidant preparation based on plant extracts for the treatment of circulation and adiposity problems.	Preparation based on plant extracts which has an anti-oxidant effect and is particularly useful in treatment of circulation problems such as phlebitis, varicosevein, arteriosclerosis, haemorrhoid and high blood pressure.	EP1214084	123
Compositions comprising *Ginkgo biloba* derivatives for the treatment of asthmatic and allergic conditions.	Compositions containing fractions deriving from *Ginkgo biloba*, useful for the treatment of asthmatic and allergic conditions.	EP1813280	124
Complexes of saponins with phospholipid and pharmaceutical and cosmetic compositions containing them.	Complexes of saponins with natural or synthetic phospholipid have high lipophilic and improved bioavailability and are suitable for use as active principle in pharmaceutical, dermatologic and cosmetic compositions.	EP0283713	125
Cosmetic and dermatological composition for the treatment of aging or photo damaged skin.	Composition for topical treatment of the skin comprises a substance that stimulates collagen synthesis and a substance that enhances the interaction between extracellular matrix and fibroblasts Cosmetic or dermatological composition for topical treatment.	EP1640041	126
Fatty acid monoesters of sorbityl furfural and compositions for cosmetic and dermatological use.	Fatty acid monoesters of sorbityl furfural selected from two diff series of compounds in which the side chain is a linear or branched C3-C19 alkyl radical optionally containing at least one ethylenic unsaturation at least one ethylenic unsaturation.	EP1690862	127
Phospholipid complexes of olive fruits or leaves extracts having improved bioavailability	Phospholipid complexes of olive fruits or leaves extracts or compositions containing it having improved bioavailability	EP/1844785	128
Soluble isoflavone compositions	Isoflavone compositions exhibiting improved solubility (e.g., light transmittance), taste, colour, and texture characteristics, and methods for making the same	WO/2004/ 045541	129
Treatment of skin, and wound repair, with thymosin β4	Compositions and methods for treatment of skin utilizing thymosin β4.	US/2007/ 0015698	130

Table3: Patent technologies of phytosomes were highlighted in the given table with Patent title, Innovation and patent Number.

Table4: Commercial Phytosomes Available In Market.131-133

Phytosomes	Phytoconstituents complexes	Dose	Indication	Side effects
Ginkgo Phytosome	24%ginkgo flavonoids from Ginkgo biloba	120 mg	Protects brain and vascular linings, anti-skin ageing	It can cause some minor side effects such as stomach upset, headache, dizziness, constipation, forceful heartbeat, and allergic skin reactions.
Ginseng Phytosome	37.5% ginsenosides from Panax ginseng	150 mg	Nutraceutical, immunomodulator	Nausea, diarrhea, euphoria, insomnia, headaches, hypertension, hypotension, mastalgia,
Grape Seed Phytosome	Procyanidins from Vitis vinifera	50-100 mg	Nutraceutical, systemic antioxidant, cardio-protective	Headache, sore throat, dizziness, itchy scalp, Stomachache, nausea.
Green Tea Phytosome	Epigallocatechin from Thea sinesis	50-100 mg	Nutraceutical, systemic antioxidant, anticancer	In some people, green tea extract can cause stomach upset and constipation.
Hawthorn Phytosome	Flavonoids from Crataegus sp.	50-60 mg	Nutraceutical, cardio-protective and antihypertensive	In some people, hawthorn can cause nausea, stomach upset, fatigue, sweating.
Leucoselect® phytosome	Procyanidolic oligomers (PCOs) from grape seeds	450 mg	Systemic antioxidant, specific. Best choice for most people under age	Headache, sore throat, dizziness, itchy scalp, Stomachache, nausea.
Silybin Phytosome	Silybin from Silybum marianum	160 mg	Hepatoprotective, antioxidant for liver and skin	Adverse effects associated with oral ingestion of silybin include mainly

				gastrointestinal problems, but these are rare.
Bilberry phytosomes	Extract of Bilberry which provides anthocyanosides	---	Improve capillary tone, reduce abnormal Bloodvessel permeability, and are potent antioxidants.	Weight loss, muscle loss, fatigue, weakness, loss of appetite, anemia, yellowing skin and eyes.
Super milk thistle extractTM	Silybin from Silymarin Food product	150 mg	Antioxidant for liver and skin.	Abdominal bloating/pain, allergic reactions, diarrhea, gas, indigestion, itching, loss of appetite, nausea.
Centella phytosomes	Terpenes	---	Used to treat Vein and Skin disorders	Skin allergy and burning sensations (with external use), headache, stomach upset, nausea, dizziness.
Palmetto berries Phytosomes	Fatty acids, alcohols and sterols	---	Used for the treatment of Non-cancerous Prostate enlargement.	Diarrhea, headache, fatigue, decreased libido, nausea, vomiting, and vertigo.
Olive oil Phytosomes	Polyphenols from Olea europaea oil	---	Inhibit oxidation of LDL cholesterol, and also have anti-inflammatory activity.	Stomach upset, nausea, dizziness.
Sericoside Phytosome	Sericosides from Terminalia sericea	---	Skin Improver	Diarrhea, headache, fatigue, decreased libido, nausea
Echinacea Phytosome	Echinacosides from Echinacea angustifolia	---	Immuno modulator, nutraceuticals	Stomach pain, constipation, diarrhea, heartburn, vomiting, and rash.
Visnadine Phytosome	Visnadine from Ammi visnaga	---	Circulation Improver	Abdominal bloating/pain, allergic reactions, diarrhea, indigestion, itching, loss of appetite, nausea.

Table4: Illustrate the various commercial phytosomes available in the market with their Phytoconstituents complexes, Dose, indications and side effects.

Table5: Different Additives Employed In Herbal Formulation Of Phytosomes

Class	Example	Uses
Aprotic solvent (Gabetta et al. 2000)	dioxane, acetone, methylene chloride	As a solvent.
Alcohol(Basnet et al. 2011; Maghraby et al. 2008; Vanden et al. 1993	Ethanol, Methanol.	As a solvent.
Buffering agent(Vanden et al. 1993; Maghraby et al. 2008)	Saline phosphate buffer (pH 6.5) 7 % v/v Ethanol Tris buffer ((pH 6.5).	As a hydrating medium.
Dye(Aad et al. 2012)	Rhodamine-123 Rhodamine-DHPE Fluorescein-DHPE Nile-Red 6 Carboxy fluorescence	For CSLM study.
Non-solvent (Gabetta et al. 2000)	N-hexane and non- solvent i.e. aliphatic hydrocarbon.	Complex precipitating
Phospholipid (Fuzzati et al. 1999; Zhang et al. 1994)	Soya phosphatidylcholine, Egg phosphatidylcholine, Dipalmitoylphosphatidylcholine, Distearyl phosphatidylcholine	Component

Table5: Highlights the different forms of additives employed in herbal formulation of phytosomes with their classes, examples and uses.

Table6: Therapeutic Applications With Dosages Forms Of Phytosomes

Phytosomes	Phyto-constituent complexes with PC	Daily dosage	Uses
Ginkgoselect® phytosome	24 % ginkgo flavono glycosides from *Ginkgo biloba*	120 mg	Best choice for most people over the age of 50. Protects brain and vascular lining
Greenselect® phytosome	Epigallocatechin 3-*O*-gallate from *camelia sinensis* (Green tea)	50–100 mg	Systemic antioxidant. Best choice for protection against cancer and damage to cholesterol
Leucoselect® phytosome	Procyanidolic oligomers (PCOs) from grape seeds	50–100 mg	Systemic antioxidant, Best choice for most people Under the age of fifty. Also specific for the eyes, lungs, diabetes,Varicose veins and protection against heart disease.
*Siliphos*TM milk thistle phytosome	Silybin from silymarin	150 mg	Good choice for liver or skin support
Hawthorn phytosome	Flavonoids	100 mg	Best choice in heart disease
Panax ginseng phytosome	37.5% ginsenosides from roots of *Panax ginseng*	150 mg	As a Food Product

Table6: Illustrate the therapeuticapplications with dosage forms of phytosomes.

Table7: Table showing difference between phytosome andliposome[134-136]

Property	Phytosome	Liposome
Bonding	It is a unit of few molecules bonded together	It is an aggregate of many phospholipid molecules that encloses other phytoactive molecules without specifically bonding to them.
Bioavailability and Absorption	It has much better bioavailability and absorption	Its bioavailability and absorption is lesser than phytosome.
Arrangement of molecules	In phytosome, phospholipid (phosphatidylcholine) and an individual phytoconstituent are present in 1:1 or 2:1 ratio depending on the substance.	In liposomes, hundreds and thousands of phosphatidylcholine molecules surround the water soluble molecule.

Table7: Highlights the differences between phytoisomes and liposomes based on bonding, bioavailability and absorption and arrangement of molecules.

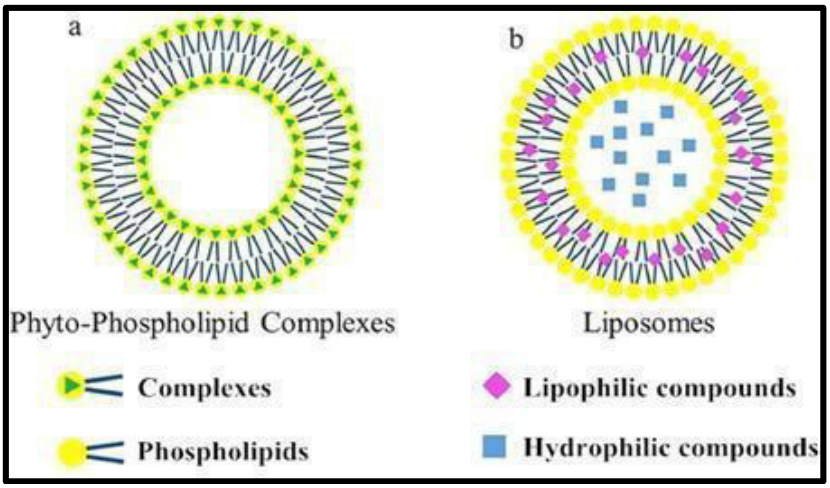


Fig5: Differences between Phyto-phospholipid complexes andLiposomes[82,137]

8.3 *Phytosomes and other lipid-based Nano-carriers: Similarities and differences*

Phytosomes have been shown to deliver poorly soluble compounds successfully by incorporating these materials into the lipid bilayer membrane or conjugating them with the lipid composition. Liposomes and transferosomes are two of the most commonly utilised lipid-based vehicles in the field of drug delivery nanotechnology for topical applications, allowing water-soluble chemicals to penetrate the skin more easily. Phytosomes, liposomes, and transferosomes are examples of lipid-based delivery systems that can encapsulate bioactive phytochemicals to enhance the concentration, absorption, and stability of poorly soluble compounds. Different phytosomal and liposomal skin care products have been licenced and commercialised since their development, but only a handful transferosomal compositions have been turned into clinical products. The comparison of various lipid-based drug delivery systems is necessary due to structural similarities as shown in Fig 5. Phytosomes have some of the same properties as liposomes and transferosomes, including the potential to improve the solubility of weakly soluble compounds, such as polyphenolic phytochemicals. In topical treatments, phytosomes and transferosomes demonstrate other unique natural features, such as long-term stability and increased skin penetration. The similarities and differences between phytosomes and commonly utilized lipid-based nanocarriers prompted researchers to investigate (i.e., liposomes and transferosomes). The comparison should be made based on numerous factors pertinent to the field of nanotechnology, such as lipid vesicle structure, phospholipid composition, and production process. Understanding the unique features of phytosomes has important implications for the topical dosage form sector and may improve the quality of topical goods. In terms of structural and functional features, phytosomes are comparable to liposomes and transerosomes. Cholesterol, PC, PS, PE, and glycosphingolipids are some of the lipids that can be employed to build the lipid bilayer structure of phytosomes. Phytosomes and transferosomes showed superior physical stability in aqueous environments than liposomes, with no trace of aggregation in 4 °C and 25 °C up to three months, but liposomes must be freeze dried to retain their stability. Different bioactive chemicals, such as herbal items, can be encapsulated in these lipid-based nanocarriers and applied to the skin to aid dermal absorption. Due to their better absorption characteristics through the skin, phytosomes and transferosomes are regarded preferable to liposomes in the administration of active substances in topical applications. The similarities and differences between phytosomes and commonly utilised lipid-based nanocarriers prompted researchers to investigate (i.e., liposomes and transferosomes). The comparison should be made based on numerous factors pertinent to the field of nanotechnology, such as lipid vesicle structure, phospholipid composition, and production process. Understanding the unique features of phytosomes has important implications for the topical dosage form sector and may improve the quality of topical goods.In terms of structural and functional features; phytosomes are comparable to liposomes and transerosomes. Cholesterol, PC, PS, PE, and glycosphingolipids are some of the lipids that can be employed to build the lipid bilayer structure ofphytosomes.[138-149]

8.4 *Bioavailability enhancement of phytosomes*

Many popular herbal extracts, including as Ginkgo biloba, grape seed, hawthorn, milk thistle, green tea, and ginseng, have been subjected to the phytosome process, and current study has shown that phytosomes boost absorption and bioavailability when compared to traditional methods. When flavonoids and polyphenolics are included in photosomal preparations, many standardised extracts with increased bioavailability have been observed. Silymarin is one of the most researched drugs for improving silybin distribution by generating a silybin phospholipid complex. Yanyu et al. synthesised silymarin phytosomes and investigated their pharmacokinetics in rats. Because of an improvement in the lipophilic quality of the silybinphospholipid complex, the bioavailability of silybin in rats was significantly enhanced following oral administration in the study.[150-151] A research to show on human investigation to see if silybin could be absorbed when it was directly linked tophosphatidylcholine[152]. After giving healthy participants single oral doses of silybin phytosome and an equal amount of silybin from milk thistle, plasma silybin levels were measured. According to the findings, silybin absorption from silybin phytosome is approximately seven times more than silybin absorption from ordinary milk thistleextract[153]. According to studies, ginkgo phytosome (made from a standardized extract of Ginkgo biloba leaves) outperformed the plant's regular standardised extract (GBE, which contains 24 percent ginkgo flavone glycoside and 6 percent terpene lactones). The levels of GBE constituents (flavonoids and terpenes) from the phytosome form peaked after 3 hours and lasted for at least 5 hours following oral treatment in a bioavailability investigation with healthy human volunteers. The phytosome GBE produced a 24 times higher plasma concentration of terpenes than the nonphytosome GBE, according to the findings. Ginkgo phytosome has been demonstrated to generate a 30-60% higher improvement in patients with peripheral vascular illness (e.g. Raynaud's disease and intermittent circulation) in studies. Compared to a conventional standardized GBE, this is animprovement[154].A polyphenolic fraction (not less than 66.5 percent, containing epigallocatechin and its derivatives) isolated from Green tea leaves (*Thea sinensis*) and primarily defined by the presence of epigallocatechin 3-O-gallate, the major constituent, is found in a standardized Green tea extract. These compounds are potent modulators of several biochemical processes linked to the breakdown of homeostasis in major chronic-degenerative diseases like cancer and atherosclerosis, as well as having several long-term beneficial activities like antioxidant, anticarcinogenic, antimutagenic, antiatherosclerotic, hypocholesterolemic, cardioprotective, antibacterial, and anticariogenic effects. Despite these potential benefits, polyphenols are complexed with phospholipids to improve their poor oralbioavailability[155]. The research produced the quercetin-phospholipid phytosome complex using a simple and repeatable process, and shown that the formulation was more effective than the molecule in treating rat liver injury caused by carbontetrachloride[156]. Hesperetin and hydrogenated phosphatidylcholinewere combined and complexed,In addition,investigated its antioxidant activities and pharmacokinetic investigations in CC14-intoxicated rats. The phytosome has a significant antioxidant activity,

- In skincare productsPhytosome is mostuseful as compared to liposomes.
- Phytosome helpsto provide greater clinical benefit.

according to the study's findings. Phytosomes have better bioavailability than the parent molecule at the same dose, according to pharmacokineticstudies[157].

8.5 Advantage Of Phytosomes

Phytosome technology has transformed the nutraceutical sector by providing the followingadvantages[158-162].

- The composition of the phytosome is safe and the components are approved for pharmaceutical use.
- The absorption and bioavailability of water soluble phytoconstituents is increased. This results in better therapeutic effects.
- Phosphatidylcholine, one of the components of phytosome, has a dual function that acts as a carrier as well as has a health benefit such as hepatoprotective effect.
- Because the bioavailability of phytoconstituents is increased, therefore, the dosage required to produce desirable effect is reduced.
- The phytosomes have a better stability than liposomes. This is because the former consists of chemical bonds while it is absent in the later.
- Phospholipids add to the nutritional value of the plant extract.
- High market demand for products.
- The process of manufacturing phytosomes is relatively simple.
- Phytosomes have the ability to permeate through skin with quite ease and thus enhances their effectiveness.
- The water soluble phytoconstituents are enveloped by phospholipid which prevents them from destruction by digestive enzymes and gut bacteria. It helps in proper drug delivery to targeted tissue.
- Phosphatidylcholine nourishes skin besides acting as a carrier because it is part of the cellmembrane.
- They can be used for systematic targeting as phytosomes are able to transit from the hydrophilic environment into the lipophilic environment of the enterocyte cell and from there into the cell.
- Phytosome produces a mini cell where the crucial components of herbal extracts are protected from destruction by gut bacteria and digestive secretions.
- Ensure proper delivery of drugs to the target tissues.
- The Secure of the nutrients of the phyto constituent need not be arranged by the herbal drug as means of Phytosome.
- The absorption of the active component is modified; its small dose can produce the required results.
- The bioavailability of the drug has increased remarkably.
- The efficiency of entrapment is high and moreover predetermined because the drug itself is in-conjugation with lipids in forming vesicles.
- Formulation is easy so it is easy to drug entrapment.
- Phytosome is better stabledue to the formation of chemical bonds between Phytoconstituent and the Phosphatidylcholine particles.
- Except acting as a carrier, Phosphatidyl choline used in formulating the Phytosome process also nourishes the skin as it is an important part of a cell membrane.
- Phospholipid (Phosphatidylcholine) used as a carrier in preparation of phytosome,which is usedas a hepatoprotective substance.

- Phytosomes are less soluble in aqueous media which helps to the formation of stable emulsions or creams

8.6 Limitations Of Phytosomes

Despite many potential advantages of phytosomes, some serious drawbacks have been reported, such as the ability of phospholipids (lecithin) to cause proliferation in the MCF-7 breast cancer cellline[163-165]. No *In-vivo* actions due to their poor lipid solubility or improper molecular size or both, resulting in poorabsorption[166-169]. The key disadvantage of phytosome phytophosphate is leaching of the phytoconstituents from some which reduces the desired drug concentration indicating their unstable nature.[170]

9. CONCLUSION

Phytosomes are the upgraded advanced form of natural phospholipid delivery system extract, which are better absorbed than the traditional nature extracts. The article thus reviews the history, physical & chemical characteristics, phytosome technology, preparation, formulation of phytosomes, interactions, solvents systems, chemical properties, therapeutic utilization with dosages forms, side effects, latest patented technology, difference between phytosome and liposome, Phyto-phospholipid complexes, Lamellarity and Stability, Solubility and partition coefficient, SEM & TEM, FTIR spectroscopy, bioavailability, advantages, other lipid-based Nano-carriers: similarities and differences,biological or pharmacological properties, interactions between active constituents and phospholipids, vesicular systems for phytosome development, commercial marketed phytosomes products, recent advancements and limitations. Phospholipids based drug delivery system have been recorded for better and effective delivery systematic ways. The preparation of phytosome is easy and can be progressed without much efforts to make it commercial. Phytosomes have enhanced pharmacokinetic and pharmacological parameter, which is appropriate for the drugs like anticancer, anti-inflammatory, cardiovascular, etc. They have a number of specific advantages over traditional formulations. The phytosome formulation technology is straightforward and may readily be scaled up to commercial levels. For this type of new formulation, the characterization approaches and analytical tools are well established. Many patents have previously been granted for novel phytosome formulations, techniques, and applications. In terms of phytosome technology's potential, it has a bright future for usage in formulation technology and hydrophilic plant chemical applications.

10. AUTHOR CONTRIBUTION STATEMENT

A.P and SB, were responsible for selection of the topic. SB and AP, contributed for collecting, drafting and formatting this review article and communicating with scientific esteemed journal. AB, VT, BS and DR, responsible for arranging the references as per the requirement of the journal. SB, AP and BS completed the overall screening of the write up. All the Authors have read and approved the manuscript.

11. CONFLICT OF INTEREST

Conflict of interest declared none.

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