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A Review on Phytosomes: Promising Approach for Drug Delivery of Herbal Phytochemicals

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ABSTRACT: Novel drug delivery system is a novel approach to drug delivery that addresses the limitations of the traditional drug delivery systems. Phytosome is a novel patented technology developed to incorporate standardized plant extracts into phospholipids to give a lipid soluble molecular complexes, with improved bioavailability and absorption, which is called as "phytosomes''.The term "Phyto" means plant, while "some" means cell-like. Phytosomes results from the reaction of stoichiometric amount of phospholipid with standardized herbal extract or polyphenolic constituents in an aprotic solvent. Phytosomes have better stability due to formation of chemical bonds between phosphatidylcholine molecules and phytoconstituents. Phosphatidylcholine is not only carrier; it is also having hepatoprotective activity and nutritional value. There are number of products available in market that contains phytosomal drug delivery system such as silybum marianum, ginkgo bilioba, camellia sinensis. The present review describes the overview of phytosomes technology, comparison of liposome and phytosome, preparation methods, properties, characterization and applications of phytosomes.

KEYWORDS: Phytosomes, Phytoconstituents, Phospholipid, Silybin, Bioavailability.

I. INTRODUCTION:

Novel drug delivery system is a novel approach to drug delivery that addresses the limitations of the traditional drug delivery systems. Our country has a vast knowledge of Ayurveda whose potential is only being realized in the recent years. However, the traditional drug delivery system used for administering the herbal medicine is out-of-date,resulting in reduced efficacy of the drug. If the novel drug delivery technology is applied in herbal medicine, it may help in increasing the efficacy and reducing the side effects of various herbal compounds and herbs. This is the basic idea for incorporating novel method of drug delivery in herbal medicines. Fora longtime, herbal medicines were not considered for development as novel formulations because of owing to lack of scientific justification and difficulties in processing, such as extraction, standardization and identification of individual drug components in complex poly herbal systems. However, modern phytopharmaceutical research can solve the scientific needs such as nanoparticles, microemulsions, matrix systems, phytosomes, liposomes, solid dispersions, solid lipid nanoparticles and so on.

There are three main reasons for the popularity of herbal medicines:

1. There is a growing concern over the reliance and safety of drugs and surgery.
2. Modern medicine is failing to treat effectively many of the most common health conditions.
3. Many more natural measures are being shown to produce better results than drugs or surgery without side effects.

There is increasing evidence that many current drug therapies simply suppress the symptoms and ignore the underlying diseases processes. In contrast, many natural products appear to address the cause of many diseases and yields superior clinical results. Unfortunately, most physicians and patients are not aware that these natural alternatives exist. Some drugs have an optimum concentration range within, from which maximum benefit is derived, and the concentrations above or below this range can be toxic or produce no therapeutic effect at all.

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ADVANTAGES OF HERBAL MEDICINES:

1) Herbal medicines are very cheap in cost when compare to the conventional form of medication.
2) Herbal medicines are known to be more productive in comparison to others forms of medication in curing certain conditions.
3) The greatest benefit associated with herbal medicine is the less existence of side effects.
4) Obesity is a growing problem which is known to have hazardous effects on an individual health. Herbal medicine deals very effectively with the problem of obesity without consuming much time and efforts.

Disadvantages Of Herbal Medicines:

1) In some instances, individuals switch to herbal medicine without realizing that the symptoms can be linked to different ailment.
2) Although herbal medicines have the potential to cure many different ailments, the curing period is usually longer in comparison to conventional form of medication. Patient needs to have more patience while undergoing herbal treatment.
3) Herbal medicines can cause allergic reactions in patients in some cases. Before resorting to herbal medication, you need to ensure that you are not allergic to the particular herb that you will be consuming. [1,2]

PHYTOSOMES:

Phytosome is a novel patented technology developed to incorporate standardized plant extracts into phospholipids to give a lipid compatible molecular complexes, with improved bioavailability and absorption, which is called as phytosomes. Phytosomes also known as Herbosomes [3]. The term "Phyto" means plant, while "some" means cell-like. Most of the biologically active constituents of the plants are polar or water-soluble molecules. However, water soluble phytoconstituents like flavonoids, tannins, glycosidic aglycones etc are poorly absorbed either due to their large molecular size which cannot absorbed by passive diffusion, or due to their lipid solubility; severely limiting their ability to pass through the lipid rich biological membranes, resulting poor bioavailability [4]. Increased bioavailability of the phytosomes over the simpler, non-complex plant extracts has been demonstrated by pharmacokinetic and activity studies, conducted in both animals and humans. Phytosomes exhibit better pharmacokinetic and pharmacodynamic profile than conventional herbal extracts [5].

Phytosomes means herbal drug loadedin vesicles, which is available in the nano form. The phytosomes provide an envelope, like coating around the active constituent of the drug and due to this the chief constituent of the herbal extract remains safe from degradation by digestive secretion and bacteria. Phytosome is effectively able to absorb from a water loving environment into lipid loving environment of the cell membrane and finally reaching to blood circulation [6]. Phytosomes are obtained by reacting phospholipid with selected botanical constituents with a suitable solvent, and due to their physical and chemical efficiency, these Phyto-complex can be considered as a novel entity [7].

Phospholipids are complex molecules which are used in the formation of cell membranes. In humans and other higher animals, the phospholipids are also employed as natural digestive aids and acts as carrier for both fat-soluble and water-soluble nutrients which are easily absorbed orally. The phospholipid mainly used to make phytosomes, is phosphatidylcholine, obtained from soya bean [8]. Phosphatidylcholine, phosphatidylserine, phosphatidylethanolamine, phosphatidylinositol are the phospholipids used, but phosphatidylcholine widely used because of their certain therapeutic value in case of liver diseases, alcoholic steatosis, drug induced liver damage and hepatitis [9]. Phytosomes can easily travel across the lipophilic path of the enterohepatic cell membranes [10] and also stratum corneum layer of the skin [11].

ADVANTAGES OF PHYTOSOMES:

- Phytosomes have better stability due to formation of chemical bonds between phytoconstituents and the phosphatidylcholine molecules [12].
- Phytosomes produces a little cell where the active components of herbal extracts are protected from destruction by gut and digestive secretions [13].
- Small dose can produce desired results, as the absorption of active component is improved [14].
- Formulation of phytosomes is easy as there is no problem in drug entrapment [15].
- Phytosomes have better stability profile [16].
- Phytosomes increases the solubility of bile to herbal constituents [17].

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- Duration of action of phytosomes is increased [18].
- Phytosomes shows better drug entrapment efficiency [19].
- Phosphatidylcholine is not only a carrier; it is also having hepatoprotective activity and nutritional value [20].
- Cosmetic and other topical use of herbal constituents can be done by phytosome formulations [21].

Mechanism Of Phytosome Technology:

Phytosomes results from the reaction of a stoichiometric amount of the phospholipid (phosphatidylcholine) with the standardized extract or polyphenolic constituents (simple flavonoids) in an aprotic solvent [22]. Phosphatidylcholine is a bifunctional compound, the phosphatidyl moiety is lipophilic and the choline moiety is hydrophilic in nature. The choline head of the phosphatidylcholine molecule binds to polyphenolic constituents while the lipid soluble phosphatidyl portion comprising the body which then envelopes the choline bound material. Hence, the phytomolecules produce a lipid soluble molecular complex with phospholipids, also called as phytophospholipid complex. Molecules are anchored through the chemical bonds to the hydrophilic head of the phospholipids, as can be demonstrated by the specific spectroscopic techniques [23,24].

Precise chemical analysis indicates that the unit phytosome is usually a flavonoid molecule linked with at least one phosphatidylcholine molecule. The phytosome technology produces a little cell, where the plant extract or its active constituent is protected from destruction b gastric secretions and gut bacteria owing to the gastroprotective property of phosphatidylcholine [25].

FIGURE 1: A FLAVONOID MOLECULE IS ENVELOPED BY A PHOSPHOLIPID MOLECULE

DIFFERENCE BETWEEN LIPOSOME AND PHYTOSOME:

Likephytosomes,a liposomeis formed by mixing a waterconstituent with phosphatidylcholine in definite ratio under specific conditions. Here, no chemical bonds are formed; the phosphatidylcholine molecules just surround the water-soluble substance. There may be hundreds and thousands of phosphatidylcholine molecules which are surrounding the water-soluble compound. In contrast, with the phytosme the phosphatidylcholine and the herbal constituents actually form a 1:1 or 1:2 molecular complex depending on the chemical bonds involved in the complex. This difference makes the phytosome much better absorbed than liposomes showing better availability. Phytosomes have also been found to be superiorto liposomes in topical and skin care products [26]. The phytosome is a unit of a few molecules bonded together while the liposome is an aggregate of many phospholipid molecules that can enclose other Phyto active molecules without specifically bonding to them [27,28].

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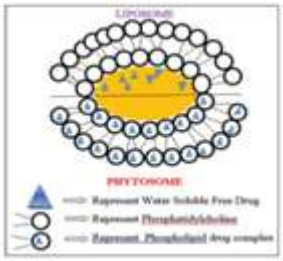

FIGURE 2: DIFFERENCE BETWEEN THE LIPOSOME AND PHYTOSOME

Preparation Techniques For Phytosomes:

A. Thin layer rotary evaporator method: Phytosomes vesicles were made by thin layer rotary evaporator vacuum method. The phytosomal complex was mixed in anhydrous ethanol in 250ml round bottom flask. The flask was attached to a rotary evaporator. The solvent will evaporate at a temperature about 60˚C forming a thin layer film around the flask. The film is hydrated by phosphate buffer having Ph 6.8, and the lipid layer will peel off in phosphate buffer forming vesicle suspension. The phytosomal suspension will be stored in the refrigerator for 24hrs, before characterization [29].

B. Solvent evaporation method: Phospholipid, i.e., soya lecithin was reacted with polyphenolic extract in an equal ratio with 5 ml of dichloromethane with stirring until evaporate. Once the dichloromethane was evaporated 5 ml of n-hexane, was added to the thin film with stirring and left in a fume hood for complete removal of the solvent. After complete removal of n-hexane, the thin film was hydrated and sonicated for desired phytosomal complex [30].

C. Reflux method: Phytosomes can also be prepared by reflux method. Polyphenolic extract and phospholipid were placed in 100ml round bottom flask and refluxed in dichloromethane for 1hr not exceeding 40˚C. the clear solution was evaporated and add 15ml of n-hexane until a precipitatewas obtained. The precipitate was taken and placed in a desiccator [31].

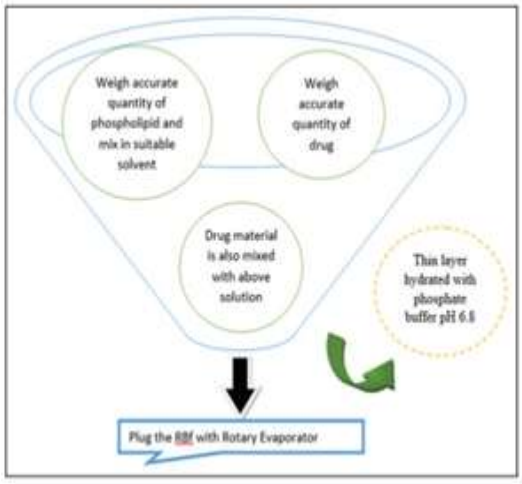

FIGURE 3: PREPARATION METHOD OF PHYTOSOMES

PROPERTIES OF PHYTOSOMES:

The term phytosome is used to define a complex between a natural product and natural phospholipids, like soy phospholipids. Phytosomes are obtained by the reaction of stoichiometric amounts of phospholipids and phytoconstituents in an appropriate solvent.

1. Phytosomes can accommodate the active principle, that is anchored to the polar head of the membrane, becoming an integral a part of the membrane [32].
2. Phosphatidylcholine: Study of comparisons of nuclear magnetic resonance of the complex with those of the pure precursors indicates that the signals of the fatty chain are unchanged [33].
3. Phytosomes are advanced forms of herbal products that are better absorbed, utilized. As a result, produce better results than conventional botanical herbal extracts. The increased bioavailability of the phytosome over the non-complexed botanical derivatives has been demonstrated by pharmacokinetic studies or by pharmacodynamic tests in experimental animals and human subjects [34].
4. Phytosomes are lipophilic substances with a definite melting point, they are freely soluble in non-polar solvents, and moderately soluble in fats [35].
5. Phytosomes when treated with water, they assume a micellar shape, forming structures that resemble liposomes exhibiting fundamental differences [36].

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CHARACTERIZATION OF PHYTOSOMES:

1. **Visualization:** Visualization of phytosomes can be done by using transmission electron microscopy (TEM) and by scanning electron microscopy (SEM).
2. **Vesicle size and zeta potential:** The particle size and zeta potential of phytosomes can be determined by dynamic light scattering (DLS) using a computerized inspection system and photon correlation spectroscopy (PCS).
3. **Entrapment efficiency:** The entrapment efficiency of drug by phytosomes can be measured by the Ultracentrifugation technique [37].
4. **Transition temperature:**The transition temperature of the vesicular lipid systems can be determined by the differential scanning calorimeter [38].
5. **Surface tension activity measurement:** The surface tension activity of the drug in aqueous solution be measured by ring method in a Du Nouy ring tensiometer.
6. **Vesicle stability:** The stability of vesicles can be determined by assessing the size and structure of the vesicles over time. The mean size is measured by differential light scattering (DLS) and structural changes are monitored by transmission electron microscopy (TEM) [39].
7. **Drug content:** The amount of drug can be quantified by a modified high-performance liquid chromatographic method or by a suitable spectroscopic technique [40].

CHARACTERIZATION TECHNIQUES:

A. **Differential scanning calorimetry:** Drug polyphenolic extract, phosphatidylcholine, a physical mixture of drug extract and phosphatidylcholine, and drug-phospholipid complex were placed in an aluminium cell and heated to a temperatureof 50-250˚C/ mins from 0 to 400˚C in the atmosphere of nitrogen [41].

B. **Scanning electron microscopy (SEM):** SEM was used to determine the size of the particle and its appearance. Dry sample was placed on Electron microscope brass stub coated with gold in an ion sputter. Random scanning of the complex at 100.

C. **Transition electron microscopy (TEM):** TEM was used to characterize the size of phytosomal vesicles with magnification at 1000 [42].

D. **Fourier transform infrared spectroscopy (FTIR):** FTIR analysis will be done for checking the structure as well as chemical stability of the drug and phospholipid. Scanning will be done between the ranges of 4000-400 cm^{-1}[43].

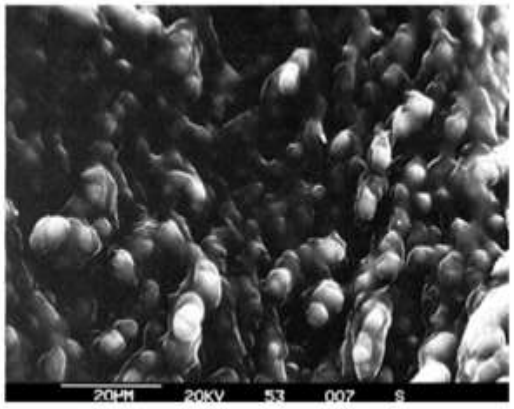

FIGURE 4: SEM PHOTOMICROGRAPH OF PHYTOSOMES

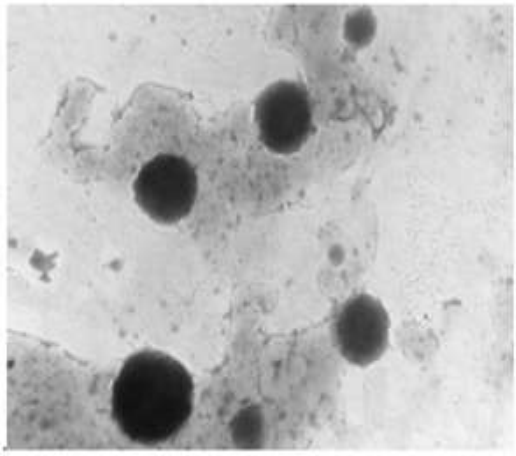

FIGURE 5: TEM PHOTGRAPH OF PHYTOSOMES

APPLICATIONS OF PHYTOSOMES:

- The primordial study of phytosomes was focused on Silybum marianum (family: Steraceae), whose fruit contains flavonoids known for hepatoprotective effects and has shown convincing outcomes in treating liver diseases like hepatitis, cirrhosis, fatty infiltration of the liver and inflammation of the bile duct. Silymarin chiefly contains three flavonoids out of which silybin overrule, supressed by silychristin silydianin. Silybinis the one which is most potent as it shields the liver by conserving glutathione in parenchymal cells [44,45,46].
- Francesco et al. studied an oral formulation of coated tablets (Monoselect Camellia®)

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containing greatly bioavailable green tea extract (GreenSelect®Phytosome) for analysing overweight subjects [n=100] of both genders on a hypocaloric diet which results into the total absence adverse effects and thus appears to be an effective and safe tool for weight loss [47,48].

- Mukerjee et al. developed a novel hesperetinphytosome by making complex of hesperetin with hydrogenated phosphatidylcholine. The complex was evaluated for antioxidant activity, which communicate that the phytosomes had higher relative bioavailability than that of active drug entity [49,50,51].
- Ravorotto et al, asserted that silymarin phytsome shows better Anti-hepatotoxic activity than crude silymarin [52].

TABLE 1: COMMERCIAL PHYTOSOME PRODUCTS [53,54,55,56]

Phytosomes Phosphatidyicholine	Phytoconstituent complexed	Indication	Dose
Silybin Phytosome	Silybin from silymarin marium	Nutraceutical, antioxidant for Liver and skin	120mg
Ginkgo Phytosome	24%ginkgo flavonoids from *Ginkgo biloba*	Protect brain and vascular lining	120mg
Olive oil Phytosome	Polyphenols from Europaea oil	Antioxidant, antiinflammatory, Anti-hyperlipidemic	-
Grape seed phytosome	Procynid ins from *Vitis vinifera*	Nutraceutical, systemic antioxidant	50-100mg
Haw thorn Phytosome	Flavonoids from carteagus sp.	Nutraceutical, cardio protective, Anti hypertensive	100mg
Centella Phytosome	Terpenes	Vein and skin disorders	-
Ecdhinacea Phytosome	Echinacoside from *Echinacea augustifolia*	Nutraceutical, immunomodulator	-

II. CONCLUSION:

This review is an attempt to present a concise profile of phytosomes as a delivery system. Phytosomes are novel formulations which offer improved bioavailability of water-solubleherbal constituents through skin and gastrointestinal tract. Phytosomes are one of the phospholipid-based drug delivery system with a better absorption and stability profile as compared to other drug delivery systems. Phytosomes have improved pharmacokinetic and pharmacological parameter, which enable them to be used for different therapeutic purposes like cardiovascular, anti-inflammatory, anticancer, immunomodulator, antidiabetic etc. They have many advantages over the conventional formulations. The formulation methodology for phytosomes is simple and can be easily upgraded to a commercial scale. Phytosomes has a great future for use in formulation technology and applications of hydrophilic plant compounds.

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