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PHYTOSOMES: AN INNOVATIVE APPROACH TO ENHANCE THE BIOAVAILABILITY AND THERAPEUTIC EFFICACY OF HERBAL EXTRACT

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ABSTRACT: The use of herbal medicines to treat various disorders is widespread around the world. People are drawn to therapeutic herbs because of their minimal side effects. The low absorption, lower bioavailability, and restricted penetration through biological membranes of the traditional dosage form limit the usage of herbal medicines. In order to address all of these problems with herbal extract or plant actives, a revolutionary drug delivery system known as Phyto-Phospholipid Complexes (Phytosome) approaches was introduced. Using this cutting-edge technology technique, the desired therapeutic effect was produced at little dose. Enhanced pharmacokinetic properties, skin penetration via strategic targeting to switch from hydrophilic to lipophilic environments, and better stability as a result of chemical coupling. The most recent research on the potential use of phytosome complexes for treating various disease conditions, their marketable form, the mechanism of phytosome transportation, and the prospects for the future are summarized in this article. The description of Phytosomes method is able to provide new ways and boundless limit as revolutionary medicinal therapy.

KEYWORDS: Phytosomes, Herbal Extract, Delivery System, Herbal medicines, Bioavailability

I. INTRODUCTION

Since the beginning of time, people have employed herbal remedies. In order to treat illness and enhance people's general health and wellness, it involves using plants as medications.[1] The majority of herbal medications' bioactive ingredients are polar or water-soluble compounds.[2] It has frequently been noted that the natural ingredient synergy is lost when the constituents of an extract are isolated and purified, which may result in either a partial or total loss of particular bio-activity for the pure constituent.[3] The progression of innovative drug delivery systems (NDDS) for plant medicines has drawn a great focus in recent years. Idealistically, the novel carriers should adhere to two criteria. First, the medication should be administered over the course of therapy with a pace determined by the body's necessities. Second, it must guide the active component of the plant medicine on the site of action. Numerous innovative formulations utilizing bioactive and plant extracts have been reported, including polymeric nanoparticles, phytosomes, transferosomes, nanocapsules, herbosomes, liposomes, nanoemulsions, microspheres, and ethosomes.[4]

The phyto-phospholipid complex (also known as a phytosome) is a innovative medication delivery method. They are more capable of penetrating lipid-rich biomembranes and reaching the blood eventually.[5] Phospholipids from soy, particularly phosphatidylcholine (PC), can be used as lipid-phase components to create phytoconstituents that are compatible with lipids.[6] Phytosomes are more adept at moving from a hydrophilic state to the enterocyte cell membrane's lipid-friendly environment than they are in doing so into the cell and ultimately into the circulation.[7,8] Therefore, the most beneficial use of phytosomes is the drug absorption via reversible compounds with phospholipids, which demonstrated that these complexes have more potent anti-inflammatory and vasokinetic effects as compared to those seen after administering the equal amount of the substance in free form.[9] A potential technique for the delivery of herbal medicines and nutraceuticals is phytosomes. Numerous well-known plant extracts, like grape seed, ginseng, milk thistle, ginkgo biloba, green tea and hawthorn have experienced phytosomes procedure.[10]

II. METHOD OF PREPARATION OF PHYTOSOMES –

Different processes are used to combine 1 mole of phytoconstituents with 3-2 moles natural or synthesized phospholipid, primarily phosphotidylcholine. The range from 0.5 to 2.0 moles is the most ideal ratio for the development of complexes between these two moieties.[11-12] The table below describes numerous phytosome preparation techniques.

Table 1- Methods for the preparation of Phytosomes

Methods	Procedure
Solvent evaporation method	The required quantity of plant material, phospholipids, and 20 mL of acetone were added to a 100 mL round bottom flask, which was then refluxed for two hours at 50–60°C. The mixture was reduced to 5–10 mL and then filtered to remove the precipitation. In an amber-colored glass container, the dried precipitate phytosome complex was kept at room temperature. [13]
Rotary evaporation technique	A rotating circular bottom flask was used to dissolve the appropriate amount of plant material and phospholipid in 30 mL of tetrahydrofuran. Then the mixture was agitated for three hours below 40°C. N-hexane was introduced after a thin layer of the sample was collected, and the mixture was continually agitated with magnetic stirrer. The precipitate was taken out and cooled to room temperature in a glass container that was amber in colour.[14]
Ether-injection technique	In this process, an organic solvent was used to break down the drug lipid complex. After that, by gradually infusing the combination into a heated aqueous agent, vesicles are produced. The focus of amphiphiles determines their state. When the concentration was low, amphiphiles take on a monomer form, but as the concentration increases, other configurations, such as disc, cylinder, cubic, circular, or hexagonal structures, may develop.[15]
Mechanical Dispersion method	In this procedure, the drug-containing aqueous phase comes into touch with the lipids wherein an organic solvent has been used to dissolve. The phytoconstituents to be encapsulated are initially dissolved in diethyl ether, which was then gently added to an aqueous solution. The subsequent removal of the organic solvent under reduced pressure results in the production of the phytophospholipid complex. Supercritical fluids (SCF), which comprise the compressed anti-solvent procedure (PCA), supercritical anti-solvent method (SAS), and gas anti-solvent technique (GAS), were new techniques for producing phospholipid complexes.[16,17]
Lyophilization technique	Both the natural and the synthetic phospholipids and phytoconstituents were disbanded in various solvents, and then additional solutions containing the phytoconstituent were put into solutions already containing the phospholipids, which were then stirred until complex formation occurred. By lyophilization, the produced complex is isolated.[18]
Salting out method	Phosphatidylcholine and phytoconstituents were dispersed in an aprotic solvent, such as dioxane or acetone, where the solution was agitated overnight. Precipitation was then used to separate the created complex from a non-solvent, such as n-hexane.[19]
Antisolvent precipitation technique	The correct amount of medication and soy lecithin was placed in a 100 ml round bottom flask, and it was refluxed for two hours with 20 ml of dichloromethane at a temperature of no higher than 60 oC. The mixture was condensed to 5–10 ml. Hexane (20 ml) was carefully added while being continually stirred to produce the precipitate. After filtering and collecting, the precipitate was stored overnight in vacuum desiccators. The dry precipitate was crushed in a mortar, and it was afterwards sieved through #100 meshes. Complex was crushed up and kept at room temperature in a glass bottle with an amber hue.[20]
Super Critical Fluids (SCF)	Three separate traditional procedures were used to create the complex. Comparing the complex created by the supercritical anti-solvent precipitation process favourably to solvent evaporation, lyophilization, and micronized purarin. Two SCF techniques used. GAS (Gas anti-solvent technique) and SEDS (Solution enhanced dispersion by supercritical fluids) were used for the preparation of complexes. The drug and phospholipid solutions were individually assorted with a supercritical antisolvent in the GAS method until the desired final pressure was attained. The reaction vessel was then maintained at a constant 38 °C and 10 mPa pressure for 3 hours without

	any agitation. In the SEDS method, the supercritical anti-solvent and liquid solution were constantly added to the precipitation unit. A 0.1 mm diameter nozzle was used to introduce carbon dioxide gas into a solvent-containing combination of phospholipids and purarin. With a drug-to-phospholipid mass ratio of 1%, a temperature of 35 °C, a purarin concentration of 100 mg/ml and a pressure of 10 mPa, the experimental conditions were optimized. The final procedure generated a 93% yield complex.[16,21]

III. VARIOUS PROPERTIES OF PHYTOSOMES:

Chemical properties: To create phytosomes, a natural material and organic phospholipids like soy phospholipids are combined. By reacting stoichiometric concentrations of the substrate and phospholipid in the right solvent, one can create this complex. Spectroscopic studies have signified that the primary phospholipid-substrate interaction results from creating the hydrogen bonds between the polar functionalities of substrate and phosphate and ammonium groups of phospholipids.[22]

Phosphatidylcholine: This can be inferred by contrasting the NMR of the complex with that of its pure predecessors. The fatty chain's signals essentially remain unaltered. These findings suggested that the two long aliphatic chains wrap all over the active ingredient to create a lipophilic envelope for protecting the catechin and the polar head of the phospholipid.[23]

Biological properties: Modern herbal compounds called phytosomes are better absorbed, used, and hence offer better effects as compared to the traditional plant extracts. It has been shown that the phytosome has a more bioavailability than the less complexed botanical derivatives.by conducting pharmacodynamic and pharmacokinetic testing on humans, animals, and other test subjects.[24]

IV. CHARACTERIZATION AND EVALUATION OF PHYTOSOMES-

Physical size, percentage of solutes entrapped, purity and quantity of the starting ingredients, membrane permeability and chemical composition are only a few examples of the parameters that affect how phytosomes behave in physical and biological systems. The phytosomes are therefore evaluated for their physical characteristics, like their size, shape, distribution, percentage of drug capture, percentage of drug release, and chemical make-up. Infrared spectroscopy (IR), differential scan calorimetry, nuclear magnetic resonance (NMR), transmission electron microscopy (TEM), photon correlation spectroscopy (PCS), percentage drug entrapment, solubility studies, etc. are used to characterize them. [25]

A. Characterization techniques:

1.Visualization: Transmission electron microscopy (TEM) and scanning electron microscopy (SEM) are both able to make phytosomes visible.[26]

2. Particle size and zeta potential: By employing a computerised inspection system and photon correlation spectroscopy (PCS), dynamic light scattering (DLS) can be utilized for deciding particle size and zeta potential. [27]

3. Transition temperature: To determine the vesicular lipid system's transition temperature, differential scanning calorimetry is performed.[28]

4. Surface tension measurement: the evaluation of the surface tension activity of a medication in dilute solution can be done by using the ring method in a Du Nouy ring tensiometer. [29]

5. Entrapment efficiency: To ascertain how well phytosomes are capable of capturing a drug, employ the ultracentrifugation technique.[30]

6. Vesicle stability: By tracking the evolution of vesicle size and shape, the stability of vesicles can be predicted. Mean size can be measured with DLS, while structural changes can be tracked with TEM. [31]

7. Drug content: A customized high performance liquid chromatography method or proper spectroscopic method can be employed for quantifying the medication amount. [32]

B. Evaluation of Phytosomes:

The following spectroscopic techniques are immersed to confirm the complex development or to inspect the reciprocal interaction in between the phytoconstituent and phospholipids.

Proton-Nuclear Magnetic Resonance (¹H-NMR): Bombardelli *et al*. examined the (+) catechin's NMR spectra as well as that of its stoichiometric combination with distearoylphosphatidylcholine. The 1H-NMR signal coming from the atoms involved in the complex's creation undergoes a noticeable change in nonpolar solvents, but there is no summation of the signal specific to each individual molecule. In order to prevent the proton from being released, the signals from the flavonoids' protons must be strengthened. When it comes to phospholipids, all of the signals expand while the singlet corresponding to the choline's N(CH3)3 undergoes an upward shift. The sample is heated to 60 °C, which causes the emergence of certain new broad bands that primarily correspond to the resonance of the flavonoid moiety. [33]

Fourier-Transformed Infra-Red (FT-IR) Spectroscopy (FTRI): By contrasting the spectrum of the complex with the spectra of the individual components and their mechanical mixes, IR spectroscopy can also be used to confirm the complex's creation. When microdispersed in water or included in very basic cosmetic gels, FTIR spectroscopy is also a helpful method for controlling the stability of phytosomes Furthermore, the stability may be verified by contrasting the complex's spectra in solid form (phytosomes) with that of its microdispersion in water following lyophilization, at various times. For simple formulations, it is required to subtract the cosmetic form's spectrum at various points and then contrast the resulting spectrum of the complex as a whole. [34]

X-ray diffraction (XRD): The structure of crystalline materials, including atomic arrangement, crystalline size, and flaws, can be studied via XRD analysis. Results utilising a graphite monochromatic at a count rate of 103.99 C with a Phillips X-Ray diffractometer (Model 1130/90). Currently, X-ray diffraction is a useful technique for analysing the microstructure of some amorphous materials as well as crystalline ones. On active ingredients or active constituents of phytophospholipid complexes, PCs, and their physical mixes, X-ray diffraction is generally conducted. [35]

C. *In vitro* and *In vivo* evaluations

Selection of *in-vitro* and *in-vivo* evaluation models is depend on the anticipated therapeutic efficacy of phytoconstituents obtainable from the phytosome. For instance, the antioxidant and free radical scavenging activity of phytosomes can be used to evaluate *in-vitro* antihepatotoxic efficacy. To evaluate produced phytosomes' *in-vivo* anti-hepatotoxic activity, their impact on animals when exposed to thioacetamide, paracetamol, or alcohol-induced liver damage, examining hepatotoxicity is possible. The *in-vivo* safety evaluation process is described in research on the skin sensitivity and tolerability of a commercial product called glycyrrhetinic acid phytosome ointment. [10,36]

V. APPLICATIONS OF PHYTOSOME TECHNOLOGY

When compared to the traditional plant extracts, other phytosome compounds have shown meaningful therapeutic results.

a. Hepatoprotective Effect of Phytosome.

Phosphatidylcholine is a crude component that, like other carriers used in different drug delivery methods, also has a lot of medicinal advantages. [37] It will be demonstrated that phosphatidylcholine's synergistic impact protects the liver. Phospholipids can occasionally have a nutritional purpose. Silybum marianum, also known as milk thistle, is the subject of the majority of phytosome investigations because it contains powerful liver-protecting flavonoids. Three flavonoids with a fully saturated C ring, or flavonols, make up the majority of silymarin. The three main compounds are silybin, silydianin, and silychristin. Silybin is a flavonolignan that probably formed naturally in the plant when a flavonol and a coniferyl alcohol combined. The strongest of the three is now understood to be silybin. Silymarin has been demonstrated to be effective in treating a variety of liver conditions, like cirrhosis, hepatitis, fatty infiltration of the liver (chemical and alcohol-induced fatty liver), and bile duct inflammation. Silymarin's antioxidant abilities significantly increase the liver's tolerance to harmful substances. The Milk thistle plant produces flavonoids in its fruit that have been shown to have hepatoprotective properties. The main and most effective component of Silymarin, the milk thistle flavonoids complex, is silybin. Although Silybum marinum's standardised extract is a great liver protector, it is not well absorbed when taken orally. [38,39] According to Busby et al., a Silymarin phytosome demonstrated superior fetoprotectant action against ethanol-induced behavioural impairments to uncomplexed Silymarin. [40] A human investigation has been executed by Barzaghi et al. [41] to evaluate the absorption of Silybin when it was directly linked to PC.

b. Cardiovascular properties of phytosomes: An anthocyanidin-based phytosome preparation called Leucoselect® PHYTOSOME is available. Polyphenols and phospholipids have formed a complex to form the grape seed phytosome. It is cardioprotective and exhibits significant antioxidant activity.[42] The effectiveness of ginkgo selected phytosomes was shown to be 30–60% higher than that

of ginkgo selected to treat the peripheral vascular illness (such as Raynaud's disease and intermittent claudication). Additionally recently confirmed as a cardioprotective agent is ginkgoselet phytosome. [43]

c. Anti-aging properties of Phytosome: The utilisation of phytosomes as a delivery mechanism in the cosmetic industry presents novel potential for the use of active substances. Investigations into the Ginkgo Biloba PHYTOSOME for the treatment of skin ageing linked to superficial capillary blood flow have been conducted. Oral G. biloba extracts are used to increase peripheral circulation, and topical G. biloba phospholipid complexes have been shown to increase skin microcirculation. The use of Silymarin PHYTOSOME® in treating ageing skin has additionally documented, along with a study of PHYTOSOME®'s function in functional cosmetics.[44,45,46]

d. Improved bioavailability and anti-oxidant properties: Greenselect phytosome contains a standardized polyphenol fraction (not less than 66.5%) which is obtained from the leaves of green tea and largely characterized by the presence of epigallocatechin and its derivatives. These substances are potent homeostasis-breaking biochemical process modulators in major chronic degenerative disorders like cancer and atherosclerosis. Bilberry (Vaccinium myritillus) extract anthocyanosides were complexed to produce the mirtoselect phytosome. It strengthens capillaries, lowers aberrant blood vessel permeability, and has strong antioxidant properties. According to numerous research, phyto-phospholipid complexes can enhance topical absorption, hence raising bioavailability and lowering the required dose. Therefore, it has the potential to greatly increase therapeutic advantages. Hesperetin was combined and complexed with hydrogenated phosphatidyl choline to create a new hesperetin. Additionally, Mukherjee et.al. investigated its antioxidant activity and pharmacokinetic studies in CC14-impaired rats. The study's findings revealed that the phytosome had strong antioxidant activity. According to pharmacokinetic studies, phytosomes have a higher bioavailability than the parent molecule at the same dosage.[47,48] OleaselectTM PHYTOSOME, a commercially available phytosome based on the polyphenols in olive oil, is on the market. It has strong anti-inflammatory, antioxidant, and antihyperlipidemic properties. It is cardioprotective and prevents LDL cholesterol from being oxidized. [30,49]

VI. COMMERCIAL PHYTOSOMES PRODUCTS:

Pharmacokinetic and pharmacodynamic studies in laboratory animals and human volunteers have shown that the phytosome has a higher bioavailability as compared to non-complexed botanical counterparts. Associated issues have been researched using various commercially accessible goods. The table below describes the formulation of phytosomes that is accessible commercially and has a variety of medicinal uses.

Table 2- Commercially available Phytosomes of various therapeutic applications [50-58]

Commercial product	Biological Source	Indication
SILYBIN PHYTOSOME™ (SILIPHOS®)	Silybium maranium	Hepatoprotective, cirrhosis, hepatitis, and Inflammation, antioxidant for liver and skin, Food Product
NARINGENIN PHYTOSOME™	Citrus aurantium	Antioxidant activity
GINKGOSELECT PHYTOSOME®	*Ginkgo biloba* L.	Healthy brain function, Antioxidant activity, Vascular health, Cognitive health support
GINKGO BILOBA PHYTOSOME™	*Ginkgo biloba* L.	Cardio-protective, antioxidant activity
LEUCOSELECT PHYTOSOME®	Vitis vinifera L.	Antioxidant, UV protectant
GREEN TEA PHYTOSOME™	Camellia sinensis	Food Product, Nutraceutical, hepatoprotective, anticancer, Antioxidant, anti-inflammatory, atherosclerosis, antidiabetic
VIRTIVA®	Ginkgo biloba L.	Cognition Increaser.
CURCUMIN PHYTOSOME™, CURCUVET®(MERIVA®)	Curcuma longa	Osteoarthritis, Anticancer, Anti-inflammatory
SERICOSIDE	Terminalia serica	Anti-Wrinkle

ECHNIACEA PHYTOSOME™	Echniacea angustifolia	Nutraceutical, immunomodulatory
ESCIN ß SITOSTEROL, PHYTOSOME™	Aesculus hippocastanum	Anti-oedema and vasoactive property
ESCULOSIDE PHYTOSOME™	Fraxinus ornus	Vasoactive, anticellulite
VISNADEX™	Ammi visnaga	Improve microcirculation
CENTELLA TRITERPENOID PHYTOSOME™	Centella asiatica	Skin disorders, anti-hair loss agent, wound healing, antiulcer
NARINGENIN PHYTOSOME™	Citrus aurantium	Antioxidant
HAWTHRON PHYTOSOME™	Crategus oxyacanthoides	Nutraceutical, cardioprotective and antihypertensive
CUCURBITA PHYTOSOME™	Cucurbita pepo	Anti-inflammatory, Benign prostatic hyperplasia
ESCULOSIDE PHYTOSOME™	Fraxinus ornus	Vasoactive, anticellulite
PYCNOGENOL PHYTOSOME™	Pinus maritime	Anti-inflammatory, Antiallergic, antiwrinkle,
MILLET PHYTOSOMETM	Panicum miliaceum	Beauty food for skin, nails and hairs, Antistress
ZANTHALENE PHYTOSOME™	Zanthoxylum bungeanum	Soothing and Anti-reddening
SWERTIA PHYTOSOME™	Swertia alternifolia	Antidiabetic
XIMILENE AND XIMENOIL PHYTOSOME™	Santalum album	Improve microcirculation
MADEGLUCYL PHYTOSOME™	Syzygium cumini	Antihyperglycemic,anti-inflammatory, antioxidant

VII. PHYTOSOMES CONTAINING DOSAGE FORMS-

Oral and topical administration of phytosome preparations are both options, but to maximise the formulation's bioavailability, it's essential to research the disintegration and dissolution time of dosage forms. Below are few examples of phytosome dosage forms. [59]

Hard gelatin capsules: the maximum quantity of powder which may be placed within a size 0 capsule, which is typically 300 mg. Though pre-compression may affect the disintegration time, by using a piston tamp capsule filling method the quantity of powder which can be put inside a capsule can be enhanced. [60]

Soft gelatin capsules: Vegetable or semi-synthetic oils are utilised for this, with Indena recommending a granulometry of 100% < 200 μm in the suspension form. [61]

Tablets: The best manufacturing method for producing tablets with greater unitary dosages is dry granulation. Due to the negative impact on the phospholipid complex, wet granulation is avoided. The concentration of phytosome complex needs to be lowered with 60–70% excipients if a direct compression technique is utilized to maximize its technical qualities and to produce tablets with a suitable shape. [62]

Topical product: To get the greatest outcome from the phospholipid complex, the emulsion is utilized in this process. A previously created emulsion needs to have a phospholipidic complex spread in modest volume of the lipid phase. For the purpose of incorporating the phytosome complex into the emulsion at a temperatures less than 40°C.[63]

VIII. PATENTS APPROVED ON PHYTOSOME:

Table 3- List of some patented technologies related to Phytosomes

Title of patent	Innovation	Patent no.	Ref.
Phospholipid complexes of olive fruits or leaves extracts having improved bioavailability	improved bioavailability	EP/1844785	**[64]**
Complexes of saponins with phospholipids and pharmaceutical and cosmetic compositions Containing them	Complexes of saponins with natural or synthetic phospholipids have high lipophilia and improved bioavailability and are suitable for use as active principle in pharmaceutical, dermatologic and cosmetic compositions	EP0283713	**[65]**
An anti-oxidant preparation based on plant extracts for the treatment of circulation and adiposity problems	Haemorrhoids, varicose veins, arteriosclerosis, phlebitis, and high blood pressure can all be treated using repair made from plant extracts that has an antioxidant effect**.**	EP1214084	**[66]**
Treatment of skin and wound repair with thymosin beta-4	Compositions and methods for treatment of skin utilizing thymosin β4.	US/2007/0015698	**[67]**
Compositions comprising Ginkgo biloba derivatives for the treatment of asthmatic and allergic conditions.	Useful for asthma and allergic condition	EP1813280	**[68]**
Complex compounds of bioflavonoids with phospholipids, their preparation and use, and pharmaceutical and cosmetic compositions containing them	Complex compounds of flavonoids with phospholipids, characterized by high lipophilia and improved bio-availability and therapeutic properties as compared with free, not complexed flavonoids.	**US5043323**	**[69]**
An anti-oxidant preparation based on plant extracts for the treatment of circulation and adiposity problems	Treatment for circulation issues such phlebitis, varicose veins, arteriosclerosis, haemorrhoids, and high blood pressure that is based on plant extracts and has an antioxidant impact.	**EP1214084**	**[70]**
Soluble isoflavone compositions	Isoflavone compositions exhibiting improved solubility (e.g., light transmittance), taste, color, and texture characteristics, and methods for Making the same.	**WO/2004/045541**	**[71]**
Fatty acid monoesters of sorbityl furfural and composition for cosmetic and dermatological use	Fatty acid monosester of sorbityl furfural selected from two different series of compounds in which side chain is linear alkyl radical optionally containing at least one ethylenic unsaturation	EP1690862	**[72]**
Oral compositions for the treatment of cellulite	Oral pharmaceutical and cosmetic compositions containing ingredients of vegetable origin for the treatment of cellulite.	US 7691422	**[73]**

IX. CONCLUSION-

The aim of this article is to provide a brief review of phytosomes as the delivery system. With the improvement of the bioavailability of hydrophilic flavonoids and further related compounds through the skin or digestive tract, phytosomes are novel formulations. They differ from other traditional formulas in numerous notable ways. Phytosome formulation is a straightforward process that is easily scaled up for commercial use. The characterization methods and analytical instruments are well established for this kind of novel formulation. Numerous patents for innovative phytosome formulations, methods, and applications have already been approved.

Phytosome technology has a bright future as far as applications for hydrophilic plant chemicals and formulation technology are concerned.

X. REFERENCES-

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