Review Article

Phytosomes - A New Herbal Drug Delivery System

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1) Herbal Medicine

1.1) Introduction

Herbal medicines are the synthesis of therapeutic experiences of generations of practicing physicians of indigenous systems of medicine for over hundreds of years[1]. The World Health Organisation (WHO) has recently defined traditional medicine including herbal drugs as therapeutic practices that have been in existence for hundreds of years before the development and spread of modern medicine and are still in use today. The traditional preparations comprise of medicinal plants, minerals and organic matter. Herbal drugs constitute only those traditional medicines which are primarily used as medicinal plant preparations for therapy[2]. Herbal medicines are also termed as phytotherapeutic agents or phytomedicines. These phytomedicines are also available as standardized herbal preparations consisting of complex mixtures of one or more plants, which are used in many countries[3].

1.2) Importance of Herbal Medicine

The use of medicinal plants for health reasons started thousands of years ago and is still a part of medical practice in China, Egypt, India and other developing countries. Over the centuries, the use of medicinal herbs has become an important part of daily life in the western world despite significant progress in modern medicine and pharmaceutical research. Increasing knowledge of metabolic processes and effects of plants on human physiology has enlarged the range of application of medicinal plants[4].

WHO estimates that 4 billion people, i.e. about 80 % of the world population, presently use herbal medicine for some aspect of primary health care? Major pharmaceutical companies are currently conducting extensive research on plant materials gathered from the rain forests and other places for their potential medicinal value.

Substances derived from the plants remain the basis for a large proportion of the commercial medications used today for the treatment of heart disease, high blood pressure, pain, asthma, and other problems. For example, Ephedra is an herb used in Traditional Chinese Medicine for more than two thousand years to treat asthma and other respiratory problems. Ephedrine, an active ingredient in Ephedra, is used in the commercial pharmaceutical preparations for the relief of asthma symptoms and other respiratory problems. It helps the patients to breathe more easily.

Another example of the use of the herbal preparation in modern medicine is the foxglove plant. This herb had been in use since 1775. At present the powdered leaf of this plant is known as the cardiac stimulant digitalis to the millions of heart patients.

Herbal medicine can be broadly classified into various basic systems: Traditional Chinese herbalism, which is part of Traditional Oriental Medicine, Ayurvedic herbalism, which is derived from ayurveda, and Western herbalism, which originally came from Greece and Rome to Europe and then spread to North and South America

There are some Ayurvedic herbs that are useful for reducing cholesterol, diabetes etc. Similarly the popularity of Ginseng and Ginkgo biloba (Ginkgo) is rising due to its effects like immunomodulatory[5]. Herbal medicines have stood the test of time for their safety, efficacy, cultural acceptability and lesser side effects [2].

In comparison to well defined synthetic drugs, herbal medicines exhibit some marked differences[6] viz

1. Long history of use and better patient tolerance
2. Renewable resource
3. Environment friendly
4. Local availability
5. Important recent breakthrough
6. Major source of new lead generation

Apart from this, they also offer therapeutics for age-related disorders like memory loss, osteoporosis, immune disorders, diabetes, cancer etc; for which modern medicine has no complete cure. Herbals, mainly in developing countries, are known for their better cultural acceptability and lesser side effects[2].

2) Phytosomes

The term "phyto" means plant while "some" means cell-like. Phytosome are created when the standardized extract and active ingredients of an herb are bound to the phospholipids on a molecular level.

Phytosome structures contain the active ingredients of the herb surrounded by the phospholipids. The phospholipid molecular structure includes a water-soluble head and two fat-soluble tails, because of this dual solubility, the phospholipid acts as an effective emulsifier, which is also one of the chief components of the membranes in our cells. Phytosomes are advanced forms of herbal products that are better absorbed, utilized, and as a result produce better results than conventional herbal extracts.

2.1) Introduction

Preparations of plants or parts of them were widely used in popular medicine since ancient times and till today the use of phytomedicines are widespread in most of the world's population. During the last century chemical and pharmacological studies have been performed on a lot of plant extracts in order to know their chemical composition and confirm the indications of traditional medicine. The Phytosome process produces a little cell because of that the valuable components of the herbal extract are protected from destruction by digestive secretions and gut bacteria. Phytosomes are better able to transition from a hydrophilic environment into the lipid-friendly environment of the enterocyte cell membrane and from there into the cell[7], finally reaching the blood. Most of the bioactive constituents of phytomedicines are flavonoids (e.g., anthocyanidins from bilberry, catechins from green tea, silymarin from milk thistle). However, many flavonoids are poorly absorbed the poor absorption of flavonoid nutrients is likely due to two factors. First, they are having multiple-ring molecules that are too large to be absorbed by simple diffusion. Secondly flavonoid molecules typically have poor miscibility with oils and other lipids, which limited their ability to pass across the lipid-rich outer membranes of the enterocytes of the small intestine. Water-soluble flavonoid molecules can be converted into lipid-compatible molecular complexes, aptly called phytosomes. The lipid-phase substances employed to make flavonoids lipid-compatible are phospholipids from soy, mainly phosphatidylcholine (PC). Phosphatidylcholine is the principal molecular building block of cell membranes miscible both in water and in oil environments, and is well absorbed when taken by mouth. Chemical analysis indicates that in phytosome is usually a flavonoid molecule linked with at least one phosphatidylcholine molecule. A bond is formed between these two molecules, creating a hybrid molecule. This highly lipid-miscible hybrid bond is better suited to merge into the lipid phase of the enterocyte's outer cell membrane. Phosphatidylcholine is not merely a passive "carrier" for the bioactive flavonoids of the phytosomes, but is itself a bioactive nutrient with documented clinical efficacy for liver disease, including alcoholic hepatic steatosis, drug-induced liver damage, and hepatitis. The intakes of phytosome preparations sufficient to provide reliable clinical benefit often also provide substantial phosphatidylcholine intakes. The phytosome process has been applied to many popular herbal extracts including Ginkgo biloba, grape seed, hawthorn, milk thistle, green tea, and ginseng. The flavonoid and terpenoid components of these herbal extracts lend themselves quite well for the direct binding to phosphatidylcholine. Specifically, the choline head of the phosphatidylcholine molecule binds to these compounds while the fat-soluble phosphatidyl portion comprising the body and tail then envelopes the choline-bound material. The result is a little micro sphere or cell is produced[8]. Phytosomes have improved pharmacokinetic and pharmacological parameter which in result can advantageously be used in the treatment of the acute and chronic liver disease of toxic metabolic or infective origin or of degenerative nature. It can also be used in anti-inflammatory activity as well as in pharmaceutical and cosmetic compositions[8.]

2.2) Preparation of Phytosome

Phytosomes are novel complexes which are prepared by reacting from 3-2 moles but preferably with one mole of a natural or synthetic phospholipid, such as phosphatidylcholine, phosphatidylethanolamine or phosphatidyiserine with one mole of component for example- flavolignanans, either alone or in the natural mixture in aprotic solvent such as- dioxane or acetone from which complex can be isolated by precipitation with non solvent such as aliphatic hydrocarbons or lyophilization or by spary drying. In the complex formation of phytosomes the ratio between these two moieties is in the range from 0.5-2.0 moles. The most preferable ratio of phospholipid to flavonoids is 1:1 [9].

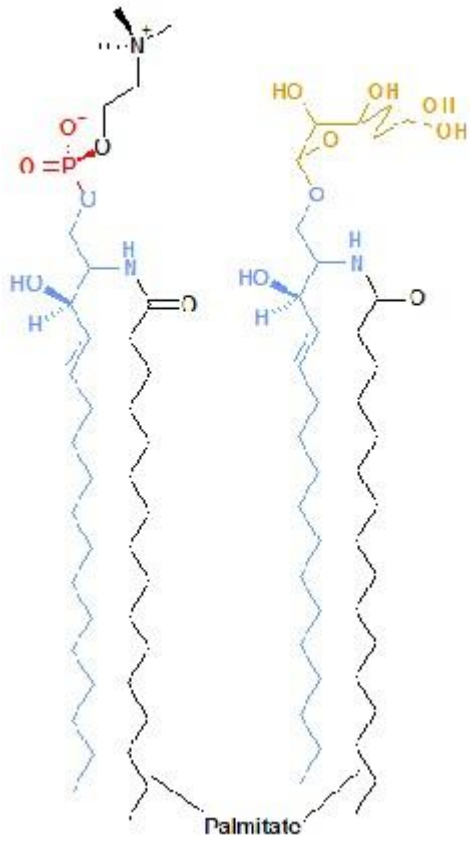
In the phytosome preparations, phospholipids are selected from the group consisting of soy lecithin, from bovine or swine brain or dermis, phosphatidylcholine, phosphatidylethanolamine, phosphatidyiserine in which acyl group may be same or different and mostly derived from palmitic, stearic, oleic and linoleic acid. Selection of flavonoids are done from the group consisting of quercetin, kaempferol, quercretin-3, rhamnoglucoside, quercetin-3-rhamnoside, hyperoside, vitexine, diosmine, 3- rhamnoside, (+) catechin, (-) epicatechin, apigenin-7-glucoside, luteolin, luteolinglucoside, ginkgonetine, isoginkgonetine and bilobetine. Some liposomal drugs complex operate in the presence of the water or buffer solution where as

phytosomes operate with the solvent having a reduced dielectric constant. Starting material of component like flavonoids are insoluble in chloroform, ethyl ether or benzene. They become extremely soluble in these solvents after forming phytosomes. This chemical and physical property change is due to the formation of a true stable complex [10].

2.3) Properties of Phytosomes

2.3.1) Chemical properties

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 internal pocket 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 catechindistearoylphosphatidylcholine complex, in this there is the formation of H-bonds between the phenolic hydroxyls of the flavone moiety and the phosphate ion on the phosphatidylcholine side.



Phosphatidylcholine

This can be deduced from the comparison of the NMR of the complex with those of the pure precursors. The signals of the fatty chain are almost unchanged. Such evidences inferred that the two long aliphatics chains are wrapped around the active principle, producing a lipophilic envelope, which shields the polar head of the phospholipid and the catechin[11.]

2.3.2) Biological Properties

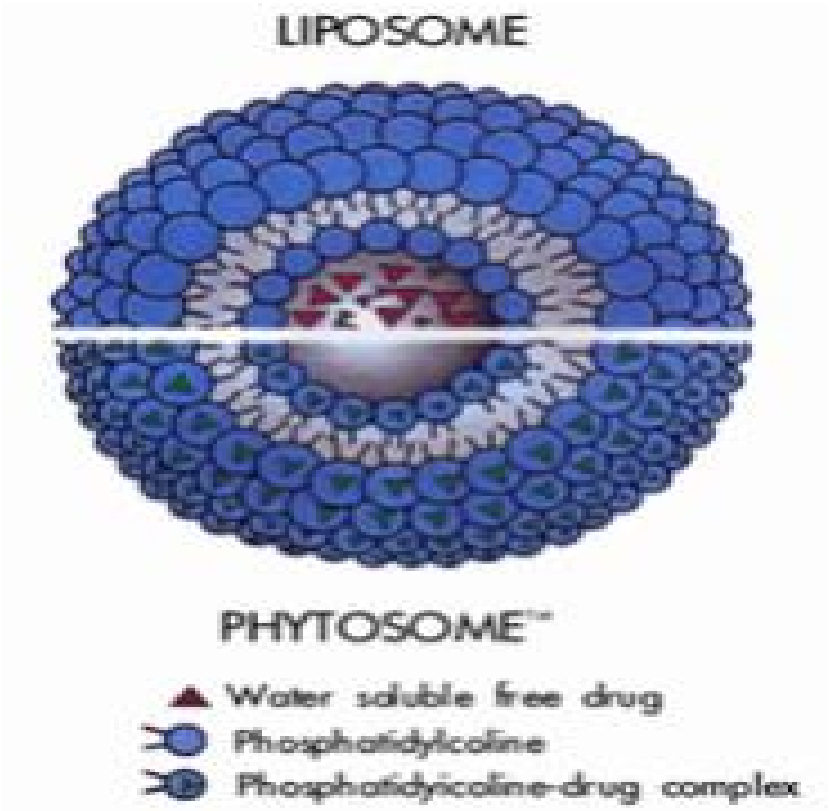
Phytosome are advanced forms of herbal products that are better absorbed, utilized and as a result produce better results than conventional herbal extracts the increased bioavailability of the phytosome over the non complexed botanical derivatives has been demonstrated by pharmacokinetics studies or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

2.4) 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 [13].

2.5) Difference between Phytosome and liposome

Liposomes are used primarily in cosmetics to deliver water-soluble substances to the skin. Mixing a water-soluble substance with phosphatidylcholine forms a liposome. No chemical bond is formed and 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 individual plant components actually from a 1:1 or a 2:1 complex depending on the substance[17].



Phytosomes are not liposome - structurally, the two are distinctly different as shown in fig. no.1. The phytosome is a unit of a few molecules this makes difference so the phytosomes being much better absorbed that liposomes. Not surprisingly, Phytosomes are also superior to liposomes in skin care products while the liposome is an aggregate of many phospholipid molecules that can enclose other phytoactive molecules but

without specifically bonding to them. Liposomes are touted delivery vehicles, but for dietary supplements their promise has not been fulfilled. But for phytosome products numerous studies prove they are markedly better absorbed and have substantially greater clinical efficacy. Companies have successfully applied this technology to a number of standardized flavonoid preparations.

The phytosomes technology is a breakthrough model for [18.]

· Marked enhancement of bioavailability
· Significantly greater clinical benefit
· Assured delivery to the tissues
· No compromise of nutrient safety

2.6) Advantages over the conventional dosage form,

The various advantages of phytosome are mentioned below;

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. Phytosome permeates the non-lipophillic botanical extract to be better absorbed in intestinal lumen.
3. Phytosome will be given in small quantity and desired results can be achieved.
4. Phytosome is widely used in cosmetics due to there more skin penetration and have a high lipid profile.
5. Phytosome are been used to give liver protectant flavonoids because they were easily bioavailable.

Phytosomes Herbal Support[14-19]

The Phytosome process has been applied to many popular herbal extracts including Ginkgo biloba, grape seed, hawthorn, milk thistle, green tea, and ginseng. The flavonoid and terpenoid components of these herbal extracts lend themselves quite well for the direct binding to phosphatidylcholine. Specifically, the choline head of the phosphatidylcholine molecule binds to these compounds while the fat-soluble phosphatidyl portion comprising the body and tail then envelopes the choline-bound material. The result is a little micro sphere or cell is produced. What the Phytosome process produces is a little cell whereby the valuable components of the herbal extract are protected from destruction by digestive secretions and gut bacteria.

The effectiveness of any herbal product (or medication) is dependent upon delivering an effective level of the active compounds. For milk thistle, this means delivering an effective level of silybin for Pan ax ginseng it's the compounds known as ginsenosides for Ginkgo biloba extract it is the flavonoids and the terpenes; and for green tea it is epigallocatechin 3-O- gallate. It only makes sense that if you can increase the absorption and utilization of these components that you will see better results. And, that is exactly what has been shown in several studies with various Phytosomes.

For example, several clinical studies have also shown SILYBIN PHYTOSOME™ is more effective and produces better results compared to regular milk thistle extracts. In one study of 232 patients with chronic hepatitis (viral, alcohol, or drug induced) treated with SILYBIN PHYTOSOME™ at a dosage either 120 mg twice daily or 120 mg three times daily for up to 120 days, liver function returned to normal faster in the patients taking SILYBIN PHYTOSOME ™ compared to a group of controls (49 treated with a commercially available silymarin; 117 untreated or given placebo).

Preliminary studies have also shown Ginkgo Phytosome and Grape Seed Phytosome to produce better results compared to the conventional extract forms of these plants.

For example in studies with Ginkgo Phytosome in peripheral vascular disease (e.g., Raynaud's disease and intermittent claudication) Ginkgo Phytosome was shown to produce a 30-
60% greater improvement compared to regular Ginkgo biloba extract (24% ginkgo flavone glycoside and 6% terpene lactones).

CONCLUSION

Phytosomes are novel compounds comprising of lipophillic complexes of components of various plants like *Silybum Marianum, Ginkgo Biloba, ginseng* etc with phospholipids. Phytosome prepration is done by non-convectional method. Absorption of phytosome in gastro-intestinal tract is appreciably greater resulting in increased plasma level than the individual component. Complex formation ratio of component and phospholipids is 1:1 and 2:1. Phytosomes are used as a medicament and have wide scope in cosmetology. Many areas of phytosome are to be revealed in future in the prospect of pharmaceutical application. Phytosomes forms a bridge between the convectional delivery system and novel delivery system.

REFERENCES

1. Houdret J., A Visual Dictionary of Herbs, South water. 2000, 1.
2. Kambhoj V.P., Current Science, 2000, 1 (10), 35.
3. Calixio J.B., Braz. J. Med. Boil. Res., 2000, 33(2), 179.
4. Bentley R. and Trimet H., Medicinal Plants, International Book Distributors, 1992, 1, 1079.
5. Samanta M.K., Mukherjee P.K., Prasad N.K. and Suresh B., the Eastern Pharmacist., 2000, 23.
6. Mascarella S., 1993, Therapeutic and antilipoperoxidant effects of silybin-phosphatidylcholine complex in chronic liver disease, Preliminary results. Curr Ther.Res., 53(1), 98-102.
7. .Magistretti Maria Jose, Bombardelli Ezio, 1987, U.S. Patent No-EPO209037 Pharmaceutical compositions containing flavanolignans and phospholipida active principles.
8. Sharma Shalini, Sikarwar Mukesh, Phytosome: a review, Planta Indica, Vol.1, No. 2, April 2005, 1-3.
9. Bombardelli Ezio, Mustich Giuseppe, 1991, U.S. Patent No.EPO-275005 bilobalide phospholipid comlex, their uses and formulation contaning them.
10. Franco P.G., Bombardelli, Ezio, 1998, U.S. Patent No-EPO 275005, Complex coppouns of bioflavonoids with phospholipids, their preparation and uses and pharmaceutical and cosmatic compositions containing them.
11. Jain N.K, Controlled and novel drug delivery, 1 st edition, CBS publisher, 2005, 321-326.
12. U.S. Department of Health and human Services, Cosmetic Handbook, U.S. Government Printing Office.
13. Bombardelli Ezio, Phytosome in functional cosmetics, Fitoterapia LXV (5): 1994, 387-401.
14. Parris Kidd, Kathleen H, A review of the bioavailibility and clinical efficacy of milk thiatle phytosome: a silybin-phosphatidylcholine complex, Altern Med Rev 2005; 10(3): 193-203.
15. Kingom A.D., Pharmacognosy in 21 st century, Journal of Pharmacognosy and pharmacology, 2001, 53,135-148.
16. Gabetta Bruno, Bombardelli Ezio, Pifferi Giorgia, 1986, U.S. Patent No- 4764508 Complexes of

flavanolignans with phospholipids, preparation there of and associated pharmaceutical compositions.
17. Schandalik R, Gatti G, and Perucca E: Pharmacokinetics of silybin in bile following administration of silipide and silymarin in cholecystectomy patients. Arzneim Forsch 1992; 42(7):964-8.
18. Barzaghi N, et al.: Pharmacokinetic studies on IdB 1016, a silybin-phosphatidylcholine complex, in healthy human subjects. Eur J Drug Metab Pharmacokinet 1990; 15(4):333-8.
19. www.natural-wellness.com.