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PHYTOSOMES: A NOVEL DOSAGE FORM FOR ENHANCEMENT OF BIOAVAILABILITY OF BOTANICALS AND NE UTRACEUTICALS

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ABSTRACT

Phytomedicines, complex chemical mixtures prepared from plants, have been used for health maintenance since ancient times. But many phytomedicines are limited in their effectiveness because they are poorly absorbed when taken by mouth. The PHYTOSOMETM technology, developed by Indena S.p.A. of Italy, markedly enhances the bioavailability of select phytomedicines. Most of the bioactive constituents of phytomedicines are flavonoids. However, a majority of the flavonoids are poorly bioavailable when taken by mouth—only a small fraction of a given dose reaches the blood.3 this report presents the evidence that by converting certain flavonoid nutrients to their phytosome equivalents, Indena's proprietary process increases their bioavailability by 2 xs to 6x, perhaps more.

Key words: *flavonoids, phytomedicines, Phytosome, bioavailability*

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INTRODUCTION

Over the past century pharmacological and chemical studies have been performed on a lot of plant extracts in order to know their chemical composition and confirm their indications of traditional medicine. Herbal drugs containing bioactive constituents are mainly water soluble molecules. However, many flavonoid which are water soluble phytoconstituents like to be poorly absorbed[1] due to their poor miscibility with oils and other lipids or due to their multiple- ring large size molecules which cannot be absorbed by simple diffusion, severely limiting factors are available for their ability to pass across the lipid- rich outer membranes of the enterocytes of the small intestine. Polyphenols (Water-soluble phytoconstituents) molecules can be converted into lipid-compatible molecular complexes, which are called Phytosomes.

Phytosomes are more bioavailable in comparison to simple herbal extracts. They have enhanced capacity to cross the lipid rich biomembranes and finally reaching the blood[2]. The lipid-phase substances employed to make phytoconstituents, lipid compatible are phospholipids from soy, mainly phosphatidylcholine (PC). Phospholipids are complex molecules that are used in all known life forms to make cell membranes. The term "Phyto" means plant while "some" means cell-like. The

Phytosomes process itself produces a little cell whereby the valuable component of the herbal extract is protected from destruction by digestive secretions and gut bacteria[3].

Flavonoids are the most important group of phytochemicals. Flavonoids are the class of compounds that have referred to be a natural biological response modifier which acts as powerful antioxidants that providing remarkable protection against oxidative and free radical damage. Various flavonoids which have shown antioxidant activity 50 to 200 times more potent than vitamin C or E. we can use certain flavonoids-rich extracts that referred as “tissue specific antioxidants” due to their ability of concentrated in specific body tissue[4].

Phytosomes is a patented technology developed by a leading manufacturer of drugs and nutraceuticals, whereby the individual component of a standardized plant extracts are bound to phosphatidylcholine - an emulsifying component to produce lipid compatible molecular complexes, called as Phytosomes and so vastly improve their absorption and bioavailability[5].

There are many plant drugs that are incorporated to Phytosomes process as herbal extracts including Ginkgo biloba, grape seed, hawthorn, milk thistle, green tea, and ginseng .Phytosomes are more bioavailable as compared to conventional herbal extracts owing to their enhanced capacity to cross the lipoidal biomembrane and finally reaching the systemic circulation. So, Phytosomes has been a novel approach for the herbal drug delivery[6].

FORMULATION OF PHYTOSOMES:

Phytosomes are prepared by reacting the herbal extract in an aprotic solvent such as methylene chloride, dioxane and ethyl acetate with the phospholipid such as phosphatidylcholine, phosphatidylethanolamine or phosphatidyiserine dissolved in the same solvent. After solubilization has been completed, the complex compounds are isolated by removing the solvent under vacuum, by freeze drying or by precipitation with non solvents such as n- hexane. Thus the obtained complexes are lipophilic in character and soluble in a polar and aprotic solvent, in which the individual components of the complex are normally insoluble[7].

DIFFERENCE BETWEEN PHYTOSOME AND LIPOSOME:

Likewise phytosomes, a liposome is formed by mixing a water soluble substance with phosphatidylcholine in definite ratio under specific conditions. Here, no chemical bond is formed; the phosphatidylcholine molecules surround the water soluble substance. There may be hundreds or even thousands of phosphatidylcholine molecules surrounding the water-soluble compound. In contrast, with the phytosome process the phosphatidylcholine and the plant components actually form a 1:1 or a 2:1 molecular complex depending on the substance(s) complexes, involving chemical bonds. This difference results in phytosome being much better absorbed than liposomes showing better bioavailability. Phytosomes have also been found superior to liposomes in topical and skin care products[8](Fig. 1).

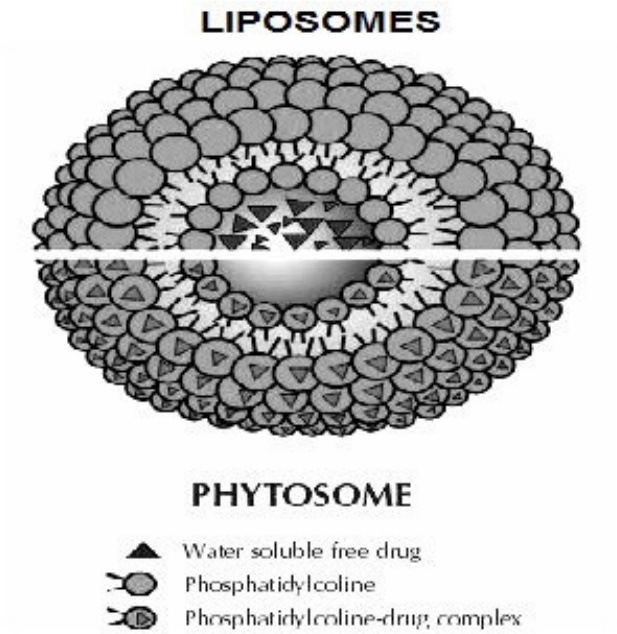

Fig. 1: Shows difference between liposome and phytosome.
The molecular organization of the liposome (upper segment)
The molecular organization of phytosomes (lower segment)

TABLE 1: COMMERCIAL PHYTOSOME PREPARATIONS[9,10]

S/N	Phytosomes	Phytoconstituents complexed	Dose	Indications
1	Silybin Phytosome	Silybin from *Silybum marianum*	120 mg	Hepatoprotective, antioxidant for liver and skin
2	Ginkgo Phytosome	24 % ginkgoflavonoids from *Ginkgo biloba*	120 mg	Protects brain and vascular linings,antiskin
3	Ginseng Phytosome	37.5 % ginsenosides from *Panax ginseng*	150 mg	Nutraceutical, immunomodulator
4	Green Tea Phytosome	Epigallocatechin from*Thea sinensis*	50-100 Mg	Nutraceutical, systemic antioxidant, anti-cancer
5	Grape Seed Phytosome	Procyanidins from *Vitis vinifera*	50-100mg	Nutraceutical, systemic antioxidant, cardioprotective.
6	Hawthorn Phytosome	Flavonoids from *Crataegus sp.*	100 mg	Nutraceutical, cardioprotective and antihypertensive
7	Olive oil Phytosome	Polyphenols from *Olea europaea* oil	-	Antioxidant, antiinflammatory, anti-hyperlipidemic
8	Echinacea Phytosome	Echinacosides from *Echinacea angustifolia*	-	Nutraceutical, immunomodulator

VARIOUS PROPERTIES OF PHYTOSOMES:

Chemical:

Phytosomes is a complex between a natural product and natural phospholipids, like soy phospholipids. Such a complex is obtained by reaction of stoichiometric amounts of phospholipid and the substrate in an appropriate solvent. On the basis of spectroscopic data it has been shown that the main phospholipid-substrate interaction is due to the formation of hydrogen bonds between the polar head of phospholipids (i.e. phosphate and ammonium groups) and the polar functionalities of the substrate. When treated with water, phytosomes assumes a micellar shape forming liposomial-like structures, In liposomes the active principle is dissolved in the internalpocket or it is floating in the layer membrane, while in phytosomes the active principle is anchored to the polar head of phospholipids, becoming an integral part of the membrane for example in the case of the catechin-distearoylphosphatidylcholine complex, in this there is the formation of H-bonds between the phenolic hydroxyls of the flavones moiety and the phosphate ion on the phosphatidylcholine side[11].

Pharmacological:

Phytosome are advanced forms of herbal products that are better absorbed, utilized and as a result produce better results than conventional herbal extracts the increased bioavailability of the phytosomes over the non complexed botanical derivatives has been demonstrated by pharmacokinetics studies or by pharmacodynamic tests in experimental animals and in human subjects[12] .

MECHANISM OF PHYTOPHOSPHOLIPID COMPLEX FORMATION:

The poor absorption of flavonoid nutrients is likely due to two main factors. First, these are multiple ring molecules not quite small enough to be absorbed from the intestine into the blood by simple diffusion, Nor does the intestinal lining actively absorb them, as occurs with some vitamins and minerals. Second, flavonoid molecules typically have poor miscibility with oils and other lipids. This severely limits their ability to pass across the lipid-rich outer membranes of the enterocytes, the cells that line the small intestine. The phytosome technology meets this challenge. Phytosomes results from the reaction of a stoichiometric amount of the phospholipid (phosphatidylcholine) with the standardized extract or polyphenolic constituents (like simple flavonoids) in a non polar solvent. Phosphatidylcholine is a bifunctional compound, the phosphatidyl moiety being lipophilic and the choline moiety being hydrophilic in nature. Specifically the choline head of the phosphatidylcholine molecule binds to thesecompounds while the lipid soluble phosphatidyl portion comprising the body and tail which then envelopes the choline bound material. Hence, the phytoconstituents produce a lipid compatible molecular complex with phospholipids, also called as phytophospholipid complex. Molecules are anchored through chemical bonds to the polar choline head of the phospholipids, as can be demonstrated by specific spectroscopic techniques. Precise chemical analysis indicates the unit phytosome is usually a flavonoid molecule linked with at least one phosphatidylcholine molecule. The result is a little microsphere or cell is produced[12].

ADVANTAGES OF PHYTOSOME[13,14,15]

Phytosomes have following advantages

1) Phytosome are better bioavailable botanical extracts, dramatically enhance bioavailability due to their complex with phospholipids and delivers faster and improved absorption in intestinal tract

2) They enhance the absorption of lipid insoluble polar phytoconstituents through oral as well as topical route showing better bioavailability with significantly better therapeutic benefit

3) Dose requirement can be minimized as the bioavailability is increased.

4) Phosphatidylcholine used in preparation of phytosomes besides acting as a carrier also acts as a hepatoprotective substance showing the synergistic effect when hepatoprotective substances like flavanoids are employed to form complex.

5) Phytosome are widely used in cosmetics due to there more skin penetration and high lipid profile.
6) Phytosomes show better stability profile owing to the chemical bonds formed between phosphatidylcholine molecule and phytoconstituents.

CHARACTERIZATION OF PHYTOSOMES:

The behavior of phytosomes in both physical and biological system is governed by the factors such as physical size membrane permeability; percent entrapped solutes, chemical composition as well as the quantity and purity of the starting materials. Therefore, the phytosomes are characterized for physical attributes i.e. shape, size, its distribution, percentage drug capture entrapped volume, percentage drug released and chemical composition[16].

ADVANCES IN PHYTOSOME TECHNOLOGY:

In a very recent study the tissue and blood effects of high-dose silybin-phytosome in prostate cancer patients was determined. Patients received silybin-phytosome for 14-31 days (mean was 20 days) prior to surgery. Silibinin blood levels were measured 1 h after the first silybin-phytosome dose with a mean value of 19.7 μM. One of the treated patients developed a grade 4 post-operative thromboembolic event. The other observed toxicities in the treatment group were mild: four subjects had diarrhea and one had asymptomatic grade 2 hyperbilirubinemia which was transient. The results indicate that high-dose oral silybin-phytosome achieves high blood concentrations transiently, but low levels of silibinin are seen in prostate tissue[17].

Green Phytosome were prepared and studied in 100 obese subjects (both male and female, divided into 2 groups of 50 each). Group 1 was given hypocaloric diet with green tea phytosome. Group 2 was given only hypocaloric diet. After 90 days, parameters like weight, body mass index, low density lipid, High density lipid, total cholestrol, triglycerides, insulin, growth factor, cortisol were determined. All parameters were improved in both groups but there was more weight loss in green tea phytosome group than in diet only group (14 kg loss versus 5 kg loss). Also, no adverse effects were reported during and after trial[18].

Another method currently being investigated is complexing curcumin with a phospholipid, known as a phytosome. The phosphatidylcholine-curcumin complex (Meriva®) is more readily incorporated into lipophilic cell membranes, making it significantly more bioavailable than unbound curcumin. In rats, peak plasma concentration and AUC were five times higher for Meriva than for unbound curcumin[19].

Phytosomes of curcumin (flavonoid from turmeric, Curcuma longa) and naringenin (flavonoid from grape fruit, vitis vinifera) showed higher antioxidant activity than pure curcumin in all dose levels tested[20]. In a study the bioavailability of silybin in rats was found to increase remarkably after oral administration of prepared silybin-phospholipid complex Phytosome due to an impressive improvement of the lipophilic property of silybin-phospholipid complex and improvement of the biological effect of silybin[21].

Ginkgo biloba phytosome treatment was found to increase superoxide dismutase, catalase, glutathione peroxidase and glutathione reductase activities in all the brain regions compared with those treated only with sodium nitrite. *Ginkgo biloba* phytosomes were administered to Wistar rats at 50 mg/kg and 100 mg/kg for 7 and 14 days. Chemical hypoxia was induced by administration of sodium nitrite (75 mg/kg) 1 h after the last administration of treatment. Thirty minutes after sodium nitrite administration, the animals were killed and the cerebral cortex, cerebellum, hippocampus and striatum were isolated and homogenized. The supernatants were used for the estimation of the antioxidant enzymes superoxide dismutase, catalase, glutathione peroxidase and glutathione reductase[22].

Herba Epimedii flavonoid phytosomes (EFP) were prepared by means of solvent evaporation technique and the accumulative dissolution of different ratios of EFP-PVP precipitates was investigated by means of dissolution release. For optimized preparation solvent-tetrahydrofuran, lecithin to PVP 2.5 times,

temperature 40 °C and reaction 3 h. Oil/water apparent partition coefficient of icariin was enhanced more than 4 times by phospholipid. The accumulative dissolution of *Herba Epimedii* flavonoids of EFP-PVP precipitate was significantly higher than that of its physical mixture and *Herba Epimedii* extract tablet[23].

Patients suffering from chronic hepatitis (viral, alcohol or drug induced) treated with silybin phytosome at a dose of 120 mg either twice daily or thrice daily for up to 120 days, liver function returned to normal faster in patients taking silybin phytosome compared to a group of controls (49 treated with commercially available silymarin,117 untreated or given placebo)[24].

In a study silymarin (a standardized mixture of flavanolignans extracted from the fruits of *S. marianum*) phytosomes showed much higher specific activity and a longer lasting action than the single constituents, to percent reduction of odema and inhibition of myeloperoxidase activity[25].

A human study was conducted to design the absorption profile of silybin when directly bound to phosphatadylcholine. Plasma levels of silybin were determined after administration of single oral doses of silybin phytosome and a similar amount of silybin from milk thistle in healthy volunteers. The results indicated that the absorption of silybin from silybin phytosome was approximately seven times greater compared to the absorption of silybin from regular milk thistle extract[26].

CONCLUSION

Thorough study of literature different phytosome products has demonstrated significant therapeutic or health promoting properties when compared with the conventional plant extracts. Phytosomes can be developed for different therapeutic purposes like hepatoprotective, cardiovascular, liver diseases, anti- inflammatory, immunomodulator, anticancer, antidiabetic etc or for prophylactic and health purposes as nutraceuticals, in due course.

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