Phytosomes: A Cutting-Edge Platform for Phytochemicals Delivery by Enhancing Bioavailability

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ABSTRACT

The word "Phyto" signifies plant, while "some" is for cell. This innovative patented technology involves combining plant extracts or hydrophilic phytoconstituents with phospholipids to create lipid-suitable molecular complexes, resulting in not only enhanced absorption but also bioavailability. Extensive research has been conducted by various scientists to explore the transdermal way as an excellent method for delivering phytoconstituents. Phyto products or Phyto extracts are gaining significant consideration as dietary complements in managing inflammation, toxicity, cancer, weight loss, and various chronic degenerative conditions. Nevertheless, continuous advancements and studies are being conducted in this fieldthese products frequently encounter issues with stability and bioavailability. Once extracted, plant products become susceptible to instability and may not be suitable for passage through a biological membrane. This technique enhances the hydrophilicity of highly lipophilic drugs, manufacturing them convenient for drug delivery, and adequately enhance the lipophilicity of Phyto constituents to facilitate permeation through the bio- membrane. The use of Phytosomes for beautifying purposes has already been scientifically established. Additionally, this review offers a relative analysis of liposomes and Phytosomes, highlighting current developments in Phytosomes technology, mostly in transdermal drug delivery. Incorporation of polyphenol compounds into a self-assembled phospholipid-based delivery system, known as a Phytosomes, can significantly improve their poor oral bioavailability.

Keywords: Phytosomes, phospholipid complex, bioavailability, phytoconstituents, nanocarrier.

INTRODUCTION

Phytochemicals are natural bioactive compounds produced by plants, which react with various elements of living creatures to provide useful effects. These compounds, including phenolics, alkaloids, carbohydrates, terpenoids, and other nitrogen-containing compounds, have different structures and are categorized as phytochemicals [1-5]. Additionally, differentiations in biogenesis or biosynthetic pathways result in different kinds of phytochemicals. Only phytochemicals with active H_2 atoms, such as polyphenols, can be incorporated into the structure of plants. Polyphenols, a foremost group of plant chemicals commonly found in plant-based foods, have demonstrated potential health effects in various studies. diseases including malignance, inflammation, neuron degeneration and heart diseases, type 2 diabetes and overweight [6-10]. In fact, they consist of sugar residues attached to the hydroxyl group; On the other hand, sugar residues and aromatic carbon can form direct bonds. Polyphenols can be divided into two primary groups: flavonoids and non-flavonoids. This review centers on the

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usage of Phytosomes to utilize polyphenols, including their structure, research, and biological processes associated with the uptake of phytochemical-rich Phytosomes [10-17]. Because of their small size (1-100 nm) and large volume, nano-based preparations can improve therapeutic efficacy. This carrier can be utilized for the intended delivery spot in addition to its size and shape. Furthermore, a variety of nanocarriers have been investigated for delivery, including liposomes, micellar systems, metallic and polymeric nanoparticles, nanostructured lipid carriers, and nano and microemulsions. The qualities of drug release, bioavailability, and consistency can all be enhanced by these nano-based transporters. At the moment, safe and sustainable nano-based formulations are also being investigated [18-25].

Principle of Phytosomes

An ordinary extraction or polyphenolic element in a nonpolar solvent combined with a stoichiometric quantity of phospholipid results in the creation of Phytosomes [26]. The flavonoids and terpenoids present in the extract enable direct complexation with phosphatidylcholine. A lipophilic phosphatidyl and a hydrophilic choline group come together to form a bivalent phosphatidylcholine molecule. The choline portion of the phosphatidylcholine molecule attaches to phytocomponents, while the lipophilic phosphatidyl moiety's body and tail encase the choline-bound substance [26-29]. Consequently, phytoconstituents develop lipid-compatible molecular complexes with phospholipids, also referred to as Phyto-phospholipid complexes. The decreased bioavailability and absorption of polyphenolic components can be attributed to two primary reasons. Firstly, these major components are composed of molecules with multiple rings that are too bulky to be absorbed through diffusion. Secondly, flavonoid molecules, the primary constituents of polyphenols, have low solubility in lipids, which hinders their passage through the cellular membrane [30-35].

Different Methods of Preparation of Phytosomes:

Phytosomes are advanced forms of herbal formulations that increase the absorption and bioavailability of phytochemicals. These are prepared by complexing the hydrophilic phytoconstituents with hydrophobic phospholipids. Various methods can be employed to prepare phytosomes, each with unique steps and benefits. Here are a few common methods:

Solvent evaporation method: The solvent evaporation method involves combining phosphatidylcholines and active pharmaceutical ingredients (APIs) or phytochemicals on a common circular base. This mixture is heated at a constant temperature for a specific duration and dissolved in a suitable solution. The resultant complex can be obtained by evaporating the solvent under vacuum conditions [36-38].

For instance, researchers developed phytosomes containing mitomycin C (MMC) complexed with soybean phosphatidylcholine using the solvent evaporation method. They dissolved 10 mg of MMC powder and 30 mg of soy phosphatidylcholine (SPC) in 12.5 ml of tetrahydrofuran (THF). This solution was stirred in a glass pressure vessel for 4 hours at 40°C, resulting in a light magenta mixture. Subsequently, THF was removed using a rotary evaporator and rotary vacuum evaporation techniques [39-45].

This process ensures the formation of phytosomes, enhancing the bioavailability and efficacy of the active compounds like MMC.

Anti-solvent precipitation method: The anti-solvent precipitation method is widely used for Phytosome preparation, leveraging soy milk (a plant-based milk rich in nutrients) and lecithin (a natural phospholipid mixture) irradiated with dichloromethane. Afterward, N-hexane is added to the resulting precipitate for overnight desiccation in vacuum desiccators. This process incorporates Icariin (a flavonoid from Epimedium) into ICA-Phytosomes through solvent precipitation. Precisely weighed ICA and Phospholipid 90H in dichloromethane produce a concentrated solution, irradiated as per experimental

parameters. The Phytosomal extract is obtained via lyophilization for 72 hours, stored briefly in an airtight amber glass container for subsequent use. This method's efficiency and standardization are evidenced by its widespread use and detailed experimental protocols [48-53].

Lyophilization method-

Lyophilization, or freeze-drying, is vital in creating Phytosomes. It starts with a solution of the active compound and phospholipids (like Soy Phosphatidylcholine, SPC), often with a solvent like Dimethyl sulfoxide (DMSO). These form a stable complex due to their chemical affinity. The solution is frozen to solidify the complex, then subjected to lyophilization, removing the frozen solvent under vacuum. This transforms the complex into Phytosomes, which are dried and stored for use in pharmaceutical or nutraceutical products. Phytosomes, with enhanced bioavailability, are achieved through this process by improving absorption and delivery of the active compound [54-60].

The figure labeled as "Figure 1" presents a graphical depiction of the preparation process of Phytosomes.

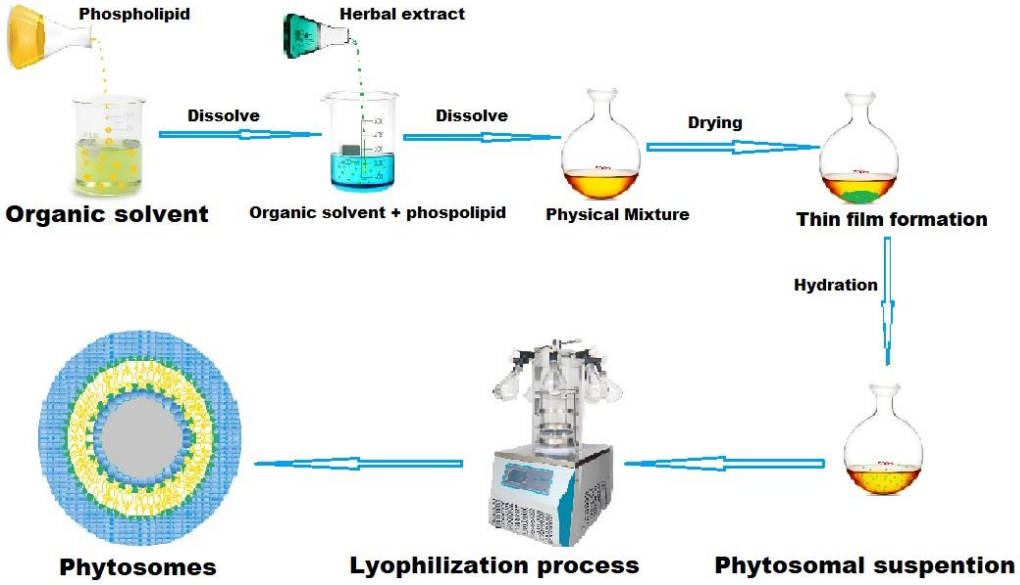

Figure1: Graphical presentation of preparation of Phytosomes.

Biological Properties of Phytosomes:

Phytosomes exhibit several biological properties that make them advantageous in various applications. Phytosomes, a technology integrating drugs, are utilized to address various medical conditions

Cardiovascular properties- Phytosomes are effective in treating peripheral vascular diseases such as Raynaud's disease and coronary artery disease. They also exhibit leuko-selective activity, reducing oxidation and oxidative stress damage to low-density lipoproteins, yielding positive results [61-63].

Anti-inflammatory properties- Phytosomes complex shows better anti-inflammatory activity than complex plant extract. Croton oil-coated dermatitis was used to evaluate the anti-inflammatory activity of the Phytosome complex in animals involving tissue and blood vessel damage. Glycyrrhizin acid, a potent anti-inflammatory agent, contributed to these beneficial outcomes [64-66].

Anti-ageing property- Phytosomes as a delivery system offers interesting applications and opens new

possibilities for the use of APIs in cosmetics [67]. G. biloba Phytosomes has been studied for the treatment of skin aging related to superficial capillary circulation. Ginkgo biloba extract is commonly taken orally to enhance peripheral circulation, while phospholipid complexes have been discovered to enhance skin microcirculation when applied topically. Microcirculation associated with dystrophic changes of the epidermis and dermis is activated in ameliorative skin aging [68-70].

Hepatoprotective property- Milk thistle (Silybum marianum) fruit flavonoids show hepatoprotective properties. Silymarin has been shown to be effective in the treatment of various types of liver diseases, including hepatitis, cirrhosis, fatty liver infiltration (chemical and alcoholic fatty liver), and inflammation of the biliary tract [71-74].

Anti-cancer property- Formulations containing Phytosomes have important pharmacological benefits, such as anti-inflammatory, antioxidant, and neuroprotective properties, and can improve the penetration and bioavailability of phytoconstituents. Although it has been studied as an anticancer agent in the treatment of many types of tumours [75-79].

Physicochemical Properties:

The physicochemical properties of Phytosomes encompass a range of characteristics:

1. The stoichiometric number of phospholipids is mixed with a standard Phyto extract as a substrate to form Phytosomes. The reaction between the phospholipid and the substrate involves the formation of H_2 bonds between the charged head of the phospholipid and the polar function of the substrate [80-83].
2. When the Phytosomes is disclosed to water, it forms micelles like liposomes, and photon correlation spectroscopy (PCS) shows that the Phytosome has this liposome structure [84].
3. Phytosomes vary in size from 51 nm to several 100 meters [85].
4. Using H1 NMR and C13 NMR data, ~~it was found that~~ fatty chains emit similar signals in free and complexed phospholipids. This suggests that the API is placed in a long aliphatic chain, creating a lipophilic envelope [86-88].

Characterization of Phytosomes-

Spectroscopy- Complex and molecular reactions of phytoconstituents and phosphatidylcholine in solution were studied by 1H-NMR, 13C-NMR, P-NMR, and Infrared spectroscopy. Complex development is related with changes in the chemical shift and line broadening of several characteristic signals in the nuclear magnetic resonance spectrum as well as the appearance of non-correlated IR spectrum [89-93].

Zeta potential- Determining the charge of Phytosomes in emulsions, which can be negative, positive, or neutral based on composition. A zeta potential greater or less than 30 mV indicates stability [94-98].

Thermal Analysis (TGA/DSC))- Determination and measurement of temperature effects such as fusion, solid-solid transition, glass transition, solvent loss and dispersion can be utilized to characterize solid Phytosome [99,100].

Entrapment efficiency- Assessing drug entrapment using ultracentrifugation and calculating efficiency (%) based on actual vs. theoretical drug amounts [101].

Particle size- Particle size and zeta potential are significant complex properties related to stability and reproducibility. Typical particle sizes of phospholipid complexes vary from 50 to 100 nm [102,103].

Advantages and Disadvatages of Phytosomes**:** Phytosomes have enhanced bioavailability, better absorption, and controlled release compared to traditional formulations, making them beneficial in pharmaceutical and cosmetic fields. They improve the solubility of poorly water-soluble compounds, expanding their applicability to various drugs and herbal extracts [104-110].

However, Phytosomes are complex and costly to prepare, requiring specialized equipment and expertise. Their stability over time can also be a concern, impacting

quality and shelf-life. Despite these challenges, Phytosomes remain valuable for enhancing drug delivery and efficacy, albeit requiring careful consideration of cost-effectiveness and stability [111].

Dosage Form of Phytosomes-

1. **Soft gelatin capsule**-These types of Phytosomes are developed in the form of heterogeneous mixtures (suspensions) with phytoconstituents as a dispersed phase such as vegetable oil or semi-synthetic oil as a dispersing media and are used to make soft gelatin phytosomes capsules for oral drug delivery e.g.- Curcumin Phyto some [112,114].
2. **Hard gelatin capsule**- Phytosomes can be used directly in the volumetric process. In powder form, it can be poured into hard gelatin capsules. For low density Phytosomes, the capsule size should not exceed 300 mg and should be zero size [115].
3. **Tablet**- Phyto-phospholipid complex powder ideal? cannot have better technological properties due to its potential viscosity, flowability and low apparent density. When the direct compression process is used for the material, it must be diluted by 60-70% of the binder and its physical and chemical properties must be optimized. For primary processing, a dry granulation process may be optimal to achieve dose uniformity and optimal bioavailability. To put it differently, it is advisable to steer clear of the wet granulation process because water and heat (utilized for granulation/drying) have an adverse impact on the constancy of the phospholipid complex [116-120].
4. **Topical dosage form**- Phyto-phospholipid complexes can be manufactured mainly in the form of creams, gel, or ointments. The innovative process, which includes a complex of Phytosomes, dispersed in a minor amount of oily phase and added to the emulsion has been formed at a low temperature (not higher than 40 °C). If the outer phase is an aqueous phase, the Phyto some complex can dissolve into the aqueous phase and add another formulation after 40°C [121].

Challenges in Developing Phytosome Products: —

Phytosomes have been developed as a potential nanocarrier delivery system. However, it is a lengthy method from product synthesis to successful marketing. As a substitute of all supplements, only phytosomal products were presented to the market [122]. After emerging an effective formulation, proving nontoxicity is the main obstacle to bringing Phytosomes to market. Phytosomes are an impartial biological system, so their entry into the body continues without problems related to safety or immunological effects. Nevertheless, prior to being marketed, it is imperative to thoroughly investigate various factors including bioaccumulation, biocompatibility, metabolism, and excretion due to the minuscule dimensions of these particles [123]. Curcumin was successfully synthesized in Phytosomes for intravenous administration in mice and was found to accumulate more in spleen tissue. Another factor to be evaluated is the passive targeting of healthy cells by Phytosomes binding to biological membranes. Therefore, the precise biological effects should be investigated in well-structured pre- clinical trials. Several studies in this area have discovered the biological protection of Phytosomes. After creating the Phytosomes, pharmacokinetics (pk) and pharmacodynamics (pd) test should be performed in animals and humans to confirm its advantage over purity of phytocomponents. Identifying the finest dosage form to maximize absorption and potency of the Phytosomes is another step for commercialization.

Additional task is the large-scale manufacturing of Phytosomes. However, the properties of the product must be maintained during upscaling. This relates to laboratory protocol practices in production settings. However, the method to produce some types of Phytosomes is sometimes easy compared to pH-sensitive Phytosomes; Low physical and chemical stability makes commercial production difficult. Similar to pharmaceuticals, Phytosomes must be able to reproduce and their properties must be tested over time. Popularity is another reason for

effective product marketing. Taken together, the biocompatibility, cost and safety of phytochemicals have influenced people to such treatments in recent years. Furthermore, due to the simple production method and the ease of commercializing phytosomal technology on a business scale of Phytosomes is a fast process [124].

Structure of Phyto-Phospholipid Complexes-

According to Bombard Elli's theory, phospholipids can combine stoichiometrically with APIs that are isolated from plants to form phospholipid complexes. This preliminary explanation of Phyto-phospholipid complexes has been questioned in light of later research. We have suggested a recent list of the four necessary elements depend on the literature: solvents, Phyto-APIs, phospholipids, and the stoichiometric proportion tangled in the creation of Phyto-phospholipid complexes.

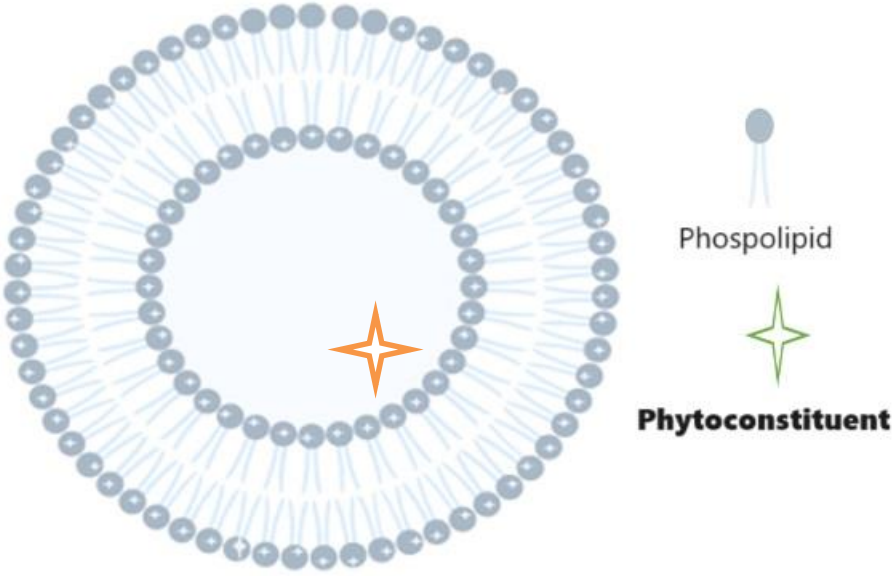

Figure 2: Phytosomes as Carriers for Herbal Drugs

Plant seeds and egg yolk are rich in phospholipids. Phospholipids made in an industrial setting are already accessible. Depending on the backbone, phospholipids can be classified as Glycerophospholipids or sphingomyelins (PC), phosphatidylethanolamine (PE), phosphatidylserine (PS), phosphatidic acid (PA), phosphatidylinositol (PI), and phosphatidylglycerol (PG) are additional glycerophospholipids.

The main phospholipids used to manufacture complexes with a water-soluble head group and two lipid soluble hydrocarbon chains are PC, PE, and PS. The most often utilized phospholipid among these is PC, which is utilized to create phospholipid complexes. the PC is structured as follows. One of PC's advantages is its amphipathic qualities, which allow it to dissolve somewhat in lipid and water-based environments. Furthermore, PC has strong biocompatibility and minimal toxicity because it is a necessary part of cell membranes. PC molecules have been shown to demonstrate clinical benefits in the treatment of and exhibit hepatoprotective properties include hepatocirrhosis, fatty liver, and hepatitis.

Phyto-active Constituents-

Rather than in vivo activities, scientists frequently designate the APIs of plant extracts based on strong in vitro pharmacological effects. These substances are mostly polyphenols. The medications made of polyphenols are

displayed below. cirantin is one of the physiologically active elements of plants that has a preference for the water phase and is impotent to cross bio-membranes. However, some, like rutin and curcumin, are very lipid soluble and not able to dissolve in aqueous phase and in gastrointestinal fluids. In addition to increasing lipophilic solubility in water phase, Phyto-phospholipid complexes to increase hydrophilic polyphenols' ability to pass across membranes from a water phase. Moreover, the formation of complexes can shield polyphenols from degradation [124].

Solvents-

Solvents of different kinds have been effectively explored. Ethanol is a common and helpful solvent that leaves behind phospholipid complexes when the yield is high enough. less damage and leaves less residue behind. Certain liposomal drug complexes function when H_2O or buffer solution is present, allowing the Phytosomes to be mixed with a solvent that has a lower dielectric constants technique has been implemented in numerous studies recently to control the morphology, size. One of the SCF technologies that is showing promise for manufacturing micro and sub micro particles with regulated sizes and size distributions is the supercritical anti solvent method (SAS) [124].

Stoichiometric Ratio of Active Constituents and Phospholipids-

The stoichiometric ratio of active constituents to phospholipids varies, with ratios ranging from 0.4:1 to 1.9:1 commonly used for phospholipid complexes. While a 1:1 ratio is often considered optimal, other ratios like 1:10, 1:15, and even 3:1 have been tested, with some studies showing better results at non-1:1 ratios. Therefore, a 1:1 ratio may not always be the most effective when creating phospholipid compounds.

Reaction Between Active Constituents and Phospholipids-

The chemical interaction between flavonoids and phospholipids was discovered in 1989 by Bombard Elli, resolving previous debates on Phyto-phospholipid complex formation. Molecular analysis revealed that the hydrogen bond formation between the polar head and polar functionalities of the Phyto API drives the phospholipid-API interaction in these complexes. When combined, phospholipid complexes with free active constituents show enhanced absorption and higher bioavailability. This discovery has sparked increased interest in Phytosome creation, particularly in the pharmaceutical industry where phytosomal formulations are extensively used. Marketed products based on Phytosomes, such as curcumin Phytosomes for antioxidants and green tea leaf Phytosomes for weight management, exemplify this trend [123, 124].

Factors influencing Phospholipid Complexes include solvent proportion of API, reaction temperature, and duration.

Complexation Rate of Phospholipid Complexes-

The complexation rate of phospholipid complexes is a critical measure in drug screening, determined by various factors such as the stoichiometric ratio of active components, temperature, duration, drug concentration, and solvent-to-phospholipid ratio. The productivity (%) of the complexes can be calculated using the formula: Productivity (%) = $[(x-y)/x] \times 100\%$, where "x" represents the initial mass of the active constituent, "y" is the mass of the free active component, and "(x – y)" indicates the mass or content of the phospholipid complexes. UV spectrophotometry or HPLC methods are commonly used to assess the yield of these complexes.

Industrial application of Phytosomes-

Phytosomes, formed by combining phospholipids with plant extracts like glycosides, flavonoids, and terpenoids, are advanced liposomes with excellent skin penetration and lipid content, making them ideal carriers and skin-nourishing agents in herbal cosmetics. Their chemical bonds with α-phosphatidylcholine and plant constituents enhance stability and absorption, reducing dosage requirements. Commercial products like Ginkgo biloba terpenes, known for their anti-inflammatory and calming

effects, are available in Phytosome-based topical formulations. Italian pharmaceutical companies are leading in Phytosome products, using standard plant extracts like polyphenols and terpenoids to address various health issues. Manufacturers like Natural Factors (Canada) and Nature's Herbs (USA) offer a range of Phytosome formulations with details on source, dosage, and pharmacological activity. Table 1 presents the Marketed Products of Phytosomes, while Table 2 showcases Patented Phytosomes Formulations, and Table 3 details Phytosomes and Their Activity.

Table1: Marketed Products of Phytosomes

No	**Marketed Phytosomes**	**Sources**	**Biological Activity**	**Application of technology**
1.	Silybin Phytosomes	Silybum marianum	Hepatoprotective and Antioxidant	Increase in therapeutic effect
2.	Ginkgo Phytosomes	Ginkgo biloba	heart protective, anti-asthmatic and anti-glycaemic	Increase hepatoprotective effect
3.	Ginseng Phytosomes	Panax ginseng	Nutraceutical, Immunomodulator	Increase absorption
4.	Green tea Phytosomes	Camellia sinensis	Nutraceutical, antioxidant, Anticancer	Increase absorption

Table 2: Patented Phytosomes Formulation

Serial Number	**Patent Name**	**Description of Innovation**	**Patent Number**
1.	Olive fruit phospholipid complex or extract composition deposit	Increase bioavailability	WO/2007/118631
2.	treatment of aging and skin damage by cosmetic preparation	topical treatment by cosmetic and dermatological composition	EP/1640041
3.	plant-based antioxidant preparation transfer	For treatment of adiposity problems	US/6756065
4.	wound healing by thymosin beta-4	Thymosin beta-4 for skin and wound healing	US/2007/0015698

Table 3: Phytosomes and Their Activity

Phytosomes	**Phytosomes Activity**
Curcumin	Wound Healing
Rutin	Anti-carcinogenic, Vaso protective
Houttuynia cordata	Anti-ageing, Anti-inflammatory
Silymarin	Free Radical scavenging
Grape seed extract	Reduce oxidative stress
Green tea	Anti-oxidant

Conclusion- Phytosomes is an advanced form of herbal drug administration technology that can control the disadvantages associated with regular dosage forms, such as bioavailability issues, dose omission, and site-specific delivery. Initially, this concept was used by the cosmetics industry. Today, its importance as a plant carrier has emerged in the pharmaceutical, pharmaceutical and preservative industries. Although many herbal medicines eliminate the root cause of the disease, it is hard to achieve therapeutic effectiveness. Therefore, the Phyto-

phospholipid complex of small size delivers active action directly to the site of need and acts with minimal side effects associated with minimal synthetic drugs. Phospholipids form complexes with Phyto active substances and keep active by forming bonds, thereby feeding lipophilic and hydrophilic components to the membrane. The formulation method for Phyto some is easy and can be quickly scaled up to commercial scale. It is commonly employed in both oral and topical medications, enhancing stability and improving their efficacy as narcotics.

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الفايتوزومات: منصة متطورة لتوصيل المواد الكيميائية النباتية من خلال تعزيز التوافر البيولوجي

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ملخص

كلمة "phyto"تعني النبات، بينما كلمة "some"تعني الخلية .تتضمن هذه التقنية المبتكرة الحاصلة على براءة اختراع الجمع بين المستخلصات النباتية أو المكونات النباتية المحبة للماء مع الدهون الفوسفاتية لإنشاء مجمعات جزيئية مناسبة للدهون، مما يؤدي ليس فقط إلى تعزيز الامتصاص، ولكن أيضًا إلى التوافر البيولوجي .تم إجراء أبحاث واسعة النطاق من قبل العديد من العلماء لاستكشاف الطريقة عبر الجلد كوسيلة ممتازة لتوصيل المكونات النباتية .تحظى منتجات Phyto أو مستخلصات Phyto باهتمام كبير كمكملات غذائية في إدارة الالتهابات والسمية والسرطان وفقدان الوزن ومختلف الحالات التنكسية المزمنة .ومع ذلك، يتم إجراء تطورات ودراسات مستمرة في هذا المجال .كثيرًا ما تواجه هذه المنتجات مشكلات تتعلق بالاستقرار والتوافر البيولوجي .بمجرد استخراجها، تصبح المنتجات النباتية عرضة لعدم الاستقرار وقد لا تكون مناسبة للمرور عبر الغشاء البيولوجي .تعمل هذه التقنية على تعزيز محبة الماء للأدوية شديدة المحبة للدهون، وتصنيعها بشكل مناسب لتوصيل الدواء، وتعزيز محبة الدهون للمكونات النباتية بشكل مناسب لتسهيل التخلل عبر الغشاء الحيوي .لقد تم بالفعل إثبات استخدام الفايتوسومات لأغراض التجميل علميا .بالإضافة إلى ذلك، تقدم هذه المراجعة تحليلًا نسبيًا للجسيمات الشحمية والفايتوسومات، مع تسليط الضوء على التطورات الحالية في تكنولوجيا الفايتوسومات، ومعظمها في توصيل الأدوية عبر الجلد .يمكن أن يؤدي دمج مركبات البوليفينول في نظام توصيل قائم على الفوسفوليبيد مُجمَّع ذاتيًا، والمعروف باسم الفايتوسومات، إلى تحسين التوافر البيولوجي الضعيف عن طريق الفم بشكل كبير.

الكلمات الدالة: الفايتوسومات، مجمع الفسفوليبيد، التوافر البيولوجي، المكونات النباتية، الناقل النانوي.

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