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Emergence Of Phytosomes : As Nanoparticles And Nanocarriers

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Abstract-

The emergence of phytosomes as nanoparticles and nanocarriers represents a significant advancement in drug delivery and natural compound utilization. Phytosomes, specialized formulations involving the complexation of plant compounds with phospholipids, have garnered attention for their ability to enhance the bioavailability, stability, and targeted delivery of active ingredients. This review explores the evolution of phytosomes, elucidating their preparation methods and mechanisms of action as nanocarriers. The unique amphiphilic nature of phospholipids allows them to encapsulate hydrophobic plant compounds, forming lipid bilayers reminiscent of cell membranes. This encapsulation improves solubility and protects compounds from degradation. The resultant nanoparticles offer advantages such as improved absorption, reduced irritation, and versatile formulation possibilities. Through a comprehensive analysis of existing research, this review highlights the promise of phytosomes in pharmaceuticals, cosmetics, and nutraceuticals. The synthesis of knowledge underscores the potential of phytosomes as a bridge between traditional herbal remedies and modern nanotechnology, paving the way for enhanced therapeutic applications and innovation in natural product utilization.

Keywords- Phytosomes, Nanoparticles, Nanocarriers, Novel drug delivery system

Introduction of Phytosomes-

A Novel Drug Delivery System (NDDS) refers to innovative approaches and technologies designed to improve the delivery of pharmaceutical compounds to the body in order to achieve better therapeutic outcomes. Traditional drug delivery methods, such as oral tablets or injections, may have limitations in terms of efficacy, safety, and patient compliance. NDDS aims to address these limitations by controlling the release, targeting, and absorption of drugs in a more precise and efficient manner.

Phytosomes are cell like structure “Phyto” means plant while “some” means cell like and phytosome is a novel approach to drug delivery system that addresses the limitations of the traditional drug delivery systems. Phytosomes contains the bioactive phytoconstituents of herb extracts surrounded and bound by lipid. Phytosomes are developed by incorporating standardized plant extract or water soluble phytoconstituents into phospholipids to produce lipid compatible molecular complexes called phytosomes and so vastly improve their absorption and bioavailability.[(1)]

The examples of phytosomes are gingko phytosomes, Curcumin phytosomes,etc;it has high potential benefit and improve the bioavailability.

The emergence of phytosome nanotechnology has a potential impact in the field of drug delivery and could revolutionize the current state of topical bioactive phytochemicals delivery. Phytosomes as lipid-based nanocarriers play a crucial function in the enhancement of pharmacokinetic and pharmacodynamic properties of herbal-originated polyphenolic compounds, and make this nanotechnology a promising tool for the development of new topical formulations. The implementation of this nanosized delivery system could enhance the penetration of phytochemicals across biological barriers due to their unique physiochemical characteristics, improving their bioavail-ability.[2]

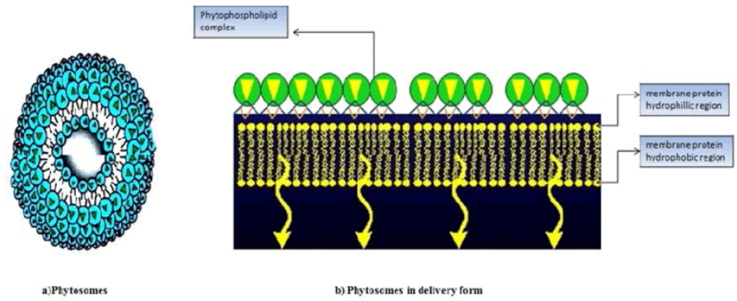

Figure 1: Phytosomes herbal complex. (3)

Figure-1 Phytosomes-A detailed overview.

Advantages of Phytosomes-

1. Enhanced Bioavailability: Phytosomes improve the absorption of plant compounds by increasing their solubility in both water and lipids. This leads to better bioavailability and effectiveness.

2. Targeted Delivery: They can be designed to deliver specific compounds to certain cells or tissues, increasing the targeted effects of the active ingredients.

3. Improved Stability: Phytosomes protect sensitive plant compounds from degradation, extending their shelf life and maintaining their potency.

4. Reduced Irritation: Phytosomes can minimize potential skin irritation and gastrointestinal distress that might be caused by the direct application or ingestion of certain plant extracts.

5. Natural Ingredients: Phytosomes are derived from natural sources and are often used to enhance the therapeutic benefits of plant extracts.

6.Compatibility: They are compatible with both hydrophilic and lipophilic compounds, allowing for the incorporation of a wide range of active ingredients.

7. Scientific Validation: The concept of phytosomes is supported by scientific research and has been studied for its efficacy in enhancing the bioavailability of herbal extracts.[4]

Disadvantages of Phytosomes-

1. Phytoconstituents are easily abolished from the phytosomes.
2. There is stability problem in phytosome.

Preparation of Phytosomes:-

1) Solvent evaporation method:-
   The solvent evaporation methods involve integration of the phytoconstituents and phosphatidycholine in a flask containing organic solvent. This reaction mixture is kept at an optimum temperature usually 40°C for specific interval of 1 hr to achieve maximum drug entrapment within the phytosomes formed. Thin film phytosomes are separated by 100 mesh sieves and stored in desiccators for overnight.

2) Mechanical Dispersion method:-

In the experiments, the lipids dissolved in organic solvent are brought be in contact with aqueous phase containing the drug. The next removal of the organic solvent under reduced pressure results in the formation of Phyto phospholipid complex.[5]

3) Salting out technique :-

An important method of phytosome preparation that done by dissolving both Phosphatidycholine and the plant extract during a suitable organic solvent then n-hexane was added until the extract Phospholipid complex precipitation occurs.

4) Lyophilization Methods:-

In lyophilization technique Diosmin was dissolved in Dimethyl Sulphoxide. The resulting solution (2.5% weight/volume) was added to Soyphosphatidycholine dissolved in t-butyl alcohol (1.5%weight/volume) followed by stirring for 3 hours on a magnetic stirrer until complex formation. The complex was then isolated by lyophilization dissolved in t-butyl alcohol (1.5%weight/volume) followed by stirring for 3 hours on a magnetic stirrer until complex formation. The complex was then isolated by lyophilization.[6]

Phytosomes as Nanoparticles and Nanocarriers:-

Phytochemicals or plant chemicals are comprised of a wide range of naturally occurring bioactive compounds produced by plants. The term bioactive refers to the ability of these compounds to interact with different components of living organisms, thereby exerting their beneficial effects. Phenolics, alkaloids, carbohydrates, lipids, terpenoids, and other nitrogen-containing compounds are the most structurally different major categories of phytochemicals. Moreover, there are several subcategories of phytochemicals based on differences in biogenesis or biosynthetic pathway.

Between all the phytochemicals, only those having an active hydrogen atom (-COOH, -OH, -NH2, -NH, etc.), like polyphenols, can be integrated into a phytosome structure. An active hydrogen atom can form a hydrogen bond between the herbal derivatives and the hydrophilic parts of amphiphile molecules. Polyphenols are the major group of phytochemicals extensively found in plant-based foods. Potential health effects of polyphenols were shown in different diseases including cancer, inflammation, neurodegenerative and cardiovascular diseases, type 2 diabetes, and obesity. Essentially, they are found in conjugated forms composed of sugar residues (one or more) attached to hydroxyl groups; however, the sugar residues may directly attach to an aromatic carbon. Flavonoids and non-flavonoids are two major subgroups of polyphenols ,the use of polyphenols through phytosomes, paying attention to their structure, preparation, and the biological activities associated with the use of phytochemicals-loaded phytosome.[7]

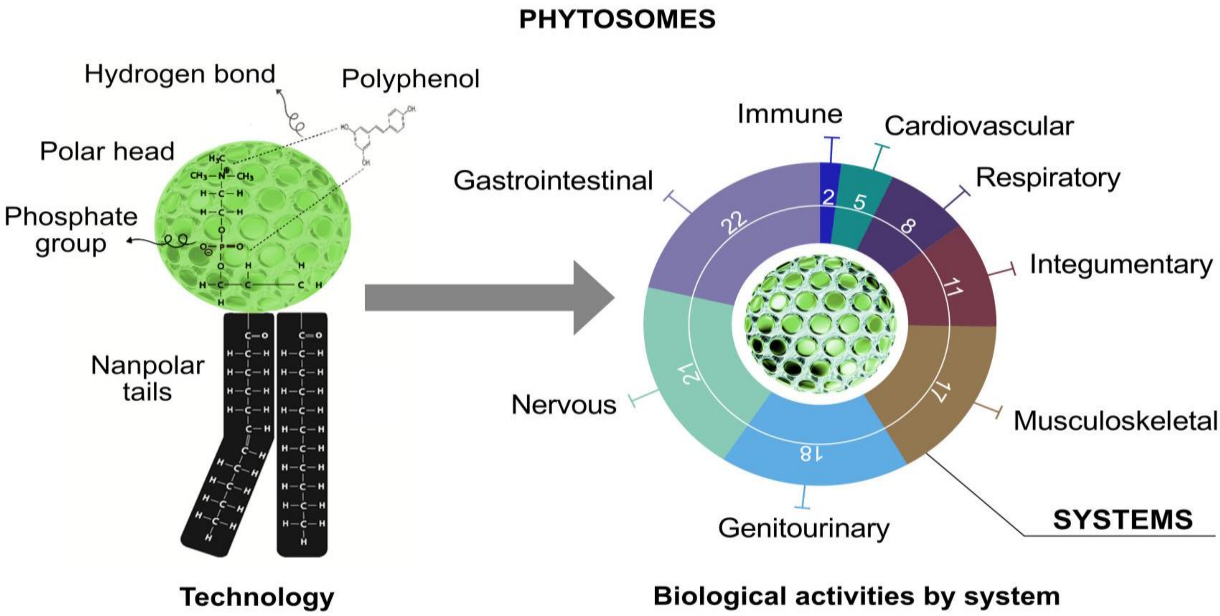

Fig-2-Phytosomes Nanotechnology linked with biological activites(8)

Preparation of nanosized phytosomes:-

1. **Selection of Plant Extract and Phospholipids**: Choose the plant extract that contains the active compound you want to encapsulate. Select compatible phospholipids that will form the bilayer structure around the compound.

2. **Solvent System**: Dissolve the plant extract and phospholipids in a suitable solvent system. Typically, a mixture of water and a water-miscible organic solvent (such as ethanol or methanol) is used.

3. **Complex Formation**: Mix the plant extract solution with the phospholipid solution in a specific ratio. The hydrophobic components of the plant extract will interact with the hydrophobic tails of the phospholipids, forming complexes.

4. **Solvent Evaporation**: Evaporate the solvent mixture under reduced pressure or through other methods to form a thin lipid film. This lipid film will contain the encapsulated active compounds.

5. **Hydration**: Rehydrate the lipid film with an aqueous solution, causing the lipid film to swell and form lipid vesicles or liposomes containing the plant extract.

6. **Size Reduction**: Depending on the desired size of the nanoparticles, the lipid vesicles can be subjected to size reduction techniques such as sonication or homogenization. This breaks down larger vesicles into smaller nanoparticles.

7. **Purification**: Remove excess plant extract, phospholipids, and other impurities through processes like centrifugation or filtration.

8. **Characterization**: Characterize the phytosome nanoparticles for size, encapsulation formulated into various products such as creams, gels, capsules, or tablets.

9. **Formulation**: Depending on the intended application, the phytosome nanoparticles can be formulated into various products,such as tablets,capsules.

10. **Testing and Validation**: Test the formulated phytosome products for bioavailability, efficacy, and safety. These tests ensure that the nanoparticles effectively deliver the active compounds and are well-tolerated.[9][10]

Materials used to prepare nanophytosomes-[11]

Solvents	Tetrahydrofuran,n-octanol,ethanol, dioxane, dichloromethane, methylene chloride, ethyl acetate, n-hexane.
Phospholipids	Phosphatidylcholine (P.C.), Phosphatidylethanolamine, and Phosphatidylserine
Phytoconstituents (vesicles)	Nanosized vesicle composed of Monascin (MNS) and ankaflavin (ANK)-loaded casein micelles (CAS MCs)
Nanocarriers	L-carnosine, Phosphatidic acid.

Instances of Nanophytosomes-

1. Propolis, a bee product, is one example of a natural product with promising antioxidant activity. Propolis is often referred to as "bee glue" and is described as a resinous material produced by honeybees from leaves, flowers, sprouts, or other parts of various plants. The excellent antioxidant activity of propolis has been attributed to the high content of flavonoid and other phenolic compounds,
   Additionally, caffeic acid (CA), quercetin (QU) and kaempferol (KP) contained in propolis have all shown strong antioxidant capacity to protect body tissues from oxidative stress.These three compounds have also been reported to have anti-aging properties. However, significant problem arises because of the nature of these compounds. They have all been reported to exhibit low solubility, poor dissolution profiles and reduced skin permeation abilities. This will consequently hinder the permeability of the substances through biological membranes. Thus, the development of nanophytosomes delivery systems to help increase the permeability of these natural substances is necessary to achieve optimum therapeutic efficacy.

2. Apigenin ,*Centella asiatica* extract,*Vitis vinifera* L. seed extract showing that the formulation of these natural products into nanophytosomes exhibited greater dissolution, stability, bioavailability profiles and dermal retention profiles.

3. Silybin, the active ingredient of *Silybum marianum* (milk thistle), is a water-soluble flavonoid reported to have potent hepatoprotective and antioxidant activities. However, silybin has poor solubility and absorption in a lipid-rich biological membrane. The formulation of the milk thistle extract as a phytosome delivery system increased its absorption and led to a sevenfold increase in antioxidant activity in comparison to free silybin. Moreover, oral administration of silybin-phytosome preparation showed remarkable enhancement in bioavailability in rats.

4. Preparation of *Centella asiatica* in the form of nanophytosomes was found to reduce the oxidative stress in diabetic patients and enhance protection against ischemic-reperfusion damage in rat heart
5. Quercetin is a phenolic phytochemical compound found in various vegetables, fruits, and leaves, and has soothing antioxidant and anti-itching effects. In a study by Maramaldi et al., the formulation of quercetin complexed with phytosomes nanoparticles exhibited potent dermal activity above that of standard quercetin and similar to the conventional anti-inflammatory drugs that are usually used. The quercetin-phytosomes

complex had a significant impact by reducing redness, itching, and inflammation of damaged skin. Research also suggested that this complex may also support restoration of the skin barrier function, increasing hydration, and reducing water loss.[12]

Mechanism of Nanophytosomes formation-

The phytoactive components of herbal extracts are well suited to direct binding to phosphatidylcholine from soy. Phosphatidyl choline is a bifunctional compound, the phosphatidyl moiety being lipophilic and the choline moiety being hydrophilic in nature. Phospholipids are small lipid molecules in which the glycerol is bound to only two fatty acids, instead of three as in triglycerides, with the remaining site is occupied by a phosphate group

Specifically, the choline head of the phosphatidylcholine molecule binds to phytoconstituents while the fat soluble phosphatidyl portion, comprising the body and tail, then envelopes the choline-bound material. This results in small microspheres or the production of cells known as phytosomes

Thus, phytosomes are also considered as a phytolipid delivery system. The phytosome process produces small cells which protect the valuable components entrapped in a nanocarriers such as phosphatidic acid of the herbal extract results in improved absorption and targeted therapy.
They improve transition of constituents from the water phase to the lipid friendly environment of the enterocyte cell membrane and from there into the cell, finally reaching the circulation[13]

Characterization and Evaluation of Nanophytosomes-

1. Visualization:-
Transmission electron microscopy (TEM), atomic force microscopy (AFM), and scanning electron microscopy (SEM) can be used in studying the morphology of phytosomes. Studying the surface morphology of phytosomes is often an essential way to detect the entrapment mechanisms and the presence of probable impurities on the surface.
Suitable magnification of the phytosomal structures can be provided by the SEM after an appropriate coating or sputtering them with a gold layer. In general, the phytosomes surface characterizations do not show any crystalline structures or any impurities. The morphological studies have confirmed that the phytosomal structures have a spherical shape.

2. Vesicular Size and Zeta Potential
Particle Size, average mean diameter, and zeta potential (ZP) of phytosome complexes can be investigated by dynamic light, scattering (DLS) and photon correlation spectroscopy (PCS). Zeta Potential is regarded as an important parameter in determining the physical stability of phytosomes by providing enough electrostatic repulsion and subsequently good in vitro stability.
This phenomenon prevents phytosomal vesicles from precipitation or aggregation which cause low cellular uptake of nutraceuticals. The photon correlation spectroscopy (PCS) technique is introduced as a good method for investigating the size of the phytosome. It can confirm whether the shape of the phytosomes are vesicular or not. The polydispersity index is another parameter of size distributions of phytosomes, which can be obtained from PCS.[14]

3. Vesicle Stability:-
DLS, SEM, and TEM are the main techniques for assessing the stability of phytosomal vesicles regarding their changes in size and shape over appropriate time intervals.
The average vesicular size can be measured by DLS and SEM. Both TEM and SEM can be applied for monitoring the changes in structure and shape of phytosomes.

4. **Entrapment Efficiency (EE):-**

The EE of a phytoconstituents loaded with phytosomes can be assessed using the ultracentrifugation method. For this purpose, the ultracentrifugation at lower rpm-longer periods or higher rpm-shorter periods can be applied for determining the EE%. Moreover, the supernatant should be estimated in order to detect phytoactive compounds either by UV-Visible spectroscopy or more precisely with high performance liquid chromatography (HPLC).(15)

Physicochemical Properties of a Nanophytosomes-

Phytosome has lipophilic substances with a clear melting point. Average size of phytosome range is 50 nm to a few hundred μm. They are easily soluble in non-polar solvents, insoluble in water and moderately soluble in fats and unstable in alcohol. Liposomal like structures of micellar shape are formed when phytosome are treated with water.

On the basis of their physicochemical and spectroscopic data, it has been shown that, the phospholipids-substrate interaction is due to the formation of hydrogen bond between the polar heads of phospholipids (i.e. phosphate and ammonium groups) and the polar functional groups of substrate, In phytosomes the active principle is anchored to the polar head of phospholipids, becoming an integral part of the membrane.(16)

Recent advances and applications of Nanophytosomes:-

1. Phytosomes as antioxidant-

   The Ginkgo biloba has various health benefits. The results obtained were promising when studying the influence of its phytosome on antioxidant effects on the rat model. The effects of phytosome were due to free-radical scavenging activity and providing liver protection.(17)

2. Phytosomes as Cardiac protectant-

   Ginkgo biloba phytosome has a protective effect on Isoproterenol induced cardiotoxicity.(18)

3. Phytosome action on nervous system-

   Annona muricata for major depressive disorder (MDD). To enhance the permeation through the blood-brain barrier (BBB) and minimize gastric biotransformation, liposome, and phytosome prepare.(19)

4. Phytosomes as anti-asthmatic-

   Boswellia phytosome (Casperome 500 mg/day) as the complementary intervention and the standardized treatment regimen (inhaled corticosteroids) beta-agonists) for four week period in asthma.(20)

5. Phytosomes as cancer treatment-

   Icarrin phytosomes against ovarian cancer cells (OVCAR-3 cells).

   Thymoquinone-loaded phytosome possesses anticancer potential against human lung cancer cells.

   Diosgenin structure to ensure new derivatives with enhanced cytotoxic effects and antiproliferative effects against human lung cancer cells.(21)

Conclusion-

Phytosomes is novel drug targeted delivery system having least complications and greater therapeutic action at targeted site. This review describes how nanocarriers are efficient by giving specific action at targeted site in case of various ailments. It also describes what is the exact mechanism of nanophytosomes and recent advances. Nanophytosomes is technique which is currently being used in various formulation and acts as best alternative for conventional dosage form. Nanophytosomes are being tremendously used in ailments of cancer, hepatoprotective, asthma, etc.(22)

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