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Phytosomes: Phyto-Phospholipid Complexes as Innovative Delivery Systems to improve the bioavailability of active constituents

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ABSTRACT

The term "Phyto" means plant and "some" means cell. It is also mentioned as 'herbosomes' this is a new patented technology, where standardized plant extracts or water soluble phytoconstituents are complexed with phospholipids to produce lipid compatible molecular complexes, there by greatly increasing absorption and bioavailability." Phytosomes have improved the therapeutic benefits of plant extracts and herbal lead molecules by increasing bioavailability in the target site when compared to standard herbal extracts. The poor oral bioavailability of polyphenolic compounds can be improved by incorporating them into a Phytosome, a phospholipids-based self-assembled delivery system. Phospholipids are employed as natural digestive aids and carriers for water soluble and lipid soluble nutrients. Typically, one or two moles of polyphenolic phytoconstituents and phospholipids are used to create phytosomes. This review will provide information regarding various properties and advantages of phytosomes.

I. INTRODUCTION

Phytosome is a combination of phospholipids and naturally active components. Phytosome enhances plant extract absorption when applied topically or orally [1]. Phytosomes are phospholipid complexes that are lipid compatible and contain plant extract coupled with phospholipids [2]. It is a phytoconstituent-encased lipid-encased vesicular drug delivery technique. Phytosome improves phytoconstituent bioavailability by boosting phytoconstituent absorption through the gastrointestinal tract. Phytoconstituents and phospholipids are present in a 1:1 or 1:2 ratio in phytosomes, whereas water soluble components in liposomes are surrounded by numerous phosphatidyl choline units [3]. Phytosomes are lipophilic vesicular drug delivery devices with a set melting point, a high solubility in nonpolar solvents, and a moderate solubility in lipids. Phytosomes, when applied topically or orally, are a mixture of natural active components and phospholipids, improve the absorption of herbal extracts or isolated active compounds.[4] Phytosomes are cell-like structures formed by the stoichiometric reaction of phospholipids (phosphatidylcholine, phosphatidylserine, etc.) with standardized extracts or polyphenolic constituents (such as flavonoids, terpenoids, tannins, and xanthones) in a non-polar solvent, and are better absorbed, utilized, and thus produce better results than conventional herbal extracts [5]. Phospholipids are one of the most important components of cellular membranes and are one of the most important building blocks of life. Because the phytosomes method creates a small cell, the beneficial components of the herbal extract are protected from digestive secretions and gut microbes.[6] Phytosomes have improved pharmacokinetic and pharmacological parameters. Phytosomes have improved pharmacokinetic and pharmacological characteristics. Phytosomes are more accessible than herbal extracts because of their improved capacity to cross lipid-rich bio membranes and eventually reach the blood. [7] It has increased bioavailability and can be used to treat a wide range of fatal diseases without deactivating the active phytocompounds. Phytosomes are formed by interacting phospholipids (natural or synthetic) with a specific plant element in an appropriate solvent, and due to their physical and chemical efficiency, these Phyto-complexes can be considered a distinct entity [8].

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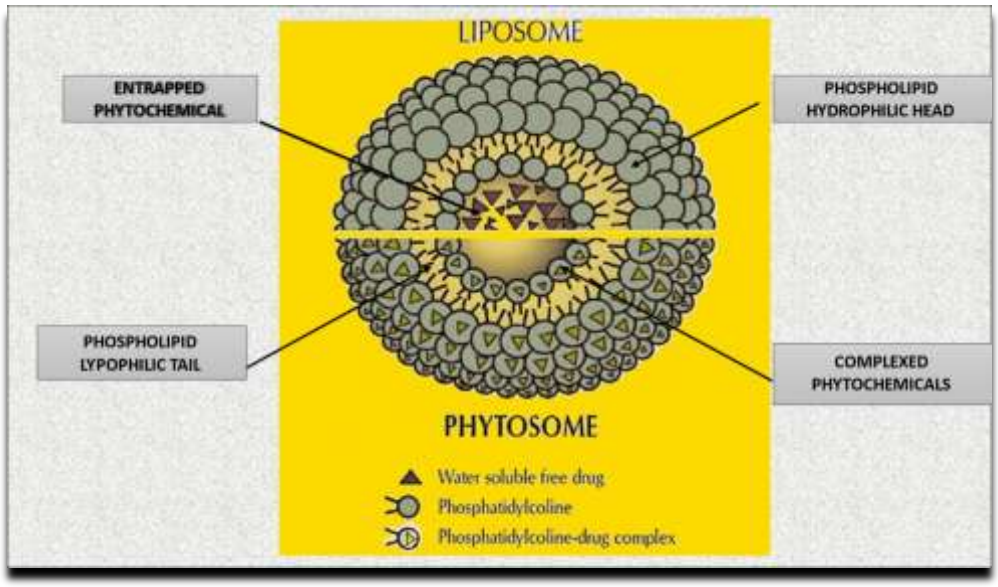

Figure 1: Structural difference between phytosome and liposome.

II. PROPERTIES OF PHYTOSOMES:

2.1 Physical properties:

Phytosomes are lipophilic by nature and are freely soluble in non-polar solvents. Water insoluble. Lipid soluble to a moderate extent.[9]

2.2 Chemical properties:

Phytosomes are a compound composed of a natural product and natural phospholipids, such as soy phospholipids, produced by reacting stoichiometric amounts of phospholipid with the substrate in the appropriate solvent. According to spectroscopic studies, the primary phospholipid-substrate interaction is caused by the formation of hydrogen bonds between the polar head of phospholipids (i.e., phosphate and ammonium groups) and the polar functionality of the substrate. When exposed to water, phytosomes acquire a micellar shape and form liposomal-like structures.[10]

2.3 Biological Properties:

In terms of absorption, application, and results, phytosomes outperform traditional herbal extracts. Several pharmacokinetic and pharmacodynamic investigations on experimental animal models and humans have explained and demonstrated the increased bioavailability of phytosomes over non-complexed plant derivatives [11].

2.4 Absorption Mechanism of Phytosome Technology:

Polyphenolic components have a decreased absorption and bioavailability due to two reasons. These main constituents are a large number of ringed molecules that aren't too tiny to be absorbed by diffusion. The second aspect is that the flavonoid molecule, or the main component of polyphenols, is poorly soluble in lipids. These are the constraints that prevent them from passing through biological membranes.[12]

III. PREPARATION METHODS FOR PHYTOSOMES

Phytosomes are prepared by different methods by interacting 3-2 moles natural or synthetic phospholipid, mainly phosphatidylcholine with one mole of phytoconstituent. The most preferable ratio for complexes formation between these two moieties is in the range from 0.5 to 2.0 moles.[13] For the large-scale preparation of phytosomes, several methods have been developed. In general, the procedures listed below are applied.

3.1 Mechanical Dispersion Method

In this method, lipids dissolved in an organic solvent are brought into contact with an aqueous phase containing the drug. After dissolving phosphatidylcholine in diethyl ether, it is gently injected into an aqueous solution containing the phytoconstituents to be encapsulated. After the organic solvent is withdrawn at reduced pressure,

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the production of Phyto-phospholipid complex takes place.[14]

3.2 Solvent Evaporation Method

The phytoconstituents and phosphatidylcholine are mixed in a flask containing an organic solvent in this method. This reaction mixture is kept at an appropriate temperature of 40° C for a specific time interval of 1 hour to achieve maximum drug entrapment in the phytosomes produced. The organic solvent is subsequently extracted using a rotatory evaporator. Thin film phytosomes are sieved through 100 mesh sieves and placed in desiccators overnight. To achieve stability, the phytosomes are stored at room temperature in a light-resistant amber-colored glass bottle that has been flushed with nitrogen.[15]

3.3 Salting Out

The phytoconstituent or standardized extract and phosphatidylcholine is dissolved in an aprotic solvent, such as dioxane or acetone where the solution is being stirred overnight then the formed complex is isolated from by precipitation from non-solvent like n-hexane.[16]

3.4 Lyophilization Technique

Both natural or synthetic phospholipid and phytoconstituent is dissolved in different solvent and further solution containing phytoconstituent were added to a solution containing phospholipid followed by stirring till complex formation takes place. The formed complex is isolated by lyophilization. [17]

3.5 LAB PRODUCTION METHOD FOR PHYTOSOMES

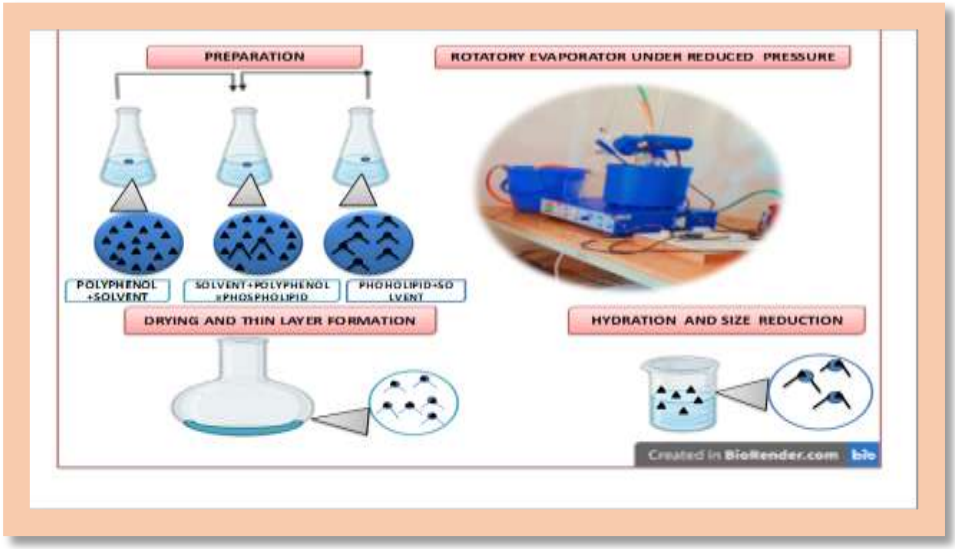

Figure2: Thin-film hydration as the most common method for phytosome preparation. Steps 1 to 4 are the procedures of phytosome preparation [18]

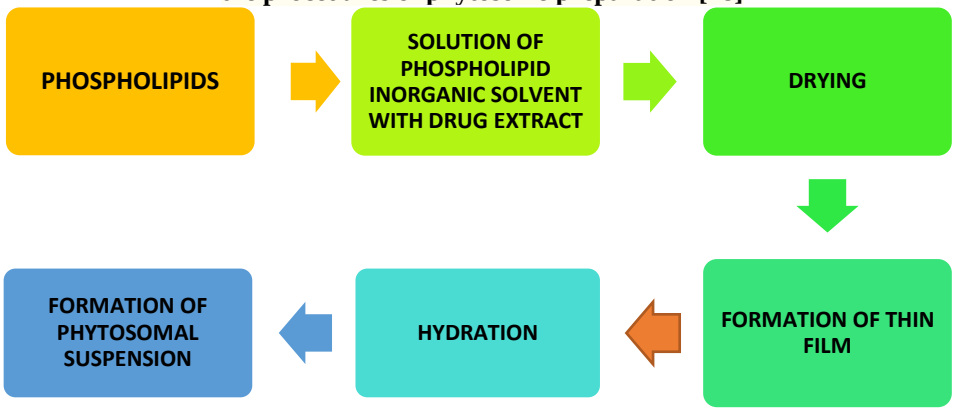

Figure3: Common stages of preparation of phytosomes.

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IV. PHYTOSOME EVALUATION

4.1 Characterization technique:

4.1.1 Visualization: Transmission electron microscopy (TEM) and scanning electron microscopy (SEM) can both be used to visualise phytosomes (SEM).[19]

4.1.2. Zeta potential and vesicle size: Dynamic light scattering (DLS) using a computerised inspection system and photon correlation spectroscopy can be used to detect particle size and zeta potential (PCS).[19]

4.1.3. Effectiveness of entrapment: The ultracentrifugation technique can be used to determine the entrapment efficiency of a drug by phytosomes [20].

4.1.4. Temperature of transition: A differential scanning calorimeter can be used to determine the transition temperature of vesicular lipid systems [21].

4.1.5 Stability of the vesicle: The size and shape of vesicles can be assessed over time to determine their stability. DLS is used to determine the average size, while TEM is used to monitor structural changes [22]

4.2 Spectroscopic evaluations:

The following spectroscopic approaches are used to confirm the development of a complex or to analyze the reciprocal interaction between the phytoconstituent and the phospholipids.

4.2.1. ^{1}HNMR: The NMR spectra of (+) catechin and its stoichiometric complex with distearoylphosphatidylcholine choline.[23] The 1HNMR signal arising from the atoms involved in the creation of the complex changes dramatically in nonpolar solvents, with no accumulation of the signal distinctive to the individual molecules. The signals from the flavonoids' protons must be widened so that the proton cannot be relieved. All of the signals in phospholipids expand, whereas the singlet corresponding to the N(CH3)3 of choline is uplifted. When the sample is heated to 60°C, new broad bands develop, which primarily correlate to the flavonoid moiety's resonance.[23]

4.2.2. ^{13}CNMR: All of the flavonoid carbons are clearly visible in the ^{13}CNMR spectrum of (+) catechin and its stoichiometric complex with distearoyl phosphatidylcholine, especially when recorded in C6D6 at room temperature. The signals corresponding to the lipid's glycerol and choline portions (between 60–80 ppm) are widened and some displaced, but the fatty acid chains' resonances keep their crisp line structure. All of the flavonoid moieties' signals reemerge after heating to 60°C, however they are still very broad and somewhat overlapping.[24]

4.2.3 FTIR: IR spectroscopy can also be used to confirm the complex's creation by comparing the spectrum of the complex to the spectrum of the individual components and their mechanical mixes. When phytosomes are micro dispersed in water or incorporated into extremely simple cosmetic gels, FTIR spectroscopy is a valuable technique for controlling their stability. [25]

4.3 In vitro and in vivo evaluations:

In vitro and in vivo assessment models are chosen based on the physiologically active phytoconstituents present in phytosomes' predicted therapeutic potential. [26] The antioxidant and free radical scavenging activity of phytosomes, for example, can be used to assess in-vitro antihepatotoxic activity [27].

4.4 Evaluation of phytosomes in terms of physicochemical properties:

4.4.1 Solubility: A solubility study can be carried out by dissolving an excess of the drug in various solvents such as water, phosphate buffer (pH 6.8), and acetate buffer (pH 4.5) [28]

4.4.2 Particle Size Distribution: To investigate particle size distribution, prepared phytosomes can be dispersed in an alcoholic solution (isopropyl alcohol) and analyzed with a size analyser.[29]

4.4.3 Pharmacosome Stability: The stability of a complex can be investigated by comparing the spectrum of the complex in the solid state with the spectrum of a dispersion of small particles in water.[29]

4.4.4Dissolution Studies: In vitro dissolution studies are carried out in a variety of media with varying pH using standard dissolution apparatus. The results are assessed on the basis of apprehended activity of the active ingredients therapeutically. [28,29]

V. APPLICATIONS OF PHYTOSOMES:

When compared to traditional herbal extracts, many phytosome products have shown to offer considerable therapeutic effects.[30]

5.1 Bioavailability Improvement: Evodiamine (Evodia rutaecarpa), a quinoline alkaloid, has a wide range of pharmacological properties, including anti-tumor, anti-inflammatory, anti-obesity, and thermoregulatory actions. Evodiamine inhibits cell proliferation, induces apoptosis, and reduces invasion and metastasis in a wide range of tumour cells. Evodiamine phytosomes were found

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to have a greater rate of in vitro dissolution, absorption, action time, and bioavailability.[31]

5.2 Hepatoprotective Ingredients: Ginkgo biloba (Ginkgoaceae) leaf extracts have been discovered to exhibit cardioprotective, anti-asthmatic, anti-diabetic, antioxidant, hepatoprotective, and strong CNS effects. Isoproterenol-induced myocardial necrosis was significantly reduced by phytosomes of G. biloba (200mg/kg) in this study. The cardioprotective properties of phytosomes were further validated by histopathological study of the myocardium. Reduced myocardial necrosis (as demonstrated by lower AST, LDH, and CPK levels, as well as histoarchitectural alterations) and increased endogenous antioxidants all contribute to its cardioprotective impact. Clinical hepatitis affects 1.1 percent of persons using rifampicin, according to the literature.[32]

5.3 Cancer Treatment: Antioxidant capabilities of medicinal plant chemical components such as flavones, isoflavones, flavonoids, coumarins, lignin's, catechins, and isocatechins contribute to their anticancer potential. However, at greater doses, a few plant-based chemicals are poisonous and cause negative effects. Chemotherapy and radiotherapy, which are already accessible but expensive, have a multitude of side effects such as myelosuppression and neurological, cardiac, pulmonary, and renal toxicity, all of which have a negative impact on quality of life. The use of a bipolar moiety to entrap these plant-derived medicines improves their solubility, dispersibility, and permeability, resulting in a strong anti-cancer agent. [33,34]

VI. STRENGTHS OF PHYTOSOMES

Phytosomes are more stable because a chemical bond is formed between the phospholipid molecule and the phytoconstituent (s)and as phytoconstituents are more accessible in complex form, phytoconstituent dose is reduced. The action's duration has been increased. Phytoconstituents complexed with phospholipids are more stable in gastric sections and can tolerate the activity of gut bacteria. Increased permeability of phytoconstituents across biological membranes. Different routes of absorption of lipid insoluble polar phytoconstituents show enhanced absorption, leading in much greater therapeutic effects. Phosphatidylcholine, which is employed in the synthesis of phytosomes, has a variety of therapeutic properties in addition to acting as a carrier, resulting in a synergistic effect when a specific medicine is administered. According to the animal model used for testing, drug entrapment is not a concern with phytosomes because the complex is biodegradable. [35,36,37,38].

VII. ADVANCES IN PHYTOSOME TECHNOLOGY

Numerous studies have demonstrated the superiority of phytosomal delivery systems over traditional herbal extracts. The following advances in phytosomal delivery systems have been made:

a) Bacopaside, a well-known antiamnesic main constituent of the Bacopa monnieri plant. The goal of this study is to develop a phytosome from bacopaside and test it on rodents in vivo. The therapeutic activity of the phospholipid-derived molecule differs significantly from that of plain B. monnieri extract [39].

b) Another study discloses how to make berberine phospholipid complex solid dispersion, which not only increases the compound's solubility but also its flow ability and dissolving rate for commercial manufacturing [40].

c) Another study suggests that sinigrin phytosome preparation is possible. The research looked at the potential for in vitro wound healing, and the results were positive when compared to sinigrin alone [41].

d) According to one study, silymarin phytosomes have greater antihepatotoxic action than silymarin alone, and they play an important role in protecting broiler chicks against B1 aflatoxin [42].

e) Oral administration of phytosomes obtained from a standardized extract of S. marianum seeds, which has a substantial effect on the foetus caused by maternal alcohol use [43]

f) One clinical trial discovered that giving silybin phytosome to 232 individuals with chronic hepatitis at a dose of 120 mg twice or thrice a day for 120 days had a substantial impact on liver function recovery [44].

g) Grape seed phytosomes protect against atherosclerosis and play an essential role in ischemia-induced heart damage. The key components involved for this are proanthocyanins/procyanidins [45].

h) When compared to uncomplexed green tea extract, Camellia sinensis or green tea extract included in phytosomes has increased oral bioavailability. The primary active constituent of green tea is epigallocatechin 3-o-gallate [46,47]

i) Additional clinical trials revealed that caffeine-free phytosomes of green tea have anti-obesity and

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antioxidant activity. Low-density lipoprotein (LDL) is also affected [48,49,50]

j) In rat liver injury induced by carbon tetra chloride, the quercetin phytosomal complex has a better therapeutic property [51].

VIII. PHYTOSOME PREPARATION TECHNIQUES:

The thin layer rotary evaporator vacuum approach was used to create phytosomal vesicles. In a 250 mL round bottom flask, the phytosomal complex was combined in anhydrous ethanol. A rotating evaporator was connected to the flask. At a temperature of roughly 60°C, the solvent will evaporate, leaving a thin layer film around the flask. Phosphate buffer with a pH of 7.4 hydrates the film, and the lipid layer peels off in the phosphate buffer, generating vesicle suspension. Probe sonication with a 60 percent amplitude was used on the phytosomal suspension. Before characterization, the phytosomal suspension will be kept in the refrigerator for 24 hours. [52] This mixture was sonicated in an ice bath. Phytosomes were prepared and stored in an amber-colored bottle. [53]

IX. PATENTS BASED ON PHYTOSOMES:

S.NO.	TITLE	INNOVATION	PATENT NO. AND YEAR
1	Curcumin phospholipid complex with increased bioavailability.	Phospholipid complexes of curcumin produce a larger systemic level of parent substance than curcumin that has not been complexed.	PATENT NO. AND YEAR WO2009/101551 (2009) [54]
2	Improved bioavailability of the phospholipid complexes from olive fruits or leaves extract.	Bioavailability of olive fruit/leaf extracts improved with the phospholipid's complexes.	PATENT NO. AND YEAR: EP1844785 (2007) [55]
3	Ginkgo biloba derivative-based compositions for the treatment of asthmatic and allergic conditions.	Compositions of Ginkgo biloba fractions for the treatment of asthma and allergic diseases.	PATENT NO. AND YEAR: EP1813280 (2007) [56]

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4	Thymosin-4 for skin treatment and wound healing.	A wound-healing formulation incorporating Thymosin 4 was developed.	PATENT NO. AND YEAR: US/2007/0015698 (2007) [57]
5	Oral compositions for cellulite treatment.	Oral and cosmetic pharmaceutical formulation of Centella asiatica triterpenes, Vitis vinifera extracts, and Ginkgo biloba flavonoids in free or complex form with phospholipids.	PATENT NO. AND YEAR:US7691422 (2007) [58]
6	Sorbitol furfural fatty acid monoesters and compositions for cosmetic and dermatological use.	Sorbitol furfural's chosen fatty acid monoesters are lipophilic agents with specialised anti-hydroxyl radical activity.	PATENT NO. AND YEAR: EP1690862 (2006) [59]
7	A dermatological and cosmetic composition for the treatment of ageing or photodamaged skin.	A topical cosmetic or dermatological preparation for anti-wrinkle treatment that contains at least one collagen synthesis-stimulating ingredient	PATENT NO. AND YEAR: EP1640041 (2006) [60]
8	Composition of soluble isoflavones.	Isoflavone compositions improved the formulation's solubility, taste, and colour.	PATENT NO. AND YEAR: WO/2004/045541 (2005) [61]
9	An anti-oxidant medicine based on plant extracts for circulation and obesity issues.	Plant extracts with anti-oxidant activity were used to create a formulation for the treatment of phlebitis, haemorrhoids, arteriosclerosis, varicose veins, and high blood pressure.	PATENT NO. AND YEAR: EP1214084 (2004) [62]

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10.	Anti-atherosclerotic phospholipid complexes derived from Vitis vinifera extracts.	Phospholipid complexes derived from Vitis vinifera extract for the prevention and treatment of atherosclerosis.	PATENT NO. AND YEAR: US6297218 (2001) [63]
11	Bilobalide phospholipid complexes, applications, and formulations.	Complexes including synthetic or natural phospholipids and bilobalide (a sesquiterpene found in the leaves of Ginkgo biloba) are described, as well as their formulation and use in inflammatory and neurotic diseases. Because it has a better bioavailability than free bilobalide, it can be used for both parenteral and topical administration.	PATENT NO. AND YEAR: EP 0441279 (1991) [64]
12	Neolignane derivatives complexed with phospholipids, their usage,	Antibacterial, antimycotic, and antiradical properties were observed in complexes of lipophilic extracts	PATENT NO. AND YEAR: EP 0464297 (1990) [65]
	and pharmaceutical and cosmetic formulations that contain them extracts.	of Krameria or Eupomatia plant genera and certain neolignanes derived from the same. As a result, it's a new active principle for cosmetics and pharmaceuticals, as well as a good preservative in cosmetics.	
13	Saponin-phospholipid complexes and medicinal and cosmetic formulations containing them.	Improved bioavailability of saponins complexed with natural phospholipids, which can be used in cosmetic, medicinal, and dermatological applications.	PATENT NO. AND YEAR: EP0209038 (1988) [65]

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14	Flavonolignan-phospholipid complexes, their synthesis, and associated medicinal formulations.	This innovation involves. using non-traditional ways to create lipophilic silidianin, silybin, and silicrist complexes. When compared to individual flavonolignans, the complex produced had a greater gastrointestinal absorption and plasma levels. The chemical can be used to treat both acute and chronic liver disorders because of its increased pharmacokinetic action	PATENT NO. AND YEAR: EP 0209038(1988)[66]
15	Bioflavonoid-phospholipid complexes, their synthesis and application, as well as medicinal and cosmetic compositions comprising them.	In comparison to free flavonoids, complex flavonoids with phospholipids have a higher lipophilic, enhanced bioavailability, and medicinal effects.	PATENT NO. AND YEAR: EP 0275005(1983)[65]

X. LATEST PHYTOSOMES RESEARCH:

10.1 Anwar E. et.al 2018 used the thin layer hydration method to formulate and evaluate the phytosomes of Camellia sinensis extract. Using maltodextrin and gum Arabic as a carrier, different formulations (F1, F2, and F3) were created, and selected phytosomes were formed into microspheres. The stability research and the dissolution study were both evaluated. Formulation F3 was the best, with a spherical shape, D mean volume of 42.58 nm, a polydispersity index of 0.276, a zeta potential of -48.2 1.78 mV, and a 50.610.93% entrapment efficiency. After a four-hour dissolving test, the total amount of EGCG was 85.21 percent. It demonstrated good physicochemical stability in a 6-week examination of organoleptic, water content, and physicochemical qualities at varied temperatures. [67]

10.2. El-Bata A. et.al 2018 prepared nanocrystals by dissolving them in various solvents (acetone, acetonitrile, ethanol, and methanol), and phytosomes by combining lecithin and silymarin. The effect of gamma irradiation on physicochemical characteristics, such as solubility and drug content in crystals or phytosomes, was investigated. SEM and TEM were used to determine crystal morphology. XRD, DSC, and FT-IR were used to describe the solid state, while DLS was used to quantify particle size. Nanocrystals and phytosomes were tested for drug release in vitro. The nanocrystal (NCy6) and phytosome (Phy1) considerably enhanced the solubility of silymarin by 17.12 percent, according to the researchers.[68]

10.3 B.J. Jevana et.al 2019 used a rotary evaporation method and an antisolvent precipitation method with seven different formulations of soya lecithin to manufacture and assess the phytosomes of Naringin. Drug entrapment efficiency, in vitro drug release, and drug-excipient interaction investigations were all performed on the produced phytosomes. They came to the conclusion that phytosomes prepared by rotary evaporation have greater dissolving values than phytosomes prepared by antisolvent precipitation. Formulation F7 had the highest percentage release, with 84.50.39% in 60 minutes

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and 99.70.24% in 120 minutes. [69]

10.4 Sachin et.al 2019 developed and evaluated curcumin phytosomes, using rotatory evaporation method. SEM, particle size measurement, zeta potential, drug content, drug entrapment efficiency, percentage yield, in-vitro drug release investigations, and the release kinetics of curcumin phytosomes complex were all performed on the phytosomes. They came to the conclusion that Curcumin phytosomes have greater physical properties and improved permeability and solubility than curcumin medication, allowing them to overcome the ability to traverse lipid-rich biological membranes, resulting in increased oral bioavailability. [70]

10.5 Palachai N et.al 2020 prepared phytosome loading with a ginger rhizome extract and ripe mulberry fruit extract (PMG). Male Wistar rats were induced MetS by a high-carbohydrate high-fat diet (HCHF) for 16 weeks and then subjected to cerebral ischemia/reperfusion injury (CIRI) at the right middle cerebral artery to investigate the neuroprotective effect and possible underlying mechanism of PMG on brain damage in cerebral ischemic rat with MetS. (Rt. MCAO). PMG at all doses improved brain infarction, brain oedema, and neurological deficit score significantly. The study discovered that the MetS condition had a neuroprotective effect against cerebral ischemia. In the MetS condition, they found that PMG is a viable neuroprotectant candidate against ischemic stroke. [71]

XI. CONCLUSION:

The purpose of this paper is to provide a comprehensive overview of phytosomes as a novel medication delivery mechanism. The phytosome is a lipid-based vesicular delivery method that can be used to encapsulate pharmaceuticals as well as plant-derived nutraceuticals including polyphenolic substances. Furthermore, phytosomes can improve polyphenolic component bioavailability through the gastrointestinal system while lowering administration dosage. Furthermore, the phytosome preparation technique is simple to implement and can be scaled up commercially. The phytosome technology is a wonderful encapsulation platform to use in the nano formulation of nutraceuticals in the future since it is a strong contender for putting herbal-derived polyphenolic chemicals into effective cancer and other disease treatments.

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