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PHYTOSOMES: A NOVEL HERBAL DRUG DELIVERY CARRIER FOR VARIOUS TREATMENTS

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ABSTRACT

Novel drug delivery system called as phytosomes was developed to incorporate standardized plant extract or water-soluble phytoconstituents into phospholipids to produce lipid compatible molecular complexes. Phytosomes is made up of two words and expressed the meaning of "Phyto" means plant and "some" means cell-like. There is and intermolecular bonding between the lipids used and the polyphenol. Formulations which are administered orally or topically, they have some limitations in bioavailability. For the enhancement of bioavailability of herbal extracts, this emerging technology is applied for various applications for orally as well as topically. These are the herbosomes that can travel from a hydrophilic to the lipid environment of the cell membrane and lastly to the blood. Herbal extract in form of phytosomes is generally bioavailable than the original extract due to enhancement in absorption and crossing lipid-rich biomembrane. For phytosomes mainly flavonoids are used as bioactive constituents as they show poor bioavailability. There is a dual advantage of phytosomes for topical pharmaceutical agents and cosmetics with improved efficacy and it can be used effectively as functional cosmetics. Phytosome is a connection between conventional drug delivery and novel drug delivery systems. The present review represents the recent advances and applications of herbal extract phytosome as a tool for drug delivery for various treatments.

KEYWORDS: phytosome, phytoconstituent, phosphatidylcholine, bioavailability, anti-inflammatory, flavonoid.

INTRODUCTION

The major drawback of plant extracts is their inability to properly cross the lipid membrane and deliver the drug at specific site of action.[1] Herbal plant extracts have reported therapeutic benefit. There always exhibit limited clinical utility as the synergistic effect of various natural ingredients after individual extraction of compounds.[2] For improvement of bioavailability, herbal products must have proper homeostasis between hydrophilic (for absorption into gastrointestinal tract fluid) and lipophilic (to cross lipid bio membrane balance).[3] The biologically active constituents of plants are mostly polar or water-soluble molecules. Toxicity and absorption problem limit the use of these constituents.[4] Due to their large molecular size, which cannot be absorbed by passive diffusion or due to their poor lipid solubility, water-soluble phytoconstituents like flavonoids, tannins, glycosidal aglycones etc are poorly absorbed thus severely limiting their ability to transport across lipid-rich biological membranes, resulting in their poor bioavailability.[5] In this novel drug delivery technology control of the distribution of drug, is achieved by incorporating the drug (plant actives) in carrier system or in changing the structure of the drug at molecular level. This mechanism aids in increasing solubility, stability, protection from toxicity, pharmacological activity, improved tissue macrophage distribution and sustained delivery.[6] The term phyto means "plant" while "some" means cell like. This are advanced forms of herbal formulation that contains bioactive phytoconstituents of herbal extract surrounded by a lipid.[7] Phytosomes show better physical stability, due to the creation of an H- bond between phospholipids and the phytoconstituents enhancing absorption of hydrophilic polar phytoconstituents resulting in enhanced bioavailability and greater therapeutic benefits.[8] Phosphatidylcholine, phosphatidylserine, phosphatidylethanolamine, phosphatidylinositol are the phospholipids used, but phosphatidylcholine are widely used because of their certain therapeutic value in case of liver diseases, alcoholic steatosis, drug induced liver damage and hepatitis.[9] These are better absorbed, utilized, and have better results. It has higher bioavailability than conventional drug. There are increased pharmacokinetic and pharmacodynamic properties.[10] The current review highlights the future scope and emerging technologies in the field of NDDS for the benefit of herbal and traditional medicines prepared from plant origins.[11]

PHYTOSOME STRUCTURE

These phyto-complex can be considered as a novel entity by reacting phospholipid (either of natural or synthetic origin) with selected botanical constituents with an appropriate solvent, and due to their physical and chemical efficiency.[12] The choline part attached with

hydrophilic chief active constituents as shown in Fig. 1.where the phosphatidyl part lipid soluble compound attached with choline bound complex. It results in the formation of lipid complex with better stability and bioavailability.[11] One class of phytomedicines currently receiving increased scrutiny is the polyphenols used as extract. These number in the thousands and include, but are not limited to, the various flavonoid subclasses. But many polyphenols are very poorly absorbed when taken orally, posing the greatest obstacle to routine clinical application.[5]

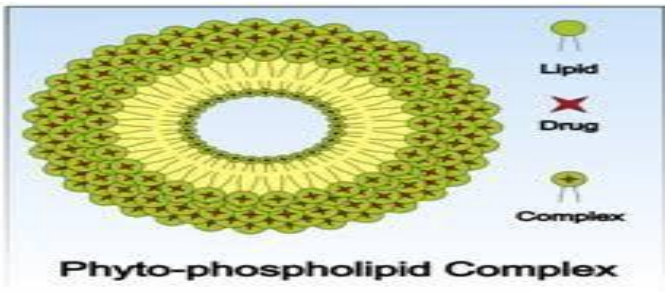

Fig. 1: Diagrammatic representation of a phytosome. It shows the complex formation between the phospholipid and the phytochemical extract. It also involves chemical bond (hydrogen bond).

DIFFERENCE BETWEEN THE LIPOSOMES AND PHYTOSOMES

The active principle is dissolved in the medium contained in the cavity or in the layers of the membrane in liposome, whereas in the phytosome it is an integral part of the membrane, being the molecules anchored through chemical bonds to the polar head of the phospholipids.[13,14] Several hundred phospholipid molecules are involved in liposomes for the entrapment and are usually now being used for cosmetic purposes. There is an interaction of 1- 4 phospholipid molecules with the phytoconstituents which are chemically anchored to each other in phytosome formation.[15] This difference results in phytosomes being much better absorbed that liposomes as shown in Fig. 3.Phytosomes are superior to liposomes in skin care products.[16,17] Comparison between phytosomes and liposomes is represented.[18]

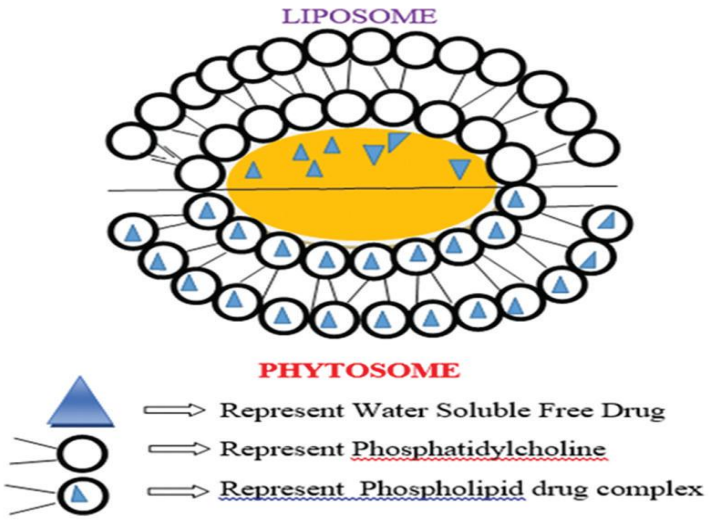

Fig. 2. Schematic representation between liposome (upper segment) and Phytosome (lower segment). In phytosomes the molecules are bonded together having chemical bond. While the liposome is an aggregate of many phospholipid molecules that can enclose other phytoactive molecules but without specifically bonding to them and having no chemical bond.

DRUG-PHOSPHOLIPID COMPLEX

By reacting with the standardized plant extract and a synthetic or natural phospholipid in a ratio ranging from 0.5-2.0 but usually 1:1 ratio is preferable phytosomes are prepared. Phospholipid is selected from group in which acyl group may be same or different and mostly derived from palmitic, stearic, oleic and linoleic acid like soya lecithin, from bovine or swine brain or dermis, phosphatidylcholine, phosphatidylethanolamine, phosphatidylserine.[19-23] The phytosomes are prepared by dissolving the phospholipid such as phosphatidylcholine, phosphatidyl ethanolamine, or phosphatidylserine and the herbal extract in the aprotic solvent such as methylene chloride, dioxane, and ethyl acetate.[24] After solubilisation, this mixture is concentrated to ensure bonding of reactants. Complex thus formed is isolated by solvent removal under vacuum, by lyophilisation or by precipitation with non-solvents.[22,25]

- **Phytochemicals for Phytosomes**

Crucial candidates of phytosome are usually terpenes, edusmocoides, ginsenoside, flavonoids, epigallocatechi-3-o-gallate, procyanidins, flavones polyphenols. Phytochemicals are defined as the substances found in edible fruits and vegetables that exhibit a potential for modulating human metabolism in a manner beneficial for the prevention of chronic and degenerative diseases.[26] Health promoting effects of flavonoids are reported by many

researchers. The scavenging of oxygen derived free radicals is an important effect of flavonoid. In vitro experimental systems also showed that flavonoids possess anti-inflammatory, antioxidant, anti-viral, and anti-carcinogenic properties.[27] This article includes some examples of medicinal plants in Table. 1 with different families and parts of plants containing flavonoid.[28]

Table 1: List of medicinal plants having the phytoconstituent as a flavonoid.

Botanical Name	Family	Common name	Plant type	Part used
Adhatoda vasica Nees	Acanthaceae	Adulsa	Shrub	Leaf
Catharanthus roseus Linn.	Apocynaceae	Sadafuli	Herb	Leaf and Root
Phyllanthus emblica Linn.	Euphorbiaceae	Awala	Tree	Fruit and Bark
Coriandrum salivum Linn.	Umbelliferae	Dhaniya	Herb	Leaf and Flower

- **Solvents**

Different solvents have been utilized by different researchers as the reaction medium for formulating phyto-phospholipid complexes. Aprotic solvents, such as aromatic hydrocarbons, halogen derivatives, methylene chloride, ethyl acetate, or cyclic ethers have been used to prepare phyto- phospholipid complexes but they have been largely replaced by protic solvents like ethanol and methanol as they have been successfully used for complex formation.[29,30]

- **Phospholipid**

A human biological membrane constitutes different classes of phospholipids, like phosphatidylethanolamine (PE), phosphatidylinositol (PI), phosphatidylcholine (PC), phosphatidic acid (PA), and phosphatidylserine (PS).[31] Phosphatidylcholine is an effective emulsifier because it consists of head or hydrophilic moiety choline (serine) and a tail or lipophilic moiety phosphatidyl. Hence phosphatidylcholine produce a lipid compatible molecular complex with phytoconstituents.[32] In phytosome preparation, the phosphatidylcholine having a great role in biological membrane and also act as hepatoprotective(18). The structural representation is shown in Fig. 3. PC molecules exhibit hepatoprotective activities, and have been reported to show clinical effects in the treatment of liver diseases, such as hepatitis, fatty liver, and hepatocirrhosis.[33,34]

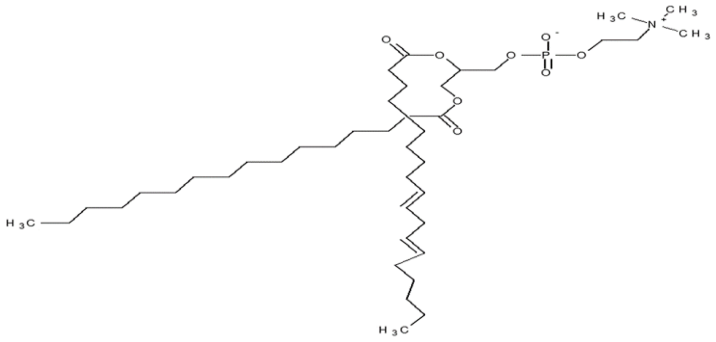

Fig. 3. Molecular structure of phosphatidylcholine. This phospholipid is composed of a choline head group and glycerol phosphoric acid, with a variety of fatty acids. Usually, one is a saturated fatty acid (in the given figure, this is palmitic acid (hexadecanoic acid, H_3C-$(CH_2)_{14}$-COOH; margaric acid (heptadecanoic acid, H_3C-$(CH_2)_{15}$-COOH).

PREPARATION OF EXTRACT OF VARIOUS PARTS OF PLANTS

- **Extract of flowers**

The flowers were washed, air dried, homogenized to fine powder and stored in airtight bottles for future use. 30g of dried powder was first defatted with petroleum ether and then extracted by soxhlation using 80% methanol. The extract was concentrated in a rotatory vaccum evaporator and further dried in desiccator till use.[35]

- **Extract of leaves**

The leaves of plant were air-dried until dryness at room temperature and under shade. The dried leaves were then powdered to a fine grade by using laboratory scale mill. Further it was sequentially extracted successively with ethanol using soxhlet apparatus. The solvent was removed and concentrated in a rotary evaporator and water bath. The dried extracts were stored in refrigerator for further studies.[36,37]

- **Extract of seeds**

Seeds were finely powdered to yield flour, then for example 100 g of flour was accurately weighed and soaked in 1 L of methanol at room temperature (25°C) with continuous agitation for 24 hours using a magnetic stirrer. The obtained extract solution was filtered and methanol was evaporated using a rotary evaporator at 30°C and 120 rpm. After complete solvent evaporation, the yielded dry extract was stored at 4°C until further use.[38]

PROPERTIES OF PHYTOSOMES

- **Physicochemical properties**

Phytosome, a product is obtained from the stoichiometric reaction between phospholipid and plant extracts.[39] Cell like structure is observed when in contact with hydrophilic environment in phytosomes, but in a liposome the chief constituent interacts within the internal pocket while in phytosome the chief active constituents are enveloped the polar head of phospholipid and becoming an integral part of the membrane.[2] Solubility of Phytosome varies as: soluble in aprotic solvents, moderately soluble in fats, insoluble in water and relatively unstable in alcohol.[40,41] It can be deduced that the fatty chain gives unchanged signals both in free phospholipid and in the complex from the 1HNMR and 13CNMR data, which indicates that long aliphatic chains are wrapped around the active principle, producing lipophilic envelope.[42] Phytosome size varies from 50 nm - 100 μm.[8]

- **Biological properties**

Phytosomes shows better result than the conventional herbal extract or non-complexed extracts as they absorbed and utilized better, hence they produce more bioavailability, which has been demonstrated by pharmacokinetic studies or by pharmacodynamic tests in experimental animals and inhuman subjects.[42] Phytosomes improve absorption of phytoconstituents through skin, to regulate the physiology of skin compositions. The improvement in the functioning of skin suggests the functional importance of the phytosomes.[43]

MECHANISM OF PHYTOSOME TECHNOLOGY

Phytosomes technology is mainly result with complexation of polyphenols with phospholipid in 1:1 ratio or 1:2 results in the formation of phytosomal complex with lipid covering around the constituents.[44] Molecules are anchored through chemical bonds to the polar choline head of the phospholipid. Precise chemical analysis indicates the unit phytosome is usually a flavonoid or polyphenol molecule linked with at least one phosphatidylcholine molecule. The result is a little microsphere or cell is produced.[42] Phospholipid complexes may be absorbed from the GIT through enterocyte based transport, and drug transport to the systemic circulation as shown in Fig. 4 via intestinal lymphatic system which has widespread network throughout the body. The major advantage of lymphatic transport is to bypass the first-pass metabolism and applicable for targeted drug delivery.[45]

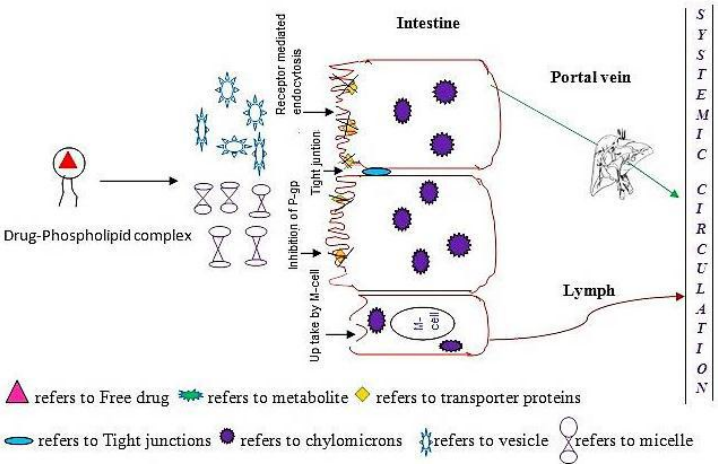

Fig. 4. Representation of mechanism of phospholipid complex. Phytosomes enhances the absorption of lipid insoluble polar phytoconstituents through oral as well as topical route showing better bioavailability, hence significantly greater therapeutic benefit. Absorption takes place towards systemic circulation via lymphatic system as it bypass the first pass metabolism.

ADVANTAGES

- Due to their more skin penetration and high lipid profile phytosomes are widely used in cosmetic preparation.
- As the absorption of chief phytoconstituent is improved, its dose requirement is also reduced.[25]
- Herbal phytosome process produces a little cell whereby the valuable components of the herbal extracts are protected from destruction by digestive secretions and gut bacteria.
- in the phytosome process phosphatiylcholine is used which acting as a carrier and also nourishes the skin, as it is the essential part of cell membrane.[11,46]

DISADVANTAGES

- Although Phytosome having so many advantages but instead of that this technology has some disadvantages like rapidly elimination of phytoconstituents from the phytosome.[47]

METHODS OF PREPARATION

- **Solvent evaporation method**

The specific amount of herbal extract and soya lecithin were taken into a 100 ml round bottom flask and refluxed with 20 ml of acetone at a temperature 50 - 60^{o}C for 2 h. The mixture is concentrated to 5-10 ml to obtain the precipitate which was filtered and collected.

The dried precipitate phytosome complex was placed in amber coloured glass bottle and stored at room temperature.[29]

- **Rotatory evaporator method**

The specific amount of extract e.g. curcumin was prepared by this method and soya lecithin were dissolved in dichloromethane in a rotary round bottom flask followed by stirring for 1 hour at a temperature not exceeding 40°C. Thin film of the sample was obtained to which n-hexane was added and continuously stirred until monolayer of phospholipid and then add phosphate buffer 6.8 and precipitate obtained was collected, placed in amber coloured glass bottle and stored at room temperature.[48]

- **Antisolvent precipitation technique**

Known quantity of drug, phospholipids and polymer is taken in round bottom flask (RBF) and refluxed with specific solvent not exceeding 600C for 2 hours. The mixture is concentrated to 5-10ml and n –Hexane is carefully added to it with continuous stirring to get the precipitate, which is filtered and kept in vacuum desiccator overnight. The dried precipitate is crushed in mortar and sieved through 100- mesh size. As a result, phytosomes loaded with drug are obtained, which are placed in amber coloured glass bottles at room temperature.[42]

- **Mechanical dispersion method**

In this method, the lipids dissolved in organic solvent are brought in contact with aqueous phase containing the drug.[48] Initially, pc is dissolved in diethyl ether which is later slowly injected to an aqueous solution of the phytoconstituents to be encapsulated. Phyto-phospholipid complex formation takes places by subsequent removal of the organic solvent under reduced pressure. Novel methods for the phospholipid complex preparation includes super critical fluids (SCF), which include gas anti-solvent technique (GAS) compressed anti solvent process (PCA), supercritical anti solvent method (SAS).[49,50]

EVALUATION OF PHYTOSOMES

- **Visualization**

For visualization, transmission electron microscopy (TEM) and by scanning electron microscopy (SEM) can be used.[51]

- **Determination of % yield**

% yield of phytosome complex was determined by the following formula:

$$(\%)\ \text{Yield} = \frac{\text{(Practical yield)}}{\text{(Theoretical yield)}} \times 100$$

- **Determination of drug content**

100mg complex is dissolved in 10ml methanol ti determine the drug content. After suitable dilution absorbance was determined by UV Spectrophotometer at 269 nm and drug content was determined.[52]

- **Entrapment efficiency**

The entrapment efficiency of a phytosomal formulation can be determined by subjecting the formulation to ultracentrifugation technique.[53]

- **Transition temperature**

Differential scanning calorimetry can be used for the determination of transition temperature of the vesicular lipid systems.[51]

- **Spectroscopic evaluations**

The interaction between the phytoconstituent molecule and the phospholipid molecule is very important which can be determined with the help of following spectroscopic methods:

- **1H-NMR**

There are several examples whose examples whose NMR spectra can help to determine the interaction between the phospholipid and phytoconstituent. By NMR evaluation a marked change can be seen in 1H-NMR signal of those particular atoms which take part in the complex formation.[51,54]

- **13C-NMR**

The signals are broadened and some are shifted, while most of the resonances retain their original sharp line shape of fatty acid chains which are corresponding to the glycerol and choline portion of the lipid (between 60–80 ppm). After heating to 60˚, all the signals belonging to the flavonoid moieties reappear, although they are still very broad and partially overlapping.[55]

- **Ultraviolet spectra**

Samples that reflect different absorption in the UV wave- length range can be used to characterize own structural properties. Most studies have revealed no differences in the UV ab- sorption characteristics of constituents before and after complexation. Xu et al. prepared luteolin-phospholipid complexes and found that the characteristic peaks of luteolin remained present.[56]

- **Biological evaluation**

For evaluation of Phytosome using in-vitro and in-vivo models can be selected based upon the phytoconstituents the therapeutic activity which are present in the formulation. For example, for the assessment of ant-diabetic Phytosome formulation, the blood glucose or sugar is analysed.[8]

EXAMPLES OF PHYTOSOME FORMULATION

Plant extract or phytoconstituents that are incorporated in the Phytosome technology are reported in the literature but some examples are from them such as Ginkgo biloba, Grape seed, Centella, Green tea, and Ginseng.[8] In Table. 2 some commercial phytosomes formulations are listed.[22,54,57-61]

Table 2: Some Examples of Phytosome Formulations.

Phytosomes	Phytoconstituents	Indications
Green Tea PhytosomeTM	Epigallocatechin from Thea sinensis	Nutraceutical, systemic antioxidant. Anticancer
Ginseng PhytosomeTM	37.5 % ginsenosides from immunomodulator Panax ginseng	Nutraceutical and immunomodulator
Ginkgo biloba Phytosome TM	24 % Ginkgo flavone glycosides from Ginkgo biloba	Protects brain and vascular lining, anti-ageing agent.
Centella	Terpenes	Used to treat Vein and skin disorders.
Grape seed phytosomeTM	Procyanidins from vitis vinifera	Nutraceutical, systemic anticancer, antioxidant
Curcumin (Merinoselect) Phytosomes	Polyphenol from Curcuma Longa	Cancer chemo preventive agent improving the oral bioavailability and the plasma.
Glycyrrhiza phytosome	18-beta glycyrrhetinic acid	Anti-inflammatory activity
Hawthorn phytosome TM	Flavonoids from Crataegus sp.	Nutraceutical, cardio-protective and antihypertensive

APPLICATIONS OF PHYTOSOMES

- Ginkgo phytosome, prepared from Ginkgo biloba leaves showed better therapeutic effects in the treatment of Raynaud's disease and intermittent circulationin comparison to the conventional standardized plant extract.[62]
- Bacopa monnieri plant having antiamnesic activity has Bacopaside well-known chief constituents present in it. To prepare phytosome from bacopaside and its in vivo evaluation on rodents is an attempt that needed to be studied. There is remarkably great change in the therapeutic efficacy of the compound prepared by phospholipid as compare to simple B. monnnieri extract.[63]
- Then the single constituent the silymarin phytosomes showed much higher specific activity and a longer lasting action, with respect to percent reduction of edema, inhibition of myeloperoxidase activity, antioxidant and free radical scavenging activity.[64]
- Then the single constituent the silymarin phytosomes showed much higher specific activity and a longer lasting action, with respect to percent reduction of edema, inhibition of myeloperoxidase activity, antioxidant and free radical scavenging activity.[64]
- Merivaselect® phytosomes Curcumin polyphenols,[65] obtained from Curcuma longa family Zingiberaceae, are powerful scavengers of superoxide and hydroxyl free radicals.[66] They also lower the incidence of mutations and genetic disorders by the ability to prevent DNA oxidative damage.[67] Potential effect in cancer chemoprevention,[68] inflammation[69] and neuro-degenerative diseases.[70]
- The quercetin phospholipid phytosomal complex was developed by a simple and reproducible method showed that the formulation exerted better therapeutic efficacy as compared to the non-phytosomal conventional in rat liver injury induced by carbon tetrachloride.[21]
- The rutin in its free form it was observed that the Rutin phytosomes were better able to penetrate the impermeable stratum corneum. Skin uptake of Rutin phytosomes was 33 ± 1.33% whereas that of Rutin was 13 ± 0.87%.[71]
- Later formulated and characterized phytosome suspension of Urtica dioica (UD). These findings suggest that herbosome suspension of Urtica dioica(100 mg/kg) shows better antidiabetic activity in comparisons to the powdered marketed formulations of Urtica dioica.[72]

CONCLUSION

Preparation of phytosomes is reproducible and simple. For plant extract a plant will be selected for flavonoid isolation and phytosome utilization for the treatment severe disease condition. The technology shows cost effective delivery of phytoconstituents and synergistic effects as functional cosmetics. Apart from that the phospholipids used have their own beneficial effect to the body. The information gathered herein will be useful for the researchers who wish to explore a vesicular drug delivery system which encompasses effective drug on target site without its metabolism. The formulation methodology for phytosome is simple and can easily be used on commercial scale. Phytosome is very useful in cosmetology also. It has a great future for use in formulation technology and applications of hydrophilic plant compounds as far as the potential of phytosome technology is concerned.

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