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Review Article

A review on Phytosome loaded with novel herbal drug and their formulation, standardization and applications

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ABSTRACT

Novel Drug Delivery System is need of time, as it makes bioavailability, security and overall therapeutics of a drug easy-going and in the bat of an eye. In the recent days, most of the regnant maladies and nutritional disorders are treated with herbal medicines because of their less after math, economical and easily accessible. The potency of any herbal medication is contingent on the delivery of the effectual level of the therapeutically active constituent. But because of high polarity and poor lipophilicity, the active contents are incompletely assimilated resulting in poor bioavailability. Herbal drugs comprises of a vast array of active contents which furnishes us with a number of applications. But due to high polarity and poor lipophilicity the active contents are poorly absorbed resulting in poor bioavailability. These problems can be overcome by formulating a suitable novel preparation of the herbal extract. Phytosomes are one of the novel drug delivery system containing hydrophilic bioactive phytoconstituents of herbs surround and bound by phospholipids. This phytophospholipid complex resembles a little cell which exhibit better pharmacokinetic and pharmacodynamic profile than the conventional herbal extract resulting in better bioavailability. This article highlights recent information, commercial preparation of phytosomes as well as the various other novel approaches for delivery of herbal constituents.

Keywords: Phytosomes, Bioavailability, Phosphatidylcholine, Phytoconstituents.

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INTRODUCTION

Plants are endowed with health promoting substances which are mainly the secondary metabolites like flavonoids. Most of the biologically active constituents of plants are polar or water soluble molecules. Toxicity and absorption problem limit the use of these constituents. Apart from that the herbal extracts are destroyed by the digestive secretions and gut bacteria. Extensive researches have been conducted for successful delivery of these plant derived products since the last century^{1,2}. The term "phyto" means plant and "some" means cell like. 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, thereby greatly increasing absorption and bioavailability. Phosphatidylcholine, phosphatidylserine, phosphatidylethanolamine, phosphatidylinositol are the phospholipids used, but phosphatidylcholine are widely used because of their certain therapeutic value in case of

liver diseases, alcoholic steatosis, drug induced liver damage and hepatitis. Phospholipids are also employed as natural digestive aids and as carriers for both fat miscible and water miscible nutrients. Phytosomes can easily traverse the lipophilic path of the enterohepatic cell membranes and also stratum corneum layer of the skin. Standardized plant extracts mainly flavonoids are derived as phytosomes. Selection of flavonoids are done from the groups consisting of quercetin, kaempferol, quercetin-3, rhamnogluconide, quercetin-3-rhamnoside, hyperoside, vitexine, diosmine, 3-rhamnoside, (+) catechin, (-) epicatechin, apigenin-7-glucoside, luteolin, luteolin-glucoside, ginkgonetone, isoginkgonetone and bilobetine etc.^{3,4}

PROPERTIES OF PHYTOSOME

Phytosomes are complex between a natural phytoconstituents and natural phospholipids, like soy phospholipids mostly phosphatidylcholine. These complex results from the reaction of stoichiometric amounts of

phospholipids with the phytoconstituents in an aprotic solvent.

1. Phytosomes can accommodate the active principle that is anchored to the polar head of the phospholipids, which finally becomes an integral part of the membrane.

2. Phytosomes are advanced form of herbal an drug which are better absorbed, utilized and which finally leads to better results than conventional dosage form. The increased bioavailability has been demonstrated by the pharmacokinetic studies as well as by pharmacokinetic tests in experimental animals and human subjects.

3. Phytosomes are lipophilic substances with definite melting point, freely soluble in non-polar solvents, and moderately soluble in fats.

4. Phytosomes when treated with water assume a micellar shape, forming structure that resemble liposomes exhibiting fundamental difference.^{5,6}

METHODS FOR PREPARATION OF PHYTOSOME LOADED DRUG DELIVERY

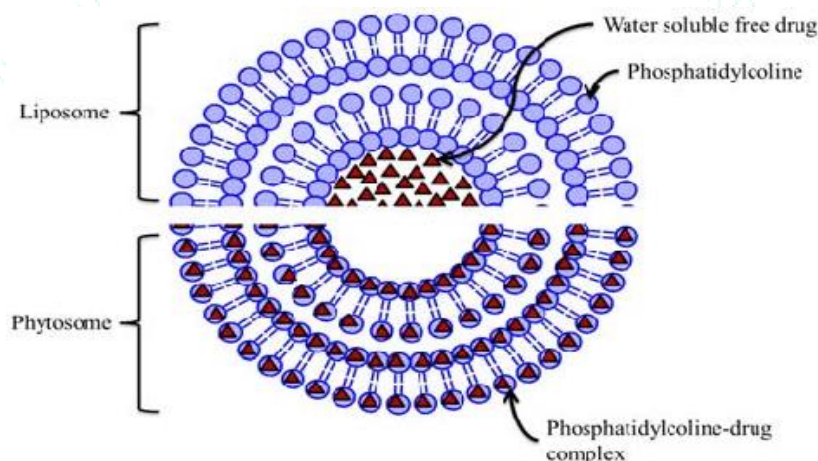
There are numerous methods are offered for preparation of phytosome loaded drug delivery and common steps for preparation of phytosome loaded drug delivery

1. Solvent Evaporation Method: The particular quantity of drug, polymer and phospholipids can be taken into a

spherical bottom flask and reflux with specific solvent at a temperature 50 - 60°C for 2 h. The mixture may be concentrated to 5-10 ml to get the precipitate which can be filtered and collected. The dried precipitate phytosome loaded can be placed in amber colored glass bottle and stored at room temperature.

2. Rotary Evaporation Technique: The particular quantity of drug, polymer and phospholipids can be dissolved in specific solvent in a rotary spherical bottom flask followed by stirring for 3 hours at a temperature not exceeding 40°C. Thin film of the sample can be obtained to which n-hexane is added and continuously stirred using a magnetic stirrer. The precipitate phytosome loaded obtained can be collected, placed in amber colored glass bottle and stored at room temperature.

3. Antisolvent Precipitation Technique: The particular quantity of drug, phospholipids and polymer may be taken into a spherical bottom flask and reflux with specific solvent at a temperature not exceeding 60°C for 2 h. The mixture can be concentrated to 5-10 ml. N-hexane can be added carefully with continuous stirring to get the precipitate which has filtered and collected and stored in vacuum desiccators overnight. The dried precipitate is crushed in mortar and sieved through #100 meshes. The dried precipitate phytosome loaded can be placed in amber colored glass bottle and stored at room temperature.^{7,8}



PHYTOSOME TECHNOLOGY

Phytosome is also known as a Phytolipids delivery system, which forms a link between the traditional delivery system and novel delivery system. Novel vesicular drug delivery systems designs to deliver the drug at a rate directed by the demand of the body during the course of therapy, and convey the active substance to the location of the action. Countless novel vesicular drug delivery systems have been appearing enclosing distinct paths of administration, to accomplish targeted and controlled drug delivery. Phytosome is a novel form of botanical preparation, which includes the bioactive phytoconstituents of botanical essence complexed with phospholipids e.g. Phosphatidylcholine to generate lipid aggregable molecular complexes. Water-soluble Phytoconstituent molecules (mainly polyphenols) can be transformed into lipid-compatible molecular complexes, which are termed as phytosomes. This phytosome technology is an innovative model for the pronounced amelioration of bioavailability, considerably higher clinical advantage, satisfied delivery to the tissues, and without complaining nutrient safety. At this time, the progress of phytosomes is still in the foundation stages in republics

such as India and in a foreign country. Up to now, this technology has been effective with herbal extracts for instance *Curcumin*, *ginkgo Biloba*, grape seed, ginseng, milk thistle, and other goods used as widespread nutritional supplements. Numerous compound, which had revealed the extensive diversity of health welfares but scientists were at no time able to capture it because it broke down to effortlessly when it come in the body. This technology permitted the compound to be appropriately assimilated into the body and carried to the appropriate site. In order for the herbal formulation to have good bioavailability, they need to have a proper equilibrium among hydrophilicity and lipophilicity. In additional, they need to be able to dissolve into solutions present in the intestines besides cross biomembranes. This is why phytosomes deliver extra bioavailability than simple herbal essence.^{9,10}

MECHANISM OF PHYTOSOME FORMATION

The polyphenolic elements of herbal essence made themselves relatively healthy for straight conjugation with phosphatidylcholine. Phytosome ensues from the response of a stoichiometric quantity of the phospholipid-like

phosphatidylcholine with the polyphenolic ingredients like simple flavonoids in an aprotic solvent. phosphatidylcholine is a multifunctional complex, the phosphatidyl part being lipophilic and the choline part being hydrophilic in behavior. The choline head of the phosphatidylcholine conjugate to these compounds while lipid-soluble phosphatidyl part containing the body and tail which then covers the choline bound material. Hence, the Phytomolecules yield a lipid soluble molecular compound with phospholipids named as phytospholipid complex. Phytomolecules are anchored through chemical bonds to the polar choline head of phospholipids, as can be confirmed by precise spectroscopic methods. Frequently, detailed chemical examination designates that, the unit phytosome is typically a flavonoid molecule connected with not less than one phosphatidylcholine molecule. The outcome is a tiny microsphere or cell is formed. In the blue phytosome spectrum, the spectrum from the polyphenol (red) is obscured by the orange spectrum from phosphatidylcholine. This is consistent with a physical entrapment of the polyphenol by the phosphatidylcholine molecule.^{11,12}

BENEFIT OF PHYTOSOME LOADED DRUG DELIVERY FOR HERBAL DRUGS

Numerous researches is being conducted by the researchers and therefore the recent works reveals that the phytosome loaded drug delivery may be a novel technique for rising the absorption and bioavailability of plant extracts considerably reducing the dose level. Some plant extracts are becoming more focus now-a-days because of their potential pharmacological effects, such as, silymarin, grape seed extract, quercetin, curcumin, hesperidins, ginkgo biloba extract, and rographolide etc. The suitability of this type of drug delivery system and raised demand for treatment of various diseases in current scenario has sealed the benefits for herb medicines. The summary of phytosome loaded drug delivery for herbal drugs.

Four polyphenol preparations like Silybin and the alternative silymarin flavonolignans from milk thistle, Curcumin and its related diphenolic curcuminoids, green tea flavan-3-ol catechins and grape seed proanthocyanidin combine (including catechin and epicatechin monomers and oligomers) with poor bioavailability and their complexation into phytosomes to bypass this drawback and reported that for each of those preparations, conversion into phytosomes has improved efficacy without compromising safety. The phytosome technology creates intermolecular bonding between individual polyphenol molecules and one or more molecules of the phospholipid, phosphatidylcholine (PC). Molecular imaging suggests that PC molecule(s) cover each polyphenol; upon oral intake the amphipathic PC molecules probably "usher" the polyphenol through the intestinal epithelial cell outer membrane, later on accessing the blood. PC itself has proven clinical effectivity that contributes to phytosome in vivo actions. As a molecular delivery vehicle, phytosome technology considerably improves the clinical applicabilities of polyphenols and other poorly absorbed plant medicinal.

Investigated that the oral bioavailability of Rutin is incredibly low necessitating its novel drug delivery approach. Phyto-phospholipid complex (phytosomes) is useful in enhancing oral bioavailability and transdermic permeation of polyphenols and discovered phyto-phospholipid complex of Rutin enhanced its skin uptake to treat inflammatory conditions in inflammatory disease, rheumatism, athletic aches and delivered the drug for a long duration avoiding the issues related to oral administration. Compared FA-PEG-functionalized MMC loaded phytosomes

(FFA-PEG-MMC-loaded phytosomes included enhanced cellular uptake in HeLa cells and better accumulation in H22 tumor-bearing mice over that of the PEG-MMC-loaded phytosomes. furthermore, FA-PEG- MMC-loaded phytosomes related to increased cytotoxic activity in vitro and an improved antitumor effect in vivo compared to it resulting from free MMC injection. They recommended that FA-PEG-MMC-loaded phytosomes could also be helpful drug delivery systems for widening the therapeutic window of MMC in clinical trials.

Nano phytosomes of luteolin to enhance the bioavailability of luteolin and improve passive targeting in carcinoma cells and discovered that co-treatment of cells with nano particles containing luteolin and antibiotic drug resulted within the highest percentage cell death in MDA-MB 231cells ($p < 0.05$). They advised that luteolin-loaded nanoparticles reduced Nrf2 gene expression at the mRNA level in cells to a greater extent than luteolin alone ($p < 0.05$) and equally, expression of downstream genes for Nrf2 including Ho1 and MDR1 reduced significantly ($p < 0.05$). Inhibition of Nrf-2 expression caused a marked increase in cancer cell death ($p < 0.05$). They also advised that phytosome technology can improve the effectivity of chemotherapy by overcoming resistance and enhancing porosity of cancer cells to chemical agents and may therefore be considered as a potential delivery system to boost therapeutic protocols for cancer patients. Developed a curcumin phytosome loaded chitosan microspheres (Cur-PS-CMs) by encapsulating curcumin phytosomes (Cur-PSs) in chitosan microspheres using ionotropic gelation and reported that the new Cur-PS-CMs system combined the benefits of chitosan microspheres and phytosomes, that had higher effects of promoting oral absorption and prolonging retention time of curcumin than single Cur-PSs or Cur-CMs. Therefore, the PS-CMs may be used as a sustained delivery system for lipophilic compounds with poor water solubility and low oral bioavailability. Prepared completely different formulations like daidzein-loaded PLGA nanoparticles, daidzein-loaded phospholipid complexes PLGA nanoparticles and daidzein loaded cyclodextrin inclusion complexes PLGA nanoparticles and reported that the oral administration of daidzein-loaded phospholipid complexes PLGA nanoparticles and daidzein - loaded cyclodextrin inclusion complexes PLGA nanoparticles to rats, relative bioavailability increased, compared to daidzein suspension as control by pharmacokinetic studies. These results describe an efficient strategy for oral delivery of daidzein loaded PLGA nanoparticles and may offer a recent approach to enhancing the bioavailability of drugs with poor lipophilic and poor hydrophilic properties.

Prepared luteolin - phospholipid complex and reported that luteolin and phospholipid within the complex joined by non-covalent-bonds and didn't form a new compound. They advised that the complex has an efficient scavenger of DPPH radicals and powerful inhibitor activity within the Rancimat antioxidant test using animal oil as substrate.

Prepared Quercetin-loaded nanophytosomes by using phosphatidylcholine (PC) and cholesterol (CH) and reported that Nano phytosomal formulation of Quercetin: PC: CH molar ratio of 1: 2: 0.2 has promising potential in fortification of food products with water insoluble antioxidants.

Developed phytosomes loaded with mitomycin C-Soybean phosphatidylcholine (MMC-SPC) complex (MMC-loaded phytosomes) by a solvent evaporation method combined with a nano precipitation technique for the aim of development of an MMC drug delivery system and discovered that In vitro drug release profiles indicated

biphasic behavior with an initial burst release, followed by a subsequent prolonged sustained release. In vitro cytotoxicity assays with H22 cells showed that the MMC-loaded phytosomes had exceptional cytotoxicity. In vivo antitumor effect of the MMC loaded phytosomes additionally discovered a dose-dependent and superior curative inhibitory effect on tumour growth without loss of body weight compared to free MMC. Histopathological analysis of specimens taken from tumour tissues indicated that MMC-loaded phytosomes had deadly effect to hepato cellular carcinoma cell. They also advised that the MMC-loaded phytosomes can serve as a promising and effective formulation for drug delivery and cancer therapy.¹³

ADVANTAGES OF PHYTOSOMES

1. Phytosomes produces a little cell where the valuable components of herbal extracts are protected from destruction by digestive secretions and gut bacteria.
2. It assures proper delivery of drug to the respective tissues.
3. The nutrient safety of the herbal extracts need not be compromised by conveying the herbal drug as means of phytosomes.
4. Dose requirement has been reduced due to the maximum absorption of chief constituents.
5. Marked enhancement in the bioavailability of drug occurs.
6. Entrapment efficiency is high and more over predetermined because drug itself is in conjugation with lipids in forming vesicles.
7. There is no problem in drug entrapment while formulating phytosomes.
8. Phytosomes shows better stability profile due to the formation of chemical bonds between phosphatidylcholine molecules and the phytoconstituents.
9. Phosphatidylcholine used in formulating phytosome process besides acting as a carrier also nourishes the skin as it is an essential part of a cell membrane.
10. Phytosomes are also superior to liposomes in skin care products.
11. Phytosomes proves to be of significantly greater clinical benefit.
12. Phosphatidylcholine used in preparation of phytosomes, besides acting as a carrier also acts as a hepatoprotective as a result it imparts a synergistic effect when hepatoprotective substances are employed.^{14,15,16}

EVALUATION

Evaluation Techniques for Phytosome Loaded Drug Delivery

The activities of phytosomes loaded drug delivery system can be evaluated by % yield, particle size and shape, percentage drug entrapped, chemical composition, percentage drug release.

Different Evaluation Technics

1. **% Yield Determination of moral yield of phytosome loaded can be calculated by the subsequent formula:**

$$(\%) \text{ Yield} = (\text{Practical yield}) \times 100 \quad (\text{Theoretical yield})$$

2. Differential Scanning Calorimetry (DSC)-

The drug sample, phospholipids, polymer, physical mixture and phytosome loaded can be placed within the aluminum crimp cell and heated at 10oC/min from 0 to 400oC in the nitrogen atmosphere. Peak transition onset temperatures may be recorded by means of an instrument.

3. FTIR Spectrographic Analysis-

FTIR spectral data can be taken to determine the structure and chemical stability of phytosome loaded, phospholipids, polymer and drug sample. Samples can be crushed with KBr to get pellets at 600 kg/cm² pressure. Spectral scanning may be done in the range between 4000 - 400 cm⁻¹.

4. Particle Size-

The average diameter and zeta potential of the phytosome loaded may be each measured employing a Zetasizer ZEN 3600 at a fixed scattering angle of 90oat 25oC.

5. Entrapment Efficiency

Phytosome loaded with drug can be diluted 1-fold with 10 ml of solvent and so centrifuged at 18,000 rpm for 1/2 h at -4oC using cooling centrifuge machine. The supernatant was isolated and the quantity of free drug may be determined by UV/Vis spectrometry. To determine the entire quantity of drug, 0.1 ml of the phytosome loaded suspension can be diluted in fuel, adjusting the volume to 10 ml. The entrapment efficiency may be calculated according to the subsequent formula:

$$\text{Entrapment efficiency (\%)} = \frac{(\text{Total amount of drug}) - (\text{amount of free drug}) \times 100}{(\text{Total amount of drug})}$$

Drug Content Drug content of phytosome loaded can be determined by dissolving accurately weighed 100 mg of phytosome loaded in 10 ml solvent. After appropriate dilution absorbance may be determined by UV - Spectrophotometer.

The drug content can be calculated by the subsequent formula:

$$\text{Drug Content (\%)} = \frac{(\text{Total amount of drug}) - (\text{amount of free drug}) \times 100}{(\text{Total amount of drug})}$$

6. Scanning Electron Microscopy (SEM)-

Scanning electron microscopy can be used to confirm particle size distribution and surface morphology of the phytosome loaded. Dry samples may be placed on an electron microscope brass stub and coated with gold in an ion sputter. Digital pictures of phytosome loaded may be taken by random scanning of the stub at 1000, 5000, 10000 and 30000 X magnifications.

7. In-Vitro and In-Vivo Evaluations-

In vitro and in vivo evaluations can be done according to therapeutic activity measurement parameters of the biologically active phytoconstituents present in the phytosomes loaded with the help of suitable animal models.

- i. Antioxidant activity:

The ability of the compound to scavenge H₂O₂ was determined using spectrophotometric method by measuring the absorption with extinction coefficient for H₂O₂ of 81M-1cm⁻¹. For assay 40mM solution of H₂O₂ was prepared in phosphate buffer (pH 7.4). Solutions of ME of leaves of a marmelos at different concentrations (10µg/ml to 100µg/ml) were prepared in phosphate buffer. H₂O₂ solution (40mM) 0.6ml added to solutions of extract. Absorbance of all solutions determined at 230 nm after 10min incubation

against a blank solution containing phosphate buffer without H₂O₂. Ascorbic acid was taken as reference. Same procedure was repeated for phytosomes. The percentage of scavenging of H₂O₂ was calculated by following equation:

Formula-

$$\% \text{ scavenged} = \frac{AB - AA}{AR} \times 100$$

Where, AB- Absorbance of blank, AA- Absorbance of sample

ii. Antiproliferative activity:

Preparation of yeast inoculums Yeast was inoculated in a conical flask containing 100 ml sterilized nutrient broth and incubated at 37°C for 24hrs. This was referred as seeded broth. 1ml of seeded broth was taken and diluted with sterilized distilled water to contain 25.4 x 10⁴ cells. Preparation of potato dextrose broth The sliced potatoes (200g) were boiled in 1L of distilled water for 1 hour and then filtered through muslin cloth. The volume of filtrate was made up to 1000ml with distilled water and then glucose (20g) was added. The medium was sterilized by autoclaving. Cell viability count 0.5 ml of yeast inoculum and 2.5ml of potato dextrose broth was treated with each 1 ml of various concentration methotrexate (50ng/ml), ME of leaves of a marmelos(4mg/ml), phytosomes(4mg/ml). It was then incubated for 24 hours at 37°C with control. This cell suspension was then mixed with 0.1% methylene blue and examined under low-power microscope. The number of viable cells (those transparent, oval shape and do not take stain) and dead cells (those get stained and stained blue) were counted in hemocytometer. The mean was calculated.

The cells per ml and percentage of cell viability were calculated by following formula:

Viable cells/ ml = average no of viable cell in one square x dilution factor x 10⁴

Percentage of cell viability = Total viable cells / Total cells x 100^{17,18,19}

APPLICATIONS

1. Enhancing Bioavailability
2. Delivery of large and diverse drugs, eg., peptides and proteins
3. Safe composition
4. Hepato-Protective
5. Approved for cosmetic and pharmaceutical applications
7. Low-risk profile
8. Toxicological properties of phospholipids have been well documented
9. High market attraction²⁰

Limitations of Phytosome:

Phytosomes, despite of having numerous advantages as drug delivery system, are not prevalent in the market. Phospholipids (lecithin) can induce proliferation on MCF-7 breast cancer cell line. A major drawback of phytosome could be leaching of the phytoconstituents off the 'some'

which reduces the desired drug concentration indicating their unstable nature.²¹

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