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PHYTOSOMES: EFFECTIVE SYSTEM FOR THE TARGETED DELIVERY OF BIOACTIVE PLANT EXTRACTS

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ABSTRACT

Due to low lipid solubility and molecular size, herbal medicines with a high concentration of active components exhibit significant bioactivity *in vitro* but limited bioactivity *in vivo*. As a consequence, the herbal extract's active ingredients are poorly absorbed and accessible. Phytosomes are a phytophospholipid complex vesicle that may increase the bioavailability of herbal extracts and phytoconstituents in medicines. Phytosomes are advanced herbal formulations that contain the bioactive phytoconstituents of herbal extracts and have the ability to shift the cell membrane from a hydrophilic to a lipophilic state, resulting in a more potent pharmacokinetic and pharmacodynamic profile than traditional herbal extracts. They are available in a variety of forms, including suspensions, pills, creams, and gels. The goal of this article is to provide a thorough research on phytosomes as a potential drug delivery mechanism by discussing current developments in phytosomes as well as their usage in various standardized herbal extracts.

KEYWORDS: Phytosomes, Herbal Extract, Delivery System, Formulations, Production methods, Characterization.

1. INTRODUCTION

Plant active compounds derived from herbal extracts, which have been employed in home treatments for centuries, are increasingly finding their way into contemporary medicine. On the other hand, certain phytoconstituents contain long side chains and high polarity, which prevents passive diffusion through lipidic skin. The majority of phytoconstituents have been found to be highly polar or water-soluble compounds, such as flavonoids, terpenoids, and polyphenolics.[1] These water-soluble components are unable to permeate highly lipid-rich cellular membranes due to their limited lipid solubility, resulting in poor bioavailability. A variety of techniques for enhancing bioavailability have been developed, including the use of solubility and bioavailability enhancers, structural modification, and entrapment in a lipophilic carrier. The chemical complexity of the crude or partially distilled extract seems to be important for the bioavailability of the active components.[2] When eaten orally, any components in water-soluble extracts may be destroyed in the stomach environment. The phytosome, a new phyto-phospholipid complexation approach that improves absorption and bioavailability, has emerged as one of the most efficient ways for boosting the bioavailability of phytopharmaceuticals with poor solubility and difficulties penetrating biological membranes. Despite having strong *in vitro* pharmacological activity, many plant actives have failed to demonstrate similar *in vivo* responses.[3] By combining these plant actives with dietary phospholipids, novel amphipathic cellular structures have been created, making them more systemically effective. Indena, a major supplier of nutraceuticals components, developed the Phytosome patent to add phospholipids to a standardized extract to improve absorption, bioavailability, and consumption.[4]

2. Phyto-Phospholipid Complex Vesicles

Phytosomes are cellular-like structures (**Figure 1**). Phytosome is a novel medication delivery method that

addresses the flaws of conventional drug delivery technologies. "Phyto" refers to a herb, and "some" refers to a cell-like structure. Phytosomes contain the bioactive phytoconstituents of plant extracts, which are encased in lipids.[5] Phytosomes are made by combining uniform plant extracts or water-soluble bioactive plant components with phospholipids to create lipid-compatible molecular complexes that improve absorption and bioavailability. The phytosome process produces a cell, which is a useful component of herbal extract that is not destroyed by digestive secretions or gut flora.[6] Phytosomes have a better ability to shift from a hydrophilic condition to the lipid-friendly environment of the enterocyte cell membrane, and then through the cell to the bloodstream. Hydrophilic phytoconstituents may be complexed with therapeutically relevant phospholipids to create lipid-soluble complexes. Phytosomes, which are liposome-like vesicles, may be made using these complexes.[7]

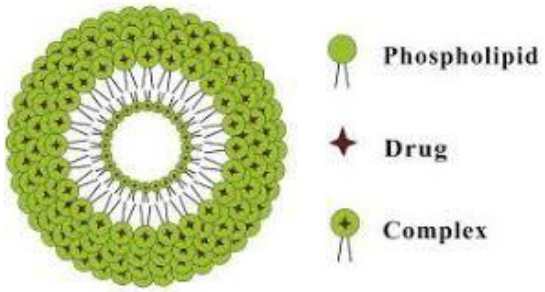

Figure 1: Structure of Phytosomes.

When phospholipids and water-soluble active plant components are complexed in phytosomes, chemical linkages are created, making them more stable. Phytosomes significantly increase the bioavailability of these polar active compounds. For phytosome production, soya phospholipids, egg lecithin, phosphatidylcholine, and other phospholipids have been discovered (**Figure 2**). Phytosomes may rapidly cross lipid biomembranes and have been demonstrated to enhance the bioavailability of lipid-insoluble extracts by boosting absorption in the gastrointestinal system.[8]

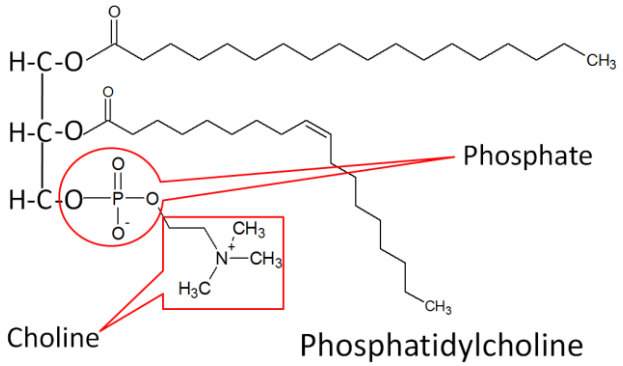

Figure 2: Structure of common Phospholipid (Soya phosphatidylcholine).

3. Advantages of Phytosome Vesicles

1. They enter the cell rapidly after passing through the cell membrane.
2. The drug's bioavailability has increased noticeably.
3. Phytosomes guarantee that herbal medications may be used for a long period.
4. Phytosomes increase the absorption of hydrophilic polar phytoconstituents via nasal, topical, and other routes, improving their bioavailability.
5. Phytosomes are a kind of small cell that protects the beneficial components of herbal extracts from digestive secretions and microorganisms in the intestine.
6. Phytosomes encourage medicine to be delivered to the correct tissues.
7. The nutritional integrity of the herbal extracts does not have to be jeopardized by assigning the herbal medication as phytosomes.
8. The dosage required has been decreased due to the maximal absorption of the major components.
9. They improve the absorption of physiologically active constituents while lowering dose requirements.
10. The phosphatidylcholine molecule forms chemical connections with phytoconstituents, indicating that phytosomes have a high stability profile.
11. Because of their enhanced skin penetration and high lipid profile, phytosomes are frequently utilized in cosmetics to improve phytoconstituent transdermal absorption.
12. Phytoconstituents in phytosomes are best absorbed when they move rapidly through tissue walls in the gut.
13. Because the phytosome complex is biodegradable, there is no risk of drug entrapment.
14. Phytosomes improve the impact of herbal compounds by improving absorption, boosting biological activity, and delivering to the target area; as a consequence, they are suitable for medication administration.
15. Entrapment effectiveness is great because the chemical is coupled with lipids during vesicle formation.
16. When making phytosomes, drug entrapment is not a problem.
17. Phosphatidylcholine, which is utilized to create phytosomes, is a component of the cell membrane that not only serves as a messenger but also nourishes the skin.
18. Phytosomes surpass liposomes in skincare products.
19. Phytosomes have been shown to have a significant therapeutic benefit.
20. When coupled with hepatoprotective chemicals, phosphatidylcholine, which is utilised in the production of phytosomes and acts as a transporter as well as a hepatoprotective, has a synergistic effect.
21. Because of their limited water solubility, they may be made into a strong semisolid dose form.

22. Increases the solubility of bile salts, making liver targeting easier.[9,10]

4. Properties of Phytosomes

4.1. Physicochemical properties

Phytosomes are synthetic compounds containing phospholipids. To make this combination, stoichiometric amounts of phospholipids and the substrate are mixed in a suitable solvent. According to spectroscopic findings, the main phospholipid-substrate interaction is due to the formation of hydrogen bonds between the polar head of phospholipids (*i.e.* phosphate and ammonium groups) and the polar functions of the substrate. When exposed to water, phytosomes take on a micellar shape, forming a liposomal structure. This may be determined by comparing the NMR of the complex to that of the pure predecessors. The indications of the fatty chain remain almost unchanged. The two long aliphatic chains wrap around the active material, creating a lipophilic envelope that protects the phospholipid's polar head and active components, according to these results.[11]

4.2. Biological properties

Phytosomes are sophisticated herbal components that are easier to ingest, use, and therefore provide better results than traditional herbal extracts. The phytosome has a higher bioavailability than non-complexed botanical derivatives, according to pharmacokinetic and pharmacodynamic studies in laboratory animals and human subjects.[12]

5. Prospects of Phytosome Technology

Phytosomes offer the following advantages over traditional herbal formulations:

1) They improve lipid insoluble polar plant extracts' oral and topical absorption, resulting in increased bioavailability and therefore therapeutic efficacy.
2) When the absorption of the active constituent(s) increases, a low dose will provide the desired results.
3) Phytosomes have a better stability profile due to the formation of chemical linkages between the phosphatidylcholine molecule and the botanical extract.
4) Phytosomes are better at transitioning from a hydrophilic condition to the lipid-friendly environment of the enterocyte cell membrane and subsequently inside the cell, enabling systemic targeting.
5) Because phytosomes penetrate the skin effectively and have a high lipid profile, they are often utilized in cosmetics.
6) Phytosomes increase the solubility of bile in herbal components, which aids liver targeting.[13,14]

6. Methods of Preparation

6.1. Anti-solvent precipitation technique

The specified volume of plant extract and phospholipid were combined with 20 mL dichloromethane in a 100 mL circular bottom flask and refluxed for 2 hours at a temperature of not more than 60°C. The mixture is condensed to 5-10 mL. After carefully applying hexane (20 mL) with continuous stirring, the precipitate was filtered, collected, and put in desiccators overnight. In a mortar, the crushed dry precipitate is sieved into #100 meshes. In an amber-colored glass container, the powdered compound was maintained at room temperature.[15]

6.2. Rotary evaporation technique

The specified volume of plant material and phospholipid were dissolved in 30 mL of tetrahydrofuran in a rotating circular bottom flask, then agitated for 3 hours at a temperature not exceeding 40°C. A thin layer of the sample was collected, then n-hexane was added and the mixture was continuously stirred using a magnetic stirrer. The precipitate was removed and placed in an amber-colored glass container at room temperature.[16]

6.3. Solvent evaporation technique

The specified volume of plant material and phospholipids is combined with 20 mL acetone in a 100 mL circular bottom flask and refluxed for 2 hrs at 50-60°C. After the mixture was condensed to 5-10 mL, the precipitate was filtered and removed. In an amber-colored glass container, the dry precipitate phytosome complex was maintained at room temperature.[17]

6.4. Ether-injection technique

In this procedure, the drug lipid complex is dissolved in an organic solvent. After that, the mixture is slowly injected into a heated aqueous agent, causing vesicles to form. The condition of amphiphiles is governed by their focus. When the concentration is low, amphiphiles adopt a monomer form; however, when the concentration increases, a variety of configurations, such as circular, cylindrical, disc, cubic, or hexagonal structures, may emerge.[18]

7. Characterization Techniques

7.1. Visualization

Phytosomes may be seen using transmission electron microscopy (TEM). Internal structure, as well as many other characteristics of phytosomes, such as anatomy, crystallization, heat, and magnetic domains, may be revealed via TEM. The surface of phytosomes is examined using scanning electron microscopy (SEM), which provides morphological information.

7.2. Particle size and zeta potential

Particle size and zeta potential may be determined using dynamic light scattering (DLS) using an automated inspection technique and photon similarity spectroscopy.

7.3. Entrapment efficiency

The ultracentrifugation method may be used to assess a drug's entrapment efficiency or potential to be entrapped in phytosomes. It calculates the proportion of medicine that is securely entrapped in phytosomes.

7.4. Transition temperature

In vesicular lipid systems, differential scanning calorimetry (DSC) may be used to determine the transfer temperature.[19]

7.5. Surface tension activity measurement

The surface tension response of a medication in an aqueous solution may be calculated using the ring method in a Du Nouy ring tensiometer.

7.6. Vesicle stability

The size and form of vesicles may be monitored over time in order to determine their long-term durability. The average scale is determined by DLS, while structural changes are monitored by TEM.

7.7. Drug content

It is possible to determine the volume of medication current using an updated high-performance liquid chromatographic technique or a suitable spectroscopic approach, depending on the situation.

7.8. Proton-Nuclear Magnetic Resonance (^{1}H-NMR)

As a typical method of validating the formation of complexes between phytoconstituents and the phospholipids moiety, as well as of analyzing the resulting association, spectroscopic investigations are often used. In order to simulate the complex formation between active phytoconstituents and the phosphatidylcholine molecule, this method may be employed.[20]

7.9. Carbon-Nuclear Magnetic Resonance (^{13}C-NMR)

When the ^{13}C-NMR of the phytoconstituents and the stoichiometric compound with phosphatidylcholine was recorded, it was found that the carbons of the phytoconstituents were not detectable in the results. Even though the signals relating to the glycerol and choline sections have been widened and others have been relocated, the resonance of the bulk of the fatty acid chains has maintained its original crisp line shape.

7.10. Fourier-Transformed Infra-Red (FT-IR) Spectroscopy

If the complex's spectrum matches up with the spectrum of the individual components and their mechanical mixes, then the complex's creation may be verified using Fourier transform infrared spectroscopy. When phytosomes are micro-dispersed in water or incorporated into very simple cosmetic gels, FT-IR spectroscopy is a useful tool for determining the stability of the phytosomes in question. When it comes to practice, it is possible to determine the stability of a complex by comparing the spectrum of the complex in solid form (phytosomes) with the spectrum of its micro-dispersion in water after lyophilization at different times.[21]

7.11. *In-vitro* and *in-vivo* evaluations

The physiologically active phytoconstituents present in plants are expected to have a medicinal effect. *In-vitro* and *in-vivo* assessment models are chosen using phytosomes.

8. Phytosome Formulations Development

Pharmaceutical companies may convert and manufacture phytosome complexes into a range of dose formulations for oral administration and topically applied administration. It is possible to develop a variety of products to get the most benefits from this technological breakthrough, both in terms of formulation manageability and improved bioavailability.

8.1.1. Capsules

8.1.1. Hard gelatin capsules

The phytosome complex may also be used to make hard gelatin capsules, which are more difficult to swallow. It is possible to use a direct volumetric filling procedure (without pre-compression) even though the phytosome complex's obvious low density tends to limit the overall amount of powder that can be filled into a capsule (usually not more than 300 mg for a size 0 capsule). The quantity of powder that can be packed in a capsule may be increased by employing a piston tamp capsule filling method, although pre-compression can have an effect on the disintegration time. Keeping a careful watch on the key metrics is recommended by Indena while a product or process is growing. In this case, a preliminary dry granulation procedure is used to define the optimal production technique. The phytosome complex may also be used to make hard gelatin capsules, which are more difficult to swallow. It is possible to use a direct volumetric filling procedure (without pre-compression) even though the phytosome complex's obvious low density tends to limit the overall amount of powder that can be filled into a capsule (usually not more than 300 mg for a size 0 capsule). The quantity of powder that can be packed in a capsule may be increased by employing a piston tamp capsule filling method, although pre-compression can have an effect on the disintegration time. Keeping a careful watch on the key metrics is recommended by Indena while a product or process is growing. In this case, a preliminary dry granulation procedure is used to define the optimal production technique.[22]

8.1.2. Soft gelatin capsules

The phytosome complex may also be used to make hard gelatin capsules, which are more difficult to swallow. It is possible to use a direct volumetric filling procedure (without pre-compression) even though the phytosome complex's obvious low density tends to limit the overall amount of powder that can be filled into a capsule (usually not more than 300 mg for a size 0 capsule). The quantity of powder that can be packed in a capsule may be increased by employing a piston tamp capsule filling method, although pre-compression can have an effect on the disintegration time. Keeping a careful watch on the key metrics is recommended by Indena while a product or process is growing. In this case, a preliminary dry

granulation procedure is used to define the optimal production technique.[23]

8.3. Tablets

For producing tablets with larger unitary dosages and adequate technical and biological characteristics, dry granulation is the safest method available. Because of the phytosome complex's limited flow capacity, potential stickiness, and low apparent density, it should only be used for low unitary doses. It is important to note that if a direct compression process is used, the phytosome complex should be diluted with 60-70 percent excipients in order to maximize its technical properties and obtain tablets with sufficient morphology. However, wet granulation should be avoided because of the negative impact that water and heat (granulation/drying) have on the stability of phospholipid complexes.[24]

8.4. Topical product

On top of that, the phytosome complex may be administered topically. A phospholipidic complex must be distributed in a small volume of the lipidic phase and applied to an emulsion that has previously been produced at low temperatures (less than 40°C) in order to integrate the phytosome complex into the emulsion. The phytosome complexes are soluble in the majority of lipidic solvents that are often employed in topically applied formulations. The phytosome complex should be dispersed in the watery process and then added to the final formulation at a temperature lower than 40°C when working with formulations with low lipid content.[25]

9. Reported Phytosomes Products From Plant Extracts

9.1. *Aegle marmelos*

Phytosomes of *Aegle marmelos* leaves extract were created from phosphatidylcholine and cholesterol using a solvent evaporation method in order to address difficulties with solubility, bioavailability, and fast removal from the body. The improved formulation, with a size range of 200-300 nm and a ratio of 1:5:5, was tested for medicinal properties and found to be stable. The modified formulation showed improved anti-proliferative efficacy compared to the crude extract, with a percent growth decrease of -62.9 percent at 10 µg/mL.[26]

9.2. *Allium cepa*

Using the solvent evaporation technique, *Allium cepa*-phospholipid complex (ACP) was made from *Allium cepa* extract (ACE) and hydrogenated soya phosphatidylcholine (HSPC) in a 1:1 ratio and developed into the matching phytosome formulation. The comprehensive characterization was carried out utilizing advanced methods to determine the complex's genesis. The phospholipid complex was tested for anti-hyperglycemic properties in normoglycemic and STZ-induced diabetic mice at 50 mg/kg and 100 mg/kg. ACP significantly increased glucose tolerance in normal animals, as well as a substantial decrease in SG levels and a considerable improvement in lipid markers in STZ-induced diabetic rats, according to the findings. During the bioavailability research, HPLC examination of the rat serum showed a high quercetin content, which may be considered an active principle for regulating glycemic levels. The bioavailability of ACP was greater in phytosomal vesicles containing HSPC and ACE intercalated in the lipid layer, indicating considerable pharmacological potential.[27]

9.3. *Allium sativum*

For the control and sustained release of the methanolic extract of *Allium sativum*, researchers designed a vesicular drug delivery system. With the zero-order release, phytosomal carriers produced using the solvent evaporation method in a 1:1 phosphatidylcholine ratio showed a substantially sustained release of 82.31 percent at 6 hours (independent of concentration and time-dependent). With IC_{50} values of 0.42µg/mL and 25.76µg/mL, the extract showed significant antioxidant and cytotoxicity against the MCF-7 breast cancer cell line. The manufactured phytosomal product had a better pharmacokinetic profile than the traditional *A. sativum* extract in terms of reactive free radical scavenging, and it may be used as an adjuvant treatment in modern chemotherapeutics.[28]

9.4. *Bacopa monnieri*

Investigators used phosphatidylcholine to make phytosomes of *Bacopa monnieri* leaf extract for potential improvement of anti-amnesic efficacy in natural aging-induced amnesic mice. In the elevated plus-maze (EPM), Morris water maze (MWM), and passive shock avoidance (PSA) tests, the bacopa-phospholipid complex (BPC) (at 40 mg/kg b.w.) in irregular size vesicles showed substantially greater anti-amnesic action than the bacopa extract (BE). The increased absorption of phytoconstituents from the formulation, which significantly corrected cognitive impairments in aged mice, may account for the BPC's greater pharmacological potential as an anti-amnesic drug. In bioavailability tests, phytosomal administration resulted in greater blood concentrations of bacopaside-I (12.21 mg/ml) and bacopaside-II (12.28 mg/ml) of BPC, indicating substantially stronger acetylcholinesterase inhibitory action and therefore higher biological activity than BE. The research has reintroduced the value of several traditional neuroprotective herbs in contemporary applications.[29]

9.5. *Boswellia serrata*

Laboratory-oriented research was planned and phytosomes of boswellic acid were developed utilizing a variety of concentrations of cholesterol (1-3%) and ethanol (20-40%) to improve the product's bioavailability. The entrapment effectiveness of uniform spherical shaped nano-vesicles with a size range of 179 nm to 514.8 nm and a size range of 39.8-74.2 percent was observed to improve with the addition of more cholesterol and ethanol. The optimized formulation with

the smallest morphology and greatest entrapment included 2% cholesterol and 40% ethanol, resulting in the highest dissolving rate of 82 percent and sustained release properties. This promising research concludes that the nano-sized vesicles may penetrate the skin quickly, allowing for topical administration.[30]

9.6. *Butea monosperma*

To address pharmacokinetics difficulties in the absorption and intrinsic bioavailability of the key phytoconstituents contained in the extract, the phytosome was produced using the solvent evaporation technique (mainly, flavonoids). The phytosomes were made from soy lecithin at a 1:1 ratio and tested for antioxidant activity using the DPPH procedure, which showed that the extract-loaded phytosomes scavenged the reactive free radical by 97.22 percent at 100 g/mL. The increased radical scavenging action may be attributed to the synergistic combination of extract (containing flavonoid) and phospholipids. The scientists found that manufacturing phytosomes significantly improved therapeutic effectiveness while reducing administration frequency.[31]

9.7. *Calendula officinalis*

Gold nanoparticles offer a wide range of biological applications, including antioxidant, wound healing, anti-inflammatory, and other properties. Formulators used the thin film hydration technique to create a phytosomal sac containing *Calendula officinalis* extract and gold nanoparticles of size 80 nm. In comparison to the plant extract and gold nanoparticles, cell-based antioxidant activity and cytotoxicity activity against the Vero cell line showed substantially greater biological activity. The phytosomes protected the cells from H_2O_2-induced damage by 81 percent, while the *in vitro* scratch test for wound healing revealed a 58.7% gap closure in the injured region. This groundbreaking research celebrated the use of a plant extract and a metallic nanomaterial in a vesicle system to produce synergistic results.[32]

9.8. *Centella asiatica*

In the case of traumatic brain injury, innovator created a *Centella asiatica* extract phytosome as a new method for the targeted delivery of citicoline, which has the property of neuroprotection, induces the repair of injured neural cell membranes, and prevents future damage to neurons. When compared to crude citicoline (at 250 mg/kg), the phytosome formulations (at 90 mg/kg) provided better neuroprotection by preventing the generation of free radicals and enhancing repair of damaged nerve myelination, as evidenced by increased expression of neuregulin-1 (NRG-1), activation of Krox-20, which triggers the formation of new phospholipids, and augment higher pTH levels.[33]

9.9. *Ginkgo biloba*

According to current research, *Ginkgo biloba* improves cerebral and peripheral blood flow in experimental animals. Experimenters produced *G. biloba* leaf extract phytosomes from di-stearoylphosphatidylcholine and used the Croton oil test to screen against topical inflammation in mice. The phospholipid-complex generated high blood serum concentrations of ginkgolides, bilobalides, and biflavones in mice, which had much higher anti-inflammatory action than the free drug extract concentration or the conventional medication indomethacin, according to the research.[34]

9.10. *Glycine max*

Researchers developed a nano-sized soy phytosome-based thermogel and tested its anti-obesity properties based on body weight increase, adipose tissue size, and lipid profile data. The spherical shape of *Glycine max* (L.) Merrill phytosomes were developed using Design Expert® software and produced using three distinct techniques: solvent evaporation, cosolvency, and salting out. High penetration, high percent entrapment effectiveness, drug release, and optimal rheological behavior were found when the produced formulation was evaluated for pharmaceutical characteristics. The thermogel had a local anti-obesity impact on the abdomens of experimental male albino rats, as well as a little systemic influence on lipid profile data.[35]

9.11. *Lawsonia inermis*

Lawsonia inermis L. phytosomes were made with soy lecithin at molar ratios of 1:1, 1:2, and 2:1 and tested for antifungal properties against *Candida albicans*. The DSC and FTIR findings showed that the antisolvent precipitated phytosomes contained drug particles linked with the phospholipid, creating complexes with irregular particle shapes and intercalated in the lipid layer. As indicated by the zone of inhibition (24 mm), the optimized formulation (1:1) had the greatest anti-fungal activity than the plain extract and had anti-*Candida* efficacy similar to that of the standard medication ketoconazole. The extract including lipid sacs was then synthesized as a topical gel that showed impressive cumulative *in-vitro* drug penetration (92.91 percent up to 6 hrs), pharmacological properties, and significant *in vivo* anti-inflammatory efficacy in rat skin. The research revealed several specific strategies for addressing difficulties such as poor bioavailability, solubility concerns, and fast elimination by expanding pathways and improving the plant extract's pharmacodynamic profile.[36]

9.12. *Mentha pulegium*

Investigators used a nutraceutical nootropic approach to create *Mentha pulegium* L. phytosomes that can treat a variety of neurodegenerative diseases caused by an increase in monoamine oxidase-A (MAO-A) levels in the central nervous system. The aqueous extract was encapsulated in lipid vesicles made from egg yolk lipids, which were enriched in high amounts of phenolic principles. The produced phytosomes exhibited a high entrapment efficiency of 75.05 percent, owing to well-defined phenolic-phospholipid connections, a mean vesicle diameter of less than 200 nm, and a zeta potential

of -15.84 mV, indicating excellent stability. The produced phytosomes reduced MAO-A by 48.24 percent in human neuroblastoma SH-SY5Y cells, which may be attributed to rosmarinic acid, the most active and abundant active principle.[37]

9.13. *Momordica dioica*

Formulators created a phytosome formulation of *Momordica dioica* fruit and used a streptozotocin-nicotinamide paradigm in rats to test its anti-diabetic potential. The research found that phytosomes at a modest dosage (100 mg/kg) reduced blood glucose levels more effectively than methanolic plant extract at a dose of 250 mg/kg b.w. The findings were found to be similar to those of the commonly prescribed medication metformin (50 mg/kg). The presence of a significant quantity of gallic acid and other flavonoidal components in the extract (208 mg/g) may be responsible for the rats' anti-diabetic effect. In comparison to its crude form, the plant extract in the phytosomal format showed superior pharmacodynamic and pharmacokinetic potentials.[38]

9.14. *Phyllanthus amarus*

Phyllanthus amarus phytosomal complex tablets were developed and tested for sustained administration of the extract using a new method. The phytosomes were made utilizing the solvent evaporation method using Phospholipon 85G at 1:1 and 1:2 molar ratios. The development of a phytosome complex with an uneven spherical shape as indicated by the characterization data. The tablets were also made from DCP and Avicel using a dry granulation method and a flat-faced punch, and they were properly described. The six manufactured batches' *in vitro* dissolution showed a sustained release characteristic, with a release of 112.28 percent after 12 hours. The research emphasized the importance of phytosomes in ensuring the extract's long-term release.[39]

9.15. *Phyllanthus emblica*

Innovators developed a photoprotective phytosome cream based on *Phyllanthus emblica* extract. The phytosomes were first produced and described using phospholipid ratios of 1:1, 1:2, 1:3, and 2:1 using the solvent evaporation method. Furthermore, seven batches of the phytosome-containing cream formulation were produced and evaluated using the standard technique, with the optimized batch exhibiting greater skin retention of the extract than the conventional cream. The strong antioxidant activity of *P. emblica* produced a sustained photoprotective effect (SPF 2.09) in the wavelength range of 290-400 nm in the cream. The complex's phospholipid content also aided in the feeding of the skin by increasing its moisture and preserving the collagen structure's integrity. Because it helps maintain the release of actives in the epidermis over time and makes it appropriate for cosmetic goods that operate on the skin, the complex cream exhibited greater localization of phytoconstituents in the skin when compared to traditional cream. Phospholipids, which make up the majority of the stratum corneum, may carry medicines to specific skin cells.[40]

9.16. *Tecomella undulate*

For the creation of phytosomes, an aqueous extract of *Tecomella undulata* stem bark complexed with lecithin was used for efficient drug delivery of therapeutically active plant extract with increased bioavailability. The very stable manufactured unilamellar vesicles with a size of 153.2 nm exhibited a high drug release efficiency and entrapment efficiency (up to 90 percent). The findings revealed that phytosomes may boost bioavailability without the use of any pharmacological adjuvants or structural changes to the components.[41]

9.17. *Woodfordia fruticosa*

Woodfordia fruticosa dried flower methanolic extract phytosomal formulations were made from soy lecithin at ratios of 1:1, 1:2, 1:3, and 1:4 using both ethanol and reflux techniques. The pharmacological characteristics of the produced optimized nano-sized phytosome (1:3) included percent yield, entrapment efficiency (89.15 percent), *in vitro* drug release (84.06 percent), and zeta potential (31.5 mV). The use of carbopol 934, HPMC K4M, and HPMC K100 in the creation of an eighteen phytosome integrated pseudo-plastic gel system resulted in a formulation with improved drug solubility, increased antioxidant activity, and substantially higher *in vitro* drug release. The phytosomal formulation had the greatest activity (absorbance value 0.185), followed by gel formulation (absorbance value 0.67) and plain extract (absorbance value 0.67) in an *in vitro* free radical scavenging assay at 600 g/mL (absorbance value 0.56). The improved antioxidant activity of the phytosome formulation may be attributed to the complexation with phospholipids, which resulted in lipophilic moieties with higher membrane permeability.[42]

10. Recent Marketed Products

10.1. Ginkgoselect®

It is a handy absorbable form of a generic extract of *G. biloba* leaves. The most common symptoms are cerebral insufficiency and peripheral vascular disease, and it is a useful tool in situations when cerebral function is impaired. It is a good choice for long-term care because of its increased oral absorption and tolerability. It is a more readily absorbed generic extract of *G. biloba* leaves. The most frequent indications include cerebral insufficiency and peripheral vascular disorders, and they may also assist with poor cerebral circulation.[43]

10.2. Greenselect®

It is made up of a completely homogenous polyphenolic fraction (no less than 66.5 percent) isolated from green tea leaves, with epigallocatechin and derivatives being the most prominent components. These chemicals have been demonstrated to be effective *in vitro* modulators of a variety of biochemical pathways linked to the development of chronic degenerative illnesses such as cancer and atherosclerosis. Because green tea

polyphenols are complexed with phospholipids, their oral bioavailability is greatly enhanced. It is made up of a completely uniform polyphenolic fraction obtained from green tea leaves (no less than 66.5 percent), with epigallocatechin and its variations being the most prevalent. These chemicals are effective modulators of a wide range of metabolic processes involved in the breakdown of homeostasis in illnesses including cancer and atherosclerosis. When green tea polyphenols are complexed with phospholipids, their poor oral bioavailability is substantially increased.[44]

10.3. Lymphaselect™

Melilotus officinalis extract is the main component of this product. This formulation is used to treat venous disorders in the lower limbs, such as chronic venous insufficiency.[45]

10.4. Mirtoselect®

It includes anthocyanoside-producing bilberry extract. These antioxidants improve capillary tone while also increasing capillary tone and decreasing aberrant blood vessel permeability. They hold a lot of potential for treating venous insufficiency and retinal blood flow problems.[46]

10.5. Oleaselect ™

It is a more contemporary formulation derived from the polyphenols found in olive oil. These are active free radical scavengers (antioxidants) with anti-inflammatory effects that prevent LDL cholesterol from being oxidized, which is harmful.[47]

10.6. Polinacea ™

This immunomodulating preparation is made using *Echinacea angustifolia*. It is made up of echinacosides and a one-of-a-kind high-molecular-weight polysaccharide. In the face of a hazardous danger, this supplement boosts immune function. For any of these ground-breaking phytomedicines, the phytosome technology enables for cost-effective distribution and synergistic benefits from the phospholipid nutraceuticals present in nature.[48]

10.7. Sabalselect®

It contains a supercritical CO_2 (carbon dioxide) extracted saw palmetto fruit extract. It contains fatty acids, alcohols, and sterols, all of which are beneficial to the prostate. This extract is very beneficial for non-cancerous prostate enlargement.[49]

10.8. Siliphos®

It protects the liver against a number of ailments. It is presently the most absorbable source of silybin, allowing it to reach the target organ, the liver, at amounts that have been shown to be antihepatotoxic.[50]

11. CONCLUSION

Phytosomes are novel structures built up of lipophilic plant component complexes and regular phospholipids. Phytosomes are often produced using unconventional techniques. When phytosomes are used as a medication, their absorption in the GIT is somewhat greater than the real portion, resulting in a higher plasma level. Phytosomes will be studied in depth in the future, with the goal of using them in medicines. Phytosomes act as a link between conventional and non-traditional distribution networks. Phytosomes allow pharmaceutical firms to develop new products based on water-soluble medicines and include new pharmacological advances. The chemical may be delivered topically and orally using this technique. Originally employed in cosmetics, phytosome complexes are now extensively utilized as a drug delivery method in antioxidants, gastrointestinal, anti-inflammatory, hepatoprotective, and anti-cancer therapies. The phytophospholipid complexing method has revolutionized herbal therapy, allowing it to have a substantial effect *in vivo* despite promising *in vitro* findings. Phytosomes are a potential medication delivery system that may improve the efficacy, purity, and targetability of active plant components and herbal extracts.

Abbreviations

^{1}H-NMR: Proton-Nuclear Magnetic Resonance
^{13}C-NMR: Carbon-Nuclear Magnetic Resonance
DLS: Dynamic Light Scattering
DSC: Differential Scanning Calorimetry
FT-IR: Fourier-Transformed Infrared Spectroscopy
SEM: Scanning Electron Microscopy
TEM: Transmission Electron Microscopy

Conflicts of Interest

No conflict of interest is declared.

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