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PHYTOSOMES: A NOVEL TECHNOLOGY FOR HERBAL PHYTOCHEMICALS FOR ENHANCING THE BIOAVAILABLITY

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ABSTRACT

Phytosomes is a novel drug delivery system. 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, there by greatly increasing absorption and bioavailability. Phytosomes are prepared by reacting a synthetic or natural phospholipid with the standardized plant extract. Phytosomes formulation can be delivered by both routes like oral and topically. The phytosome process has been applied to many useful herbal extracts such as Ginkgo biloba, grape seed, hawthorn, milk thistle, green tea, and ginseng. Due to formation of chemical bonds, phytosomes show better stability profile. Phytosomes can be used for systemic targeting of herbal drugs, as phytosome can easily transit from hydrophilic environment into the lipid friendly environment of the enterocyte cell membrane and from there to into the cell.

KEYWORDS: Phytosomes. Herbosomes, Phospholipid.

INTRODUCTION

Phytosomes is a novel drug delivery system approach and is effective in distributing the herbal drug at a predetermined rate, distributing the drug at the site of action, reducing toxic effects, increasing drug bioavailability, regulating the distribution of the drug is accomplished by incorporating the drug into the carrier system or altering the drug structure at the molecular level. Phytosomes are newly introduced by Indian patent technologies for the production and incorporation of standardized plant extracts.[1]

In the recent past, considerable scientific works targeted on the development of novel drug delivery system (NDDS) for herbal drugs. NDDS approaches toward phytochemicals to develop polymeric nanoparticles and nanocapsules, liposomes, solid-lipid nanoparticles, transferosome, pharmacosome, phytosomes and nanoemulsions have a number of advantages for herbal drugs, including enhancement of solubility and bioavailability, protection from toxicity, enhancement of pharmacological activity, enhancement of stability, improved tissue macrophages distribution, sustained delivery and protection from physical and chemical degradation. Thus novel drug delivery of herbal drugs has significant scope for enhancing the activity and overcoming problems associated with plant medicine of conventional type. Liposomes, which are biodegradable and essentially nontoxic vehicles, can encapsulate both hydrophilic and lipophilic materials including phtyoconstituent.[2] On human body herbal cosmetic formulations can be made more efficient through NDDS approach.[3] Medicinal plants play a key role in the human health care. About 80% of the world population believes on the use of traditional medicines which is predominantly based on plant materials.[4]

Phytosome is a patented process developed by Indena, to incorporate phospholipids into standardized extracts and so vastly improve their absorption and utilization. Phytosomes are advanced herbal products produced by binding individual component of herbal extract to phosphatidylcholine resulting in a product that is better absorbed and produces better results than the conventional herbal extracts. Many phytoconstituents have multiple rings and, therefore, cannot be absorbed from the intestine into the blood by simple diffusion. Also, some herbal phytomolecules are poorly miscible with oils and other lipids and often fail to pass through the small intestine because of its lipoidal nature. The effectiveness of any herbal product is dependent upon delivering an effective level of the active compounds.[5-6]

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, there by greatly increasing absorption and

bioavailability. Phosphatidylcholine, phosphatidylserine, phosphatidylethanolamine, phosphatidylinositol are the phospholipids used, but phosphatidylcholine is 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 nutrient. Phytosomes can easily traverse the lipophilic path of the enterohepatic cell membranes6 and also stratum corneum layer of the skin.[7-8]

The phytosome process has been applied to many useful herbal extracts such as Ginkgo biloba, grape seed, hawthorn, milk thistle, green tea, and ginseng.[9] The usual scheme to produce phytosome through binding individual components of herbal extracts to phosphatidylcholine, which results in a dosage form that is better absorbed and thus leads to better results than conventional herbal extracts.[10] The results are encouraging and indicate that the absorption of silybin from silybin phytosome is approximately seven times greater compared to the absorption of silybin from regular milk thistle extract.[11] Drug can be embedded or dissolved in carrier and can also be adsorbed or coupled on the surface. Encapsulating drug within nanoparticulate carrier can improve the solubility and pharmacokinetics of drugs, and in some cases enable further clinical development of new chemical entities that have limited applicability because of poor pharmacokinetic properties.[12]

PHYTOSOME TECHNOLOGY

The phytosome technology was developed by Indena s.p. A of Italy, markedly enhancing the bioavailability of selected phytomedicines, by incorporating phospholipids into standardized plant extract, which improve their absorption and utilization. The polyphenols are little soluble both in water and in lipids. The polar functionalities of the lipophilic guest interact via hydrogen bonds and polar interaction with the charged phosphate head of phospholipids, forming a unique arrangement that can be evidenced by spectroscopy. As phosphatidylcholine is a bifunctional molecule with hydrophilic choline and hydrophobic phosphatidyl group, the choline group head binds with the compound, while phosphatidyl portion envelopes the bounded part The first phytosome generation was prepared by combining selected polyphenolic extract with phospholipids in nonpolar solvent, but recently the phytosome generations are developed by using hydro-ethanolic solvent, to comply with current food specifications

ADVANTAGES OF PHYTOSOME

As compared to conventional herbal formulation, phytosome have following advantages.[13,14,15,16]

Greater therapeutic benefits, as absorption of lipid insoluble polar botanical extracts through oral and topical route is enhanced markedly.

- Phytosomes produces a little cell where the important components of herbal extracts are protected from destruction by gut bacteria and digestive secretions.
- Small dose is required, as absorption is increased manifolds.
- Phytosomes possess better drug entrapment efficiency.
- Phosphatidylcholine is not merely a carrier; it is also having hepatoprotective activity and nutritional value.
- Due to formation of chemical bonds, phytosomes show better stability profile.
- Phytosomes can be used for systemic targeting of herbal drugs, as phytosome can easily transit from hydrophilic environment into the lipid friendly environment of the enterocyte cell membrane and from there to into the cell.
- Cosmetic and other topical use of phytoconstituents can be done by phytosome formulations.
- Phytosomes have significantly greater clinical benefit
- They are less soluble in aqueous media which allows the formation of stable emulsions or creams
- Phytosomes are more useful than liposomes in skin care products.
- As the absorption of active component is improved, its small dose can produce desired results.
- The bioavailability of drug is enhanced remarkably.

DISADVANTAGES OF PHTYOSOMES

Although phytosomes having so many advantages instead of this technology it has few disadvantages such as phospholipids (lecithin) can provoke the proliferation on MCF-7 breast cancer cell line and it has been reported that phytosomes could rapidly eliminate the phytoconstituents.[17-18]

PROPERTIES OF PHYTOSOMES

1. Physico-Chemical Properties

- Phytosomes are prepared by reaction of stoichiometric amount of phospholipid with the phyto-constituents in an aprotic solvent.[19]
- The size of phytosome varies from 50nm to a few hundred µm.[20]
- Phytosome, when treated with water, assumes a micellar shape resembling liposome and photon correlation spectroscopy (PCS) reveals this liposomal structures acquired by phytosome.[21]
- The H1NMR and C13NMR data deduced that the fatty chain gives unchanged signals both in free phospholipid and in the complex, which indicates that long aliphatic chains are protected around the active principle producing lipophilic envelope.[22]

Biological Properties

Phytosomes are novel complexes which are better

absorbed and utilized, hence they produce more bioavailability and better result than the conventional herbal extract or non-complexed extracts, which has been demonstrated by pharmacokinetic studies or by pharmacodynamics tests in experimental animals and in human subjects.[23]

PREPARATION TECHNIQUE OF PHYTOSOMES

Phytosomes are prepared by reacting a synthetic or natural phospholipid with the standardized plant extract in a ratio ranging from 0.5-2.0. But usually 1:1 ratio is preferable.

The reaction is carried out alone or in the natural mixture in aprotic solvent, such as, dioxane, methylene chloride, acetone; from which the novel complex can be isolated by precipitation with a non-solvent, usually an aliphatic hydrocarbon or by lyophilisation or by spay drying. The solubilization or complex formation is sometimes carried out by refluxing the stoichiometric ratio mixture for a specified period in the aprotic solvent.

The solvents may be evaporated by using rotary evaporators. Hence, after drying, the resulting complexes are soluble in polar and aprotic solvents, in which the individual components of the complex are usually insoluble. For the preparation of phytosome the phospholipids are choosen from the group consisting of soylecithin, from bovine or swine brain or dermis, phosphatidylcholine, phosphatidylethanolamine, phosphatidylserine, in which acyl group may be same or different and mostly derived from palmitic, stearic, oleic and linoleic acid.[24-27]

There are different types of technique employed to formulation of phytosomes which is summarized below.

- Solvent evaporation method
- Rotary evaporation method
- Anti-solvent precipitation method

Table 1: Therapeutic applications of different Phytosomes with their dose.[28-29]

Phytosomes	Phytoconstituent complexed with Phospholipid	Daily Doses	Uses
Greenselect	Epigallocatechin 3-O-gallate from camelia sinensis (Green tea)	50–100 mg	Systemic antioxidant. Best choice for protection against cancer.[28]
Leucoselect	Procyanidolic oligomers (PCOs) from grape seeds	50–100 mg	Systemic antioxidant Best choice for most people under age of fifty. Also specific for the eyes, lungs, diabetes, varicose veins, and protection against heart disease[29]
Ginkgoselect	24 % ginkgo flavono glycosides from Ginkgo biloba1	20mg	Best choice for most people over the age of 50. Protects brain and vascular lining[30]
Panax ginseng	37.5% ginsenosides from roots of Panax ginseng	150mg	As a Food Product
Glycyrrhiza	18-beta glycyrrhetinic acid	-	Anti-inflammatory Activity[31]
Silybin	Silybin from silymarin (milk thistle)	120 mg	Best choice if the liver or skin needs additional antioxidant protection
SiliphosTM milk thistle	Silybin from silymarin	150 mg	Good choice for liver or skin support
Oleaselect	Polyphenols from olive oil		As potent antioxidants, inhibit harmful oxidation of LDL cholesterol, and also have anti-inflammatory activity.[32]

FORMULATION OF PHYTOSOMES

Phytosomes formulation can be delivered by both routes like oral and topically, to obtained the best output regarding bioavailability of the phytosomes. There are different types of dosage form containing phytosomes are depicted below.[33]

Tablet: An ideal Phyto-phospholipid complex powder could not have got better technological properties due to their potential stickiness, flow ability, and low apparent density. When applying the direct compression process for material, it should be diluted with 60 to 70% of excipients and to optimize its physical & chemicals characteristics. For major process, dry granulation process can be most suitable to find the dose uniformity and convenient bioavailability. In other way, wet granulation process should be avoided owing to the negative effect of water and heat (used for granulation/drying) on the stability of the phospholipids complex.[34]

Soft gelatin capsule: These types of phytosomes are developed in form of heterogeneous mixture (suspensions) with phytoconstituents as dispersed phase such as vegetable oils or semi synthetic oils as dispersion medium it is use to make a soft gelatin phytosomes capsules for oral drug delivery.[35]

Hard gelatin capsule: Phytosomes can be used with direct volumetric process. It can be filled into hard

gelatin capsules in powder form itself. Capsule size may not have increase 300 mg for low density phytosomes it is should be in zero size.[36]

METHODS USED FOR CHARACTERIZATION OF PHYTOSOMES[37]

a. Melting point determination
b. Drug release
c. Entrapment efficiency
d. Percentage drug entrapment
e. Thin Layer Chromatography
f. Infrared- Spectroscopy
g. Nuclear magnetic resonance spectroscopy
h. Differential scanning calorimetry
i. X-Ray Diffraction analysis
j. Scanning electron microscopy
k. Transmission electron microscopy
l. Photon correlation spectroscopy

RESEARCHES ON PHYTOSOMES TECHNOLOGY

Tedesco et al., (2004) reported the phytosomes of silymarin. This study is focused on the better Anti-Hepatotoxic Activity than silymarin alone and can provide the protection against the toxic effect of aflatoxin B1 on performance of broiler chicks.[38]

Maiti et al, (2005) developed the quercetin phospholipid complex in carbon tetrachloride to overcome the absorption of herbal formulation and it exerted better therapeutic efficacy to induced acute liver injury in rats.[39]

Mukerjee et al, (2008) developed a novel hesperetin phytosome by complexing hesperetin with hydrogenated phosphatidyl choline. This complex was then evaluated for antioxidant activity in CCl4 intoxicated rats along with pharmacokinetic studies. It was found that the phytosome had sustained release property for over 24 h and enhanced antioxidant activity. Pharmacokinetic study revealed that the phytosome had higher relative bioavailability than that of parent molecule at the same dose level.[40]

Keyong Xu et al, (2009) formulated luteolin - phospholipid complex and suggest that results showed the luteolin and phospholipid complex joined by non-covalent-bonds and didnot form a new compound. They were reported that the complex has an efficient scavenger of DPPH radicals and powerful inhibitor activity within the Rancimat antioxidant test using animal oil as substrate.[41]

Cao et al, (2010) prepared Oxymatrine-phospholipid complex (OMT-PLC) to reform the lipid solubility of oxymatrine-phospholipid. The purpose of this study was to recognize the utility of the combination of a micro emulsion and an OMT-PLC as topical delivery vehicle for increasing the absorption and efficacy of OMT. The solubility of OMT-PLC was determined and phase diagram of micro emulsion were constructed. Subsequently it is concluded that the combination of a micro emulsion and phospholipids complex show the effective vehicle for topical delivery of OMT.[42]

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