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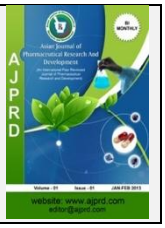

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Review Article

Review on Phytosome for Topical Drug Delivery

Mandwe S. Vrushabh*, Dr. Sandeep C. Atram, Bawankar V. Dipali, Bhonde G. Akash, Puri G. Ashutosh

Vidyabharati College of Pharmacy, Amravati

A B S T R A C T

In recent years, medicinal herbs and their constituent phytochemicals have gained considerable attention as promising therapeutic agents for various diseases. Nevertheless, limitations such as low bioavailability and insufficient selectivity may hinder their clinical efficacy. Consequently, enhancing bioavailability remains a critical challenge for improving the therapeutic potential of dietary phytochemicals. To address this, phytosome-based nanotechnology represents a significant advancement in the field of drug delivery, particularly in enhancing the topical administration of bioactive phytochemicals. To improve the absorption and inadequate permeability of phytochemicals across biological barriers, such as the skin. Phytosomes, as lipid-based nanoscale carriers, play a pivotal role in improving the pharmacokinetic and pharmacodynamic profiles of polyphenolic compounds derived from herbal sources. In this review we focus on the delivery of phytochemicals by topical route by encapsulating them in phyto-phospholipid complex, which is phytosome to improve absorption and bioavailability and penetrate the biological membrane easily.

Keywords: Phytochemical, Phyto-phospholipid complex, Topical delivery.

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*Address for Correspondence:

Mandwe S. Vrushabh, Vidyabharati College Of Pharmacy, Amravati.

INTRODUCTION:

The global interest in herbal medicines has significantly increased, primarily due to their aesthetic appeal, higher patient acceptability, and notable therapeutic efficacy. The ethnobotanical knowledge concerning these medicinal plants and their traditional use by indigenous communities plays a crucial role in preserving traditional medical systems and biodiversity, while also contributing to the advancement of healthcare practices.Numerous medicinal plants are abundantly distributed worldwide, including Withaniasomnifera, Aloe vera, Azadirachtaindica, Murrayakoenigii, Carica papaya, and Allium sativum, among others. [1]Herbal remedies possess a complex composition comprising numerous active constituents, which act synergistically to enhance their therapeutic efficacy.[2]The recommendation of herbal medicines aims to minimize adverse effects, and the application of herbal formulations and phytoconstituents has increasingly been recognized as a promising strategy for managing a wide range of health conditions.[3]The limited oral bioavailability of numerous plant-derived active compounds has emerged as a significant challenge for researchers. This issue is particularly prominent for compounds with polyphenolic structures, such as flavonoids, as well as other water-soluble constituents like terpenoids and tannins.[4]Several fundamental factors contribute to the poor bioavailability of these compounds, including limited aqueous or lipid solubility, high molecular weight or size, and inadequate permeability across the plasma membrane. Furthermore, when standardized extracts are administered orally, certain constituents may be degraded or lost due to exposure to gastric fluids. These limitations have hindered the therapeutic application of pharmacologically active polyphenolic compounds in the treatment of various diseases.[5]To enhance bioavailability, herbal formulations should maintain an optimal balance between hydrophilic properties, which facilitate absorption into gastrointestinal tract fluids, and lipophilic characteristics, which enable permeation across lipid-based biological membranes.[6]Many key constituents of herbal medicines, such as glycosides and flavonoids, exhibit good water solubility; however, their therapeutic potential is often limited due to partial solubility or hydrophobic characteristics, which reduce their efficacy when applied topically. To address these limitations, extensive research has focused on improving their bioavailability through targeted drug delivery systems. Among these, phytosomes and liposomes have emerged as

promising approaches. Incorporating such advanced delivery techniques into formulation development can significantly enhance the bioavailability of herbal drugs compared to conventional herbal extracts.[7]

History of Phytosome:

Phytosome technology was first introduced by Indena S.p.A. (Milan, Italy) in the late 1980s with the objective of enhancing the bioavailability of active compounds through complexation with phospholipids. Officially emerging in 1989, this innovative approach marked a significant advancement in the delivery of herbal phytoconstituents. Over the past century, extensive scientific research has confirmed the presence of bioactive compounds such as flavonoids, tannins, polyphenols, and terpenes in plants. However, their clinical utility has been limited due to poor solubility and hydrolytic instability in both aqueous and organic solvents under physiological conditions, resulting in minimal absorption when administered orally or topically. The application of advanced drug delivery systems, such as phytosomes, offers a promising strategy to improve bioavailability by enhancing solubilization in intestinal fluids and facilitating the permeation of these compounds across biological membranes.[8]

Phytosome:

The term "phyto" denotes plant origin, whereas "some" implies a cell-like structure. Phytosomes, also known as herbosomes, are vesicular drug delivery systems designed to improve the absorption and bioavailability of poorly soluble phytoconstituents.[9] Phytosomes, which closely resemble liposomes, represent an advanced lipid-based drug delivery system capable of encapsulating a variety of polyphenolic phytoconstituents to enhance their absorption upon administration.[10]A significant proportion of bioactive compounds in phytomedicines, particularly flavonoids, exhibit poor oral bioavailability. However, water-soluble phytoconstituents—primarily polyphenols—can be transformed into lipid-compatible molecular complexes known as phytosomes. These complexes demonstrate superior bioavailability compared to conventional herbal extracts due to their improved ability to traverse lipid-rich biological membranes and ultimately reach systemic circulation.[11]The formation of phytosomal lipid vesicles arises from hydrogen bonding interactions between the polyphenolic components of bioactive herbal extracts and the phosphate groups of the phospholipid matrix, typically occurring in non-polar solvent environments.[12]

The water-soluble polyphenolic structures of phytochemicals, such as flavonoids and terpenoids, exhibit strong affinity for the hydrophilic head group of phospholipids, particularly choline, facilitating the formation of the phytosome core. Concurrently, the lipophilic phosphatidyl portion of the phospholipid extends outward, forming a tail that encapsulates the choline-bound, water-soluble phytoconstituents.[13]The drug is conjugated with lipids to form vesicular structures, enhancing the entrapment efficiency within the phytosomal system. This approach leads to a reduced required dosage while substantially improving the drug's bioavailability.[14] Phytosomes possess the ability to penetrate the skin, thereby markedly improving therapeutic efficacy. Phospholipids, particularly phosphatidylcholine, serve as fundamental components of phytosomes, functioning as vesicular carriers while also offering additional health benefits, including hepatoprotective properties.[15]

The dual-functional characteristics of phytosomes have been shown to enhance both their pharmacodynamic and pharmacokinetic profiles compared to conventional herbal formulations when applied topically, due to their ability to traverse both lipophilic and hydrophilic barriers of the skin.[8]Phytosomes exhibit an optimized stability profile attributed to the chemical interactions formed between phosphatidylcholine and the botanical extract. Furthermore, the improved absorption of the active constituents enables the achievement of therapeutic effects even at lower dosages.[16]The potential of phytosomes to enhance the therapeutic efficacy of polyphenolic compounds derived from herbal sources highlights their promise as a nanotechnological platform for the development of advanced pharmaceutical formulations. Typically, phytosomes are synthesized by combining bioactive phytoconstituents with phospholipids—such as phosphatidylcholine (PC), phosphatidylserine (PS), and phosphatidylethanolamine (PE)—in defined stoichiometric ratios under controlled conditions.[17]

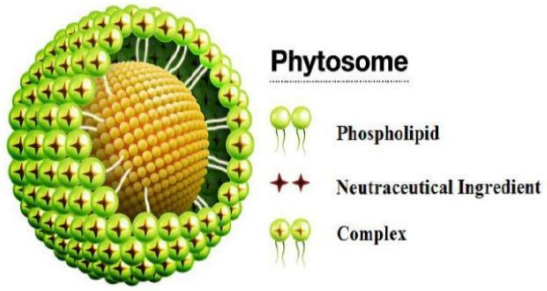

Figure 1: Phytosome

Advantages of Phytosome:

- Phytosomes improve the absorption of hydrophilic and polar phytoconstituents via both oral and topical routes, thereby enhancing their bioavailability.
- Due to the formation of chemical bonds between phosphatidylcholine molecules and phytoconstituents, phytosomes exhibit a favorable stability profile.[18]
- The enhanced absorption of the active constituent allows for a reduced dosage requirement, enabling the achievement of therapeutic effects with smaller quantities.[19]
- Phosphatidylcholine, a key component of cell membranes utilized in phytosome technology, functions as a carrier while also providing nutritional benefits to the skin.
- Phytosomes can also be employed to enhance drug permeation through the skin, facilitating both transdermal and dermal delivery.[20]

Disadvantages of Phytosome:

When administered via oral or topical routes, their bioavailability is limited.

Phytoconstituents is quickly eliminated from phytosome.

Stability problem.[21]

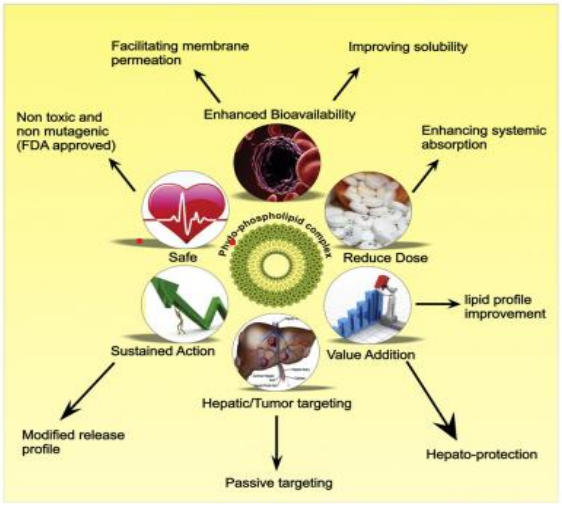

Figure 2: Benefits of Phyto-phospholipid Complexation.

Properties of Phytosome:

Chemical Properties:

Phytosomes are molecular complexes formed between natural bioactive compounds and phospholipids, typically derived from sources such as soy lecithin. These complexes are synthesized through the reaction of equimolar proportions of the bioactive substance and phospholipids in a suitable organic solvent. Spectroscopic analyses indicate that the primary mode of interaction between the phospholipid and the active compound involves hydrogen bonding, specifically between the polar functional groups of the bioactive molecule and the phosphate or ammonium moieties of the phospholipid head groups. Upon exposure to an aqueous environment, phytosomes self-assemble into micelle-like structures resembling liposomes. However, unlike liposomes where the active compound is either encapsulated within the aqueous core or integrated within the lipid bilayer, in phytosomes the bioactive molecule is covalently or non-covalently bound to the polar head of the phospholipid, ensuring improved stability and bioavailability.

The particle size of phytosomes typically ranges from approximately 50 nanometers to several hundred micrometers. [22]

Biological Properties:

Phytosomes represent advanced formulations of herbal products that exhibit superior absorption and utilization, thereby enhancing therapeutic efficacy compared to conventional herbal extracts. The improved bioavailability of phytosomes relative to non-complexed botanical constituents has been substantiated through pharmacokinetic evaluations and pharmacodynamic investigations conducted in both experimental animal models and human subjects.[23]

Method OfPreparation:

Solvent Evaporation Method:

The solvent evaporation method entails the incorporation of phytoconstituents and phosphatidylcholine (PC) within a round-bottom flask containing an appropriate organic solvent. The resulting mixture is maintained at an optimal temperature, typically around 40°C, for a duration of one hour to facilitate maximum drug entrapment within the resulting phytosomes. The thin-film phytosomes are subsequently separated using a 100-mesh sieve and stored in a desiccator overnight for stabilization.[24]

Rotary EvaporationMethod:

A defined quantity of the drug, polymer, and phospholipids is dissolved in a suitable solvent within a rotary round-bottom flask, followed by continuous stirring for 3 hours at a temperature not exceeding 40°C. A thin film is formed from the mixture, to which n-hexane is added and the solution is further stirred using a magnetic stirrer. The resulting precipitated phytosome formulation is collected, transferred into amber-colored glass containers, and stored at room temperature for further use.[25]

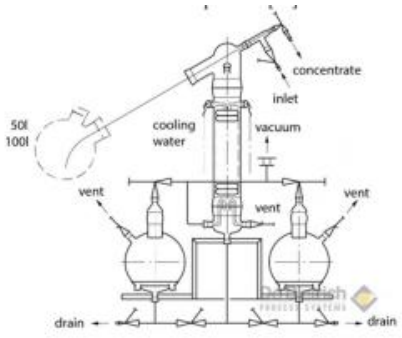

Figure 3: Rotary evaporation method

Antisolvent Precipitation Method:

A specified amount of herbal extract and phospholipids is refluxed with 20 mL of an organic solvent, such as acetone, under controlled experimental conditions at temperatures below 50°C for a duration of 2–3 hours. The reaction mixture is then concentrated to a minimum volume of approximately 10 mL. Upon the addition of a low-polarity solvent such as n-hexane with continuous stirring, a precipitate is formed. The resulting precipitate is filtered and stored in a desiccator. After drying, the precipitate is pulverized into a fine powder and the resulting complex is stored in dark amber glass bottles at room temperature.[26]

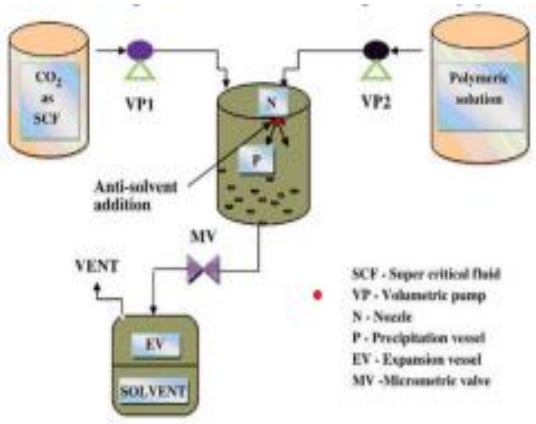

Figure 4: Antisolvent method

Solvent Ether Injection Method:

This method involves the interaction between lipids, dissolved in an organic solvent, and herbal extracts present in the aqueous phase. Phospholipids, solubilized in diethyl ether, are gradually introduced dropwise into the aqueous solution containing the phytoconstituents intended for encapsulation. This process facilitates the formation of vesicular structures upon the subsequent removal of the solvent, resulting in phytosomal complex formation. The structural characteristics of the phytosomes are influenced by the concentration of the components; at lower concentrations, monomeric amphiphilic structures are typically formed, whereas higher concentrations may lead to the generation of a diverse array of vesicular morphologies, including spherical, cylindrical, disc-shaped, cubic, or hexagonal forms.[27]

Mechanical Dispersion Method:

In this technique, lipids dissolved in an organic solvent are brought into contact with an aqueous phase containing the drug. Initially, phosphatidylcholine (PC) is dissolved in diethyl ether and then gradually injected into the aqueous solution containing the phytoconstituents intended for encapsulation. The organic solvent is subsequently removed under reduced pressure, resulting in the formation of a phyto-phospholipid complex.[28]

Salting Out Technique:

A significant method for phytosome preparation involves dissolving both phosphatidylcholine (PC) and the plant extract in an appropriate organic solvent, followed by the gradual addition of n-hexane until precipitation of the extract-PC complex is achieved.[24]

Selection of Dosage Form for Delivery Of Phytosome:

The selection of an appropriate formulation or dosage form for phytosome delivery should be guided by its capacity to enhance the effectiveness and efficiency of the incorporated bioactive compound. The chosen dosage form should support sustained therapeutic activity of the herbal constituents, thereby promoting systemic efficacy. Key factors to consider include the physicochemical properties of the herbal drug (e.g., hydrophilicity or hydrophobicity), the surface characteristics of the delivery system (such as permeability and surface charge), as well as parameters like biodegradability, tonicity, desired release profile, and the target particle size of the final formulation. Phytosomes can be developed for both oral and topical administration routes.[29]

Topical Drug Delivery:

In recent years, the topical route of drug administration has gained significant attention due to its non-invasive nature and high bioavailability. This route enables direct delivery of the drug to the target site, thereby bypassing hepatic first-pass metabolism and minimizing gastrointestinal tract-related complications.[30]Topical drug delivery refers to the administration of a pharmaceutical formulation directly onto the skin for the localized treatment of dermatological conditions. This route is particularly employed when alternative methods of drug administration—such as oral, sublingual, rectal, or parenteral—are ineffective or unsuitable, especially in cases involving localized skin disorders such as fungal infections. [31]A wide range of herbal extracts derived from various plant species have been investigated for their therapeutic potential in managing dermatological disorders. These natural compounds exhibit diverse medicinal properties, including antimicrobial and anti-inflammatory activities, as well as the ability to facilitate hemostasis, promote wound healing, and alleviate burns and other cutaneous conditions. Medicinal herbs have shown effectiveness in the treatment of several prevalent skin ailments such as eczema, acne, urticaria, pruritus, psoriasis, and various bacterial and fungal infections.[32]The topical drug delivery system encompasses two primary categories: externally applied topicals and internally applied topicals. Externally applied formulations are administered by spreading, spraying, or otherwise distributing them over the skin surface to protect or treat affected areas. Internally applied topicals are designed for application to mucosal membranes—such as oral, vaginal, or rectal tissues—to exert localized therapeutic effects. The key advantages of topical drug delivery include bypassing first-pass hepatic metabolism, minimizing gastrointestinal incompatibilities, enabling site-specific drug targeting,enhancing patient compliance, allowing for convenient self-administration, and facilitating the use of drugs with short half-lives or narrow therapeutic indices. Additionally, this system permits the prompt discontinuation of therapy when necessary. [33]

The topical drug delivery system presents several limitations, including the potential for skin irritation, contact dermatitis, and allergic reactions. Additionally, drug permeability through the skin is often limited, particularly for compounds with large molecular sizes, which are not readily absorbed. The skin's structure is inherently thick and complex, posing a significant barrier to drug penetration. For a molecule to

reach systemic circulation, it must traverse the stratum corneum, any endogenous or exogenous substances present on the skin surface, the viable epidermis, the papillary dermis, and finally, the capillary walls. Once absorbed, the compound enters the bloodstream or lymphatic system, where it is subsequently cleared from the skin. This multilayered diffusion process presents substantial analytical and formulation challenges. [34]

Routes of Drug Penetration:

Drug transport across the skin can occur via three principal pathways: through the sweat ducts, through hair follicles and associated sebaceous glands (collectively referred to as the transappendageal route), or directly across the continuous stratum corneum via the transepidermal route. Within the transepidermal pathway, two distinct mechanisms are recognized: the intercellular route, which involves diffusion through the lipid matrix between corneocytes, and the transcellular route, which entails passage through both the corneocytes and the intervening lipid domains. [35,36]It is important to recognize that these penetration pathways are not mutually exclusive; a drug may utilize multiple routes simultaneously, depending on its physicochemical characteristics. The transcellular pathway is considered a polar route through the stratum corneum, as corneocytes contain an intracellular keratin matrix that is relatively hydrated and thus polar in nature. Consequently, drug permeation via this route requires successive partitioning between the polar intracellular environment of the corneocytes and the surrounding lipophilic intercellular regions. This pathway is generally more favorable for hydrophilic compounds, although the permeant must still traverse intercellular lipid domains to move from one corneocyte to the next. [37]

Although the transcellular route offers a more direct pathway, drug transport across the stratum corneum is predominantly mediated via the intercellular route, which represents the only continuous diffusion pathway. In this mode of transport, the effective diffusional path length significantly exceeds the actual thickness of the stratum corneum (approximately 10–15 µm) due to the highly tortuous nature of the intercellular lipid matrix, potentially extending to over 150 µm. Within these intercellular spaces, permeating molecules must navigate through alternating lipophilic regions (lipid cores) and hydrophilic regions (polar head groups) of the organized lipid bilayers. [38]Although skin appendages such as glands and hair follicles have traditionally been regarded as low-resistance shunt pathways, their overall contribution to transdermal drug delivery was considered minimal due to their limited coverage—accounting for only 0.1–1% of the total skin surface area. Nevertheless, emerging evidence suggests that the appendageal route may play a dominant role during the initial lag phase of the diffusion process. In recent years, there has been a growing interest in exploiting this pathway for targeted follicular drug delivery, particularly through the use of colloidal-based formulation strategies. [39,40]

Advances In Topical Drug Delivery:

- Topical administration is considered a highly favorable route for drug delivery, as it effectively addresses the limitations associated with other conventional routes such as oral and parenteral administration.
- Oral administration of phytoceuticals is often suboptimal due to their inherent unpleasant taste and odor, along with the potential for degradation within the gastrointestinal (GI) tract prior to absorption. In contrast, the parenteral route, while bypassing the GI tract, is associated with reduced patient compliance due to its invasive nature.[41]
- However, the primary challenge associated with topical drug delivery lies in the inherently low permeability of the skin, which serves as a significant barrier to effective drug penetration.
- Traditionally, gels—particularly hydrogels and oleogels—have been the most widely utilized dosage forms for topical drug delivery. However, recent studies have introduced a diverse array of advanced gel formulations, including niosomal gels, proniosomal gels, emulgels, bigels, aerogels, and xerogels, which have demonstrated enhanced potential in achieving optimal therapeutic outcomes.[42]

Characterization And Evaluation of Phytosome :

The performance of phytosomes within physical and biological systems is influenced by several key parameters, including particle size, membrane permeability, entrapment efficiency, chemical composition, and the quality and purity of the raw materials used. Consequently, phytosomes are typically characterized based on their physicochemical properties, such as morphology, particle size and distribution, drug loading efficiency, encapsulated volume, drug release profile, and overall chemical composition.[43]

Different Characterization Technique Used For Phytosome :

a. Visualization :

The morphological characteristics of phytosomes were examined using digital microscopy, transmission electron microscopy (TEM), and scanning electron microscopy (SEM).

1. Digital Microscopy :

The phytosome formulation was dispersed in water and observed under a digital microscope using a 400X objective lens.

2. SEM :

Approximately 5 µL of the phytosomal suspension was placed onto a coverslip, which was subsequently mounted onto a specimen stub. The samples were air-dried at room temperature. Particle size analysis was conducted using a scanning electron microscope (Sigma Scan, Carl Zeiss). Prior to imaging, the samples were coated with a thin layer of platinum under vacuum pressure. The coated specimens were then visualized and photographed using a JEOL JSM-6701F field emission scanning electron microscope (FE-SEM).[24]

b. Vesicle Size And Zeta Potential :

Particle size and zeta potential can be measured using dynamic light scattering (DLS), which employs a computerized analysis system in conjunction with photon

correlation spectroscopy (PCS) for precise characterization. [44]

c. Entrapment Efficiency :

The entrapment efficiency of a drug within phytosomes can be quantitatively assessed using the ultracentrifugation method. [45]

d. Drug Content :

The drug content can be quantified using a modified high-performance liquid chromatography (HPLC) method or an appropriate spectroscopic technique. [46]

e. DSC :

The sample containing phospholipon and phytosomes was placed in an aluminum crimp cell and heated at a rate of 100 °C/min from 0 to 400 °C under a nitrogen atmosphere using a differential scanning calorimeter (DSC) (TA Instruments, USA, Model DSC Q10 V24.4 Build 116). The onset temperatures of the thermal transitions were recorded using the system's analytical software.

f. FT-IR :

Spectral analysis was conducted to evaluate the structural characteristics and chemical stability of the extract, phosphatidylcholine (PC), and the phytosome complex. The spectra were recorded within the range of 4000 to 500 cm^{-1}. [24]

CONCLUSION:

Due to the side effects of synthetic drugs, people are moving towards the herbal drug but the lack of absorption and bioavailability problems in GI tract, require another route of drug administration. In this review study we gather the knowledge on topical drug delivery by using the phytosome technology. The lipid-based composition and nanovesicular characteristics of phytosomes facilitate enhanced transdermal penetration compared to the application of phytochemical extracts in their free form.So we conclude that from above review, topical delivery of phytochemical using phytosome as carrier enhance the bioavalability and cross the biological membrane easily due to their phospholipids composition.

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