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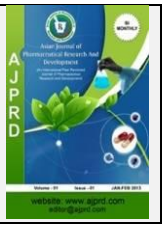

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Review Article

A Review on Phytosomes for Effective Topical Drug Delivery

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ABSTRACT

In recent years, there has been growing interest in the therapeutic potential of medicinal herbs and the bioactive compounds they contain for treating various health conditions. However, challenges such as poor bioavailability and limited targeting ability may reduce their effectiveness in clinical applications. As a result, enhancing the bioavailability of these compounds has become a critical focus to maximize their therapeutic impact. Phytosome-based nanotechnology offers a promising solution, especially for improving the topical delivery of herbal bioactives. Phytosomes, which are lipid-based nanoparticles, significantly enhance the absorption and penetration of phytochemicals across biological barriers, such as the skin. This review examines how encapsulating phytochemicals in a phytosome—a complex of plant compounds and phospholipids—can enhance their absorption, bioavailability, and ability to penetrate the skin.

KEYWORDS: Phytosome, Phyto-phospholipid complex, Topical drug delivery, Lipid-based nanocarriers, Skin penetration enhancement, Bioavailability

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INTRODUCTION

Plants and their parts have been used in traditional medicine since ancient times, and even today phytomedicines remain widely utilized across the world's population.[1] Throughout the last century, extensive chemical and pharmacological investigations have been carried out on numerous plant extracts to identify their constituents and scientifically validate the claims of traditional medicine. It has frequently been noted that isolating and purifying individual components from an extract may reduce the specific biological activity compared to the whole extract. Phytosomes represent a patented technology introduced by a major pharmaceutical and nutraceutical manufacturer to incorporate standardized plant extracts or water-soluble phytoconstituents into phospholipids, forming lipid-compatible molecular complexes known as phytosomes, which significantly enhance absorption and bioavailability.[2] This technology produces a small vesicle-like structure that protects the active constituents of herbal extracts from degradation by digestive enzymes and intestinal microflora. Phytosomes efficiently move from an aqueous environment to the lipid-rich membrane of enterocytes, then across the cell, ultimately entering systemic circulation.[3] Over the years, phytochemical and phytopharmacological research has identified the chemical profiles, biological effects, and health benefits of many plant-derived substances. Most active plant constituents are polar or water-soluble molecules; however, due to their hydrophilicity or large molecular size, many such compounds (e.g., flavonoids, tannins, terpenoids) exhibit poor lipid solubility and cannot easily cross biological membranes, resulting in low bioavailability.[4] Phytosomes enhance pharmacokinetic and pharmacological properties, making them beneficial for managing acute and chronic liver disorders of toxic, metabolic, infectious, or degenerative origin. They also show promise in anti-inflammatory therapy and have applications in pharmaceutical and cosmetic formulations.[5] Phytosomes are prepared by reacting soy phospholipids with selected botanical extracts in an appropriate solvent, and based on their physical, chemical, and spectroscopic properties, these complexes are regarded as novel entities.[6]

History of Phytosome

Phytosome technology was pioneered by Indena S.p.A. (Milan, Italy) in the late 1980s as a method to improve the

bioavailability of plant-based active compounds by forming complexes with phospholipids. Officially recognized in 1989, this technology represented a major breakthrough in enhancing the delivery of herbal phytoconstituents. Over the years, abundant scientific evidence has verified the presence of bioactive molecules such as flavonoids, tannins, polyphenols, and terpenes within medicinal plants. Despite their therapeutic potential, their practical application has been hindered by poor solubility and susceptibility to hydrolysis in both aqueous and organic media under physiological conditions, leading to very limited absorption following oral or topical administration. Incorporating advanced drug delivery approaches like phytosomes provides an effective way to improve their bioavailability by increasing solubility in intestinal fluids and promoting better permeation of these constituents across biological membranes.[7]

Phytosome

The word *"phyto"* denotes plant origin, while *"some"* refers to a cellular or vesicular structure. Phytosomes—also known as herbosomes—are vesicle-based drug delivery systems developed to improve the absorption and bioavailability of plant-derived constituents that exhibit poor solubility.[8] Although they resemble liposomes, phytosomes represent a more advanced lipid-based delivery platform capable of complexing a range of polyphenolic plant compounds to enhance their uptake following administration.[9]Many therapeutically valuable plant constituents, particularly flavonoids, show extremely low bioavailability when consumed orally. Water-soluble phytochemicals such as polyphenols can, however, be transformed into lipid-compatible molecular complexes called phytosomes. These complexes demonstrate markedly improved bioavailability compared with conventional herbal extracts due to their enhanced ability to traverse lipid-rich biological membranes and enter systemic circulation.[10]

Phytosomal vesicle formation occurs through hydrogen bonding between the polyphenolic groups of plant extracts and the phosphate moieties of phospholipids, typically within a nonpolar solvent system.[11] Hydrophilic polyphenolic structures—including flavonoids and terpenoids—exhibit strong binding affinity to the polar head groups of phospholipids, particularly choline, which enables the development of a stable phytosome core. The hydrophobic phosphatidyl tails orient outward, creating a vesicle that effectively entraps the water-soluble plant constituents bound to choline.[12] Drug–lipid binding produces vesicular assemblies that significantly enhance the incorporation and uptake of active molecules into the phytosomal system, thereby reducing the required dose while simultaneously improving bioavailability.[13]

Phytosomes also possess the capability to penetrate the skin, greatly enhancing therapeutic outcomes. Phospholipids—especially phosphatidylcholine—serve not only as structural vesicular carriers but also contribute additional biological benefits such as hepatoprotective activity.[14] These dual functionalities lead to superior pharmacokinetic and pharmacodynamic performance compared to traditional herbal formulations, particularly in topical applications, owing to their ability to cross both lipophilic and hydrophilic layers of the skin. Furthermore, phytosomes offer enhanced stability due to strong chemical interactions between phosphatidylcholine and plant extracts, improving the absorption of active compounds and enabling therapeutic efficacy at reduced doses.[15]

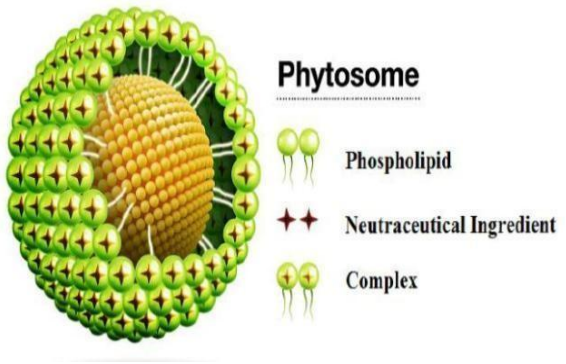

Figure1: Phytosome

The ability of phytosomes to significantly improve the delivery and therapeutic action of plant-derived polyphenols underscores their value as a nanotechnology-based platform for developing advanced pharmaceutical formulations. Typically, phytosomes are produced by reacting bioactive plant constituents with phospholipids such as phosphatidylcholine (PC), phosphatidylserine (PS), or phosphatidylethanolamine (PE) in well-defined stoichiometric proportions under controlled preparation conditions.[16]

Advantages of phytosome:[17-21]

- **Enhanced Skin Penetration:**Phytosomes boost dermal absorption by forming lipid-compatible complexes.
- **Improved Solubility:** They increase solubility of poorly water-soluble herbal actives.
- **Controlled Release:** Phytosomes enable sustained and controlled delivery of active ingredients.
- **Better Stability:** They protect herbal compounds from oxidation and degradation, improving formulation stability.
- **Biocompatible:** Natural phospholipids make phytosomes non-irritating and safe for sensitive skin.
- **Synergistic Action:** Phytosome complexes enhance anti-inflammatory, antimicrobial, and antioxidant effects.
- **Reduced Side Effects:** They are gentler than synthetic anti-acne agents and suitable for long-term use.
- **Targeted Delivery:**Lipid affinity helps them reach pilosebaceous units effectively.
- **Better Compliance:** Improved texture, spreadability, and reduced irritation promote patient adherence.
- **Natural & Safe:** They offer a safe, plant-based alternative to synthetic acne treatments.

Disadvantages of phytosome:[22-25]

- **High Production Cost:**Expensive phospholipids and equipment increase production cost.
- **Complex Formulation:** Techniques like solvent evaporation, thin-film hydration, and sonication are

required, making the process unsuitable for basic or small-scale labs.

- **Limited Scalability:** Maintaining uniformity and stability during industrial-scale production is challenging.
- **Storage Concerns**: Unstable to heat, light, and moisture; needs careful packaging.
- **Limited Clinical Data:** Few long-term studies on phytosome-based acne treatments.
- **Regulatory Difficulties:**Falls between cosmetic and pharmaceutical categories.
- **Allergy Risk:** Natural phospholipids or essential oils may cause rare allergies.
- **Shorter Shelf Life:** Improper storage leads to degradation or leakage.
- **Low Awareness:**Limited familiarity reduces acceptance among users and clinicians.

Table 1: Reported Phytosome Studies on Various Herbal Drugs for Topical Delivery[26-51]

Sr. No.	Herbal Drug andSynthetic Drugs	Topical Application	Observed Outcomes
1	Curcumin/Turmeric	Anti-inflammatory, anti-acne	Increased permeation, better antioxidant action, deeper skin retention.
2	Green Tea Polyphenols	Anti-aging	Improved dermal penetration, enhanced anti-wrinkle effect.
3	Aloe vera Extract	Wound healing	Faster wound closure, higher hydration, improved skin absorption.
4	Grape Seed Extract	Anti-aging	Better collagen protection and elasticity improvement.
5	Ginkgo biloba	Antioxidant	High stability and superior skin permeation.
6	Licorice	Skin whitening	Stronger depigmentation effect due to better penetration.
7	Kojic Acid	Anti-pigmentation	Reduced irritation and enhanced topical delivery.
8	Boswellia serrata	Anti-inflammatory	Better anti-swelling and local anti-inflammatory activity.
9	Centella asiatica	Wound healing	Improved collagen synthesis and dermal retention.
10	Silymarin	Photoprotection	Excellent antioxidant activity and UV protection.
11	Neem Extract	Anti-acne	High antimicrobial effect and enhanced sebum control.
12	Eucalyptus Oil	Anti-acne, antimicrobial	Controlled release, less irritation, better penetration.
13	Quercetin	Anti-inflammatory	Solubility and permeation significantly increased.
14	Resveratrol	Anti-aging	Superior stability, improved anti-wrinkle efficacy.
15	Chamomile Extract	Anti-inflammatory	PhytosomeBetter calming & soothing effect on irritated skin.
16	Kojic Acid	Anti-pigmentation	Increased skin penetration, reduced irritation, stronger depigmentation effect.
17	Azelaic Acid	Anti-acne, depigmentation	Improved solubility, enhanced permeation, smoother delivery, reduced skin irritation.
18	Diclofenac Sodium	Anti-inflammatory, pain relief	Higher dermal penetration, enhanced anti-inflammatory effect, prolonged release.
19	Indomethacin	Anti-inflammatory	Improved skin permeation, increased anti-inflammatory action, better drug stability.
20	Piroxicam	Anti-inflammatory	Increased permeation across skin, better localization, reduced systemic side effects.
21	Meloxicam	Anti-inflammatory	Higher solubility, enhanced skin retention, improved anti-inflammatory efficacy.
22	Ketoprofen	Anti-inflammatory	Better dermal penetration, prolonged action, reduced irritation.
23	Rutin	Antioxidant, anti-aging	Dramatically ↑ solubility, improved dermal absorption, superior antioxidant activity.
24	Silymarin	Photoprotection	Extremely high antioxidant stability, increased permeation, UV protection.
25	Quercetin	Anti-inflammatory	Solubility ↑, permeability ↑, strong antioxidant & anti-inflammatory effect.

Properties of Phytosome:

Chemical properties

Phytosomes are composed of natural bioactive substances complexed with organic phospholipids, typically soy-derived phospholipids. These complexes are produced by reacting specific stoichiometric amounts of the phospholipid and the plant substrate in an appropriate solvent system. Spectroscopic studies reveal that the major interaction stabilizing the complex is the formation of hydrogen bonds between the polar head groups of the phospholipids (such as phosphate and ammonium groups) and the polar functional groups present on the substrate. When dispersed in water, phytosomes adopt a micelle-like arrangement resembling liposomes. However, unlike liposomes—where the active ingredient is either enclosed within the aqueous core or distributed within the bilayer—phytosomes have the active constituent directly bound to the phospholipid's polar region, becoming an integral part of the membrane structure. A typical

example is the catechin–distearoyl phosphatidylcholine complex, where hydrogen bonds form between the phenolic hydroxyl groups of catechin and the phosphate moiety of phosphatidylcholine.

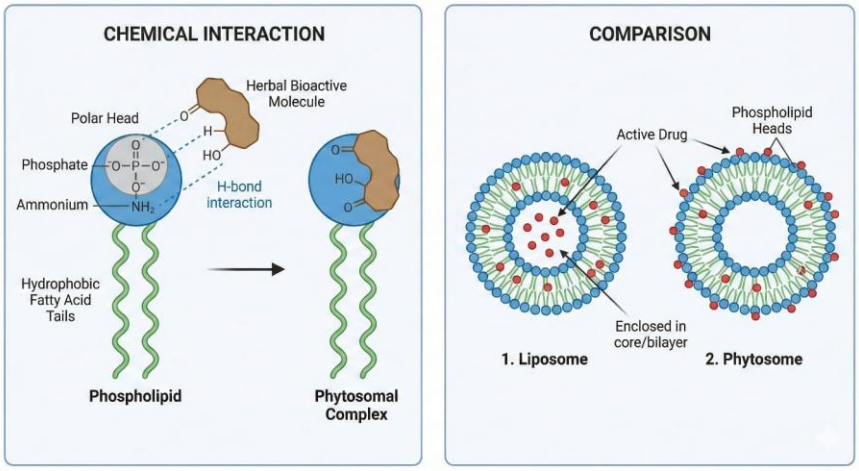

Figure 2: Phospholipid–bioactive interaction with liposome vs phytosome comparison

Biological Propertiies

Phytosomes represent advanced herbal delivery systems that exhibit superior absorption, enhanced utilization, and improved therapeutic outcomes compared to conventional herbal extracts. Their increased bioavailability relative to non-complexed plant derivatives has been confirmed through pharmacokinetic evaluations and pharmacodynamic studies conducted in both experimental animals and human subjects.[52]

METHOD OF PREPARATION

Solvent Evaporation Method:

In the solvent evaporation technique, the selected phytoconstituents and phosphatidylcholine (PC) are dissolved together in a suitable organic solvent inside a round-bottom flask. The mixture is then maintained at an optimized temperature, usually close to 40°C, for about one hour to promote efficient entrapment of the drug within the phytosomal complex. After formation, a thin phytosomal film is obtained, which is passed through a 100-mesh sieve and then placed in a desiccator overnight to allow proper stabilization.

Rotary Evaporation Method:

A measured amount of the drug, polymer, and phospholipids is dissolved in an appropriate solvent inside a rotary round-bottom flask, where the mixture is continuously stirred for approximately 3 hours at a temperature below 40°C. This process results in the formation of a thin film, after which n-hexane is introduced and the mixture is stirred again using a magnetic stirrer. The phytosomes that precipitate out are then collected, transferred into amber glass containers, and stored at room temperature for later use.

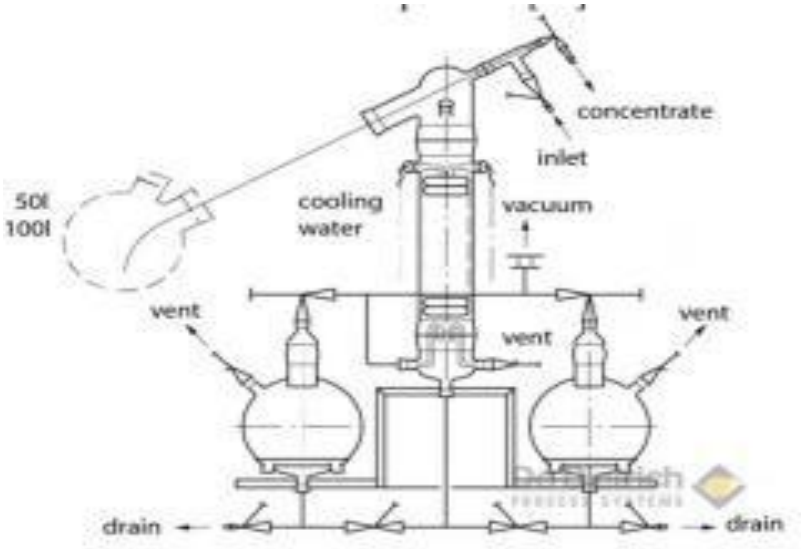

Figure 3: Rotary evaporation method

Anti solvent Precipitation Method:

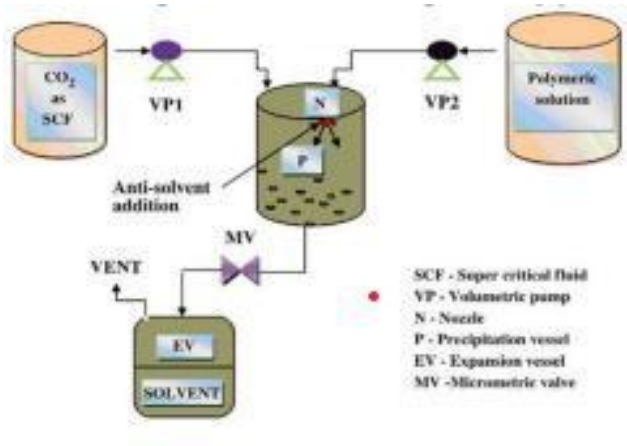

Figure 4: Anti solvent method

A measured quantity of the herbal extract and phospholipids is refluxed with 20 mL of an organic solvent—such as acetone—under controlled conditions at temperatures below 50°C for 2–3 hours. The mixture is then concentrated until its volume reduces to about 10 mL. When a low-polarity solvent like n-hexane is added with continuous stirring, a solid complex precipitates out. This precipitate is collected by filtration and kept in a desiccator for drying. Once dried, it is ground into a fine powder, and the prepared phytosomal complex is stored in dark amber glass containers at room temperature.

Solvent Ether Injection Method:

In this technique, lipids dissolved in an organic solvent are brought into contact with herbal extracts dispersed in the aqueous phase. The phospholipids, first solubilized in diethyl ether, are slowly added dropwise to the aqueous solution containing the phytoconstituents meant for encapsulation. As the solvent is subsequently removed, vesicular structures begin to form, giving rise to the phytosomal complex. The morphology of the resulting phytosomes depends on the concentrations of the interacting components: lower concentrations generally favor the formation of monomeric amphiphilic units, while higher concentrations can produce a wide range of vesicular shapes, such as spherical, cylindrical, disc-like, cubic, or hexagonal structures.

Mechanical Dispersion Method:

In this method, lipids dissolved in an organic solvent are mixed with an aqueous phase that contains the drug. Phosphatidylcholine (PC) is first solubilized in diethyl ether and then slowly injected into the aqueous solution holding the phytoconstituents targeted for encapsulation. Afterward, the organic solvent is eliminated under reduced pressure, leading to the formation of the phyto-phospholipid complex.

Salting Out Technique:

An important approach for preparing phytosomes consists of dissolving phosphatidylcholine (PC) together with the plant extract in a suitable organic solvent, after which n-hexane is slowly added to the mixture until the extract–PC complex precipitates. [53]

Selection of Dosage Form for Delivery Of Phytosome:

Choosing an appropriate dosage form for delivering phytosomes should be based on its ability to enhance the therapeutic performance and efficiency of the encapsulated bioactive compound. The selected formulation must ensure prolonged activity of the herbal constituents, thereby supporting their systemic benefits. Important considerations include the physicochemical nature of the herbal drug (such as whether it is hydrophilic or hydrophobic), the permeability and surface charge of the delivery system, and additional formulation factors like biodegradability, tonicity, the intended release pattern, and the desired particle size. Phytosomes can be formulated for various routes of administration, including both oral and topical delivery.[54]

Topical Drug Delivery:

In recent years, topical drug administration has received considerable interest due to its non-invasive application and the high bioavailability it can achieve. This delivery route enables the drug to reach the intended site directly, avoiding hepatic first-pass metabolism and reducing complications associated with the gastrointestinal tract. Topical drug delivery involves applying a pharmaceutical preparation onto the skin to treat localized dermatological conditions. It is especially useful when other administration routes—such as oral, sublingual, rectal, or injectable methods—are ineffective, impractical, or inappropriate, particularly in cases of localized skin disorders like fungal infections.

Numerous herbal extracts from diverse plant species have been evaluated for their therapeutic potential in skin-related conditions. These natural molecules possess a wide range of activities, including antimicrobial, anti-inflammatory, wound-healing, hemostatic, and burn-relief properties. Medicinal plants have demonstrated effectiveness in managing common dermatological problems such as acne, eczema, urticaria, psoriasis, pruritus, and various bacterial and fungal infections.

Topical delivery systems can be broadly categorized into externally and internally applied formulations. External topicals are applied by spreading, spraying, or otherwise distributing the formulation across the skin surface to

protect, soothe, or treat affected areas. Internal topicals are designed for application to mucosal membranes—including oral, vaginal, or rectal tissues—to provide localized therapeutic action. Topical delivery offers several advantages, such as avoidance of hepatic first-pass metabolism, reduced gastrointestinal side effects, targeted drug action at the site of application, improved patient compliance, ease of self-administration, and suitability for drugs with short half-lives or narrow therapeutic windows. Additionally, therapy can be discontinued immediately if adverse reactions occur.

Despite these advantages, topical delivery also presents limitations. Skin irritation, allergic responses, and contact dermatitis may occur. Furthermore, many drugs—particularly those with large molecular sizes—exhibit poor skin permeability, making efficient absorption challenging. The skin's complex and multilayered structure acts as a formidable barrier to penetration. For a molecule to reach systemic circulation, it must pass through the stratum corneum, any substances present on the skin surface, the viable epidermis, the papillary dermis, and finally the capillary walls. Once absorbed, the drug is transported via the bloodstream or lymphatic system and gradually cleared from the skin. This multi-step diffusion pathway creates significant formulation and analytical challenges.

Routes of Drug Penetration:

Drug molecules can penetrate the skin through three major pathways: via the sweat glands, through the hair follicles together with their sebaceous glands (collectively known as the transappendageal route), or directly across the stratum corneum through the transepidermal pathway. Within the transepidermal route, two distinct mechanisms are identified: the intercellular route, in which diffusion occurs through the lipid matrix situated between corneocytes, and the transcellular route, where molecules pass alternately through the corneocytes and the surrounding lipid layers.These pathways do not function independently; depending on the physicochemical nature of the drug, permeation may occur through more than one route simultaneously. The transcellular pathway is considered a polar route because corneocytes contain a hydrated, keratin-rich intracellular matrix. As a result, molecules traveling through this pathway must repeatedly partition between the polar corneocyte interior and the lipophilic intercellular regions. This mechanism generally favors hydrophilic substances, although they must still cross intercellular lipid layers to move from one corneocyte to the next.

Despite its more direct nature, the transcellular route contributes less to overall skin permeation compared to the intercellular route, which is regarded as the primary and continuous diffusion pathway through the stratum corneum. Because of the highly convoluted arrangement of intercellular lipids, the actual diffusional path length is far greater than the physical thickness of the stratum corneum (about 10–15 μm), and may extend beyond 150 μm. During transport through these intercellular channels, permeating molecules must pass through alternating hydrophobic (lipid core) and hydrophilic (polar head group) regions of the structured lipid bilayers.

Although cutaneous appendages such as glands and hair follicles have traditionally been considered low-resistance shunt pathways, their overall contribution to transdermal absorption was once thought to be minimal due to their limited surface coverage—only about 0.1–1% of the total skin area. However, recent research indicates that the appendageal pathway may play a significant role during the early lag phase of drug diffusion. Consequently, there is growing interest in exploiting this route for targeted follicular drug delivery, particularly through the development of colloidal and nanoparticulate formulation systems.[55]

Advances in Topical Drug Delivery:

- Topical administration is regarded as a highly advantageous route for drug delivery because it helps overcome several limitations associated with conventional methods such as oral and parenteral administration.
- The oral delivery of phytoceuticals is often inefficient due to their unpleasant taste and odor, as well as the possibility of their degradation within the gastrointestinal (GI) tract before absorption occurs. Although parenteral administration avoids GI degradation, it is invasive and therefore tends to reduce patient compliance.[56]
- Despite its benefits, the major drawback of topical delivery is the naturally low permeability of the skin, which acts as a robust barrier and restricts effective drug penetration.
- Historically, gels—especially hydrogels and oleogels—have been the most commonly used topical dosage forms. More recently, a variety of advanced gel-based formulations such as niosomal gels, proniosomal gels, emulgels, bigels, aerogels, and xerogels have been developed, each offering improved potential for achieving enhanced therapeutic efficacy.[57]

1. Characterization and Evaluation of Phytosome:

Phytosomes are evaluated based on various physical parameters, including their shape, particle size, size distribution, drug-loading capacity, entrapment efficiency, release profile, and overall chemical composition. Consequently, the performance of phytosomes in both physical and biological environments is influenced by factors such as their particle size, membrane permeability, percentage of entrapped constituents, chemical makeup, and the quality, quantity, and purity of the raw materials used in their preparation.

a) **Visualization:** The structural morphology of phytosomes can be examined using transmission electron microscopy (TEM), which provides detailed visualization of their vesicular architecture.

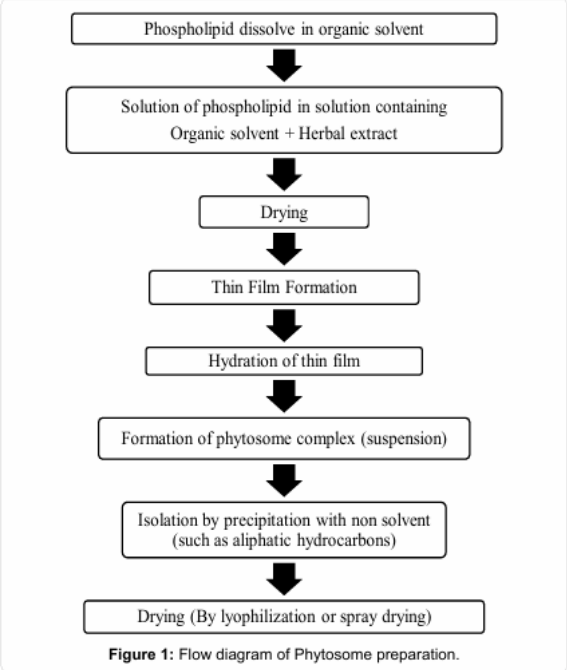

Figure 1: Flow diagram of Phytosome preparation.

b) **Drug content:** The amount of drug can be quantified by modified high performance liquid chromatographic method or by a suitable spectroscopic method.

c) **Transition temperature:**The phase transition temperature of vesicular lipid systems can be measured using differential scanning calorimetry (DSC).

d) **Surface tension activity measurement:**The surface tension of a drug in an aqueous solution can be assessed using the ring method with a Du Nouy ring tensiometer.

e) **Vesicle stability:**Vesicle stability can be evaluated by monitoring changes in their size and structural integrity over time. The average particle size is determined using Dynamic Light Scattering (DLS), while any morphological alterations are examined through Transmission Electron Microscopy (TEM).

f) Vesicle size and Zeta potential: Particle size and zeta potential can be analyzed using Dynamic Light Scattering (DLS), supported by a computerized measurement system and photon correlation spectroscopy.[54]

g) DSC: The sample containing phospholipon and the prepared phytosomes was loaded into an aluminum crimp cell and subjected to heating from 0 °C to 400 °C at a rate of 100 °C/min under a nitrogen atmosphere using a differential scanning calorimeter (DSC) (TA Instruments, USA; Model DSC Q10 V24.4 Build 116). The onset temperatures corresponding to the thermal transition events were obtained through the instrument's analytical software.

h) FTIR Spectroscopy: Spectral analysis was performed to assess the structural features and chemical stability of the extract, phosphatidylcholine (PC), and the resulting phytosomal complex. The spectra were obtained over the range of 4000 to 500 cm^{-1}. [53]

i) **Scanning electron microscopy (SEM):**The surface morphology and particle size of the phytosomal complex were examined using scanning electron microscopy. A dried sample was mounted on a brass stub and coated with a thin conductive layer using an ion sputter coater. The sample was then analyzed under the electron microscope at an appropriate scanning speed.

j) **Drug entrapment and loading capacity:**The phytosome complex was separated from the unentrapped drug by centrifugation at 10,000 rpm for 90 minutes at 4 °C. The concentration of free drug present in the supernatant was determined using UV spectrophotometric analysis. Drug entrapment efficiency was calculated using the following equation:[58]

$$\text{Entrapment Efficiency (\%)} = \frac{\text{Total drug} - \text{Free drug}}{\text{Total drug}} \times 100$$

CONCLUSION

Due to the adverse effects commonly associated with synthetic medications, there is an increasing shift toward the use of herbal therapies. However, challenges such as poor absorption and limited bioavailability in the gastrointestinal tract necessitate the exploration of alternative drug delivery routes. This review highlights the potential of topical drug delivery enhanced through phytosome technology. The lipid-based structure and nanovesicular nature of phytosomes allow for superior transdermal penetration compared to the direct application of free phytochemical extracts. Therefore, based on the findings discussed, topical delivery of phytochemicals using phytosomes as carriers significantly improves bioavailability and enables easier passage across biological membranes due to their phospholipid composition.

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