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PHYTOSOMES TECHNOLOGY

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ABSTRACT

Phyto and Some refer to plants and cells, respectively. Phytosomes are small structures that resemble cells. This is a more advanced herbal formulation in which the bioactive phytocomponents of herb extracts are surrounded and bonded by lipid. The majority of plant phyto ingredients like flavonoids are water soluble. Phytosome is a Lipid-based Vesicular Delivery method to encapsulate pharmaceuticals as well as plant based nutraceuticals. The phytosomes has the potential to reduce difficulties with polyphenolic compound solubility and bioavailability, making it useful in the creation of bioavailability within low dosage. Further, phytosome preparation is simple procedure to scale up commercially. It is a promising way to incorporating Phyto-derived compounds to bring an effective cancer and other new medicine. It helps many pharma industries encapsulate adequate amounts of phyto ingredients in the production of new supplements. Furthermore, phytosomes can increase polyphenolic compound disease treatments, phytosome technology is a promising encapsulation platform for future nutraceutical nano-formulation.

Keywords: Phytosomes, Flavonoids, Herbal and Stability.

INTRODUCTION TO PHYTOSOMES TECHNOLOGY

Phytosomes (P) increases absorption of polar phytoconstituents orally which are lipid insoluble in nature and topically shows an increase in bioavailability whichresults in greater therapeutic benefit. When the rate of absorption rate of an active constituent is increased, the dose required will be s reduced[1].

Phyto extract (PE) like flavonoid and terpenoids lend them to direct binding to phosphatidylcholine (PC). Phytosomes made by reaction of stoichiometric amount of PC with a PE like flavonoids in non-polar solvent. PC is a bifunctional substance shows lipophilicity and hydrophilicity. The phosphatidylcholine molecule's choline head specifically binds these compounds, while the lipid solubility portion of phosphatidyl envelopes the choline.

The phyto ingredient forms a lipid compatible complex known as the phyto-phospholipid complex (PPC). Specific spectroscopic techniques show that molecules are adhered to choline via chemical bonds. The phytosome unit, a flavonoid moleiety is linked to PC molecule results in the formation of small microsphere or cell. Phytosomes is a cell which protects the phytoextract.

A. Chemical Properties

P are a combination of a natural ingredient and naturally originated phospholipids. Hydrogen bonds which are present in between polar head of phospholipids and substrate, an interaction between phospholipid and substrate based on spectroscopic data. P treated with water, phytosomes forms structure similar to liposomes.

B. Biological properties

P are advanced forms phyto ingredients shows better absorption and yields good results than conventional phytoextracts. The increased bioavailability of the phytosome is observed pharmacokinetic or pharmacodynamic study in experimented animals.

Characterization of phytosomes

The behavior of P is influenced by physical

size of the membrane permeability; % entrapped solutes, chemical composition, quantity and purity. Therefore, the phytosomes are characterized by their physical attributes.

A. Advantages of phytosomes

By forming a stable complex with phospholipids, P improves bioavailability and stability and absorption from the site of action in the intestinal tract when administered as a herbal constituent alone.

- Improves liver targeting by increasing bile salt solubility.
- The required dose is reduced as active phytoconstituent absorption improves.
- PC used in phytosome preparation, Apart from acting as a carrier also produces synergistic effect.
- Because of their improved skin penetration and high lipid profile, phytosomes are widely used in cosmetics.
- Herbal extracts' valuable components are protected from destruction by digestive secretions and gut bacteria.
- Drug delivery to specific tissues.
- Because of the maximum absorption of the main constituents, the dose requirement has been reduced.
- Significant improvement in drug bioavailability occurs.
- Efficiency of entrapment is high and predetermined.
- There are no issues with drug entrapment when creating phytosomes.
- Due to the presence of chemical bonds formed in between phosphatidylcholine molecules and phytoconstituents results in higher stability.
- Phosphatidylcholine, which is used in the phytosomes process, both nourishes and acts as a carrier.
- Phytosomesworks out better than liposomes in aspects of skin care formulations.
- Phytosomesresults in significant therapeutic benefit.

B. Disadvantages of phytosomes

Despite the numerous benefits of phytosomes, it has been reported that phospholipids will induces proliferation in MCF-7 breast cancer cell line. The phytoconstituents leaching from the ‘some' is a significant disadvantage of phytosome. Phytosomes of Curcumin In two separate studies, Maiti et al. (2006) created phytosomes of curcumin, a flavonoidal content present in *C. longa*, Naringenin, a flavonoids present in grape fruits. All dose levels tested, the complex's antioxidant activity was significant over curcumin. An another study stated that the developed P of naringenin produces better antioxidant.

APPLICATIONS OF PHYTOSOMES

A. Silymarin Phytosomes

The majority of Phytosomal research has focused on Silybum marianum (milk thistles), which contains powerful liver-protecting flavonoids. Yanyu et al. (2006) synthesized silymarin phytosomes and investigated their pharmacokinetics in rats. The bioavailability of silybin in rats was significantly increased after oral administration of silybinphospholipid complex, owing to an impressive improvement in the lipophilic properties of silybinphospholipid complex and an improvement in silybin's biological effect. Tedesco et al (2004) reported that Silymarin phytosomes have greater anti-hepatotoxic activity than silymarin alone and can protect broiler chick performance from the toxic effects of aflatoxin B1.

B. Curcumin Phytosomes

In two separate studies, P of curcumin and naringenin, in all dose levels tested, the complex's antioxidant activity was significant. In earlier study, the phytosomesof naringenin shown a good radical scavenging property when compared with free compound. It also shown longer duration of action, as the rapid elimination from the body is decreased[21].

C. Quercetin-phospholipid Phytosome

Complex Maiti et al. (2005) created the quercetin PPC and demonstrated the formulation outperformed the molecule in treating liver injury in rats caused by CCl_4.

D. Grape seed Phytosomes[25]

Phytosomes made from grape seeds are comprises proanthocyanidins or Procyanidine with phospholipids. Procyanidine in grape seeds increases antioxidant property and helps in physiological defenses in plasma. In earlier studies, rabbits were given the food comprised with high cholesterol for the period of 6 weeks observed that the elevation of blood cholesterol level induces atherosclerotic lesions in aortas and carotid arteries. One group of rabbit fed with Grape Seed Phytosomes (GSP) in their feed for half a dozen week and followed by the next four weeks receives rich cholesterol diet. Less aortic plaque is developed in rabbits received conventional extract. In clinical trails in humans, healthy subjects were taken GSP

daily once for the period of 5 days. The blood samples were analysed for antioxidant Parameter. Blood Total Radical Antioxidant Parameter levels were shown significant higher when compared with control group than the group taken conventional extract[25].

E. *Gingko biloba*LeavesPhytosomes-(GbLP)

Studies about *Gb*LPresulted in better potency compared to normal extract of the plant.When bioavailability study, is carried on healthy human volunteers, the level of Gb extract(Gingko biloba leaves) constituents - flavonoids and terpenes peaked out after completion of three hours and longer persistence is observed longerperiod of time for 5 hours after oral administration. Phytosomal Gb extract produces a greater plasma concentration of terpenes than the non-Phytosomal Gb. The improved oral bioavailability and good tolerability is observed. Ginkgo phytosomes study in patients with peripheral vascular disorders shown high improvement compared to a conventional standardized GbExtract. The result indicated that GbLPbringsout bronchoconstriction. Antioxidant property is improved efficacy of ginkgo phytosomesto overcome bronchospasm resulted by allergens. This study includes, the improvised potency of GbLPover the conventional extract to protect the rats against ischemia. Obtained results had shown GbLP are better than conventional one which paves the path for their use in herbal phytoconstituents[24].

F. Phytosomes of green tea

Green tea leaves (*Theasinensis*) consists of polyphenolic compound called epigallocatechin 3-O-gallate[26]. These potent phytoconstituents in many biological chemical processes, results in breakdown of homeostasis in many chronic conditions for instancecancer, atherosclerosis etc., Green tea also furnishes many beneficial activities like antioxidant, anticarcinogenic, antimutagenic etc., but the demerit with these polyphenols are bioavailability is low. Polyphenolsin green tea strongly improvised bioavailability (oral) is observed. The study was also examined on absorption rate of developed phytosomal preparation on healthy subjects. In the study period of 6 hours the plasma concentration of flavonoids was doubled and radical trapping was measured between phytosomal and non-phytosomal substance. It was observed about 20% increase of peak antioxidant effect.

PHYTOSOMES CONTAINING DOSAGE FORMS

The prepared Phytosomes administered via orally or topically in order to achieve the best results in the form of bioavailability. It is needed to study about dissolution and disintegration parameters for the developed dosage forms. Some of the examples were listed below

A. Capsules (Soft gelatin)

A 100 % < 200 µm granule in suspension form consisting of vegetable or semi-synthetic oils is preferred.

B. Capsules (Hard gelatin)

NMT 300 mg in capsule size measures 0, without recompression is preferred to fill hard gelatin capsules.

C. Tablets

Dry granulation is preferred than Wet granulation to avoid adverse effects of phospholipids, which shows an ideal way of manufacture process inorder to get tablets (higher unitary doses).

D. Topical dosage forms

The emulsion were used should ensure good result from the phospholipids complex.

PREPARATION OF PHYTOSOMES

Preparation by various methods by an interaction between natural or synthetic phospholipid with one mole of phytoconstituents. The preferred ratio for the complex should be in the range from 0.5 to 2.0 moles.

Solvent evaporation method

The quantity of drug, polymer and phospholipids were taken in a spherical bottom flask made reflux with solvent at certain temperature for a period of 2 hrs. The mixture is made concentrated, filtered and collected. The dried precipitate P loaded stored in amber coloured glass bottle at room temperature[29].

A. Rotary evaporation technique

The specific amount of drug, soya lecithin was dissolved in tetrahydrofuran in a rotary flask, by stirring for 3 hours at 40^{o}C. Sample Thin film is produced upon addition of n-hexane and stirred in continous with the help of magnetic stirrer. Precipitate is collected and stored in glass bottle at room temperature.

B. Anti-solvent precipitation technique

Desired quantity of drug and soya lecithin was taken in RB flask. Made reflux with dichloromethane at 60^{o}C/2 h. Concentrated and precipitated by treating with 20 ml of

hexane. Precipitation is filtered, collected and stored. The dried precipitate is crushed, sieved and stored in amber colored glass bottle.

C. Salting Out method

The phytoconstituent and phosphatidecholine is dissolved in aprotic solvents like acetone. Later it is continuously stirred to form complex, later isolated by using non-solvents n-hexane.

D. Lyophilization Technique

The natural or synthetic originated phospholipid and phytoconstituent were made soluble in various solvents. The phytoingridient solution were added to a phospholipid solution. Stirred to get a complex further the complex separated out by lyophilization.

The phospholipids used in phytosomes preparation consist of acyl group which is varied in PhosphatidylCholine (PC), phosphatidylserine, phosphatidylethanolamine. In phytosome active, an integral part of the membrane because the active principle is in connection with the polar head of phospholipid.

E. Mechanical Dispersion method

The concept involves the lipids were made dissolved in organic solvent which were brings in contact with water containing the drug. Initially, phytosomes were made dissolved in diethyl ether, injected in water contains phytoingredients to be encapsulated. The organic solvent is removed under reduced pressure leads to form the complex. Novel methods for the preparation of phospholipid complex are Super Critical Fluids (SCF), Anti-Solvent technique (GAS), compressed anti solvent process (PCA) and Supercritical Anti Solvent method (SAS).

DIFFERENT ADDITIVES – PHYTOSOMES FORMULATION

Phospholipids like Phosphatidyl choline from the sources like Soya, egg, Dipalmityl etc.,
Aprotic solvents like Dioxane etc.,
Non solvent like n-hexane etc.,
Alcohols

CHARACTERIZATION TECHNIQUES OF PHYTOSOMES

A. Visualization Method

To visualize the phytosomes Transmission and Scanning Electron Microscopy are used.

B. Transition temperature

In order to determine the transition temperature of vesicular lipid system a DSC.

C. Surface tension measurement

Ring method in a Du Nouy Ring Tensiometer is choosen for the determination of Surface of drug in aqueous phase.

D. Vesicle stability

Assessment of vesicles tells about stability of vesicles. If any structural changes occurs it can be monitored by TEM and DLS.

E. SEM-(Scanning electron microscopy)

It is used for the determination of average particle size and the surface morphology in complexes. The dry sample which has to be analysed is to be placed on Scanning Electron Microscope with the help of brass stub and made coated with gold in ion sputter. Thereby the digital images of phytosome complex were taken at magnification power.

F. Entrapment efficiency

The Entrapment efficiency of phytosomes assessed by Ultracentrifugation.

EVALUATION OF PHYTOSOMES

Spectroscopic evaluation is carried to evaluate the formation of a complex or to evaluate the interaction.

A. $_1$H-NMR

Bombardelli et al in his studies, NMR spectra of (+)-catechin and its complex with distearoylphosphatidylcholine shown that in non polar solvents, alter of $_1$H-NMR signal due to atoms in complex formation. Proton signalsare broad due to flavonoids, where proton not to be relieved. In regard of phospholipids, the signals were broadened and singlet related to N-$(CH3)_3$ choline shown signal uplift. When sample is heated at 60˚C,broad bands were formed related to resonance - flavonoid moiety.

B. $_{13}$C-NMR

Spectrum (+)-catechin and its complex in C_6D_6 at room temperature, carbons in flavonoid were unclear with poor visibility. Signals of glycerol and choline of lipid esp., rests from 60–80 ppm were broadened, few were shifted, other resonance of the fattyacid chains. When heated at 60˚C, all the signals related to flavonoid moiety were reappeared even they broad and overlapping.

C. FTIR

The complex formation is confirmed by IR spectroscopy by comparing the of individual components spectrum. It is a useful tool to control the phytosomes stability when micro-dispersed in water or simple gels.

D. Evaluation byInvitro &In vivo Method

Choosing of In-vitro and In-vivo evaluation method to select the phytoconstituents for desired therapeutic activity present in the phytosome is important. For instance! Invitro liver protection can be analysed by examining the antioxidant activity of phytosome.Sensitization and tolerability studies on skin carried with glycyrrhetinic acid phytosome ointment, a commercial product, explains about invivo safety evaluation methodology[2].

MARKETED FORMULATIONS

Many marketed formulations were introduced into the market for treatment of ailments. Examples: Leucoselect® phytosomes, used as sysytemic anti- oxidant and is the best choice for the subjects under age 50.Green select® phytosome it is used for protection against cancer, the best choice. Silybin phytosome is the best choice if the liver needs additional anti – oxidant protection. Sabalselect® phytosome it increases the immunity against toxic condition.

CONCLUSION

In association with phytochemicals usage is limited because of poor solubility and sensitivity towards degradation brings less usage in pharmaceutical products. Vesicular drug delivery systems help to improvise these limitations. Vesicles show promising delivery systems at a cellular level due to their capacity of entrapment, biocompatibility and safety. These phytosomes forms a complex with vesicular drug carriers resulting in enhancement of absorption and bioavailability. Phytosomes are the one lipid-based vesicle, which helps to increase the transport of plant-based nutraceuticals. This review provides an overview on applications, preparation and evaluation methods for phytosomes. In upcoming days, clinical studies on standardized products will be superior in efficacy which will grab attention in these technologies.

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