Novel Drug Delivery Systems for Herbal Bioactives: A Comprehensive Review of Phytosomes

Prachi B. Desale[1], Kajal V. Choudhari[2], Rohit R. Khairnar[3], Rajanikat T. Kakade[4], Mohit M. Jadhav[5]
[1,2]*Research Scholar, Siddhi's Institute of Pharmacy Nandgaon, Murbad, Thane, 421401*
[3]*Principal, Departement of Pharmacology, Siddhi's Institute of Pharmacy Nandgaon, Murbad, Thane, 421401*
doi.org/10.64643/IJIRTV12I6-187630-459

Abstract*—Phytosomes are a sophisticated nanotechnology-based delivery platform built specifically to overcome the biopharmaceutical constraints of herbal phytoconstituents. Many plant-derived bioactives have poor aqueous solubility, restricted membrane permeability, fast metabolism, and low oral bioavailability, which limits their therapeutic potential. By establishing a molecular combination between phytochemicals and phospholipids, particularly phosphatidylcholine, phytosomes improve the lipophilicity, gastrointestinal absorption, membrane contact, and overall pharmacokinetic performance of poorly absorbed phytocompounds. This review offers a thorough examination of the structural design, preparation methods, characterisation techniques, and mechanistic foundation of phytosome-mediated drug delivery. It also discusses the important therapeutic applications of phytosomes in inflammation, cancer, hepatoprotection, metabolic disorders, dermatitis, and oxidative stress-related diseases. Preclinical and clinical studies show that phytosomal formulations of flavonoids, terpenoids, polyphenols, and herbal extracts have higher bioavailability, better tissue distribution, improved therapeutic efficacy, and lower dose requirements than conventional herbal preparations. Despite encouraging developments, difficulties like as large-scale manufacturing, stability, regulatory frameworks, and translational clinical data persist. Overall, phytosomes are developing as a strong and adaptable platform for phytopharmaceutical development, providing a scientifically verified strategy to updating herbal treatments for better clinical results.

***Index Terms*—Phytosomes, Nanotechnology, Herbal drug delivery, Phytoconstituents, Phospholipids, Phosphatidylcholine.**

I. OVERVIEW: INNOVATIVE DRUG DELIVERY METHODS

In contrast to traditional dosage forms (tablets, capsules, syrups, ointments), novel drug delivery systems (NDDS) refer to technological methods and formulation techniques created to deliver active pharmaceutical ingredients (APIs) to their site or sites of action in the body more safely, effectively, and predictably. In order to maximize therapeutic efficacy and minimize side effects, NDDS aims to regulate the rate, time, and/or location of medication release[1]. Many contemporary therapeutic molecules, such as biopharmaceuticals, poorly water-soluble compounds, and cytotoxic agents, have low oral bioavailability, rapid systemic clearance, limited therapeutic windows, or off-target toxicity when administered by conventional routes, which has led to a sharp increase in interest in NDDS. NDDS can enhance solubility, shield labile drugs from degradation, provide sustained/controlled release, and allow passive or active targeting to tissues or cells by employing engineered carriers (such as liposomes, polymeric nanoparticles, solid lipid nanoparticles, micelles, dendrimers) or device-based platforms (such as transdermal patches, implantable pumps, and osmotic systems)[2].

Carrier-based nanomedicines (liposomes, polymeric nanoparticles, solid lipid nanoparticles, nano micelles, nano cochleates, etc.) that combine encapsulation with surface functionalization to adjust pharmacokinetics and biodistribution; targeted delivery systems that preferentially accumulate drug at the diseased site via passive (e.g., enhanced permeability and retention) or active (ligand-mediated) mechanisms; and controlled/sustained-release systems that maintain

therapeutic concentrations for extended periods of time. Formulation decisions and clinical and regulatory translation tactics are guided by these classifications[3].

Improved patient compliance (less frequent doses), a higher therapeutic index (greater efficacy with lower systemic exposure), site-directed therapy (less off-target toxicity), and the potential to repurpose older compounds with poor pharmacokinetics are some of the benefits of NDDS. However, there are several obstacles to NDDS development, including manufacturing reproducibility and scale-up, long-term stability, immunogenicity or unexpected toxicity of novel carriers, complicated regulatory procedures, and cost-effectiveness for extensive clinical use. Research and regulatory discourse continue to focus on these translational barriers[1]. In order to increase safety and manufacturability, recent approaches focus on precision delivery (targeted at the cellular/subcellular level), stimuli-responsive systems (pH, redox, enzyme, temperature), combination platforms (drug + imaging agent = theranostics), and greener/biomimetic carriers. NDDS is moving from the bench to the bedside because to ongoing interdisciplinary advancements in materials science, surface engineering, pharmacology, and manufacturing technologies. Numerous nanomedicines and controlled-release devices have already received approval, and many more are undergoing clinical trials[4].

Need for novel herbal drug delivery system:

Although herbal remedies have been utilized for ages, basic biopharmaceutical issues frequently restrict their therapeutic usefulness. Inadequate systemic exposure and decreased therapeutic efficacy are caused by the poor aqueous solubility, limited membrane permeability, chemical instability, and substantial first-pass metabolism of several phytoconstituents.

These drawbacks underscore the increasing demand for innovative natural drug delivery systems (NDDS) that can improve the pharmacokinetic and pharmacodynamic properties of compounds derived from plants.

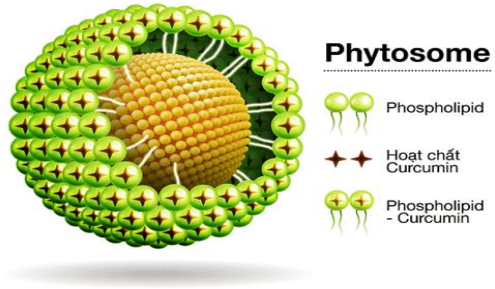
1. Low Phytoconstituent Bioavailability: The complex structures and high polarity of the majority of herbal active ingredients, such as flavonoids, alkaloids, terpenoids, and phenolics, prevent them from being absorbed through biological membranes. As a result, when given as traditional extracts or powders, these substances frequently show poor oral bioavailability. NDDS can increase therapeutic efficacy by enhancing solubility, penetration, and absorption[2].
2. Instability in Chemistry and Metabolism: A large percentage of phytochemicals break down when exposed to stomach pH, temperature, light, or metabolic enzymes. Additionally, they experience fast first-pass hepatic metabolism, which results in a short half-life and low plasma levels. Phytosomes, liposomes, nanoparticles, and nano emulsions are examples of encapsulation techniques that protect against degradation and prolong the release of active ingredients[1].
3. Insufficient Target Specificity: The active components in conventional herbal preparations are dispersed throughout the body, which frequently leads to less than ideal concentrations at the intended location. New carriers improve drug localization and reduce off-target effects by enabling both passive and active targeting[4].
4. Variability in Extracts from Herbs: Batch-to-batch variability in herbal medicines is often caused by variations in the plant source, extraction conditions, and environmental influences. New drug delivery methods make it possible to standardize active ingredients and enhance the repeatability of therapeutic results[2].
5. Enhanced Safety and Patient Compliance: Phytosome complexes, transdermal systems, and sustained-release nanoparticles are examples of NDDS technologies that lower dosage frequency and enhance patient adherence. Reduced dosages are necessary due to increased bioavailability, which lowers the possibility of toxicity and adverse effects[1].
6. Connecting Modern Pharmacology with Conventional Medicine: NDDS helps convert traditional herbal treatments into clinically acceptable, scientifically verified formulations by utilizing cutting-edge delivery technology to plant actives. This integration streamlines regulatory approval, encourages worldwide acceptability, and supports the evidence-based usage of herbal medicines[4].

II. OVERVIEW OF PHYTOSOMES

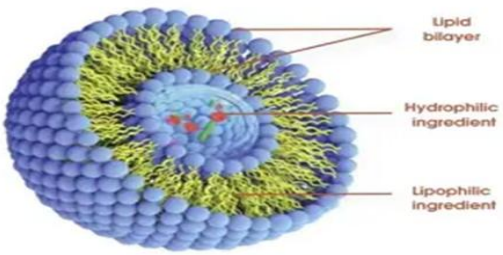
A phytosome is a complex of a natural active plant component and phospholipids that transports the phytochemical to target sites and increases its absorption and bioavailability compared with the uncomplexed extract[5].

III. DIFFERENCE BETWEEN PHYTOSOMES AND LIPOSOMES

Aspects	Phytosomes	Liposomes
Structure/Molecular intereaction	Phytosomes are molecular complexes in which the phospholipid (often phosphatidylcholine) and phytochemical (plant-derived substance) are chemically bound (for example, by hydrogen bonds)[6].	Liposomes are vesicular structures composed of a phospholipid bilayer; no strong chemical connection is formed, and the active molecule is either embedded in the lipid bilayer or enclosed in the aqueous core[7].
Phospholipid: Active compound ratio	In phytosomes, the molar ratio is frequently 1:1 or 2:1 (phospholipid: phytochemical)[6].	The active ingredient in liposomes may be surrounded by hundreds to thousands of phospholipid molecules[8].
Chemical Bonding and stability	Phytosomes are more stable and less likely to leak due to hydrogen bonding (or other polar interactions) between phospholipid and phytoconstituent[9].	Because the active is not chemically anchored, liposomes are less "tied together" and instability (such as leakage and fusion) may be an issue[8].
Size	In general, phytosomes are smaller than certain liposomal systems[6].	Depending on the formulation, liposome size might vary greatly (small unilamellar vesicles, multilamellar vesicles, etc.)[7]
Bioavailability /Absorption	Phytosomes frequently exhibit higher bioavailability (absorption) than liposomes because the active ingredient is incorporated into the phospholipid complex[9].	For some phytochemicals, liposomes may not increase absorption as much as phytosomes, but they do preserve the medication and improve solubility[9].
Applications	utilized specifically for phytochemicals and herbal active ingredients to enhance their delivery, absorption, and effectiveness[6]	Very widely used: as carriers for both hydrophilic and lipophilic medicines, in cosmetics, and in medication delivery[8].



Structure of Phytosomes



Structure of Liposome

IV. ADVANTAGES OF PHYTOSOMES

1. Improved Bioavailability: By creating a chemical combination with phospholipids, phytosomes greatly increase the bioavailability of phytoconstituents and facilitate their absorption via the digestive system. This is especially useful for phytochemicals that are polar or poorly lipophilic.
2. Enhanced Solubility: Phytosomes increase the solubility of bioactive substances that are ordinarily poorly soluble in water by complexing with phospholipids. This facilitates absorption by making them more compatible with bodily fluids.
3. Greater Stability: The phytoconstituent's stability is increased by the phospholipid structure, which shields it from deterioration (by gastric juices or enzymes, for example). A greater portion of the active ingredient will enter the systemic circulation thanks to this protection.

4. Improved Membrane Permeation: The phytosome's lipid compatibility makes it easier for it to fuse with cell membranes, increasing the phytochemical's cellular uptake. The phytosome's amphiphilic properties aid in the active compound's passage through biological membranes that are rich in lipids.
5. Potential for Targeted Delivery: Targeted distribution of phytosomes to particular tissues or organs may improve therapeutic efficacy and lessen adverse effects. Additionally, this could partially avoid first-pass metabolism (e.g., via lymphatic absorption).

V. DISADVANTAGES OF PHYTOSOMES

1. Stability Issues: Over time, phospholipids may oxidize and hydrolyze in phytosomes, decreasing their physicochemical stability[10].
2. High Cost of Production: High-purity phospholipids are costly raw materials[11].
3. Scalability Challenges: While lab-scale production can be adjusted, it is challenging to scale up without sacrificing quality (e.g., size, binding efficiency)[12].
4. Limited Clinical Translation: Clinical research is still scarce despite enhanced bioavailability in vitro and in vivo pharmacokinetics[6].
5. Potential Toxicity / Safety Concerns: Certain phospholipids employed in phytosomes, such as lecithin, may encourage cell division, as demonstrated by the MCF-7 breast cancer cell line[13].

Composition of Phytosomes :

1. Phospholipids (especially Phosphatidylcholine)

A phospholipid molecule, most frequently phosphatidylcholine (PC), forms the core of a phytosome. Phosphatidylcholine is amphiphilic because it has two lipophilic fatty acid tails and a hydrophilic "head" (the choline-phosphate). The choline head of the phospholipid interacts with the polar groups of the phytoconstituent in the complex, frequently through chemical bonding[14].

2. Phytoconstituents / Phytochemicals

Terpenoids, polyphenols (such as flavonoids), and other moderately polar plant-derived actives are common phytoconstituents that form phytosomes. A phyto-phospholipid complex" is created when these bioactive substances chemically combine with phospholipids[14].

3. Molar Ratio & Solvent :

Depending on the molecule, the complex formation frequently occurs in a stoichiometric ratio (1:1 or 1:2) between phospholipid and phytoconstituent. To aid in the synthesis of the complex, preparation is typically carried out in an aprotic solvent (such as dioxane, acetone, or methylene chloride)[15].

4. Molecular Complex :

The phospholipid head (phosphate/ammonium groups) and the polar functionalities of the phytoconstituent produce chemical bonding (usually hydrogen bonds) instead of only physical encapsulation. These interactions are confirmed by spectroscopic methods such as FTIR and NMR. The resulting structure is "lipid-compatible" and frequently behaves like a micelle or a cell[15].

Mechanism of Phytosomes

1. Improving Lipid Compatibility & Bioavailability

Due to their polarity or poor lipid solubility, many phytochemicals particularly polyphenols are poorly absorbed[16]. These phytochemicals become more "lipid-compatible" by building a compound with phospholipids, which improves their ability to interact with biological membranes (such as enterocyte membranes).Improved absorption results from the hybrid phytosome molecule's easier integration into cells' lipid-rich bio membranes[5].

2. Structural Protection

The phytophospholipid complex's synthesis shields the bioactive substance from being broken down by bacteria or gastrointestinal enzymes. PMC More of the active ingredient is so preserved and accessible for absorption[5].

3. Molecular Bonding for Stability

Chemical connection (e.g., hydrogen bonding) between the phytoconstituent and phospholipid makes the complex more stable than a simple physical combination. This stability adds to a superior pharmacokinetic profile (higher absorption, longer circulation, and probably better tissue targeting)[17] .

4. Improved Pharmacokinetics & Therapeutic Efficacy

Phytosomes can greatly boost phytochemical bioavailability by increasing solubility, improving membrane permeability, and protecting them from destruction[13]. For example, in the context of

anticancer therapy, phytosome-encapsulated secondary metabolites (such as flavonoids) exhibit increased cellular absorption and higher inhibition of cancer-related pathways[17].

Solvent systems for phytosomes detailed overview

1. Why does the solvent system matter?

Phytosomes are molecular complexes generated by the interaction (mainly hydrogen bonding) of a polar phytoconstituent (such as a polyphenol) and a phospholipid (often phosphatidylcholine). Solvents must dissolve both partners and facilitate complexation while preserving the interaction[18].

2. Common classes of solvents used:

1. Polar aprotic organic solvents –They are widely utilized because they breakdown phospholipids and other polar compounds while promoting hydrogen bond formation. Examples include dioxane, acetone, and dichloromethane (methylene chloride). These are frequently utilized in solvent-evaporation or reflux methods[18].
2. Alcohols (protic solvents) - Ethanol and methanol are commonly utilized (frequently as co-solvents) when the extract or pure phytochemical and phospholipid are soluble; ethanol is chosen for its lesser toxicity. Many studies describe ethanol or ethanol/acetone combinations[19].
3. Chlorinated solvents - Chloroform and methylene chloride dissolve phospholipids effectively and are commonly used in thin-film or solvent-evaporation procedures; however, their toxicity and regulatory constraints must be considered[20].
4. Non-polar anti-solvents - n-hexane and petroleum ether are employed for anti-solvent precipitation (to separate the phytosome complex from the reaction solvent) or to wash and remove un complexed materials[21].

3. Typical preparation methods & their solvent needs :

1) Solvent evaporation / reflux method: Dissolve the phospholipid and phytoconstituent in a common organic solvent (acetone, dioxane, chloroform) or solvent mixture; reflux or stir to allow interaction, then evaporate to obtain the complex. The solvent used must solubilize both components[21].
2) Anti-solvent precipitation: Complex is produced in a good solvent and then precipitated by adding a poor solvent (e.g., n-hexane), enhancing yield and eliminating free lipids or drugs[21].
3) Thin film hydration or rotational evaporation: Involves dissolving phospholipids and phytoconstituents in volatile solvents (e.g., chloroform, methanol), removing the solvent to form a thin film, and then hydrating to form vesicular systems or complexes[22].

Solvent evaporation method:

A phospholipid (often phosphatidylcholine) and a phytoconstituent (or plant extract) combine to generate a molecular complex using the solvent-evaporation (thin-film) approach. A thin film containing the phytosome complex is obtained by dissolving both components in a mutual organic solvent, mixing them to enable complexation, and then removing the solvent under low pressure. After the film is gathered and dried, the complex can either be transformed into a dry powder or further treated (hydration/sonication) into nanosuspensions[26].

1. Dissolve components :

   In a round-bottom flask, dissolve the weighted phospholipid (such as 100 mg PC) in a suitable volume of organic solvent (such as 10–20 mL ethanol or an ethanol:chloroform mixture). Use a small volume of the same solvent (or a minimal miscible solvent) to dissolve the plant extract or phytoconstituent separately (50–100 mg, depending on the ratio). Use ethanol or a little amount of methanol if the extract is only soluble in polar solvents; use DCM/chloroform for extremely lipophilic medicines[26].
2. Combine and (optional) reflux or mild heating In the same flask, mix the two solutions. To encourage complex formation (hydrogen bonding between polar heads of phospholipid and phytoconstituent), gently stir or reflux at 40–50 °C for 30–90 minutes. To enhance contact, some investigations employ swirling and light heating (45 °C). Prevent degradation by not overheating[27].
3. Removal of solvents using rotational evaporation (thin-film creation) Connect the flask to an evaporator that rotates. Lower the pressure and set the water bath temperature

between 40 and 50 degrees Celsius. Turn until a thin layer appears on the flask wall and the solvent has evaporated. Depending on the solvent and scale, this typically takes 20 to 60 minutes. Once the majority of the solvent has been eliminated, lower the pressure even more and remain under vacuum for at least 15 to 30 minutes to eliminate any remaining solvent. To guarantee dryness, some groups place the film in a vacuum oven set at 40 °C for two to four hours[26].

4. Collecting and drying Carefully remove the dry film from the flask; this is the phytosome complex, which is an oily, waxy material. To eliminate traces of solvent, dry under vacuum (in a desiccator or vacuum oven) to constant weight. To create a fine, dry powder with improved storage qualities, lyophilize the film (after pre-freezing)[27].
5. Particle formation / size reduction (if nanosuspension is intended) To create a nanosized phytosome dispersion, hydrate the film with a small amount of aqueous medium (such as phosphate buffer pH 7.4) and homogenize or probe-sonicate. To achieve the required particle size (usually 50–300 nm), sonication time and energy are tuned. An alternative that departs from the conventional thin-film technique is to dissolve the film in a volatile organic solvent and then carefully inject it into an aqueous phase (antisolvent approach) to create particles[26].

Anti-solvent Precipitation (also called Nanoprecipitation / Solvent Displacement):
Principle / Mechanism:

1. Anti-solvent precipitation involves dissolving your medicine (or polymer + drug) in a good solvent.
2. You then quickly add this solution to another solvent (the anti-solvent), in which the medication is poorly soluble (yet miscible with the first solvent).
3. Because to miscibility, the solvents mix, but the solute (drug) experiences a sharp decline in solubility, resulting in supersaturation[23].
4. Supersaturation causes nucleation (creation of tiny nuclei) and growth, resulting in the precipitation of very small particles (nanoparticles, nanocrystals) under regulated conditions[24].
5. Stabilizers (e.g., surfactants, polymers) are often present in the anti-solvent to prevent aggregation / growth of the particles.
6. After precipitation, the organic solvent may need to be removed (e.g., via evaporation or dialysis) so that only the nanoparticle suspension remains[24].

Key Parameters Affecting It:

1. Higher anti-solvent ratio leads to greater supersaturation and smaller particles.
2. Mixing rate / injection rate (faster mixing produces high supersaturation more quickly)
3. Higher drug concentration in the solvent leads to increased nucleation.
4. Selection and concentration of stabilizer (to prevent aggregation)
5. Temperature, sonication, and other factors can also influence the balance of nucleation and growth[25].

Thin film hydration or rotational evaporation
Principle:
By dissolving the phytoconstituent (or standardized plant extract) and a phospholipid (typically phosphatidylcholine) in a volatile mutual solvent, removing the solvent under low pressure to form a thin lipid film, and then hydrating that film to obtain vesicular/nanosized phytosomes, the thin-film hydration (rotary-evaporation) method (also known as solvent-evaporation) creates phytosome complexes. This technique is still among the most widely documented and repeatable methods in current research[26].

1. Dissolve lipid and phytochemical

Weigh the phytoconstituent and phospholipid in accordance with the selected molar ratio (e.g., PC 200 mg: quercetin 100 mg for a 2:1 w/w approximation). In a round-bottom flask, dissolve both ingredients in the same organic solvent (usually 10–50 mL solvent for 100–500 mg total solids). For poorly soluble flavonoids (like quercetin), ethanol, ethanol:chloroform (1:1), or THF are common solvent systems employed in recent research. Before continuing, make sure the solution is completely dissolved (clear)[28] .

2. Encourage complexation with mild heating and mixing.

If the solution is sensitive to oxygen, agitate it under nitrogen and heat it slowly (40–50 °C) for 30–90 minutes. According to certain research, refluxing momentarily or keeping the temperature between 40 and 45 °C can facilitate interaction without destroying delicate phytochemicals[29].

3. Rotary evaporation for the elimination of solvents (thin-film creation)

Connect the flask to an evaporator that rotates. Depending on the solvent's boiling point and the stability of the compound, set the water bath at between 40 and 50 degrees Celsius.Rotate the flask and gradually remove the solvent by applying less pressure; keep doing this until a thin, uniform layer of oil or wax (film) sticks to the flask's inner surface. Depending on the solvent and scale, typical run times range from 20 to 60 minutes.Once the majority of the solvent has been eliminated, keep the vacuum on for 15 to 60 minutes (or move it to a vacuum oven at 40 °C for 1 to 4 hours) to remove any remaining solvent. The dry phytosome film or complex is produced in this stage [26].

4. Hydration of thin film (to form vesicles / nanosuspension)

Add pre-warmed hydration buffer (e.g., PBS pH 7.4, 1–5 mL per 100 mg film) to the flask; allow to hydrate while gently rotating or stirring for 15–60 min at room temperature or slightly above.Use high-pressure homogenization or probe sonication (pulsed, ice bath, 5–15 min, depending on power) on the hydrated film to produce nanosized dispersions. After sonication, typical target sizes range from 50 to 300 nm (PDI varies on formulation and energy input)[29].

5. Drying and post-processing (optional)

If a dry powder is needed, lyophilize the hydrated dispersion (usually using cryoprotectants like sucrose or mannitol) after freezing (liquid N_2 or −80 °C) to produce a stable dry phytosome powder. An alternative is to evaporate any remaining solvent and grind the dry film into a powder; however, lyophilization usually results in improved redispersion characteristics [29].

Applications of Phytosomes in Herbal Drug Delivery (by Therapeutic Area)

1. Anti-Inflammatory:

Because the active ingredient is complexed with phospholipids, which increases membrane permeability and stability, phytosome technology enhances the bioavailability and absorption of anti-inflammatory phytochemicals (such as flavonoids and polyphenols)[30]. For instance, in LPS-induced systemic inflammation models, bioactive extracts (such as ginger and rosehip) synthesized in a phytosome demonstrated a markedly enhanced anti-inflammatory impact in vivo, with decreased inflammatory cytokines (such as TNF-α and IL-1β) in comparison to non-phytosome formulations[31]. From a therapeutic perspective, this means that phytosome formulations can enhance the anti-inflammatory properties of herbal actives, enabling lower dosages, improved tissue absorption, and fewer adverse effects[32].

2. Anti-Cancer:

By creating a stable combination with phospholipids that enhances transport to tumor locations, phytosomes assist overcome the main drawbacks of phytochemical anticancer treatments, which include poor solubility, low stability, and limited bioavailability. Phytosome formulations of substances such as curcumin, resveratrol, or quercetin have demonstrated improved pharmacokinetics, more effective absorption, and increased anticancer efficacy in cancer models[33]. Reviews have specifically shown that phytosomes containing polyphenols improve anti-angiogenic activities, reduce tumor proliferation, and increase treatment efficacy compared to free chemicals in liver cancer (hepatocellular carcinoma)[34]. In terms of therapeutics, this indicates that phytosomes can enhance chemoprevention and supplementary cancer therapy, increasing the efficacy of herbal actives and potentially lowering the toxicity of traditional chemotherapy[35].

3. Hepatoprotective (Liver Protection):

Phytosome formulations can increase the oral bioavailability of hepatoprotective medicines. For example, a silymarin-phytosome study found that absorption rose considerably. The same formulation provided better protection in liver injury models, lowering biochemical markers of liver damage and increasing histological recovery. Phospholipids (such as phosphatidylcholine) in phytosomes aid in

membrane repair by integrating into cell membranes, which helps to regenerate injured hepatocytes. Therapeutically, phytosome-based herbal hepatoprotective medicines offer more effective liver protection, possibly at lower doses, hence enhancing clinical efficacy and tolerability[36].

4. Antioxidant :

Phytosomes increase the stability, absorption, and systemic distribution of antioxidant phytochemicals (such as flavonoids and phenolics) by complexing with phospholipids. In experimental models, phytosome-formulated extracts (e.g., Ginkgo biloba in Ginkgoselect Phytosome) boosted endogenous antioxidant enzyme levels (GSH, SOD, CAT, and GPx) while decreasing oxidative stress indicators. The antioxidant benefits are not limited to the system; phytosomes also aid in the delivery of actives to target tissues, boosting therapeutic efficacy in oxidative stress-related disorders. Therapeutically, this indicates that phytosome-based formulations can operate as strong antioxidants, boosting herbal ingredients' protective action against oxidative damage in a variety of disease states[37].

5. Anti-Diabetic:

Phytosomes are employed as delivery methods for metabolic illnesses, including diabetes, since they improve the bioavailability of antidiabetic phytochemicals. In the context of diabetic wound healing (e.g., diabetic foot ulcers), phytosome-based polyherbal formulations increase skin absorption, speed up re-epithelialization, reduce inflammation, and stimulate collagen production. These phytosome formulations work by modulating inflammatory and oxidative pathways, both of which play important roles in diabetic complications. Phytosomes can improve the effectiveness of herbal treatments in diabetes, both systemically (for glycemic control or metabolic syndrome) and locally (for wound healing)[38].

6. Skin Disorders / Dermatological Applications :

Because phytosomes are phospholipid-based complexes, they improve skin penetration of herbal actives far more than unformulated extracts. According to evaluations of phytovesicular systems, phytosomes increase skin hydration and suppleness while also protecting against UV-induced oxidative damage. In wound healing (particularly diabetic wounds), phytosome formulations including polyherbal actives improve wound closure, re-epithelialization, and collagen deposition. Phytosomes are used therapeutically in topical herbal medicines to treat inflammatory skin conditions, wound healing, anti-aging, and antioxidant skin protection[30].

REFERENCE

[1] Adepu, S., & Gopinath, P. (2021). Controlled drug delivery systems: Current status and future perspectives. Pharmaceutics, 13(7), 1–24. https://doi.org/10.3390/pharmaceutics13071062

[2] Patra, J. K., Das, G., Fraceto, L. F., Campos, E. V. R., Rodriguez-Torres, M. del P., Acosta-Torres, L. S., Diaz-Torres, L. A., Grillo, R., Swamy, M. K., Sharma, S., Habtemariam, S., & Shin, H.-S. (2018). Nano based drug delivery systems: Recent developments and future prospects. Journal of Nanobiotechnology, 16(1), 71. https://doi.org/10.1186/s12951-018-0392-8

[3] Khedkar, O., Waghmare, S., & Kamble, H. V. (2022). A review: Recent updates in novel drug delivery system (NDDS). International Journal of Pharmaceutical Research and Applications, 7(1), 319–328. https://www.ijprajournal.com

[4] Chen, Q., Yang, Z., Liu, H., Man, J., Oladejo, A. O., Ibrahim, S., Wang, S., & Hao, B. (2024). Novel drug delivery systems: An important direction for drug innovation research and development. Pharmaceutics, 16(5), 674. https://doi.org/10.3390/pharmaceutics16050674

[5] Kalaivani, P., & Kamaraj, R. (2024). Phytosome technology: A novel breakthrough for the health challenges. Cureus. https://doi.org/10.7759/cureus

[6] Gaikwad, S. S., Morade, Y. Y., Kothule, A. M., Kshirsagar, S. J., Laddha, U. D., & Salunkhe, K. S. (2023). Overview of phytosomes in treating cancer: Advancement, challenges, and future outlook. Heliyon, 9(6), e16561. https://doi.org/10.1016/j.heliyon.2023.e16561

[7] Agrawal, S. S., Baliga, V., & Londhe, V. Y. (2024). Liposomal formulations: A recent update. Pharmaceutics, 17(1), 36. https://doi.org/10.3390/pharmaceutics17010036

[8] Bhakat, S. P., Modak, A., Debnath, B., Rahaman, R., Mitra, H., & Roy, S. (2024). Phytosome: An advancement technology in herbal drug delivery A review. YMER Digital, 23(8), 16. https://doi.org/10.37896/YMER23.08/49

[9] Talebi, M., Shahbazi, K., Dakkali, M. S., & Akbari, M. (2025). Phytosomes: A promising nanocarrier system for enhanced bioavailability and therapeutic efficacy of herbal products. Phytomedicine Plus. https://doi.org/10.1016/j.phyplu.2025.100779

[10] Prabu, S. L., & Umamaheswari, A. (Eds.). (2025). Dosage Forms: Emerging trends and prospective drug-delivery systems (Vol. 8). IntechOpen. https://doi.org/10.5772/intechopen.

[11] Maheshwari, R. A., Sen, D. B., & Sen, A. K. (Eds.). (2025). Emerging trends in phytomedicinal research (ISBN: 978-93-48620-04-0). Department of Pharmacy, Sumandeep Vidyapeeth Deemed to be University, Piparia, Vadodara, Gujarat, India.

[12] Author(s). (2024). Phyto-phospholipid complexes and its application in cancer therapy. In Futuristic trends in pharmacy & nursing (IIP Series, Volume 3, Book 3, Chapter 6, pp. 85–__). IIP Publications. https://doi.org.

[13] Singh, H., & Gauri. (2023). Recent development of novel drug delivery of herbal drugs. RPS Pharmacy and Pharmacology Reports, 2(4), rqad028. https://doi.org/10.1093/rpsppr/rqad028

[14] Kaur, R. (2021). Phytosomes: An emerging technology for improving phytochemical bioavailability – A review. CT Institute of Pharmaceutical Sciences, Jalandhar.

[15] Upase, A. U., Bhusnure, O. G., Gholve, S. B., Giram, P. S., & Wattamwar, P. B. (2019). A review on phytosome loaded with novel herbal drug and their formulation, standardization and applications. Channabasweshwar Pharmacy College (Degree), Latur, Maharashtra, India.

[16] Purkayastha, J., & Ghosh, J. (2018). Phytosomes: The novel drug delivery system for phytomedicine. In New age herbals (pp. 455–464). Springer. https://doi.org/10.1007/978-981-10-8291-7_21.

[17] Mardiana, L., Milanda, T., Hadisaputri, Y. E., & Chaerunisaa, A. Y. (2025). Phytosome-enhanced secondary metabolites for improved anticancer efficacy: Mechanisms and bioavailability review. https://doi.org/10.2147/DDDT.S483404

[18] Lu, M., Qiu, Q., Luo, X., Liu, X., Sun, J., Wang, C., Lin, X., Deng, Y., & Song, Y. (2018). Phyto-phospholipid complexes (phytosomes): A novel strategy to improve the bioavailability of active constituents. Asian Journal of Pharmaceutical Sciences, 14(3), 265–274. https://doi.org/10.1016/j.ajps.2018.05.011

[19] Sakure, K., Patel, A., Pradhan, M., & Badwaik, H. R. (2023). Recent trends and future prospects of phytosomes: A concise review. Advances in Phytosome Technology: Enhanced Bioavailability and Therapeutic Potential, Rungta College of Pharmaceutical Sciences and Research, Bhilai, India.

[20] Pahwa, R., Chetna, Saroha, K., Bhardwaj, B. Y., Kumar, M., & Singh, I. (2022). Insights into various approaches of phytosomes for enhanced therapeutic potential of bioactives. Research Journal of Pharmacy and Technology, 15(9), 4277–4282. https://doi.org/10.52711/0974-360X.2022.00718

[21] oma, L., Deleanu, M., Sanda, G. M., Barbălată, T., Niculescu, L. Ș., Sima, A. V., & Stancu, C. S. (2024). Bioactive compounds formulated in phytosomes administered as complementary therapy for metabolic disorders. International Journal of Molecular Sciences, 25(8), 4162. https://doi.org/10.3390/ijms25084162

[22] Gaikwad, A. R., Ahire, K. D., Gosavi, A. A., Salunkhe, K. S., & Khalkar, A. (2021). Phytosome as a novel drug delivery system for bioavailability enhancement of phytoconstituents and its applications: A review. Journal of Drug Delivery and Therapeutics, 11(3), 138–152.

[23] Kuddushi, M., Kanike, C., Xu, B. B., & Zhang, X. (2025). Recent advances in nanoprecipitation: From mechanistic insights to applications in nanomaterial synthesis. Soft Matter, 21(7), 2759–2781.

[24] Krosuri, P. K., & Mothilal, M. (2022). Recent advances in the development of nanoparticles in enhancement of solubility of poorly soluble drugs. Pharmacology and Nursing Research, 13(S10), Article 422. https://doi.org/10.47750/pnr.2022.13.S10.422

[25] Katas, H., & Hussain, Z. (2017). Influence of processing parameters on nanoparticle formation using antisolvent precipitation. Materials Science and Engineering: C, 78, 1142–1150. https://doi.org/10.1016/j.msec.2017.05.008

[26] Toma, L., et al. (2024). Bioactive compounds formulated in phytosomes: formulation, characterization and therapeutic potential. International Journal of Molecular Sciences, 25(8), 4162. https://doi.org/10.3390/ijms25084162

[27] Novel phytosomal formulation of Emblica officinalis extract: preparation and evaluation. (2024). Scientific Reports / Hindawi / Wiley prepared using a solvent-evaporation process with characterization (April 4, 2024)

[28] Quercetin phytosome innovare / IJAP (2024). Quercetin Phytosomes: Preparation & Optimization using Box–Behnken Design. International Journal of Applied Pharmaceutics

[29] Dewi, M. K., Muhaimin, M., Joni, I. M., Hermanto, F., & Chaerunisaa, A. Y. (2024). Fabrication of phytosome with enhanced activity of Sonneratia alba: formulation modeling and in vivo antimalarial study. International Journal of Nanomedicine, 19, 9411–9435. https://doi.org/10.2147/IJN.S467811

[30] Koppula, S., Shaik, B., & Maddi, S. (2025). Phytosomes as a new frontier and emerging nanotechnology platform for phytopharmaceuticals: Therapeutic and clinical applications. Phytotherapy Research, 39(5), 2217–2249. https://doi.org/10.1002/ptr.8465

[31] Guedes, J. M., Pires, A. W., Simões, C. M., & et al. (2023). Bioactive compounds formulated in phytosomes administered as complementary therapy for metabolic disorders. Oxidative Medicine and Cellular Longevity. [If this is the correct journal] or PMC article. PMC. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC11049841/

[32] Kalaivani, P., & Kamaraj, R. (2024). Phytosome Technology: A Novel Breakthrough for the Health Challenges. Cureus, 16(8), e68180. https://doi.org/10.7759/cureus.68180

[33] Saeed, M., Sadr, S., Gharib, A., Lotfalizadeh, N., Hajjafari, A., Ahmadi Simab, P., & Borji, H. (2022). Phytosomes: A promising nanocarrier for enhanced delivery of herbal compounds in cancer therapy. Journal of Life and Allied Research, 1(1), Article 8. https://doi.org/10.58803/jlar.v1i1.8

[34] Kothawade, S., Bhange, M., & Pande, V. V. (2025). Advancements in phytosomal therapies for liver cancer: A comprehensive review. Current Cancer Drug Targets, 25(9), 1066–1082. https://doi.org/10.2174/0115680096319007240703072650

[35] Chivte, P. S., Pardhi, V. S., Joshi, V. A., & Rani, A. (2017). A review on therapeutic applications of phytosomes. Volume 7, Issue 5, Sep–Oct 2017, Review.

[36] Shriram, R. G., Moin, A., Alotaibi, H. F., Khafagy, E.-S., Al Saqr, A., Abu Lila, A. S., & Charyulu, R. N. (2022). Phytosomes as a plausible nano-delivery system for enhanced oral bioavailability and improved hepatoprotective activity of silymarin. Pharmaceuticals, 15(7), 790. https://doi.org/10.3390/ph15070790

[37] Pandey, V., Rathee, S., Sen, D., Jain, S. K., & Patil, U. K. (2024). Phytovesicular nanoconstructs for advanced delivery of medicinal metabolites: An in-depth review. Current Drug Targets, 25(13), 847–865. https://doi.org/10.2174/0113894501310832240815071618

[38] Toma, L., Deleanu, M., Sanda, G. M., Barbălată, T., Niculescu, L. Ș., Sima, A. V., & Stancu, C. S. (2024). Bioactive compounds formulated in phytosomes administered as complementary therapy for metabolic disorders. International Journal of Molecular Sciences, 25(8), 4162. https://doi.org/10.3390/ijms25084162