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Phytosome based cosmeceuticals for enhancing percutaneous absorption and delivery

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ABSTRACT: The therapeutic efficacy of various phytoconstituents is improved by the use of phytosome, innovative drug delivery methods based on phytochemicals, by enhancing their absorption, bioavailability, and therapeutic availability. This exceedingly complex type of herbal formulation contains the active phytoconstituent of the herbal extract and is joined by a phospholipid molecule. They also operate as vesicular systems for a wide range of fascinating and important phytoactives. The phytosome method produces startlingly tiny spheres or cells, which is advantageous in keeping active phytochemical contents from being destroyed by the stomach environment. Phytosome also produce pharmacokinetic and pharmacodynamic effects that are more potent than those of conventional herbal extracts.
Phytosome demonstrated increased pharmacokinetics and pharmacodynamic response when compared to conventional botanical extracts. Through the use of phytosome technology, the bioavailability of several of the most widely used herbal extracts, such as milk thistle, Ginkgo biloba, grape seed, green tea, hawthorn, ginseng, etc., has been improved. These drug-phospholipid complexes can be produced as a liquid solution, suspension, emulsion, syrup, lotion, gel, cream, tablet, capsule, powder, or granule. The purpose of this review is to emphasize the application of how the phytosome technology has helped to improve the bioavailability and absorbance of the cosmeceuticals.

KEYWORDS: Phytosome; Phytoconstituents; Cosmeceuticals; Herbal extracts; Bioavailability

1. INTRODUCTION

"Phyto" refers to plant, and "Some" refers to a cell. Herbosomes is another name tha has been given for the word phytosome [1]. This are the brand-new, patented technology that combines standardized plant extracts of water-soluble phytoconstituted compounds with phospholipid molecules to create lipid-compatible molecular complexes, as it helps in greatly enhancing the dosage's absorption and bioavailability. The phytosome give an envelope,like covering around the dynamic constituent of medication and because of this the main constituent of herbal extract remainsprotected from debasement by stomach related emission and microorganisms. Phytosome is successfully ready to retain from a water cherishing climate into lipid cherishing climate of the cell film lastly coming to blood dissemination [2]. A study using different plant extracts as isolated compounds for a delivery vehicle for phytosome based cosmeceuticals formulations was done that contained a skin-whitening ingredient that is controlled to inhibit the tyrosinase enzyme was done. The solvent evaporation, thin film hydration, solvent evaporation-lyophilisation, and antisolvent precipitation methods are some of the techniques that are used to prepare the phytosome delivery system. The phytosome system is composed of the double-layer phospholipid complex, and phosphatidylcholine becomes a major carrier [3].

Many organic products have been proving to be safer and more efficient than synthetic medications. However, due to poor oral bioavailability, several active plant constituents are being contested for

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therapeutic usage. There are a few significant explanations behind the expanded utilization of home grown drugs:

1) current medication can't productively fix every one of the human pathologies,
2) there are expanding interests and consideration over the confirmation and security of engineered medications, and
3) numerous regular items are being displayed to create improved results than manufactured drugs without unfriendly effects.

Be that as it may, because of unfortunate oral bioavailability, the clinical use of various dynamic builds of plants is under debate. The feeble retention pace of such constituents might be a consequence of low lipid solvency, the presence of multi rings polyphenols in their designs, and high sub-atomic weight. Various arrangements have been proposed to face such obstacles, including getting ready emulsions, and nano-formulation, the change of atomic structure, and organization of prodrugs. Between all methodologies, phyto-phospholipid edifices (named phytosomes) are seemed, by all accounts, to be an extraordinary strategy to help their bioavailability. [4]. Some of the benefits of phytosome delivery system like the high drug encapsulation, high stability profile, high bioavailability, and high chemical bonds formation with the polar head (phytosome) as well as amphiphile of phytosomes [5]. The bulk of molecules in plants that are physiologically active belong to polar or water-soluble compounds. Various phytoconstituents present in phytosomes like Flavonoids, tannins, terpenoids, and many other phytoconstituted molecules are poorly absorbed due to their large molecular size, which prevents passive diffusion from taking place, or due to their poor lipid solubility, which severely limits the capacity to pass via lipid-rich biological membranes and results in poor bioavailability [6].

A complex sort of plant extract known as phytosomes produces a substance known as phospholipid.Phytosomes are made to improve the bioavailability of medications. Phytosomes were created for the first time by the Italian company Indena in the late 1980s [7].

1.1. Plant constituents/ Plant substance

A phytochemical is a type of bioactive substance created by plants as a form of defense. Whole grains, fruit and vegetables, nuts, herbs, and a wide range of other plants contain phytochemicals. There are currently over a thousand distinct phytochemical substances known. Among the most crucial are Carotenoids Polyphenols isoprenoids, phytosterols, saponins, consumable fibers, and polysaccharides[8].

The non-nutrients known as phytochemicals are made by plants to protect themselves from microbial and insect attacks. They also tend to protect people from a variety of chronic ailments, such as cancer and heart disease [9]. While numerous plant-based phytoconstituted substances have historically been employed to treat a variety of skin conditions, including eczema, acne, and skin eruptions, the current emphasis in dermatology and cosmetology is on the utilization of naturally bioactive compounds in a variety of curative and cosmetic applications [10]. Herbal extracts comprise plant-derived compounds that are increasingly utilised in contemporary treatments as well as conventional home cures. The strong polarity of some plant-derived compounds with lengthy side chains, however, prohibits them from bypassing lipid skin by passive diffusion [11].

The majority of compounds found in phytoconstituted substances including flavonoids, terpenoids, and polyphenols are polar or water-soluble. Because these chemicals are poorly solublility they cannot pass through the extremly lipid-rich bio-molecular systems so, water-soluble phytochemicals is poorly absorbed. Many methods have been devised to increase bioavailability, such as structure modification, entrapment in lipophilic carriers, integration of solubility and bioavailability enhancers, etc. The bioavailability of active components appears to be strongly influenced by the chemical complexities of the raw extract or minimally purified extract. Oral absorption of some water-soluble extracts is possible but he gastrointestinal tract may degrade some components [12].

Phytosomes are crucial for boosting bioavailability and enhancing absorption. One of the most popular ways to improve the bioavailability in plant-based pharmaceuticals that are poorly soluble and can pass biological membranes with the help using phytosomes as a delivery system. Despite having considerable in-vitro pharmacological activity, some plant actives do not produce the same in-vivo effects. When combined with phospholipids produced from the food to create new, amphiphagetic cellular structures, these plant-derived actives are more efficient systemically [13].

1.2 Phytosome structure

A lipid-based delivery method with a liposome-like structure is known as phytosomes. Different phytoconstituted compounds with polyphenolic bases can be captured by phytosomes to improve absorption when taken orally [14]. Standardized plant extracts are combined into phytolipids, primarily with phosphatidylcholine, to create phytosomes [7].

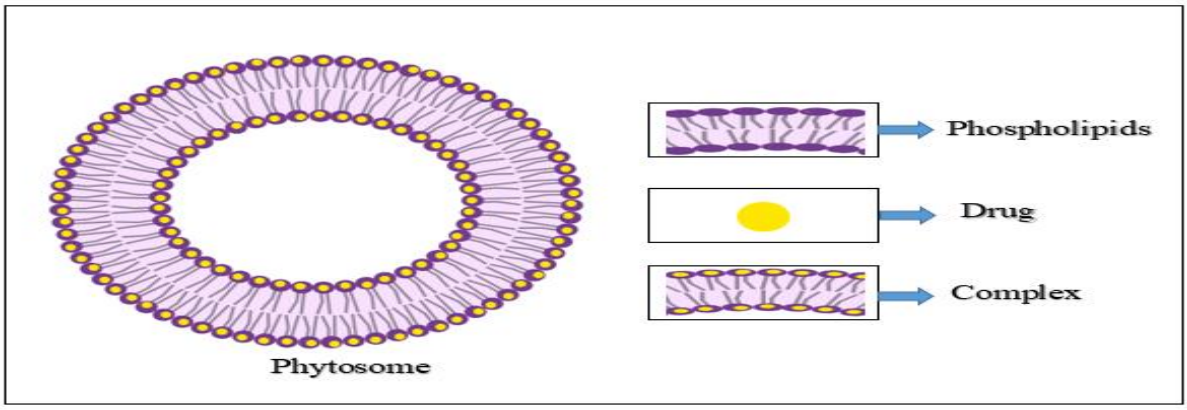

Figure 1. Structural representation of Phytosome[15].

Lipid vesicles are found in phytosomes. The phospholipid matrix phosphate group and polyphenol moiety in bioactive herbal extracts form a H-bond with each other nonpolar solvents to form the lipid vesicles[16]. Polyphenolic rings found in phytochemicals like flavonoids and terpenoids are water-soluble. To create phytosomes, these polyphenols make strong chemical bonds with the hydroxyphosphilic portion of phytolipids (choline). The phytochemicals' physical form is called a phytosome. Phytoconstitutes are created when phytochemicals link to the phospholipid moiety. The phytosomal tail is made up of phytoconstituents that bind to the phosphate moiety. Polyphenols that bind choline are water-soluble phospholipid-bound and found in phytosomal tails[17].

The encapsulation of the polyphenolic molecule into the Phytosomal Delivery System, results in greater penetration and absorption throughout the body, is a significant contributor in the increased absorption of poorly soluble substances and also ensure higher bioavailability in the biological membrane[18].

Comparing phytosomes to conventional herbal compounds, phytosomes have better pharmacodynamics and pharmacokinetics due to their capacity to work in the "lipophilic" and "hydrophilic" barriers of the skin[19]. Polyphenols derived from herbs that are used to treat a range of ailments can be enhanced by phytosomes. Because of this, phytosome nanotechnology has promise for developing novel formulations. Phytosomes are commonly created by mixing phospholipids like PC, PS, and PE with active biological phytochemicals in specified stoichiometric ratios under predetermined conditions[20].

2. COMPONENTS OF PHYTOSOMES

According to Bombardelli's idea, a stoichiometric process created phospholipids and the main component of phytosomes. The stoichiometric ratio, solvents, phytoingredients, and phospholipids are the four main components utilized to make phytosomes.

2.1 Phospholipids

The yolks of eggs and seedlings are both rich in phospholipids. Currently, industrially manufactured phospholipids can be obtained. Depending on the structure of their backbone, phospholipids can be classified as sphingomyelins or glycerophospholipids [21]. Phosphatidylcholine, phosphatidylethanolamine, phosphatidylserine, phosphatidic acid, phosphatidylinositol, as well as phosphatidylglycerol, are examples of glycerophospholipids. The major phospholipids used to construct compounds that include two hydrophobic hydrocarbon chains along with a hydrophilic head group are PE(Phosphatidylethanolamine) P(Phosphatidylcholine), and PS(Phosphatidylserine). PC is the phospholipid that is most frequently employed to make phospholipid complexes [22]. PC is only partially soluble in both aqueous and organic solutions because of its amphipathic characteristics, surroundings. PC also makes a major contribution to cell structure, this explains both its high biocompatibility and relatively low toxicity [19].

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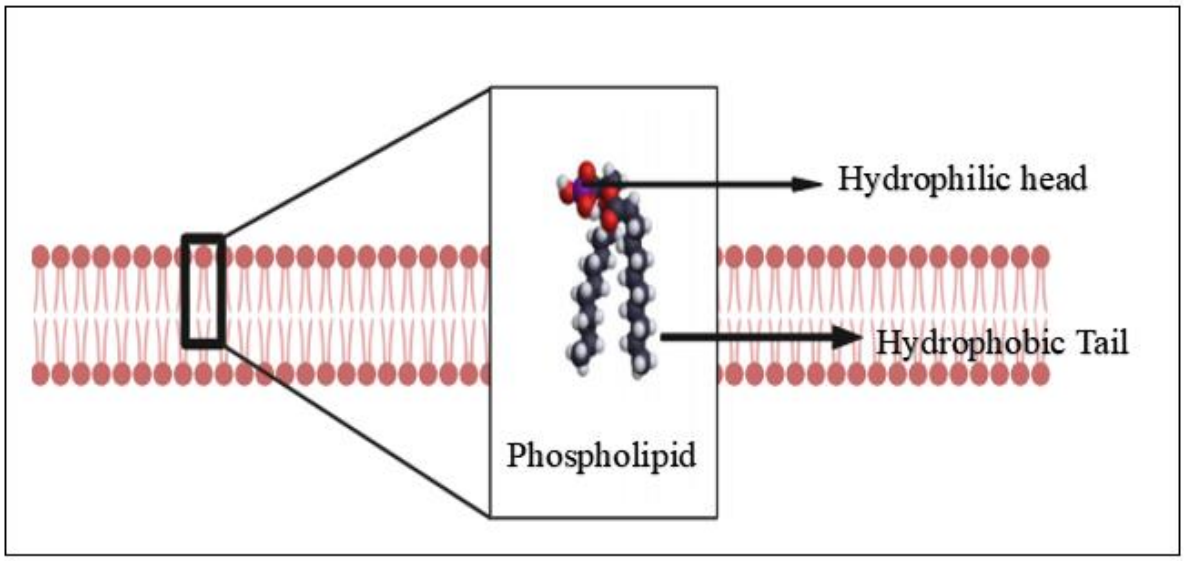

Figure 2. Representation of the phospholipid [23].

2.2. Phytoactive substances

Researchers usually categorize the main constituents of herbal materials based on their in-vitro pharmacological effects rather than on in-vivo functions. Polyphenols make up the majority of these substances. For instance, the naturally occurring polyphenol in plants called hesperidin prefers aqueous solutions and is unable to penetrate cell membranes. Some, like rutin and curcumin, are extremely lipophilic and incapable of degrading in digestive juices. In addition to enhancing the solubilisation of lipid polyphenols in water, phytosomes may improve the membrane permeability of polar polyphenols with water. Additionally, polyphenols are protected against outside forces including oxidation, hydrolysis, and photolysis by the complex formation. Any active substance can be produced using the same process; polyphenols are merely one kind of phytosome [24].

2.3. Solvents

Various solvents have been employed as the basic solution by various researchers to produce phytosomes. When creating phyto-phospholipid complexes, aprotic solvents like cyclic ethers, methylene chloride, and aromatic hydrocarbons have mainly been substituted by protic solvents like ethanol [25]. Recently, protonic solvents like ethanol and methanol have been used to successfully generate phospholipid complexes. Many solvents have been thoroughly investigated. Because it produces little waste and causes no harm, ethanol can be widely employed as a solvent when the output of phospholipid components is high enough. Some liposomal drug complexes require aqueous or buffer solutions to function properly, while phytosomes interact in a low-dielectric constant solvent. Supercritical fluids are typically used to reduce a substance's solubility. If the solvent contains a solute, carbon dioxide can be used as an anti-solvent [16].

2.4. Stoichiometric ratios of phytoactive compounds and phospholipids

Typically, the active ingredient in phospholipids is formed into phytosomes through a natural and synthetic reaction with a 0.5 to 2.0 molar ratio [26]. The ratiometric on the other hand, it is thought that the optimal ratio for forming phospholipid complexes is 1:1. Other active substances have also been used, as well as previously determined phospholipid stoichiometric ratios.

Maryana et al. created silymarin phospholipid complexes with stoichiometric ratios of 1:5, 1:10, and 1:15, and discovered that the complexes with a 1:5 stoichiometric ratio have the biggest drug and strong structural characteristics. 1.18 percent loaded. When creating phospholipid compounds with a 1:1 stoichiometric ratio, the answer is never, ever. The proportion of phospholipids to active ingredients should be modified in accordance with the various objectives for the various medications, with the most potent drug assuming the role of loading [27].

3. MECHANISM OF THE PHYTOSOME BASED DELIVERY SYSTEM

The active elements or "photoactive" in botanical extracts are excellent candidates for interacting chemically with phosphatidylcholine. Phytoconstituents, most frequently polyphenolics, saponin, and triterpenes, that can act as a site for the formation of this bond (polyphenol) with phosphatidylcholine can be transformed into phytosomes [6]. Phosphatidylcholine is a chemical with numerous uses [17]. Phosphatidylcholine, on the other hand, exhibits hydrophilic activity in nature despite having lipophilic qualities. The lipid-soluble phosphatide region, which contains the body and the tail, cover the Choline-Photochemistry site (choline-bound materials), and the choline sections of the phosphatidylcholine molecules specifically form a ligand to the phytoconstituents. As a result, it produces a molecular complex containing phospholipids that is compatible with lipids, also known as as the complex of phytophospholipids. Additionally, the rapid exchange of phospholipid acids within the bio-membrane as well as extracellular fluid transports the active ingredients into the bio-membrane, which improves its cellular capitation, while shielding them from water-activated degradation [28].

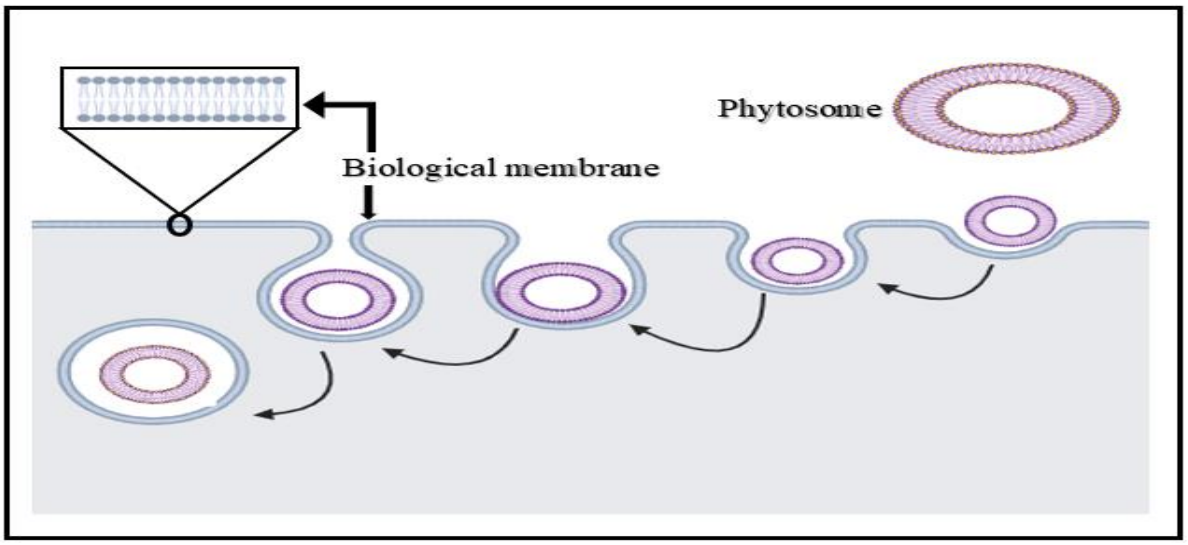

Figure 3. Mechanism of the phytosome [29].

4. USES OF PHYTOSOMES

Table 1. The table below holds the demonstration of the Phytosomes along with their phytoconstituents that are used for the cosmeceutical purpose. Production of cosmeceuticals based on phytosomes.

S.no	Source	Phytoconstituents	Cosmeceuticals Properties	Action	Reference
1	*Eysenhardtia platycarpa* leaf	Flavones are the phytoconstituents present.	Shows Enhancing Anti-Aging activity	Used for the improved anti-aging effects	[30]
2	Rice bran oil	It contains Protocatechuic acid, Coumaric acid, Caffeic acid, Catechins, Gallic acid, Ferulic acid, Hydroxybenzoic acid	Has Moisturizing effect	This can be used for Improve a number of skin conditions, including as psoriasis and atopic dermatitis	[31]
3	Lauric Acid		Possess Antimicrobial activity (skin cleanser)	Used to treat the Acne-caused by skin infections	[31]
4	Curcumin		Known for its Antimicrobial activity (skin cleanser)	Used in the treatment of Acne-caused skin infections	[31]
5	Phytoflavanoid-encapsulated poly(lactic-co-glycolic) acid		Shows Antioxidant activity	They are known to show enhanced sunscreen activity	[32]

6	Pomegranate seed oil	α- and γ-tocopherols	Has Antioxidant activity	Generally show Photodamage with enhanced antioxidant activities	[32]
7	Curcumin	cyclodextrin complex	Used as Hair growth enhancer	Helps in follicle penetration and hair growth enhancement	[33]
8	*G. biloba*	flavonolignan silybin	Anti-Aging	Can be used to decrease skin aging related to dystrophic epidermal and dermal modification and regressive abiotrophic pinnacular disease	[34]
9	*Pinus maritima* (Pine)	Procyanidins	Anti-inflammatory, Antiwrinkle, Antiallergic.	Use to inhibits the enymes which causes allergy, inflammation and wrinkles.	[35]
10	*Terminalia serica*(Silver cluster leaf)	Sericoside	Anti-aging, skin restructuring, wound healing, antioedema, anti-inflammatory	Helps in reduction in capillary permeability	[35]
11	*Centella asiatica* (Brahmi)	Asiatic acid, madecassic acid.	Skin disorders, antiulcer, wound healing, anti-hair loss agent.	Has a Protective activity on microcirculation, with reduction of abnormal increase in capillary permeability.	[35]
12	*Moringa oleifera* phytosome	Flavonoids	antioxidant activity	Can be used to Inhibit tyrosinase activity in the melanin formation process	[36]
13	Quercetin	Flavonoids	anti-itching and soothing effect	Quercetin is well known to have antioxidant and anti-inflammatory effects that might help reduce swelling	[37]
14	Pegagan (*Centella asiatica* L.)	Asiaticoside, Madecassoside, Asiatic acid, and Madecassic acid	Anti-aging, Skin whitening	Has activity in treating skin diseases and skin lesions such as excoriations, burns, hypertrophic scars, antioxidants, anti-aging, skin whitening, and as a cosmetic ingredient	[38]

15	*S. medusula*	triterpenoid	Antioxidants, photoprotective, and anti-Candida albicans	Promising sources for creating photoprotective gels to treat C. albicans-related skin infections	[39]
16	Papaya (*Carica papaya*)	Papain is a cysteine protease		anthelmintic, carminative, diuretic, oxytocic, and anti-infective effects treat colic, flu, beriberi, abortion, asthma, and cancer, eczema and psoriasis.	[40]

5. PREPERATION OF THE PHYTOSOMES

Typically, phytosomes can be produced using the solvent evaporation method. Phytoconstituents like bioflavonoids, flavonolignans, and polyphenolic compounds are combined drop by drop with the phospholipid solution, which is made up of either natural or synthetic phospholipids, which includes Phosphatidylcholine (PC), to produce pytosomes. In this manner, ginsenoside, puerarin, and kushenin phytosomes are created. Another example involves adding phospholipids in an ethanol solution prepared from the hydro-alcoholic extract of turmeric rhizomes that is further refluxed and agitated. The result is the production of curcumin phospholipid complexes. Complex phytosomes are those that have been produced by nonsolvent, freeze-drying, spray-drying, or vacuum-drying [41].

By attaching flavolignan and terpenoids to phospholipids like phosphatidylcholine (PC) through the polar end of a standardized extract that contains a standardized number of active ingredients, phytosomes are made utilizing patented processes. The phytosome process results in tiny cells that protect the beneficial components of the herb extract from being damaged by stomach acid and bacterial growth in the intestines [42].

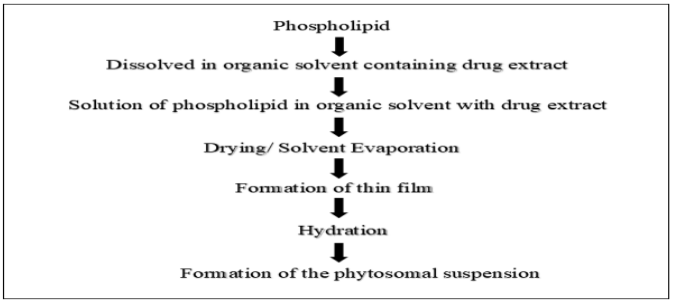

Figure 4. The process of preparation of Phytosomes [43].

To make phytosomes, active components such as bioflavonoids, flavolignans, and polyphenolic compounds are mixed with either artificial or natural phospholipids. Solvent evaporation is the procedure that produces phytosomes the most frequently. In this manner, ginsenoside, puerarin, and kushenin phytosomes are created. Mechanical dispersion is used to create marsupsin-phospholipid complexes. Phospholipids is dissolved into an appropriate solvent using a sonicator, and the active ingredient is then added drop per drop. Sometimes, with reflux plus stirring conditions, phospholipid complex is produced to accomplish thorough contact. To produce curcumin phospholipid complexes, phospholipids are added to an ethanol mixture that contains a hydroalcoholic concentration of turmeric rhizomes while it is refluxed and stirred. The nonsolvent is precipitated by lyophilization, spray deposition, or Drying or vacuum drying and can be used to separate the prepared complex which is called phytosome [44].

5.1 Selection of dosage form for the Phytosomes- Cosmeceuticals preparation

Based on its ability to increase the effectiveness and efficiency of the bioactive component, a suitable formulation or dosage form for the distribution of phytosomes can be chosen. The use of dose forms should increase their effectiveness with regard to the ongoing systemic effects of herbs on the human body. The final formulation must take into account the inherent qualities of herbal drugs, such as hydrophilic or

hydrophobicity, surface properties of systems, such as permeability and charges, percentage of biodegradability, and tonicity, as well as the release profile and size of the product required. Both oral and topical formulations of phytosome are available. For the distribution of phytosomes, the following dosage formulations are suggested [45]:

5.1.1 Soft gelatin capsules:

To create a suspension for soft gelatin capsule filling, the phytosome can be distributed in oily media (vegetable or semi-synthetic oil) [46].

5.1.2 Hard gelatin capsules:

These capsules can be filled with phytosomes. Precompression is not necessary because it can alter the disintegration time during a straight volumetric filling operation. The maximum quantity of powder that may be put into a capsule (often no more than 300 mg each size capsule) appears to be constrained by the phytosome complex's low density. We can increase the amount of powder that is loaded into capsules by using a piston pump during the capsule filling process [48].

5.1.3 Tablets:

A direct compression procedure can be used because of the phytosome complex's limited ability to flow, stickiness, and low apparent density is only used for smaller unitary doses. To create tablets with the proper properties, the phytosome complex needs to be diluted with 60–70% excipients. Due to the detrimental effects of heat and water on the stability of the phyto-phospholipid complex, wet granulation should be avoided [47].

Skin-applied dose form First, make the emulsion at a low temperature (no more than 40 °C), then add the phytosome complex. The primary lipid solvents used in topical formulation can disperse the phyto-phospholipid complexes [48].

6.PARAMETERS FOR EVALUATING PHYTOSOMES-BASED COSMETICS

The structural size, membrane permeability, proportion of entrapped solutes, and chemical composition of the preparation materials are only a few of the variables that are crucial in defining how phytosomes behave in physical and biological systems. Listed below are the characterization methods for phytosomes that were utilized to describe their physical characteristics.

6.1 Visualization technique:

The use of visualization Viewing can be done using either scanning electron microscopy (SEM) or transmission electron microscopy (TEM) [49].

6.2 % yield:

The percentage yield of the phytosome complex was calculated using the following formula: (%) Yield = 100 (Realistic yield). (Predicted yield)

6.3 Detecting the presence of drugs:

The detection of drug use 100 mg of the substance are dissolved in 10 ml of methanol to determine the drug concentration. Following the correct dilution, the amount of medication present was determined through determining the absorbance at 269 nm with a UV spectrophotometer [50].

6.4 Effectiveness of entrapment:

The ultracentrifugation method's entrapment potency will be demonstrated using a phytosomal formulation [48].

6.5 Transition temperature:

Differential scanning calorimetry can be used to determine the transition temperature of the vesicular lipid systems [49].

6.6 Vesicle size and Zeta potential:

Dynamic light scattering, which makes use of a computerized examination system and photon correlation spectroscopy, can be used to measure the particle size and zeta potential of phytosomes [51].

6.7 Evaluation using spectroscopy:

This technique is frequently used to both validate that a complex has formed among phytoconstituents and the phospholipid moiety and to examine the interaction that results from this complex. The most popular techniques include

6.7.1 ^{1}HNMR:

The complex formation between the phosphatidylcholine molecule and the active phytoconstituents is estimated using the NMR spectra. Bombardelli has examined the phytosome complex's NMR spectra. In nonpolar liquids, the 1H NMR signal noticeably changes without any accumulation of the signal specific to individual molecules and comes from atoms participating in the creation of the complex. The phytoconstituents' protons contribute to broader signals. Signals in phospholipids broaden while the singlet related to the N-(CH3)3 of choline goes through a process a field shift up [52].

6.7.2 ^{13}C NMR:

The phytoconstituents' carbons are undetectable in the 13C NMR data of the phytoconstituents and their stoichiometric complex with phosphatidylcholine when it they are recorded in C6D6 at room temperature. While most of the resonance of the fatty acids chains maintains its original sharp line shape, the signals corresponding to the glycerol and choline portion are broadened and some are shifted [53].

6.7.3 FTIR Infrared spectroscopy:

Comparisons are made between the FTIR spectra of the phytoconstituents, the phospholipid, and their phytosomes. Free hydroxyl groups interact with one another the phospholipid's choline component. A broad peak replaces the peak that once represented the free hydroxyl group. Investigations into the chemical shift value, presence, and absence of a certain proton's NMR peak can be used to characterize phytosomes [54].

7.The Application of phytosomes in cosmetics

The components of phytosomes have all received approval for use as medicinal and cosmetic ingredients, and the formulation is secure. Additionally, they can be utilized to improve the drug's penetration into the skin during transdermal and dermal delivery. Due to their enhanced skin penetration and high lipid profile, they can be widely used in cosmetics. Functional cosmetics can be made using phytosomal compositions [52].

Table 2. Representation of the already marketed formulation of phytosomes as cosmeceuticals

S.no	Phytosome Trade Name	Phytoconstituents	Application	Reference
1	Greenselect	An antioxidant is present in Greenselect	Greenselect works as an Anti-oxidant and whitening agent.	[55]
2	Centella Asiatica	Triterpenes	Works as an Anti wrinkles, collage restructuring	[55]
3	Curbilene Phytosome	Curbilene	Used in Skincare, Matting Agent	[56]
4	Gingko select PhytosomeTM	Gingko flavonoids, Gingoic acids of ginkgolides and bilobalide	Used for treating Raynaud's disease, antiageing, Vasoactive, Micro Circulation Improver, Cognition enhancer	[56]
5	Millet PhytosomeTM	Mineral salts, vitamins, unsaturated fatty acids, amino acids	This includes Beauty food for skin, nails and hairs, Antistress	[56]
6	Silybin PhytosomeTM	Silybin from Silybum marianum.	Has properties to treat Hepatoprotective, antioxidant for liver and skin.	[57]
7	Meriva	Curcumin phytosome	Works as a Soothing	[58]

			agent	
8	Super Milk thistle ExtractTM	Silybin from Silymarin Food Product	Used as an Antioxidant for liver and skin	[59]
9	Sericoside Phytosome	Sericosides from Terminalia sericea	Can be used as a Skin Improver	[60]
10	Centella Phytosome	Terpenes	Used to treat Vein and Skin disorders	[60]
11	Ginselect phytosome	Ginsenosides from *Panax ginseng* rhizome	Shows activity in Adaptogen, tonic, skin elasticity improver	[61]
12	PA2 phytosome	Proanthocyanidin A2 from horse chestnut bark	Treats Anti-wrinkles, as works as UV protectant	[62]
13	Silymarin phytosome	Silymarin from milk thistle seed	Used for Healthy liver, antioxidant, UV protection	[25]
14	Siliphos	Silybin from milk thistle seed	Acts for Healthy liver, retinoic acid-like compound	[63]

8.HOW DO PHYTOSOME IMPROVE THE ABSORPTION AND BIOAVAILABILITY OF ACTIVE PHYTOCONSTITUENTS

Phytosomes are an innovative lipid-based delivery system that have a liposomes-related structure and can be utilized for the entanglement of various types of polyphenolic-based phytoconstituents to furthermore cultivate their support when administrated [63].The improvement of phytosomes is produced using normalized polyphenolic plant take out integrated into phospholipids, dominatingly phosphatidylcholine (PC) [86]. The lipid vesicles of phytosomes are the consequence of a H-security correspondence between the polyphenolic moiety of the bioactive standard concentrates and the phosphate social event of phospholipids framework in non-polar solvents [16]. The water-dissolvable polyphenolic rings of phytochemicals (i.e., flavonoids and terpenoids) have a high warmth to falsely tie to the hydrophilic moiety of phospholipids (i.e., choline) to shape the combination of phytosomes, while the phosphatidyl lipophilic moiety of the phospholipids moves toward a tail to organize the water-dissolvable choline-bound phytoconstituents [17, 65]. The greater part of the broadly broke down phytocompounds are polyphenols, which have terrible bioavailability and lipid dissolvability because of their hydrophilic nature, restricting their in vivo improvement [86]. The phospholipid moieties of phytosomes have a high partiality to tie two or three flavonoids compounds unequivocally [66]. There are two or three typical concentrates, for example, hawthorn, grape seed, green tea, milk thorn and ginseng, that are more reasonable when they are stacked into phytosomes [67]. The exemplification of inadequately dissolvable polyphenolic compounds into the phytosomal transport structure basically impacts the update of their ingestion, inciting better passage and upkeep across the regular film and further created bioavailability [18]. The bifunctional considered phytosomes has been shown to work on their pharmacodynamic and pharmacokinetic properties in relationship with standard typical mixes when applied topically, attributable to their capacities in the headway among lipophilic and hydrophilic checks of the skin [86,19]. The likely control of phytosomes in the improvement of neighborhood began polyphenolic compounds utilized for the treatment of two or three issues makes this nanotechnology a promising device to work on new plans. Phytosomes hold two or three basic attributes of liposomes and transferosomes, for example, the capacity to develop the dissolvability of inadequately dissolvable particles as in polyphenolic phytochemicals. Unconventionally, phytosomes and transferosomes show extra adroit normal properties in the suitable applications, for example, extended length consistency and higher skin entrance [68]

Table 3. Demonstration of how phytosome improve the bioavailability and absorption of phytoconstituents.

S.no	Application	Justification	Reference
1	**Enhanced bioavailability**	By forming phyto-phospholipid structures, the layer permeability and oil-water portion coefficients of dynamic constituents get to a higher level. In this manner, phytophospholipid structures are the more quickly consumed and have extended bioavailability.	**[69]**

2	**Enhanced absorption**	Phytosomes can all the more likely travel from a hydrophilic climate into the lipid accommodating climate of the cell layer. In this way, percutaneous retention of phytoconstituents is moved along. Consequently it is generally utilized in beauty care products	**[69]**

9.USING PHYTOSOMES AS A DELIVERY SYSTEM TO INCREASE THE BIOAVAILABILITY AND ABSORPTION OF COSMECEUTICALS

Scientists are engaged in a variety of research initiatives, and the most recent results demonstrate that phytosome expertise is a ground-breaking strategy for enhancing the absorption and bioavailability of herbal extract while precisely reducing the level. The technique of new investigations has been influenced by the effectiveness of this approach and the rising demand for herbal remedies to treat a variety of illnesses in today's environment. According to pharmacokinetic and activity studies done on both people and animals. Phytosomes of olive fruits and leaves, green tea, ginseng, kushenin, marsupsin, and curcumin have a better bioavailability than the simpler, non-complex plant extract, lipid-based medication delivery [70].

A topical formulation with a high curcumin content cannot increase bioavailability, as claimed by Gupta and Dixit. They combined curcumin and phosphatidylcholine, tested them, and evaluated the results using FTIR, TLC, and DSC, as well as melting point. They evaluated how vesicle systems like phytosomes, liposomes, along niosomes performed. They discovered that the phyto-vesicles have remarkable antioxidant and anti-aging characteristics when compared to other vesicular systems due to the amphiphilic character of the complex, which significantly boosts the water and lipid miscibility of the curcumin [71].

Cao et al. developed the oxymatrine-phospholipid complex (OMT-PLC) to improve the lipid solubility and efficiency of OMT. The goal of their study was to evaluate the feasibility of using an OMT-PLC and microemulsion combination as a topical administration strategy to improve the absorption and efficacy of OMT. We looked at a variety of physicochemical properties as well as in vitro and in vitro absorption via the skin. They came to their conclusion suggested an effective topical delivery strategy for OMT is a phospholipid complex paired with a microemulsion (Cao et al. 2011) [72].

According to Forster et al.'s review, phospholipid complexation can be employed to effectively distribute plant-based formulation topically in formulations for cosmetics (Forster et al. 2009).Topical administration of medications and cosmetics [73].

To measure the blood levels of quercetin in healthy volunteers different formulations were given in single- and multiple-dose phases. Quercetin has been a key component of human diets since prehistoric times. Quercetin in particular has shown promising results in vitro and in vivo against diabetes, cancer, cardiovascular diseases, and other atopic disorders, as well as allergy, asthma, and other allergic ailments. As a result, the bioavailability and absorption of quercetin would appear to have a significant influence on bioefficacy. Research into increasing solubility has been committed to developing innovative technology. Therefore, encapsulating a component within certain vehicles seems to be a potential method for shielding the substrate from undesirable conditions like chemical or physical damage but oxidation, and it may even help cover up unpleasant tastes [74].

Herbal extracts have limited bioavailability along with absorption, however, this serious problem is resolved when they are combined with phospholipids or phytosomes. As Eucalyptus can be used for a variety of purposes, including as an expectorant, antifungal, antibacterial, antioxidant, antiseptic, for upper respiratory infections (URI), for various skin issues, as flavouring, and as an insect/mosquito repellent. Its restricted water solubility, which also contributes to its reduced absorption and bioavailability, has led to the employment of several techniques to improve it. The objective of the study was to investigate the effects of cholesterol and various. Although the enhance absorption and bioavailability was seen when eucalyptus extracts were encapsulated in phytosomes [75].

A newly developed and patented technology allows for the extraction of water-soluble phyto-ingredients for the incorporation of certain workshop passages into phospholipids to generate lipid-compatible molecular complexes. Phytosomes are filtered zones or controlled paths. Phospholipids have been refined, which increases effort and boosts bioavailability. The phytosome process enhances herb production by increasing absorption, increasing bioavailability, and improving transport to tissues [76].

Natural healthcare remedies have a very constrained range of uses but due to their unstable nature, poor solubility, and inadequate bioavailability. So, in order to get over these limitations and boost the therapeutic potential of these natural medicines novel nanoformulation-based technologies have been

created. In addition to living organisms like microalgae, crabs, and shellfish, Astaxanthin (C40H52O4), a xanthophyll carotenoid with a molecular weight of 596.84 g/mol, is present in yeast, fungus, complex plants, and bird feathers. A formulation containing astaxanthin (L-AST) was developed to study astaxanthin's function in the prevention of Atopic Dermatitis by lowering skin inflammation. The molecule's limited water solubility was enhanced by conjugation with phospholipid structures [77].

To make polyherbal phytosomes that may be administered topically, Trichosanthes curcumin and Abrus precatorius were mixed into aqueous extracts. These phytosomes proved to be equally as effective in accelerating hair growth as a course of minoxidil medication. Nanotechnology uses herbal nanomedicines to cure alopecia The development of herbal-based nanomedicines for hair [78].

Lycopene, an unsaturated linear hydrocarbon carotenoid having the lowest bioavailability of all fruits and the highest concentration, is the predominant red colour in fruits such as tomatoes. In order to increase therapeutic advantages; The bioactive phytoconstituents of herb extract are combined with phospholipids to produce lipid-compatible molecular complexes in a novel herbal formulation known as a phytosome, which mimics microscopic cell-like structures. In the current investigation, a three-level factorial design quadratic model using Design Expert was employed to assess the combined impacts of three independent variables—phosphatidylcholine (PC)% (1 and 3), tomato extraction containing lycopene% (1 and 3), and manner of preparation [79].

Commercial antiaging A. vera gel and produced antiaging phytosomal gel were compared. A. vera was incorporated in this commercial product as an antiaging component because to the presence of phenolic compounds as well as Vitamin E, and C. The phytosomal gel consisting of tender coconut water as its base and A. vera extract was compared to the antiaging A. vera gel. Using these ingredients, standard dosage forms like creams, gels. They do not, however, have as much of an antiaging effect. Herbal extracts were combined with the carrier and skin-nourishing ingredient phosphatidylcholine to form phytosomes. They were better absorbed and used to treat skin diseases, delay the indications of aging, and prevent skin cancer because of their dual solubility, which contained a head that was water-soluble and two tails that were fat-soluble [80].

As rutin has a very limited oral bioavailability, a unique drug delivery strategy is required. The oral bioavailability and transdermal penetration of polyphenols are improved by phyto-phospholipid complexes (phytosomes). Rutin phytosomes (RN-P) were created and described in the current study to determine their viability for transdermal administration in inflammatory situations. The findings of the current study suggest that the phyto-phospholipid complex of rutin might boost its skin uptake for the treatment of inflammatory conditions like arthritis, rheumatism, and athletic aches and may be able to deliver the medication for a long time without experiencing the issues related to oral administration [81].

A vesicular delivery method for curcumin in order to increase its topical bioavailability was prepared. TLC, DSC, melting point, and IR spectroscopy analyses were used to produce and characterize a complex of curcumin and phosphatidyl choline (PC). The compound was then further transformed into phyto-vesicles. Curcumin was also made into liposomes and niosomes, and all of these vesicular compositions were combined with carbopol gel to make them suitable for topical treatment on skin. In mice exposed to UV-induced oxidative stress, the anti-aging benefits of these formulations have been compared to those of pure curcumin and a physical combination of curcumin and phosphatidyl choline. The complex's creation was discovered via spectroscopic data and analytical analyses. The phyto-vesicles were shown to be more effective in the current investigation than all other formulations have the same improved antioxidant and antiaging effects. This increase could be caused by the complex's amphiphilic properties, which considerably improve the curcumin's water and lipid miscibility [82].

Using the lipid film hydration process, carotenoid-rich phytosomes of the tubular calyx of Nyctanthes arbor-tristis L. and the petals of Tagetes patula L. (standardized for crocin and lutein content) were made, and these phytosomes were then added to a gel basis. According to ICH recommendations, the gel formulation's stability was assessed. The D-galactose-induced aging model was used to assess the formulation's effectiveness. By giving albino mice D-galactose for 42 days, skin aging was caused. For 42 days, the gel composition was administered topically. Then, determination of the biochemical markers glutathione and malondialdehyde (MDA) as well as histological analyses of treated skin samples were used to assess the formulation's impact on skin aging. Studies on accelerated stability revealed an increase in the stability of the phytosomal preparation. At the end of three months, it was discovered that the formulation had 99.98% w/w to 99.85% w/w of the carotenoids crocin and lutein. In comparison to the control group, the formulation that included extract of Phytosomes of carotenoid rich extracts of Nyctanthes arbor-tristis L.

and the petals of Tagetes patula L. significantly (P 0.05) increased dermal and epidermal layers and increased GSH levels in the skin [83].

10.OTHER VESICULAR DELIVERY METHODS FOR COSMECEUTICALS

It is in our nature as humans to seek out beauty. Throughout history, products have been used to enhance skin health. In the past, organic products like milk, citrus fruits, and clay were used [84].

Cosmeceuticals are cosmeticsas well as pharmaceuticals that use substances with health advantages in an effort to enhance appearance. In 1984, Kligman created the idea by merging the fields of cosmetics and drugs. They are multipurpose products that provide the active pharmaceutical components needed to treat or enhance skin. Although they are applied to the skin as cosmetics, they include substances that support the skin's biological function. Products that enhance attractiveness and play a useful pharmacological role have been made possible by new developments and expansion in the cosmetics sector.

The traditional use of plant for skin care and fragrance relies on infusions, poultices, and other skin care products. In the last century, scientists have concentrated on plants to learn more about their safety and efficacy in the field of cosmetics. In general, herbal sources are full of vitamins, antioxidants, essential oils, hydrocolloids, proteins, terpenoids, and other bioactive substances with cosmeceutical-related properties including anti-aging, antioxidant, emollient impact, etc [85].

The primary marketed cosmetic products for many years were cosmeceuticals made of synthetic materials. But more recently, because of a surge in consumer health consciousness, there have been worries about the toxicity of synthetic chemicals. The usage of plant-derived PHYTOCs, which have previously demonstrated their ability to improve attractiveness and prevent, reduce, or treat several pathological disorders, appears to be the answer to this unwanted toxicity worry [86].

Because they may be used to treat a variety of conditions with little hazardous side effects, bad effects, or adverse consequences, herbal medicines are becoming more and more popular in the modern world. There are a number of difficulties with herbal extracts and plant actives, though, including low solubility (in water or fat), poor penetration, a lack of targeted specificity, instability in extremely acidic pH, liver metabolism, etc. Modern technology has made it possible to distribute herbal medications with better physical, chemical, pharmacokinetic, and pharmacodynamic qualities through the development of innovative drug delivery systems. Due to its use in treating a variety of illnesses with a minimum amount of harmful effects, side effects, or bad consequences, developing nano-strategies such polymeric nanoparticles, liposomes, niosomes, microspheres, and herbal medications is getting increasing appeal in the current world. But there are a number of difficulties. with plant or herbal extracts, including hepatic metabolism, low solubility (water/lipid), poor penetration, lack of targeted specificity, instability in severely acidic pH, etc [87].

Modern technology has made it possible to distribute herbal medications with better physical, chemical, pharmacokinetic, and pharmacodynamic qualities through the development of innovative drug delivery systems. The creation of nanostrategies such as polymeric nanoparticles, liposomes, niosomes, microspheres, and phytosomes [88].

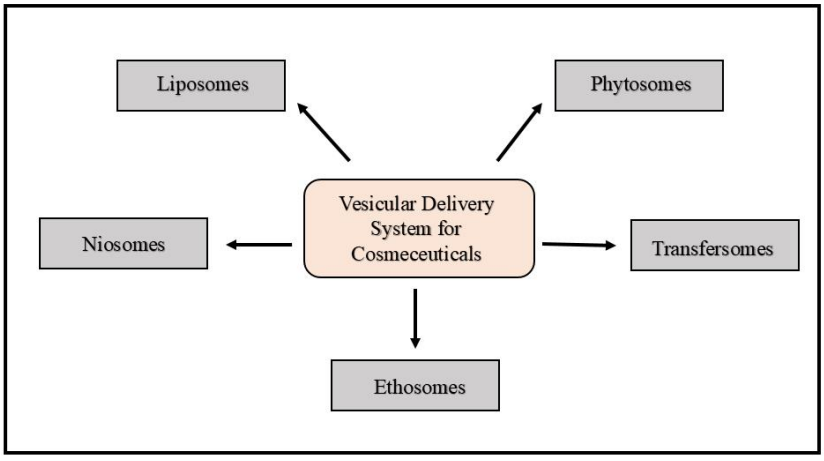

Figure 5. Some of the most commonly used vesicular delivery system for cosmeceuticals

11 TYPES OF VESİCULAR DRUG DELIVERY SYSTEM FOR COSMECEUTICALS

Solid lipid nanoparticles, nanostructured lipid carriers, and nanoemulsions are the most preferred vesicular delivery methods (liposomes, nanosomes, phytosomes, herbosomes, marinosomes, oleosomes, etc.) [89]. These systems have better stability, increased effectiveness, and decreased the allergenic potential of specific herbal components, to name a few benefits for herbal cosmetics [85].

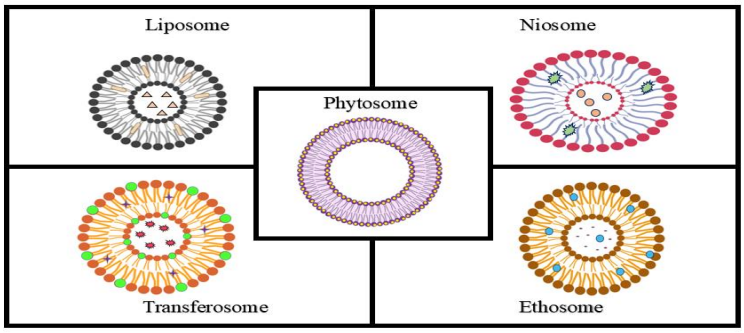

Figure 6. Representation of the structure of different delivery systems used for cosmeceuticals

11.1 Phytosomes

Phytosomes comprise of lipid-compatible molecular structures that encase water-soluble and biologically active phytochemicals in phospholipids for improved absorption and bioavailability. [Phytosome: a growing trend in the use of herbal drugs[63]. Because of their large molecules and difficulty crossing biological membranes, hydrophilic phytochemicals like polyphenols and flavonoids have poorer absorption in the body. Thanks to phytosome, these limitations have been removed. They differ from other compounds in that they create a chemical relationship between plant material and phosphatidylcholine in a ratio of either 1:1 or 1:2 [90].

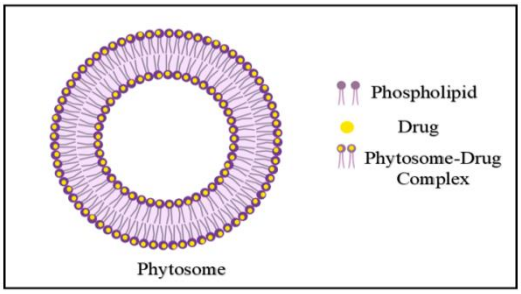

Figure 7. Detailed representation of the phytosomes structure[86].

Phytosomes are structurally similar to liposomes, with the exception of the substance being entrapped. In phytosomes, the active material is an essential component of the membrane, in contrast to liposomes where the active substance is dissolved in the medium found in the membrane layers. The enterocyte cell membrane's ability to change from a water-soluble condition to a lipid-soluble state was improved by the phytosomes. Once within the cell, they entered the circulation and shielded entrapped herbal drugs from stomach acids and gut microbes [91].

The components of phytosomes have all received approval for use in medicines and cosmetics, and the formulation is secure. Because of the chemical link created between phosphotidylcholine molecules and phytoconstituents, phytosomes have higher stability profiles [92]. Numerous studies on phytosomes have found that they outperform liposomes in terms of bioavailability, absorption, and therapeutic effectiveness. Review on phytosomes: innovative technique for herbal phytochemicals [93] like Abrus precatorius and Trichosanthes curcumerina's aqueous extracts were combined to create polyherbal phytosomes that may be applied topically. These demonstrated their ability to promote hair growth, and the formula was just as efficient as a course of minoxidil therapy. Herbal nanomedicine is utilized in nanotechnology to treat alopecia [78]. The use of phytosomal formulations as topical pharmaceutical agents and cosmetics with

better safety and efficacy leads to optimal usage of herbal medications and cost-effective pharmaceutical products.

11.2 Liposome

A market for nanotechnology has developed since Christian Dior's company created the first cosmetic in 1986 using nanocarrier technology via a liposome system, [94] and it is anticipated to reach US$ 125 billion by 2024 [95]. Liposomes are widely used in the pharmaceutical, cosmetic, and food industries. They are self-assembled, closed spherical systems in a lipid bilayer made of, among other things, one or more amphiphilic phospholipids. Liposomal vehicles are actually biocompatible, biodegradable, non-toxic, and immunogenic carriers of active substances that are both hydrophilic and hydrophobic by nature. They can be made of natural or synthetic lipids[96]. Due to their ability to biodegrade, biocompatibility, and nontoxicity as well as a number of improved characteristics of those vesicles, liposomes stand out among the numerous nano- and microparticles in a variety of fields, including pharmaceuticals, nutraceuticals, and cosmeceuticals [97].

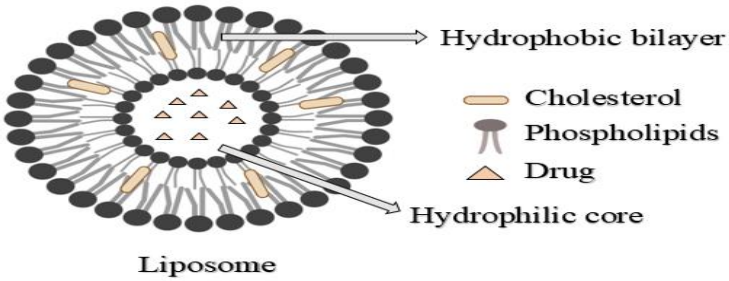

Figure 8. Detailed representation of the liposomes structure[98].

Given below are some of the examples that show effectiveness of liposomes in cosmeceuticals:

Bi et al. claim that while vitamin D3 protects skin from photoaging, it has some drawbacks such as being sensitive to air, high temperatures, and light and degrading quickly in water/ethanol when used in the creation of conventional topical preparations. So they created a new system based on vitamin D3-encapsulated liposomes, and they showed that the previous problems were diminished as well as the drug's stability [98].

In order to lessen the effects of skin aging, Lee and Tsai (2010) [87] investigated the incorporation of coenzyme Q10, a powerful antioxidant, in liposomes. Vitamin E and soy phosphatidylcholine were used to make the liposomes. According to the findings, the lipid vesicles were about 200 nm in size and had a polydispersity of about 0.3. Two formulations—coenzyme Q10 in solution while coenzyme Q10 encapsulated in liposomes—were used for these in vivo studies on rats. The findings demonstrated that cutaneous penetration of the liposomal form was significantly greater than that of the solution. Therefore, it has been demonstrated that the liposomal formulation can raise the concentration of coenzyme Q10 within the skin and keep it there for a longer period of time [100].

Retinoic acid was encapsulated in liposomes that were created by Manconi et al. in 2011. To improve skin penetration, hydrophilic excipients (Oramix NS10, Labrasol, Transcutol P, and propylene glycol) were also added in addition to soy phosphatidylcholine. The findings revealed that the vesicles were approximately 150 nm in size, had a polydispersity of 0.3, a negative zeta potential (55 mV), and a rate of encapsulation of 87%. Ex vivo studies on pig skin were used to evaluate the impact of hydrophilic excipients. The findings revealed that the epidermis accumulated more retinoic acid than the dermis [101].

Curcumin, a naturally occurring polyphenol that is derived from the roots of Curcuma longa, acts as an antioxidant and inhibits the peroxidation of lipids. This bioactive exhibits pharmacological action, including effects against toxicity, cancer, inflammation, wrinkles, and viruses [91]. Curcumin is currently sold as creams as well as gels (Vicco Turmeric cream and Emami Gold), but its skin absorption is poor [87]. Curcumin was encapsulated in liposomes and niosomes by Gupta and Dixit and then added to carbopol gel. The in vivo findings demonstrated that the formulations containing curcumin in capsule form enhanced the antioxidant and anti-aging effects [82].

The low solubility and high manufacturing costs of liposomes are some of their drawbacks. They have a brief shelf life in storage and can degrade through oxidation or hydrolysis. Depending on the drug and how the liposomes are made, drug molecules can occasionally leak out [84].

11.3. Niosomes

Niosomes are vesicles with a bilayer structure made of hydrated non-ionic surfactants that self-assemble, either containing or despite incorporation of cholesterol as well as their lipids.[102] The three types of niosomes—large unilamellar vesicles (LUVs), small unilamellar vesicles (SUVs), and multilamellar vesicles (MLVs)—depend on the size of the particle. Nonionic surfactants are essential for the formation of niosomes. Numerous studies have looked at the function, advantages, and applications of nonionic surfactants to create niosomes for the delivery of molecules, targeting a particular site or tissue, and the creation of various cosmetic products. The composition of nonionic surfactants has a big impact on how niosomes are made. They are therefore made up of a single or multiple lamellae, that comprise bilayers with hydrophilic as well as hydrophobic components joined through ester, ether, or amide bonds [103].

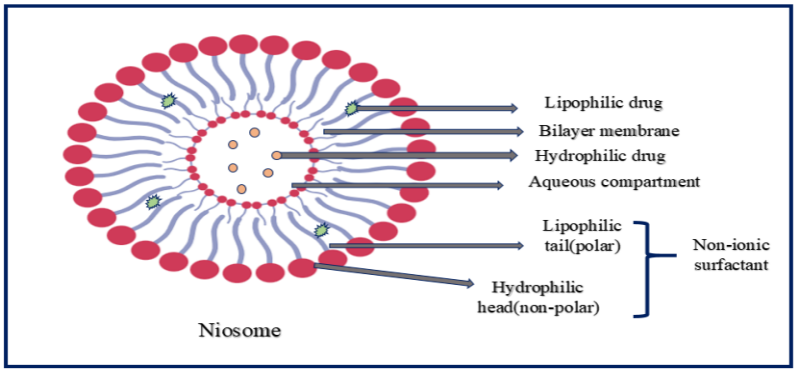

Figure 9. Detailed representation of the niosomes structure. [104]

Epigallocatechin gallate (EGCG), an antioxidant, has anti-aging, anti-inflammatory, and anti-cancer properties. However, gastrointestinal breakdown and enzymatic liver metabolism limit its effectiveness when given orally. In contrast, the SC layer develops a barrier of skin that prevents exogenous substances from penetrating the skin and prevents external molecules from entering the inner skin layer. An enhanced antioxidant effect was produced by the drug-loaded niosomes due to their biphasic drug release pattern, prolonged release, and steady drug level [105].

The benefits of physic nut (Jatropha curcas Linn.) for glowing skin and anti-aging cosmetics have been investigated. According to the outcomes, pure physic nut oil showed benefits in cosmetics, especially when the substance was encapsulated in niosomes. In vitro tyrosinase suppression and the capacity to scavenge free radicals are the first steps in the intricate process of glowing skin and oxidative stress. These two processes were found to be more common in encapsulated pure oil compared to unencapsulated oil, crude oil that had not been filtered, and crude oil the fact had been filtered. This might be because the oil is trapped inside of niosomes, increasing its stability [106].

DAV (also referred to as deer antler velvet) powder extract may promote the growth of skin and hair cells. Niosomes that were enclosed in DAV displayed loading capacities of 51.62 9.63 and 50.13 9.35, respectively. Nanometer-sized vesicles with a constrained size distribution along with a negative zeta potential were present on the niosomes. Niosomes-loaded microspicules serum was then created using the loaded niosomes. The niosome serum microspicules formulation significantly increased cumulative in vitro skin permeation study at every time interval (1-24 h) and, in contrast to other formulations, accumulation into the deepest layer of the skin encourages hair growth without causing skin problems. This formulation also increased the moisturizing effect of skin and decreased erythema [107].

11.4. Ethosomes

Ethosomal systems are more recent lipid vesicular carriers with a 20-year lifespan, but during that time, their use as a transdermal drug delivery system has increased significantly. They contain a significant

amount of ethanol. These nanocarriers transport pharmaceuticals with different physicochemical properties throughout the surface and deeper layers of the skin [108]. Ethosomes are soft, malleable vesicles made primarily of water, phospholipids, and ethanol (at a relatively high concentration). These soft vesicles are brand-new vesicle carriers for improved skin absorption. The ethosomes' vesicles can range in size from a few nanometers to several microns. Molecules were said to be successfully delivered to and through the skin through systemic circulation by ethosomes [109]. Both of hydrophilic and lipophilic drugs can be transported effectively by ethosomes. The ability of ethosomes to transport drugs through the skin and into systemic circulation is facilitated by their small particle size (microns to nanometer). The ethosomes are the most preferred carriers for topical drug delivery due to their simplicity in preparation, non-irritating nature, effectiveness in encapsulating a wide range of drug molecules, and higher stability compared to any other vesicular systems. Phospholipids are found in ethosomes, which contain alcohol and drug solutions. The formulations' phospho-lipid content can range from 0.5 to 10%. Along with glycol, alcohols can be used as a softener, vehicle, and penetration enhancer in ethosomal formulations. According to several studies, the drug delivery might be modulated by changing the alcohol and water compositions. Consequently, bioavailability can be improved [110].

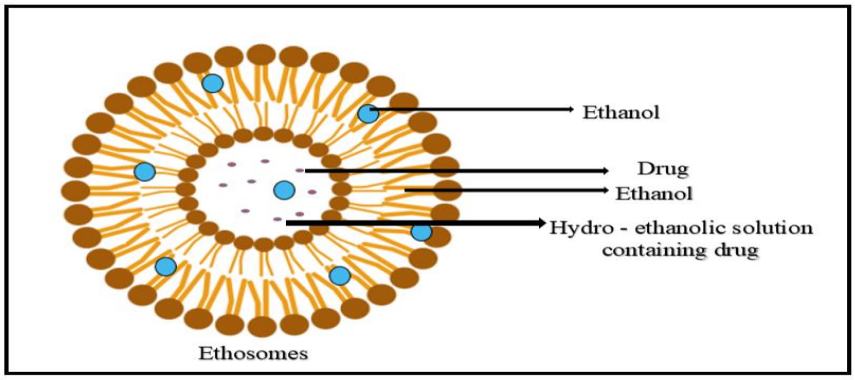

Figure 10. Detailed representation of the ethosomes structure. [109]

Ethosomes are very effective form of delivery of a wide range of drug through the skin Applications of ethosomes in various diseases are discussed below:

For the treatment of psoriasis, Fathalla et al. evaluated and contrasted Anthralin liposomal as well as ethosomal formulations. The mean change in the Psoriasis Area and Severity Index (PASI) was significantly higher after ethosomal therapy. Additionally, ethosomal gel showed greater skin penetration through the rat abdomen [111].

In a study by Yu et al., they created ethosomes that were loaded with cryptotanshinone to treat acne. Optimized ethosomes and regular hydroethanolic gel were compared for skin penetration and deposition. The gel had a more effective anti-acne effect with a slight amount of skin irritation. According to the study, ethosomes may one day prove to be a successful tool for treating acne [112].

Fisetin-loaded ethosomes were created by Moolakkadath et al. to treat skin cancer. Studies conducted in vivo revealed that mice given fisetin ethosomes had lower levels of TNF- and IL-1. According to the study, ethosomes formulation with fisetin could serve as a potential dermal delivery system for treating skin cancer [113].

In a study, Nakka et al. contrasted isotretinoin ethosomal gel with commercially available isotretinoin preparations. According to reports, ethosomal vesicles containing 30% w/w ethanol and 2% w/w lecithin had the best entrapment efficiency, and the formulation's permeation enhancers improved skin penetration and the development of drug depots in the skin [114].

Rao Peram et al. created curcumin-loaded ethosomes to treat melanoma. The in vitro studies showed that the curcumin-loaded ethosomes were superior to conventional liposomes in terms for drug penetration and skin drug deposition [115].

A critical step toward better skin penetration and absorption is the incorporation of ethosomal systems in appropriate vehicles such patches, creams, and gels. The future of all delivery methods lies with this one since it is the most efficient [116].

11.5. Transferosome

Deformable liposomes (Transfersomes) are elastic nanovesicles made of phospholipids. They are the original elastic nanovesicles that Cevc et al. introduced. Transfersomes have phospholipids as their primary component and 10–25% edge activators (such sodium cholate). Only when administered in nonocclusive circumstances were they said to penetrate undamaged skin and transport the medicines. [117] Traditional liposomes can only penetrate the SC tissue's outermost layers because of their rigid structure. Transfersomes, on the other hand, can pass through channels just one-tenth of their diameter and can penetrate the SC because they contain surfactant molecules in their structures, which give them more flexibility to do so. A transfersome is identified to improve the in vivo permeation to attain therapeutic doses that are equivalent to the SC injection as well as the in vivo skin administration of a wide variety of medications [118].

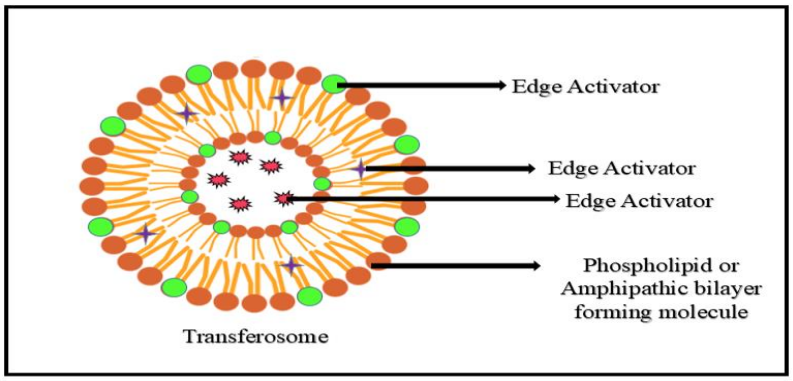

Figure 11. Detailed representation of the transferosomes structure. [119]

In terms of improving drug permeation and interactions with human skin, transfersomes have generally been found to be superior to conventional gel-state and liquid-state vesicles as well as conventional liposomes [120].

The treatment of skin cancer using transfersomal gel containing 5-Fu was examined in the current article. Different tranfersome formulations Span-80 and Tween-80 were used as edge activators during preparation. For the treatment of skin cancer, the carbopol-based transfersomal gel of 5-Fu was developed and tested. According to the findings, Tween-80 appears to be a more effective EA than Span-80 in terms of vesicle size and entrapment effectiveness. In vitro skin permeability and 5-Fu skin deposition were both enhanced by the transfersomal gel as compared to the commercial formulation. It was demonstrated to be gentle on the skin and effective at keeping 5-Fu in the deeper layers of the skin for an extended period of time [121].

The Brazilian berry, or jabuticaba, is a member of the Plinia genus, commonly known as the Myrciaria genus. According to certain research, the peel of this berry contains a significant amount of phenolic chemicals, which are what give it its high antioxidant activity in vitro antioxidant benefits in humans and anti-inflammatory and gut microbiota modification in rats. The peel's high polyphenolic content also makes it a potential natural coloring and antibacterial agent. It was integrated into ultradeformable phospholipid vesicles to increase the stability and efficiency of the extract. Hydroxyethyl cellulose and sodium hyaluronate were added to (transfersomes) to modify them, resulting in the creation of HEcellulose-transfersomes and hyaluronan-transfersomes. The inclusion of the extract in the vesicles enhanced their beneficial properties because they were more effective than the reference solution at reducing the toxic effects of hydrogen peroxide and even accelerating the healing of a wound in a monolayer of cells, particularly when the vesicles were enriched with polymers. Given this, using polymer-enriched vesicles to create cosmetic and cosmeceutical products with advantageous qualities for skin may be a smart idea [122].

Centella asiatica (CA) transfersomes along with rosemary essential oil (REO) nanoemulsion was formulated using lipid-based nanocarriers for the capacity of both biological substances to synergistically block UVB radiation, coupled with ameliorative and anti-aging benefits. By reducing the expression of malondialdehyde (MDA), and by suppressing matrix metalloproteinase-9 (MMP-9) expression, the gel comprising CA transfersomes with REO nanoemulsion inhibited lipid peroxidation and collagen degradation. Additionally, the gel of CA transfersomes and REO nanoemulsion activated the TGF-(transforming growth factor)/Smad pathway, upregulating type I collagen, and restoring the density of collagen fiber that had been lost due to UVB exposure [123].

Sinapic acid (SA) is a type of phenolic substance with antioxidant and UV protection properties against skin conditions. However, its limited therapeutic utility is a result of its weak skin penetration. According to the findings, transferosomes and ethosomes increase a drug's permeability across the skin and make it easier to treat a variety of skin conditions. To increase the permeability of SA across the skin, the current study set out to create vesicular nanoformulations like transferosomes and ethosomes. In light of this, an ethosomes-based method would be a good way to improve SA permeability via the skin [124].

Transferosomes are prone to oxidative destruction, which makes them chemically unstable. Another factor working against transferosomes' use as drug delivery systems is the purity of their natural phospholipids. Formulations containing transferosomes are expensive [125].

12 WHY TO PREFER PHYTOSOMES AS DELIVERY SYSTEM FOR COSMECEUTICALS

Cosmetics are often used to improve the look of the face and other body parts, such as the mouth, hair, nails, and eyes, among others. Just like cosmetics, cosmeceuticals covers delivery form like powder, cream, lotion, shampoo, conditioner, and nail paint. The many chemical toxins, germs, pollutants, and sunshine can harm the skin [126]. So, using a synthetic or natural agent, cosmetics together with active ingredients can lessen skin issues including wrinkles, acne, dark undereye bags, and dullness [127].

There is a current movement to return to using herbal remedies and to live a more natural lifestyle throughout the entire planet. For a healthy life, they favor natural foods, herbal remedies, and traditional medical procedures. Products made from vegetables grown biologically or organically without the use of synthetic fertilizers are quite popular a pesticide [128]. In the recent years, the use of herbal cosmetics has been increasingly popular in the fashion and beauty industries. The majority of ladies appreciate it since it has active elements that are derived from natural sources that feed the applicant. Additionally, it is free of chemicals that might cause negative effects including allergic responses from butylated hydroxyanisole (BHA) and butylated hydroxytoluene (BHT), cancer from coal tar, and genetic mutations from dibutyl phthalate. Typically used as preservatives in chemical cosmetics, parabens are quickly absorbed via the skin and can disrupt hormonal and endocrine function [129].

Many cutting-edge cosmetic delivery techniques are employed in cosmetic goods. A cosmetic delivery system is a substance or procedure that can improve the perceived or quantifiable effectiveness of a cosmetic product [130].

Any herbal product must offer a functional degree of the active components in order to be effective.The words "some" and "phyto" both refer to plant-like structures. Due to the gastro-protective nature of phosphatidyl-choline, the phytosomes technique forms a tiny cell that protects the herbal extract or its active ingredient from harm by stomach secretions and gut microbes. The phytosome are relatively new structures that contain the developing herb component contained and held in by phospholipids [131].

Ginkgo biloba, grape seed, hawthorn, milk thistle, green tea, and ginseng are just a few of the prominent herbal extracts that have undergone the phytosome process. Recent studies have shown that using phytosomes is more effective than using conventional methods for absorption and bioavailability. Numerous reports of standardized extracts with flavanoids and polyphenols when added to a phytosomal formulation, enhanced bioavailability. Phospholipids, primarily phosphatidylcholine, make up phytosomes and form a molecular complex with other components that is compatible with lipids. The majority of phytomedicine's bioactive components are water soluble substances like flavonoids. In comparison to traditional herbal extracts, phytosomes exhibit improved absorption due to their water solubility and lipophilic outer layer, which also results in better bioavailability [132].

There are a number of potential barriers that stand in the way of the research and marketing of natural goods, despite the fact that therapeutic plants have been discovered to contain promising biological qualities. By providing effective partitioning between phytochemicals placed inside the hydrophilic head of phospholipid subunits and lipid layers of cell membranes, phytosome technology aids in improving the absorption of active phytochemicals [133].

Numerous well-known herbal extracts have been subjected to the phytosome technique includes Ginkgo biloba, grape seed, hawthorn, milk thistle, green tea, and ginseng; current study demonstrates better bioavailability and absorption with phytosomes as compared to the conventional methods. When used in phytosomal preparation, several standardized extracts including flavanoids and polyphenols have been shown to have enhanced bioavailability [134]. Liposomes are less stable than phytosomes. Phytosomes are widely used in cosmetics because of their improved skin penetration, which also improves the skin's absorption of phytoconstituents [135].

13 FACTORS THAT SHOULD BE CONSIDERED WHEN CHOOSING A COSMECEUTICAL PRODUCT FOR A PARTICULAR SKIN TYPE OR CONCERN

Protection, prevention, cleansing, and moisturizing are the vital parts of a powerful skincare schedule. There is a bewildering exhibit of cleaning agents for expulsion of cosmetics, contamination, and overabundance sebum and lotions for hydration and conveyance of gainful fixings. As a general rule, gel-based and bar chemicals are best for slick appearances, though cream or moisturizer based ones are better for typical to dry skin. Lotions supply humectant specialists, which bring water into the layer corneum from the climate and dermis underneath. Creams likewise incorporate occlusive specialists that go about as a boundary to transepidermal water misfortune. In practically all cases, items contain the two humectants, as hyaluronic corrosive, urea, and allantoin, and occlusives, including petrolatum, mineral oil, and lanolin. The particular FDA-endorsed dynamic and additionally useful corrective fixings that patients ought to search for in their items will rely upon their essential skin condition, concern, or objectives, as illustrated beneath [136].

Table 4. Demonstration of the factors that should be considered when choosing a cosmeceutical product for a particular skin type or concern.

S.no	Concerns	Problem	Factors to consider when choosing a cosmeceutical product	Reference
1	**Skin type**	Dry skin	In moisturizer recipes containing humectants and occlusives, emollients are utilized to work on understanding acknowledgment of the equation. Different substances utilized in private consideration items incorporate vitamin E, vitamin A (and other retinoids), sunflower oil (linoleic corrosive), biotin, vitamin D, vitamin B, and certain organic concentrates. In the event that a portion of these substances are available at fixations adequate for restorative viability, impacts on the skin physiology can be noticed.	[137]
		Oily skin	Tretinoin, glycolic corrosive, and azelaic corrosive further develop surface and sleekness somewhat. Grimes6 revealed fantastic improvement in unpleasant and sleek skin while utilizing a progression of salicylic corrosive substance strips in patients with skin Types V and VI. Salicylic corrosive strips likewise worked on the presence of developed pores	[138]
		Sensitive skin	It is essential to fix and keep up with boundary capability and diminish irritation. Regular saturating factors, lipid edifices, and ceramides. Forestalling contact with known aggravations, allergens, solvents, surfactants, and sharpening additives Suggesting items with a predetermined number of ingredients is savvy.	[136]
2	**Specific Skin Concern**	Hyperpigmentation	M with 0.3% retinol accomplished better outcomes in examination than 0.05% tretinoin for further developing photograph related	[136]

			hyperpigmentation. A uniform coloring can kept up with "light up" specialists that incorporate fixings like kojic corrosive, AHAs, licorice root, and water-dissolvable subsidiaries of L-ascorbic acid, tracked down in different items from cleaning agents to toners and creams.	
		Acne	A treatment routine for gentle to direct grown-up skin break out, items should hydrate, be viable, and cause insignificant to no disturbance. In skin break out inclined skin, noncomedogenic, sans oil items with either zinc oxide or avobenzone as a functioning fixing are suggested. Effective cell reinforcements, including resveratrol, quercetin, and cinnamic corrosive, give likely advantage to both the provocative parts of skin inflammation and photodamage.	[136]
		Aging	A retinoid-containing item ought to be remembered for everybody's skincare munititions stockpile to address the indications of skin maturing.	[136]
		Sun damage	sunscreens for the most part founded on para- aminobenzoic corrosive, its subordinates, cinnamates, different salicylates andbenzophenones, dibenzoylmethanes, anthraline derivatives,octocrylene and homosalate are every now and again utilized as sunblocking specialists. Items might contain a fixing that providesprotection against the bright A (UVA) sun beams and anotheringredient that shields from the bright B (UVB) sun beams, whichare bound to cause burns from the sun than the UVA sun beams.	[139]
3	**Ph level**		Beauty care products, because of their broad regular use could add to skin wellbeing support, through skin pH esteem control. the impact of corrective items on the skin surface pH concerned the impact of skin purifying items. To bar or decrease the gamble of skin disturbance, different definition approaches in skin purging items improvement are being utilized, including the choice of sufficient fixings to get legitimate purifying action	[140]

		however a low skin bothering strength impact.	
4	**Fragrance**	aromas are significant reasons for unfavorably susceptible contact dermatitis. Something like 35% of all hypersensitive reac-tions to beauty care products are because of aroma fixings (61-65), and roughly 1% of the unselected populace is sharpened to scents. The antagonistic response to scents seen most fre-quently by dermatologists is hypersensitive contact der-matitis. In examinations on hypersensitive responses to corrective items, fragrances represent 4%-18% of all re-activities, and antiperspirants/antiperspirants cause 5o/o-17% of all instances of unfavorably susceptible contact dermatitis.	[141]
5	**Allergen-Free**	Large numbers of aroma fixings which are unlisted are aggravations and can cause sensitivities, serious cerebral pain and asthma side effects. Scent can demolish asthma and maybe even add to its advancement in kids. Unsafe impacts of weighty metals in different beauty care products items like facial make-up have been assessed in writings. Weighty metals which can get gathered in the body throughout some undefined time frame are known to cause different medical conditions.	[142]

14 SPECIFIC CONSIDERATION OR PRECAUTIONS WHEN USING COSMETICS CONTAINING PHYTOSOME

While beauty care products containing phytosomes are for the most part thought to be protected, remembering explicit contemplations and precautionary measures is significant. Phytosomes are intended to improve the retention and bioavailability of dynamic phytoconstituents, however individual responses can fluctuate. Here are a few contemplations:

14.1 Patch test:

Patch tests are devices utilized in the recognizable proof of the etiologic specialist (s) of hypersensitive contact dermatitis. Prior to putting on a corrective item containing phytosomes to your whole face, play out a fix test on a little, unnoticeable area of skin. This decides whether you might have an unfavorable response or aversion to any of the fixings in the definition as the fix test can likewise be utilized to explore drug responses that manifest with skin sores coming about because of a late touchiness component, for example, maculopapular rash, DRESS (drug, rush, eosinophilia, fundamental side effects), fixed drug ejection. In spite of the fact that there is definitely not a conventional contraindication, fix tests ought to be kept away from in pregnant ladies [143].

14.2 Individual Sentivities:

Delicate skin is a condition described by stinging, consuming and tingling sensations. The determination, pathophysiology and treatment of delicate skin are still being talked about. Somewhat recently, concentrates on its the study of disease transmission have been performed, showing a high predominance and effect on personal satisfaction. Brazilian populace was likewise viewed as in these examinations. Beauty care products, environment changes and skin boundary weakness are the fundamental factors that contribute for skin hyperreactivity. Thus, the individual ought to know their sentivities towards substance before applyingor considering a particular cosmeceuticals [144].

14.3 Consultation with Dermatologists:

Restorative dermatology manages the excellence and presence of the skin-a most significant component of self-perception. Medicines utilized in surface level dermatology (cleanliness, hydration, assurance, fix) mean to upgrade the attributes of the skin, its life systems, its capability, and its imperativeness, to deliver tasteful enhancements. Correspondence with the patient is fundamental in clinical conferences and we accept that it has exceptional undertones in superficial dermatology that should be considered [145].

14.4 Consistency in use:

The utilization of corrective items normally works on the appearance and assists with the attitude of the client, Use items containing phytosomes routinely and every time to accomplish ideal outcomes. Skipping applications might affect the adequacy of the item. Where their utilization can be related with numerous known and obscure unfavorable responses from less serious nearby responses like disturbance, consuming sensation, and contact urticarial rash to fundamental responses like diseases and rhinoconjunctivitis [146].

14.5 Product Compatibility:

Now and again, the determination of fitting biocompatible materials as excipients would improve conceivable harmful impacts of the center materials, which is particularly helpful for phytochemicals with possible gamble to the human body. A notable model is salicylic corrosive, and a decrease of its skin bothering possibilities has been tracked down after joining into nanostructured lipid transporters (NLCs), which in this way expanded its clinical dose. In this way, it is vital to check item similarity before use [147].

14.6 Time of Application:

Daylight is a human cancer-causing agent. Numerous retinoid-containing beauty care products are utilized to safeguard harms brought about by daylight illumination. Since retinol is thermally unsteady and retinyl palmitate (RP) is generally more steady, RP is likewise broadly utilized as a fixing in superficial definitions. As a general rule, little is had some significant awareness of the photodecomposition of retinoids and the harmfulness of retinoids and their photodecomposition items on the skin's reactions to daylight. A few dynamic fixings in cosmeceutical items, for example, retinoids, are suggested for use at explicit times (e.g., evening). Understanding the ideal season of utilization for every item can amplify their viability and limit the gamble of unfavorable impacts [148].

15 ALREADY MARKETED COSMECEUTICALS PRODUCTS AS PHYTOSOMES DELIVERY SYSTEM

Various therapeutic uses of phytosomes have been developed to investigate the numerous advantages of phytosomes, including their capacity to boost the bioavailability of polar phytoconstituents. The following is a list of commercial goods on the market and certain phytosome patents:

Table 5. Shows the patented formulation of phytosome-cosmeceuticals.

S.no	Title of Patent	Patent no	Reference
1	Treatment of skin and wound repair with thymosin beta-4	US/2007/001 5698	**[149]**
2	Cosmetic and dermatological composition for the treatment of aging or photo damaged skin	EP1640041	**[56]**
3	Cosmetic and dermatological composition for the treatment of aging or photo damaged skin	EP1640041	**[56]**
4	Fatty acid monoesters of sorbityl furfural and compositions for cosmetic and dermatological use	EP1690862	**[150]**
5	Complexes of saponins with phospholipids and pharmaceutical and cosmetic compositions containing them	EP0283713	**[151]**

6	Complex compounds of bioflavonoids with phospholipids, their preparation and use, and pharmaceutical and cosmetic compositions containing them	UUS5043323	**[152]**
7	Fatty acid monoesters of sorbitol furfural and composition for cosmetic and dermatological use	EP1690862	**[152]**
8	Cosmetic and dermatological composition for the treatment of aging or photodamaged skin	EP1640041	**[153]**
9	Fatty acid monoesters of sorbitol furfural and compositions for cosmetic and dermatological use	EP1690862	**[154]**
10	Cosmetic and dermatological composition for the treatment of aging or photo damaged skin	EP1640041	**[155]**

16.CONCLUSION

Phytocosmeceuticals benefit from the ongoing progressions in prescription conveyance and focusing on advances. Fitting drug conveyance techniques are expected for the best scattering of dynamic fixings. Specifically, plant supplements that are hydrophilic naturally and inadequately retained might be conveyed securely, precisely, and productively utilizing phytosomes, a state-of-the-art prescription conveyance method. Consequently, the review investigates the benefits, underlying particulars, compound cosmetics, and creation technique for phytosomes. Among vesicular medication transporters, phytosomes structure a complex among phytochemicals and phospholipids, which brings about the improvement of ingestion and bioavailability of bioactive particles, along with worked on generally compound strength. The formation of phytosomes is a simple method to increase to a business level. Phytosomes are valuable helpful specialists due to their upgraded pharmacological and pharmacokinetic properties. A few phytosome zones will be unveiled before long as a feature of the cosmeceuticals.

Phospholipid based drug conveyance framework has been seen as promising for better and powerful conveyance of regular medication and can upgrade the rate and degree of medication retention across the lipoidal biomembrane. Phytosomes are novel phospholipid based drug conveyance framework, which deal further developed bioavailability of hydrophilic flavonoids and other comparative mixtures through the skin or gastrointestinal parcel.

They enjoy numerous particular upper hands over other regular plans. The detailing procedure for phytosome is straightforward and can be handily moved up to a business scale. The portrayal strategies and scientific methods are deep rooted for this kind of novel plan. A huge number are now endorsed for imaginative details, processes also, utilizations of phytosomes. All things considered,it has an extraordinary future for use in definition innovation and utilizations of hydrophilic plant compounds

LIST OF ABBREVIATIONS

PC- Phosphatidylcholine
PS- Phosphatidylserine
PE- Phosphatidylethanolamine
SEM- Scanning Electron Microscopy
TEM- Transmission Electron Microscopy
NMR- Nuclear Magnetic Resonance
FTIR- Fourier Transform Infrared

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