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Review Article

Phytosomes As an Advanced Herbal Drug Delivery System

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ABSTRACT

Phytosomes are an innovative herbal drug delivery system designed to overcome the limitation of poor bioavailability, solubility, and permeability associated with phytoconstituent like polyphenols, flavonoids and glycosides. Formed by complexing phospholipid, primarily phosphatidylcholine with bioactive plants compound in aprotic solvents, phytosomes create lipid-compatible molecular complexes through hydrogen bonding. This technology pioneered by indena, significantly enhances the pharmacokinetic and pharmacological properties of herbal extracts, improving intestinal absorption, reducing dosage requirements and enabling targeted drug delivery. The amphiphilic nature of phospholipids with a hydrophilic choline head and lipophilic phosphatidyl tails ensure high entrapment efficacy, better stability and enhance membrane permeability. The phytosomes are versatile supporting oral, topical, ocular, parenteral, and nasal administration and demonstrate application in antioxidant, cardio protective, anti-inflammatory, anticancer, wound healing, and hepatoprotective therapies. Marketed product like Silymarin, Meriva, and Ginkgo biloba phytosomes highlight their commercial success. Preparation methods including solvent evaporation method , anti-solvent precipitation method, supercritical fluid technology, optimize solubility and stability, while evaluation techniques like stability, scattering and HPLC ensure quality ,advantage, elimination and limited clinical trials persist .This review synthesized recent advancements in phytosome technology, detailing their preparation, characterization, therapeutic application, and potential to revolutionize herbal medicine by enhancing the efficacy of plant-based therapeutic.

INTRODUCTION

Traditional medicines and phytomedicines have been used therapeutically for centuries to maintain health in a variety of ways. Numerous plant extracts have been subject of chemical and pharmacological investigation during the past century to determine their chemical makeup and

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validate their potential for therapeutic application. Water soluble compounds such as flavonoids, glycosides, and phenolics make up the majority of bioactive phytoconstituents. when administered locally or consumed orally, many strategies including structural alteration and entrapment within the lipophilic carriers have been devised to increase the bioavailability and absorption capability. The efficiency of any the effectiveness of herbal product depends on how well the active ingredients are delivered. This difficulty is addressed by indena's phytosome technology, which significantly increases the bioavailability of specific phytomedicines. [1]. Phytosomes the term "phyto" refer the plant, while "somes" refer to cell-like. Phytosomes are the cell-like structure that is mainly used in herbal industries to increase the effectiveness and to overcome the limitation of herbal extract.[2]. The compound of natural active phytochemicals and phospholipids known as phytosomes is formed when phosphatidylcholine (or any other hydrophilic polar head group) reacts with plant extracts in an aprotic solvent. The formulation pharmacological and pharmacokinetic characteristics are better than those of commonly used preparation. The lipid soluble phosphatidyl part covers the hydrophilic component –Coline complex entirely. Due to formation of chemical interaction between the polar heads of the amphiphilic molecules and the phytoconstituent, phytosomes exhibit superior stability profiles and excellent drug encapsulation. Their superior bioavailability results in a lower dosage of active ingredient needed to produce a biological impact due to their faster absorption rate. It has been suggested that phytosome are a potential option for delivering phytochemicals. Because of their versatility and ease of manufacture, bilayer vesicles have been widely used and accepted by scientific literature. [3] Phytoconstituent with phospholipid produces compatible Phyto-phospholipid complexes called phytosomes. The phospholipid contains one polar head and two nonpolar tails which give increased solubility and acts an affective emulsifier that provide enhanced bioavailability for lipid soluble drug in intestine tract. In phytosome technology phytoconstituent are protected from gastric destruction, like phosphatidylcholine which has a gastroprotective effect nano size of phytosome increases the solubility and permeability of phytoconstituent having larger molecular size.[4] Many plants extract poor potency, solubility, permeability, stability was thought to be the main obstacles to creating contemporary medicine from herbs. Pharmeceutical researchers have recently demonstrated a keen interest in using natural sources for drugs in the development of new therapies. In the flavonoid class of herbal medications, polyphenolic chemicals are the most abundant and have a wide range of therapeutic uses, including anti-inflammatory, anti-cancer, anti-obesity, cardio-protective, and antioxidant properties. Currently, the market offers phytosomes form of important herbs such as Ginko biloba, green tea, ginseng, curcumin, grape seeds, etc. Unquestionably, further research and idea sharing in the sphere of this innovative technology will prepare the search for more potent formulae to combat human disease. A plethora of phytosome achievements is covered in this article, along with the production and therapeutic aspect of the product and a comparison of the efficacy of several traditional herbal extracts and their phytosome form.[5]

3. Phytosome Technology:

Phytosomes or herbosomes are an advanced novel form of phytoconstituent which are better absorb orally, trans dermally, and topically. Phytosomes are a product of the stoichiometric quantity of the phospholipid(phosphatidylcholine) and the polyphenolic constituents(like –flavanoids)

reacting inside a non-polar solvent. The lipophilic component of phosphotidylcoline, a bifunctional molecule, is phosphotidyl. The other component, the choline, is hydrophilic. The latter is in charge of attaching itself to the molecules of the chemical. The choline-bound substance is enveloped by the lipid soluble phosphatidyl part,which consists of a body and a tail.As a result,the phytoconstituents and phospholipids form a lipid compatible molecular complex,also known as phytophospholipid complex in phytosomal complex.Hydrophilic phytoconstituents are standardised plant extract are then integrated into phospholipid molecules to create a lipid compatible vasicular complex.Phytosomes are a unique formulation that shows great advantages over traditional formulations of herbal extract and bioactive component. Phytosome technology primarily increases the bioavailability lipid solubility and gastrointestinal solubility of the bioactive compound. Other benefit include incremented ability to cross cell membrane, stability, sustained delivery, and prevention from toxicity and chemical or physical degradation. Research have proven the higher efficicacy of the phytosomes, in aspects of both reduced dosage and pharmacological potential. Phytosomes exhibit better transdemal drug distribution and have an extensive scope in cosmeticology. Phospholipids have outstanding properties of amphiphilicity and excellent biocompatibility. This considerable characteristics make phospholipid the most appropriate to be utilised as a crucial pharamaceutical agent and have several application in drug delivery system.[6]

4. Structure Of Phytosome:

When active ingredients interact with the polar head of phospholipids, phyto-phospholipid complexes are created relationship between phospholipid and active ingredients permit phospholipid complexes to play a crucial role in which the head group of phospholipid is anchored yet neither of the two lengthy fatty acid chains takes part in creation of complexes.[7]

PC, or phosphatidylcholine, is a chemical with two functions. In particular, the hydrophilic choline head attaches itself to these substances, and the lipophilic phosphatidyl portion which consists of the body and tail—envelops the choline-bound material to form a phyto-phospholipid complex. Phosphatidyl-choline - phospholipid Phosphatidyl moiety -lipophilic Choline moiety – Hydrophilic.[8]

Figure of phytosome:

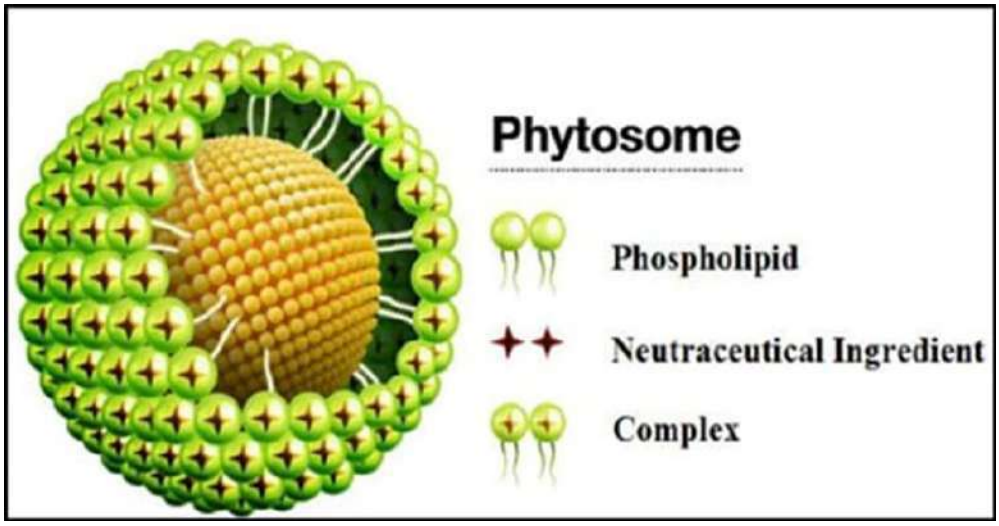

Fig: 1

5. Components Of Phytosome:

5.1Phytochemicals:

Several naturally occurring bioactive compounds that are produced by plants. The term "bioactivity" describes these compound's capacity to interact with different life components; therefore, organism is performing their beneficial effects. Alkaloids, Phenols, Lipids, Carbohydrates, Terpenoids and other nitrogen-containing compounds are the primary structurally different families of phytochemicals. Phytochemicals can also be categorized into several sub classes based on difference in the pathway of biogenesis or biosynthesis. It is only possible to incorporate phytochemicals like polyphenols that have an active hydrogen atom (-COOH, -OH, -NH2, -NH, etc.) into the structure of phytosome. An active hydrogen atom can form a hydrogen bond with the hydrophilic part of amphiphile molecules and their herbaceous derivatives. Polyphenols are the primary class of phytochemicals found in plant-based diets. Polyphenols have been connected to possible negative health effects in a variety of illness including type 2 diabetes, obesity, inflammation, cancer, cardiovascular and neurodegenerative disease. Basically, they are found in conjugated forms, which are composed of one or more sugar residues attached directly to an aromatic carbon 22 and 23 shows that flavonoids and non-flavonoids are too important sub classes of polyphenols. The current study provides the body of knowledge about the usage of polyphenol through phytosomes with a focus on their biochemical loaded phytosome's structure, synthesis and biological activities.

5.2 Phospholipid:

Both plant seeds and egg yolks are rich in phospholipids. Now, industrially manufactured there is phospholipid available [9]. Depending on their backbone, phospholipids can be classified as either sphingomyelins or glycerophospholipids. Furthermore, phosphatidylcholine (PS), phosphatidic acid (PA), phosphatidylglycerol (PG) are examples of glycerophospholipids.[10]. A hydrophilic head group and two hydrophobic hydrocarbon chains combine to form complexes, which are primarily generated using PE, PC and PS phospholipids.[11]

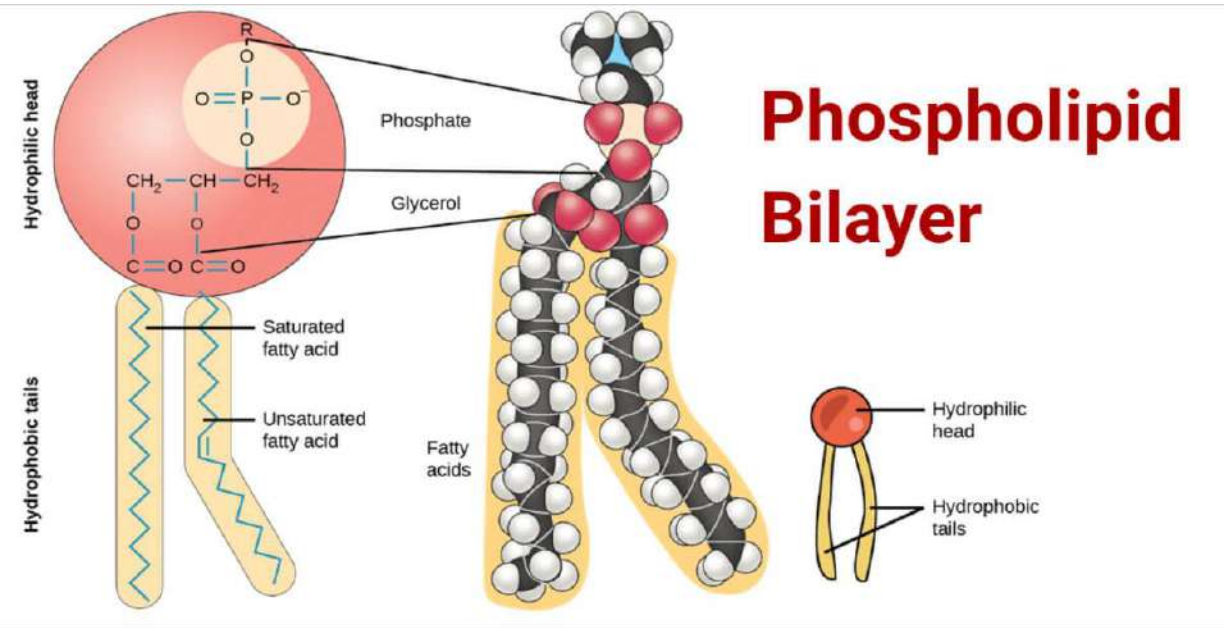

Fig: 2

Their dual nature makes them valuable carriers for herbal drugs in phytosome development. Additionally, phospholipids exhibit hepatoprotective properties, contributing to human health. In phosphatidylcholine, the hydrophilic choline moiety forms chemical bonds, such as hydrogen bonds, with bioactive compounds, while the lipophilic phosphatidyl portion surrounds the choline-bound material, creating a phyto-phospholipid complex.[12]

6. Benefits Of Phytosomes:

1. As a result of their interaction with phospholipids, the herbal extracts bioavailability is dramatically increased, increasing intestinal absorption.

2. This facilitates targeted drug delivery, ensuring that the medicine is delivered to the appropriate tissue.

3. The phytosomes improves the absorption of phytoconstituents, lowering the dosage needed and potentially lessening the harmful effects.

4. The componets of the phytosome formulation are all permitted for use in cosmetics and pharmaceuticals, and the formulation is safe. They outperform liposme –based skin care products as well.

5. Improved stability due to chemical bond formation between phytoconstituents bi-functional chemical compound such as phosphatidylcholine molecule.

6. Using a phytosomal drug delivery technology further lowers the dosage needed because these carries improved medication absorption.[13]

7. It greatly increases the therapeutic effects by improving the absorption of lipids and insoluble polar phytoconstituents through topical and oral routes, demonstrating improved bioavailability.

8. Due to the drug's presence in the entrapment system, entrapment efficiency is high and higher than predicted. Conjugation with lipids to create vesicles.[14]

9. They can be utilized to enhance the transdermal and dermal absorption of medications through the epidermis.

10. The required dosage is reduced because of improved main component absorption. To get the desired results, they can also be taken in lesser amounts.[15]

11. The complexation of botanical extracts with phospholipid and improved intestinal absorption result in a notable's improvement in bioavailability.[16]

12. This technique offers economical phytoconstituent delivery and a synergistic impact when used as functional cosmetics to shield the skin against endogenous or exogenous hazards in both normal and stressful environmental settings.

13. Chemical interactions between the bioactive substances and phospholipid molecules allow phytosomes to entrap drug more effectively and sustainably. It guarantees that drug reach the intended tissues properly.[17]

Comparison of conventional dosage form and microsphere:

S.N.	Parameter	Conventional Dosage Form	Microsphere
1	Patient compliance	Poor	Better

2	Toxicity	Toxicity level is higher	Toxicity level is lower
3	Dose Dumping	Higher Risk	No risk
4	Frequency of medication	More	Less
5	Drug release rate	Rapid and complete release	Slow/controlled release
6	Drug concentration in blood	Fluctuates	constant
7	Affect	Affect healthy tissue and organ	Do not affect and organ
8	Target	Nonspecific	specific
9	Bioavailability	less	More
10	Efficacy	Lower efficacy and therapeutic effect	Higher efficacy and therapeutic effect
11	Amount of dose required	High dosed required	Less dose required
12	Side effect	Higher side effect	Lower side effect
13	Metabolism	Undergo 1st pass metabolisms	Avoid 1st pass metabolisms
14	Long-Term/Chronic Treatment	Requires frequent dosing	Extended or sustained release, reducing dosing frequenc

7. ADVANTAGES:

● The combination of herbal medications with phospholipids and botanical herbs in the digestive tract significantly increases the bioavailability and improves their absorption.[18]

●Using phytosomes for transdermal medication administration is safe.[13]

● By accessing the non lipophilic plant extract, they raise intestinal lumen intake. [15]

● phytosomes are required in small dose and maximum absorption occurs.

●They have been used to deliver flavonoids that protect the liver since they are composed of phytosomes.[19]

● Phytosomes provide significant drug entrapment and extend the duration of action.

●The phytoconstituent and phosphatidylcholine molecule create chemical bonds, which improves the stability of the phytosomes.

● The phytosomal system can be immediately commercialized because it is non-invasive, passive, and appropriate.[8]

● Added nutritional benefit of phospholipids.[20]

DISADVANTAGES:

●Leaching of the phytoconstituents indicates the unstable nature of phytosomes and lower the required medication concentration, which is a major disadvantage.

● Rapid elimination of phytoconstituent may diminish the target drug concentration and indicted the unstable nature of phytosomes.

●Phospholipids (lecithin) can stimulate the grow of the MCF-7 breast cancer cell line, and it has been observed that phytosomes may quickly remove the phytoconstituents.[13]

● Insufficient comprehensive clinical trials have been conducted.

● The active components in phytosomes are swiftly eliminated.[20]

●Plant based products are not widely available on the market, despite their many advantages as a medicine delivery vehicle.

● It exhibits a short half-life. [17]

8. Preparation And Methods:

8.1 The Formulation of The Phyto-Phospholipid Complex: Solution and Method.

In centuries, Phytomedicine and traditional medicine have been a part of health as well as therapy. Plant extract's chemical components and structures have been the subject of much research over the past few decades. Yet, most bioactive constituents in plants, such as flavonoids, phenolics and glycosides, are water-soluble. These chemicals are not easily absorbed or accessible to human systems with any degree of efficiency due to their hydrophilic nature. Many approaches, including structural modification and entrapment in lipid carriers, have been tried over the past decade or two to overcome this problem. The creation of phyto-phospholipid complexes, commonly referred to as phytosomes, is one outcome of such initiative. They improve a phytomedicine's solubility and rate of absorption when they are directly or indirectly attached to it. Vesicular drug carriers constructed by complexing phospholipids, chiefly phosphatidylcholine, with natural bioactive compounds are called phytosomes. The formulation dramatically improves pharmacokinetic and pharmacological behaviour of drugs. It consequently has superior stability, higher drug encapsulation, and ultimately a large therapeutic efficacy. Phytosome technology has transformed the practice of herbal medicine by providing targeted drug delivery, enhanced solubility, and increased clinical efficacy. As interest in this noval drug delivery method keeps growing, it's critical to understand how solvents function in its manufacture because they're essential for complex formation, stability, and effectiveness. This article discusses several solvents applied in phyto-phospholipid complex preparation and describes the methodologies adopted, citing their importance in optimizing bioavailability and therapeutic effect.

8.2 Solvents Used in Phyto-Phospholipid Complex Preparation:

In order to guarantee that phospholipid and phytoconstituents dissolve, and stabilise properly, solvents are an essential part of the formulation process. Important factors like stability, toxicity, bioavailability, and solubility are all influenced by the solvent choice. Phytosomes preparation solvents fall within the following categories:

8.2.1 Traditional Solvents:

Aprotic Solvents: these include methylene chloride, ethyl acetate, halogen compound, and aromatic hydrocarbons. The solubilisation of phytoconstituents is aided by aprotic solvents. Nonetheless, toxicological concerns have taken precedence. Protic solvents since they facilitate the formulation of complexes and are acceptable for use in medications, ethanol and methanol are frequently utilised. Early in phytosomes research, chloroform and acetone were commonly used.' They must be eliminated because they may be harmful.

8.2.2 Advance solvent system:

Supercritical fluids or SCF are materials that are at a temperature and pressure above the critical point of the material. Solvents which Increase Solubility without Affecting Phytoconstituent Structure. Hydrotropic Solvents: Solvents which Increase Solubility without Affecting Phytoconstituent

Structure.

8.3 Techniques to Prepare Phyto-Phospholipid Compounds:

Phyto-phospholipid complexes can be prepared using a variety of techniques. These are made to optimise the stability, loading, and bioavailability of drugs. The most popular techniques are described in more detail below.

8.3.1 Solvent Evaporation Method [21,22]

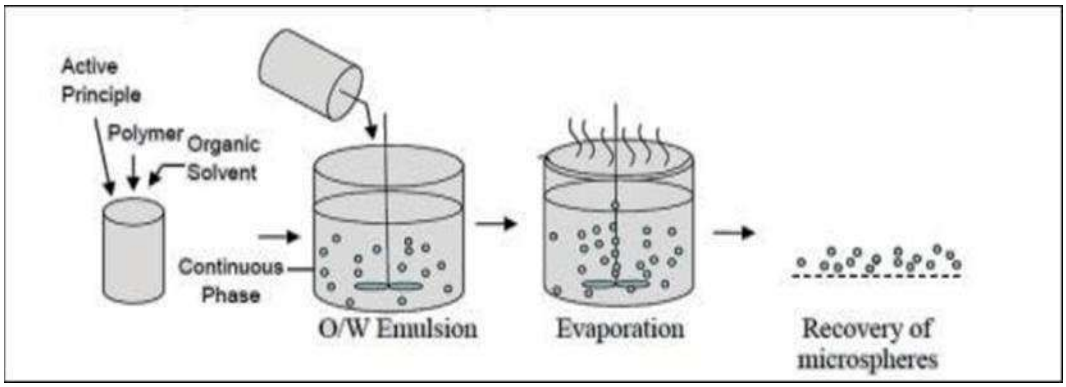

Fig:3

It is one of the most common methods because it is simple and easy to scale. A stable complex is prepared by dissolving the phytoconstituent and phospholipid in an appropriate solvent, followed by the solvent's evaporation at low pressure

Example: water-soluble curcumin can be made whose solubility in water can be increased by the addition of phospholipids. This approach substantially enhances bioavailability and uptake.

8.3.2 Anti-Solvent Precipitation Method: [23,24]

This method adds a non-solvent (n-hexane) to the complex solution of phytoconstituent-phospholipid which makes up precipitation. This provides controlled particle size and stability. For instance, Silymarin-phospholipid complexes are produced from acetone as solvent, then n-hexane is added to precipitate the complex to improve aqueous solubility. Thin film hydration technique. The organic solvent in which the phospholipid and phytonutrients are dissolve and evaporates to produce a thin layer. An aqueous solution then hydrates it to create vesicular structures.

Example: thin-film hydration has been shown to improve membrane permeability and absorption of quercetin-phospholipid complexes made with methanol and chloroform.

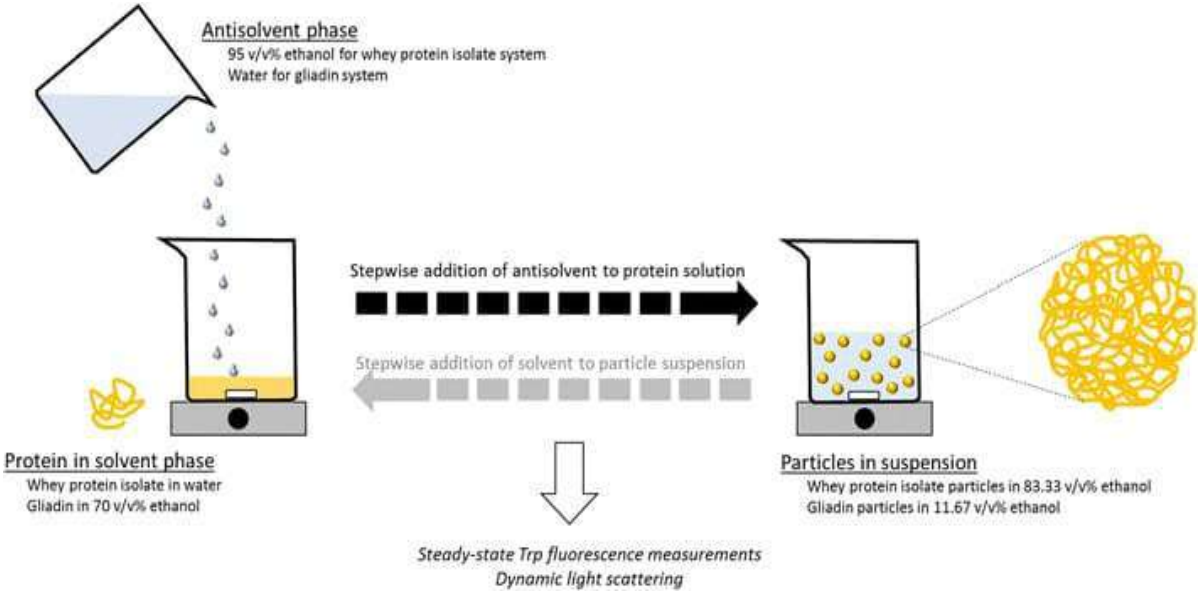

Fig:4

8.3.3 Supercritical Fluid Technology: [21,24]

SC-CO2 supercritical fluid extraction is a new method for producing phytosomes. It increases solubility and reduces residual solvent contamination.

Example: Supercritical CO2 was effectively used to prepare Ginkgo biloba phytosomes, which demonstrated improved pharmacokinetic and increased rates of dissolution.

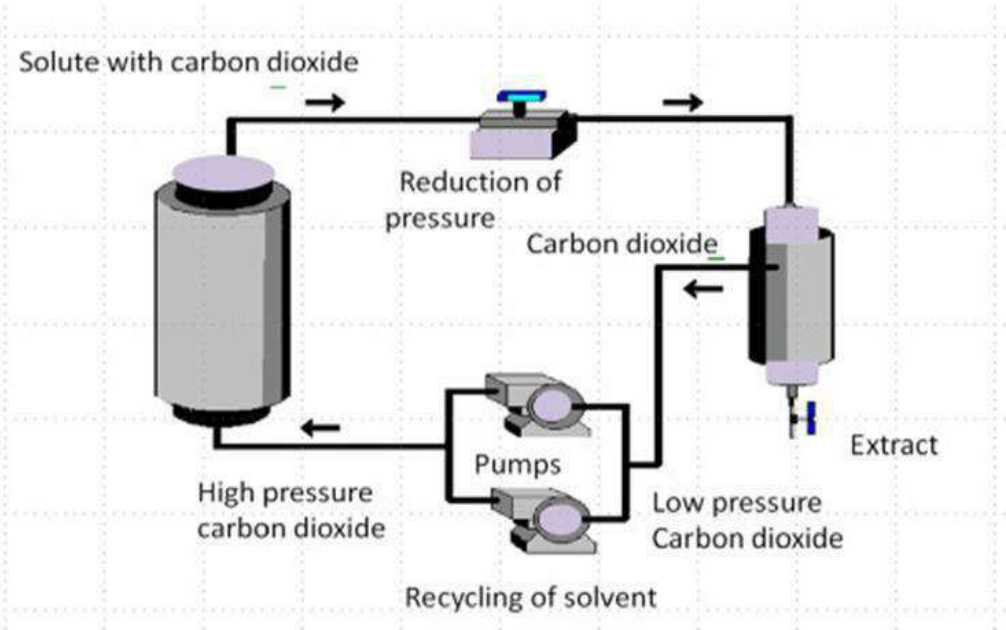

Fig:5

8.3.4 Rotary Evaporation Method: [22, 23]

Rotary evaporation is generally employed to remove efficiently the solvents under diminished pressure, providing stable phytosome complex

formation. The technique is often integrated with other preparation methods to enhance complex formation.

Example: Ethanol and rotary-evaporated milk thistle phytosomes showed better hepatoprotective activity and bioavailability.

Fig :6

9. Properties Of Phytosomes:

The process of preparing phytosome involves reacting phospholipids with plant extracts.' Spectroscopic data shows that the polar head of the phospholipids forms a hydrogen bond with the substrate (polar trail). when exposed to water, they shrink from 50nm to a few hundred micrometres, as photon. [20]

Correlation Spectroscopy

9.1 Biological properties of phytosomes:[20]

1. Phytosomes are sophisticated herbal medicines that work better than tradition herbal extracts because they are more easily absorbed and used.

2. Lipophilic compound with a distinct melting point, phytosomes are easily soluble in nonpolar solvents and only weakly soluble in lipids.

3. The active principle, which is attached to the phospholipid's polar head and ultimately forms an essential component of the membrane, can be accommodated by phytosomes.

4. Pharmacokinetic and pharmacodynamics research in both experimental animal and humans have shown that the phytosomes has a higher bioavailability than the simple botanical derivatives. [20]

9.2 Chemical properties of phytosomes:[20]

1. A natural substance and natural phospholipids combine to form phytosomes.

2. Proper concentration of phospholipid and the substrate react in a suitable solvent, like glycerol, to form the phytosomes complex.

3. The primary mechanism of phospholipid-substrate is the creation of hydrogen bond between the polar functionalities of the substrate and the polar head of phospholipids, which are phosphate and ammonium group.

4. Phytosomes takes on a micellar shape and form structures resembling liposomes when exposed to water.

9.3 Physico-chemical properties:[27]

1. A stoichiometric quantity of phospholipid react with standardises plant extracts as a substrate to prepare phytosomes. The spectroscopic data indicates that the phospholipid substrate connection results from the polar function of the substrate and the polar head (i.e., the phosphate and ammonium group) forming a hydrogen bond.

2. The size of Phytosome varies from 50 nm to a few hundred µm. Phytosomes range in size from 50 manometer to several 100 micro meter

3. When phytosomes are exposed to water, they take on a micellar shape that resembles liposomes, and photon correlation spectroscopy (PCS) shows that the phytosomes have gained liposomal structures.

4. The fatty acid chain provides sun altered signals in both the complex and free phospholipid, according to H1 and C13 NMR data. This suggests that long aliphatic chains are encircling the active principle to form a lipophilic envelope.

5. It is common for the complexes to be easily soluble in aprotic solvents, somewhat soluble in lipids, insoluble in water, and relatively unstable in alcohol. However, when complexed with phospholipid, the phytosomes of some lipophilic phytoconstituent, such as curcumin, have demonstrated an increase in water solubility.

10. Evaluation Of Phytosomes: [24, 25, 26]

The following characterization of phytosomes

10.1 Entrapment efficiency:

It's performed by the help of centrifugation technique by means of It's important to study ultracentrifugation equipment. The drug phytosomal complex is centrifuged in ultracentrifugation equipment and then the phytosome are separated from non-entrapped drug and the drug concentration is quantified by Uv-spectroscopic technique. The entrapment efficiency is calculated by using the formula

Percentage entrapment efficiency = weight of total drug – weight of free drug ÷ By entrapment weight of total drug × 100.

10.2 Zeta potential and particle analysis:

Spectroscopy methods such as dynamic light scattering and photon correlation spectroscopy can be used to assess zeta potential and particle size. Zeta potential and size analysis the Malvern Zeta sizer is used to measure the phytosomal complex's particle size. For this particle size and zeta sizer characterisation, an argon laser is employed.

10.3 Vesicle stability:

It is determined by evaluating the vesicle's size and structure over time. DLS measures the mean the mean size, and TEM tracks structural alterations.

10.4 Surface tension activity measurement:

A Du Nouy ring tentiometer can be used to assess the drug's surface tension activity in water using the ring method.

10.5 Drug content:

Both an appropriate spectroscopic approach and HPLC (high performance liquid chromatography) can be used to quantify the amount of medication.

10.6 Morphology:

Electron microscopy is one of several microscopic techniques that can be used to examine the shape and structure of phyotosomes.

10.7 Drug load:

It indicates the number of bioactive compounds that can be incorporated into the produced phytosthome. Its calculation depends on the dimensions of the incorporated phytoconstituent and the total weight phytosome formed which is crucial for dosing and efficiency.

11. Routes Of Administration:

11.1 Phytosomes for Topical Delivery [28, 29, 30]

The topical drug delivery techniques use phytosomes. Ocimum basilicum topical phytosomal gel was created using lecithin, cholesterol, and Carbopol 934. The Ocimum Basilicum extract was used to create the phytosomes, and they were evaluated for their morphology, yield, stability, and ability to prevent microbial growth. The produced phytosomes demonstrated improved cutaneous permeability. Stearic acid, cetyl alcohol, liquid paraffin, triethanolamine, glycerines, and other ingredients have all been mentioned in topical soy phytosome cream reports. This cream has been found to be naturally non-irritating. Hesperetin-loaded phospholipid-based nano vesicular systems were developed using a solvent evaporation process that included a phospholipid complex. They noted that the new formulation improved the therapeutic efficacy, solubility, and penetration (>53%) of the encapsulated Hesperetin). The phospholipid present in the phytosomes interfaces with the loaded phytoconstituent through the generation of an H-bond between the polar head of the phospholipid and the polar capabilities of the phytoconstituent. They significantly improve the skin penetration of the loaded phytoconstituents. Phytosomes enhance the permeation of loaded phytoconstituents due to their peculiar nanosized characteristics, quickly being delivered or transported across the cell membrane and into the bloodstream.

11.2 The ocular drug delivery techniques use phytosomes [31]

The use of prodrugs is increased because the presence of esterase causes N-acetyl carnosine to be hydrolysed. Here, L-carnosine and lipoid 75 were treated with methanol and Milli Q water and refluxed for one hour at 40°C.to produce a phospholipid complex. They found that L-carnosine phytosomes had 2.4 to5.6 times quicker penetration than L-carnosine solution. The phytosome technology helps phospholipids to enter the posterior portion of the eye with more selectivity and specificity. Furthermore, phytosomes enhance the effectiveness of the specific phytoconstituent loaded. when used for ocular drug delivery. The phospholipid LECIVA-S70 to make Hesperetin natrosomes using solvent evaporation have been reported. They evaluated the developed lipid-based system's compatibility, thermal behaviour, shape, and diffraction pattern. They discovered that compared to pure hesperetin, natural hesperetin is 10 times more soluble.in

water in comparison to pure hesperetin (23%) and the hesperetin-physical combination (28%), the corneal penetration of Hesperetin-naturosomes dramatically increases (>53%). This suggests that phytosomes are more effective in accelerating corneal permeation [18–20]. illustrates the advantages of phytosomes for ocular drug delivery. The challenges associated with the delivery of phytosomes through the ocular route involving poor corneal permeability, which may limit the entry of drugs loaded in the phytosomes. The presence of anatomical and Physiological barriers also limits the entry of drugs into the eye, which may lead to poor absorption and very low ocular bioavailability. The lacrimal secretions may also lead to poor retention time and decreased permeability across the corneal epithelium. Conjunctival blood.

11.3 Phytosomes for Parenteral Delivery:

The mitomycin C-loaded soybean phosphatidylcholine complex-based phytosomes employing solvent evaporation in conjunction with nanoprecipitation have been reported. They noticed that the mature phytosomes have a small size of 210.87 nm, a PDI of 0.251, and a charge of 33.38 mV. The spherical phytosomes had a biphasic release pattern, first releasing in a burst and then continuing to release over time. The produced phytosomes showed a notable lethal effect in H22 cells and a superior, dose-dependent curative inhibitory effect on tumour growth.

11.4 Phytosomes for Oral Drug Delivery: [33, 34]

Jain S et al. developed cefixime-loaded phytosomes for oral drug administration in 2019 by utilising phospholipid S100 in various millimolar ratios under vacuum drying and reflection. The formulation was found to be in the nanosized range with a prolonged release pattern. Quercetin phytosomes using food-grade lecithin have been reported to increase the solubility of quercetin. They saw improvements in both in vitro solubility and oral absorption while avoiding adverse effects. The solubility of quercetin phytosomes is unaffected by the highly acidic conditions that prevail in the gastrointestinal situation. Here, an enterocyte membrane was seen to release the hydrophilic quercetin into the lipid environment, supporting quercetin's penetration into the bloodstream.

11.5 Phytosomes for Nasal Drug Delivery:[35]

The nasal route, which involves olfactory or trigeminal nerves exiting the brain at the respiratory epithelium or olfactory neuro epithelium and entering the nasal cavity, is a dependable way to cross the blood-brain barrier. This creates quick, non-invasive access into the cerebrospinal fluid as well as interaction with the mucosal tissue. For the transfer of anti-Alzheimer's drugs into the brain, lipidic nanoparticles, emulsions, vesicles, gels, liposomes, etc., have demonstrated promising results. This increases the permeability and related bioavailability. The formulation method, size, zeta potential, and therapeutic action of the Encapsulated drugs influence the effective targeted administration via the nasal route. The standard intranasal transport system combines passive partitioning, carrier-mediated transport, and the paracellular pathway to target the brain. Our team reported the phytosomes containing "Geophilarepens methanolic leaf extract" using soy phosphatidylcholine. To provide a better penetration effect at the nasal cavity for the enhanced treatment of Alzheimer's disease, we further transformed the phytosomes into intranasal gel using hydroxypropyl methylcellulose as a gelling agent and incorporating transcutol P. We found that the mature phytosomes have a spherical form, measuring 444.93. ±25.24 nm in size and

contain 51.88 ± 1.025% of the methanolic leaf extract of Geophilarepents. At 60 minutes, it was discovered that the in vitro release was 45.84 ± 5.6%. The Geophilarepens methanolic leaf extract-based phytosome intra-nasal gel demonstrated improved nasal permeability in comparison to the Geophilarepens methanolic leaf extract, as well as better acetylcholinesterase inhibition (97.87 ± 6.84%) as compared to MEGR (69.86 ± 5.68%), which was shown to be higher and with substantial. Circulation also affects topical drug absorption. Overall, these may significantly lose the administered drugs through topical administration.

12. Application:

12.1 Antioxidant: [36]

According to research, phytosomes can decrease oxidative stress and inflammation by dramatically raising the body level of endogenous antioxidants such glutathione peroxidase (GPx) and super oxide dismutase (SOD). for instance, in preclinical setting, a phytosome formulation that included ginger and rosehip demonstrated exceptional antioxidant benefits. Has antioxidant qualities derived from silymarin that provide protection for the skin and liver.

12.2 Cardiac protectant: [37, 38]

Ginkgo bilioba phytosomes have demonstrated potentially in cardiovascular protection. Studies show that by lowering myocardial damage and raising endogenous antioxidant levels, they considerably lessen the myoproterneol-included myocardial necrosis in rats. Additionally, studies looked at mixing OCIMUM SANCTUM extract with GINKGO BILOBA phytosomes which suppressed lipid peroxidation and serum marker enzymes, through separate treatments worked better moreover, GINKGO BILOBA phytosomes have anti-inflammatory qualities through the reduction of cell adhesion molecules associated with heart conditions. Because of their increased bioavailability phytosomes are a novel approach to cardiovascular health because they improve the delivery and long-lasting therapeutic benefits of active substances.

12.3 Nervous system: [37,38]

Phytosomes have the potential to cure problems of the nervous system by improving the bioavailability and brain penetration of neuroactive substances .they have anti-depressants properties , lower the neuroinflammation ,and enhance cognitive function .Notable examples are Annona murucata for depression, Catella asiatica for cognitive support ,ginkgo biloba for migraine relief and curcumin for Alzheimer .The therapeutic effectiveness of phytochemicals in neurological illness is is increased by this method.

12.4 Anti asthmic: [37, 39]

By improving the transport of plant-based substances with anti-inflammatory and antioxidant qualities, phytosomes have the potential to be used anti asthmatic agents. While quercetin phytosomes enhance peak expiratory flow and reduce asthma symptoms, EUPHORBIA HITR phytosomes have broncho dilatory effects via preventing tracheal contractions. By increasing antioxidant defences, they reduce lung damage, fluid exudations and pro inflammatory cytokinesis like COX2 and ICAM 1.

12.5 Wound healing: [40, 41]

By improving the stability and bioavailability of chemicals originating from plants phytosomes present a viable strategy for wound healing. Phytosomes , which are created by mixing phytoconstituents with phospholipids, enhance targeted distribution, skin penetration, and

absorption. Important substances such as carvacrol, curcumin, quercetin, and crocetin have been shown in clinical trials to promote collagen deposition, decrease inflammation and speed wound closure. Phytosomes are useful invention for encouraging quicker and more efficient tissue regeneration since this technology solves the problems of poor solubility and limited therapeutic benefits in conventional wound treatment.

12.6 Cancer treatment: [42, 43, 44]

Anew approach to cancer treatment is the use of the phytosomes, which increase the bioavailability and therapeutic effectiveness of substances originating from plants such as qucdertin and curcumin. Phytosomes reduce adverse effects on healthy tissues by improving absorption, stability, and targeted delivery to cancer cells by encasing bioactive substances in phospholipid complexes. By blocking proteins like p-glyco protein, they also aid in the fight against multidrug resistance and increase the efficacy of chemotherapy .A useful tool in cancer therapy ,phytosomal formulations have demonstrated promising results in treating a variety of tumours , including liver, colorectal, and breast cancers, as well as synergetic effects with traditional medications .

12.7 Transdermal: [37, 45, 46]

By mixing herbal phytochemicals with phospholipids ,phytosomes and innovative transdermal medication delivery system improve their absorption and bioavailability. This structure allows for deeper distribution of poorly soluble chemicals by improving skin penetration, deformability, and prolonged release. Because of their long-lasting therapeutic effects, minimal toxicity and biocompatibility, phytosomes are perfect for treating inflammatory diseases, chronic wounds, and skin conditions. Their potential in contemporary herbal medicine is highlited by their capacity to improve clinical efficacy and overcome absorption issues.

12.8 Liver: [47, 48, 49]

By increasing the bioavailability and absorption of herbal extracts, phytosomes function as an efficient delivery vehicle for hepato protective drugs. They have potent antioxidant properties. Lower bilirubin, GPT, GOT, and ALP, and restore liver function by increasing the levels of antioxidant enzymes. Phosphatidylcholine in phytosomes further promotes liver protection, while silymarin and ursolic acid phytosomes greatly increase oral bioavailability. Phytosomes are a viable strategy for controlling and preventing liver problems because of their qualities.

13.Marketed Products of Phytosomes: [50]

S. No	Trade Name	Chief Constituents	Source	Use
1	Centella phytosomes	Triterpine	Centella asiatica	Cicatrizing trophodermic
2	Ginselect phytosomes	Ginsenosides	Gingko biloba	Adaptogenic
3	Greenselect phytosomes	Polyphenols	Camellia sinensis	Free radical scavenging activity
4	Leucoselect	Polyphenols	Vitis vinifera	Antioxidant
5	Meriva	Curcuminoids	Curcuma longa	Anti-inflammatory
6	Silymarin	silymarin	Silybum marianum	Anti-hepatotoxic
7	Oleaselect TM phytosome	Polyphenols of olive oil	Olea europaea	Anti-inflammatory, Antioxidant
8	Crataegus phytosomes	Vitexin z+ o rhamonoside	Crataegus Mexicana	Antioxidant

9	Visnadine	Visnadine	Ammi visnaga	Circulation improver
10	Bilberry	Triterpine	Vaccinium myritillus	Potent antioxidant
11	Ruscogenin phytosomes	Steroid saponin	Ruscus aculeatus	Anti- inflammatory
12	PA2 phytosmes	Proanthocynidin	Horse chestnut bark	Antiwrinkle, UV protectant
13	Zanthalene phytosomes	Zanthalene	Zanthoxylum bungeanum	Soothing, anti-itching
14	Lymphaselect phytosomes	Triterpenes	Melilotus officinalis	Indicated in insomnia
15	Sabal select phytosomes	Fatty acid, steroid	Serenoa repens	Benign prostate hyperplasia

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