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PHYTOSOMES: POTENTIAL CARRIERS FOR HERBAL DRUGS

ABSTRACT

Phytosomes are recently introduced herbal formulations that are better absorbed, and as a result produce better bioavailability and actions than the conventional phytomolecules or botanical extracts. This is an advanced form of herbal formulations which contains the bioactive phytoconstituents of herbal extract bounded in a lipophilic carrier. Phytosome technology has been effectively used to enhance the bioavailability of many popular herbal extracts and phytoconstituents including Ginkgo biloba, milk thistle, grape seed, green tea, hawthorn, ginseng etc and can be developed for various therapeutic uses or dietary supplements.

Keywords: Phytosomes, absorption, phospholipids, bioavailability.

INTRODUCTION

During the last century, chemical and pharmacological studies have been performed on lot of plant extracts in order to know their chemical composition and confirm the indications of traditional medicine. It has often been observed that the separation and purification of the various components of an extract may lead to a partial loss of specific activity for the purified component. Most of the biologically active constituents of plants are polar or water soluble molecules. However, water soluble phytoconstituents (like flavonoids, tannins, glycosidic aglycones etc) are poorly absorbed either due to their large molecular size which cannot be absorbed by passive diffusion, or due to their poor lipid solubility, severely limiting their ability to pass across the lipid-rich biological membranes, resulting in poor bioavailability [1,3]. 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 Phytosome® technology, developed by Indena S.p.A. of Italy, markedly enhances the bioavailability of select phytomedicines, by incorporating phospholipids into standardized extracts and thus significantly improving their absorption and utilization. Even standardization of extracts for determination of exact concentration was not able to solve this problem as poor bioavailability often limited their clinical utility. Then it was discovered that complexation with certain other clinically useful nutrients substantially improved the bioavailability of such extracts. The accipients so helpful for enhancing the absorption of other nutrients are the phospholipids which also have their own nutritive value. Phospholipids are complex molecules that are used in all known life forms to make cell membranes. They are cell membrane building blocks, making up the matrix into which fit a large variety of proteins that are enzymes, transport proteins, receptors, and other biological energy converters. In humans and other higher animals, the phospholipids are also employed as natural digestive aids and as carriers for both fat-miscible and water miscible nutrients [4, 5].

The term "phyto" means plant while "some" means cell-like [2]. The phytosome structure is a small cell in itself, as the valuable components of the herbal extract are protected from destruction by the digestive secretions and gut bacteria. Water-soluble phytoconstituents can be converted into lipid-compatible molecular complexes and therefore are aptly called phytosomes. The lipid phase substances employed to make phytoconstituents lipid compatible are phospholipids from soy, mainly phosphatidylcholine (PC) (Fig. 1). PC is the principal molecular building block of the cell membranes, miscible both in water and in oil environments, and is well absorbed when taken orally. Chemical analysis indicates that phytosome is usually a phytoconstituent molecule linked with at least one PC molecule. PC is not merely a passive "carrier" for the bioactive phytoconstituent 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 [6]. The intake of phytosome preparations is sufficient to provide reliable clinical benefit. The phytosome process, applied to many popular herbal extracts, including phytoconstituents, lends these molecules for direct binding to PC quite well, which means that the choline head binds to phytoconstituents while the fat-soluble phosphatidyl portion comprising the body and tail then envelopes

the choline-bound material. The result is a little microsphere or cell. The phytosome process has been applied to many popular herbal extracts including Ginkgo biloba, grape seed, hawthorn, milkthistle, green tea, and ginseng

1.1. VESICULAR SYSTEMS OR "SOMES" USEFUL FOR DRUG DELIVERY:

The term "Somes" indicates the cell like formulations of novel drug delivery system which are classified as vesicular systems. There are different types of somes like (Fig. 2)

• Liposomes, which encapsulate water and lipid-soluble pharmacologically and cosmetically active components.

• Phytosomes are standardized extracts or purified fractions complexed with phospholipids for a better bioavailability and enhanced activities.

• Cubosomes are bicontinuous cubic phases, consisting of two separate, continuous, but nonintersecting hydrophilic regions divided by a lipid layer that is contorted into a periodic minimal surface with zero average curvature.

• Colloidosomes are solid microcapsules formed by the self assembly of colloidal particles at the interface of emulsion droplets. "Colloidosomes" are hollow, elastic shells permeability and elasticity can be precisely controlled.

• Ethosomes are non-invasive delivery carriers that enable drugs to reach the deep skin layers and/or the systemic circulation. They contain phospholipids, alcohol (ethanol and isopropyl alcohol) in relatively high concentration and water.

• Aquasomes are spherical 60300nm particles used for drug and antigen delivery. The particle core is composed of noncrystalline calcium phosphate or ceramic diamond, vesicles and as liposomes, is bilayered structures etc.

. Pharmacosomes are the colloidal dispersions of drugs covalently bound to lipids and may exist as ultrafine vesicular, micellar, or hexagonal aggregates, depending on the chemical structure of the drug–lipid complex

• Niosomes are non- ionic surfactant vesicles and, as liposomes, are bilayered structures etc.

1.2. DIFFERENCE BETWEEN PHYTOSOMES AND LIPOSOMES

Likewise phytosomes, a liposome is formed by mixing a water soluble substance with phosphatidylcholine in definite ratio under specific conditions. However, 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) complexed, involving chemical bonds (hydrogen 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 [7] (Fig.3).

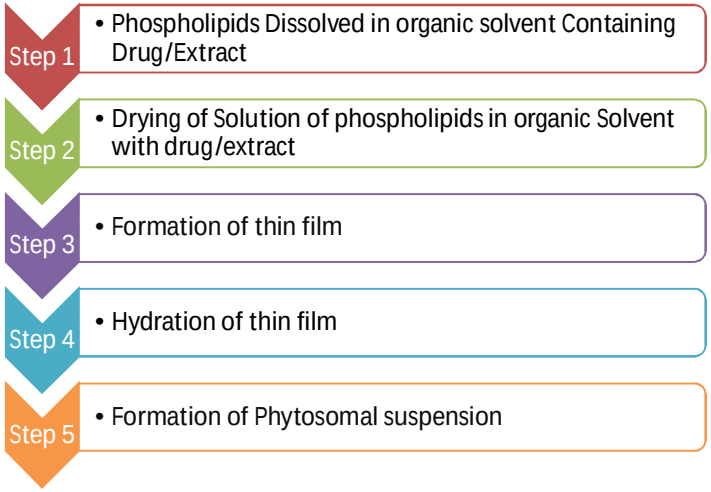
1.3. PREPARATION OF PHYTOSOME- THE PHYTOSOME TECHNOLOGY

1. 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 spray 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[8].

2. Naringenin–PC complex was prepared by taking naringenin with an equimolar concentration of phosphatidylcholine (PC). The equimolar concentration of PC and naringenin were placed in a 100 mL round bottom flask and refluxed in dichloromethane for 3 h. On concentrating the solution to 5–10 mL, 30 mL of n-hexane was added to get the complex as a precipitate followed by filtration. The precipitate was collected and placed in vacuum desiccators [9].

3. The required amounts of drug and phospholipids were placed in a 100 ml round-bottom flask and dissolved in anhydrous ethanol. After ethanol was evaporated off under vacuum at 40 ◦C, the dried residues were gathered and placed in desiccators overnight, then crushed in the mortar and sieved with a 100 mesh. The resultant Silybin-phospholipid complex was transferred into a glass bottle, flushed with nitrogen and stored in the room temperature [10].

Common steps of preparation of Phytosomes



The flavonoid and terpenoid constituents of plant extracts lend themselves quite well for the direct binding to phosphatidylcholine. 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 these compounds while the lipid soluble phosphatidyl portion comprising the body and tail which then envelopes the choline bound material.

1.4. PROPERTIES OF PHYTOSOMES [11, 12, 13, 14, 15]

The term phytosome is used to define a complex between a natural product and natural phospholipids, like soy phospholipids that are obtained by the reaction of stoichiometric amounts of phospholipids and phytoconstituents in an appropriate solvent. Spectroscopic data reveal that the main phospholipid-substrate interaction is due to the formation of hydrogen bonds between the polar head of the phospholipids (i.e., phosphate and ammonium groups) and the polar functionalities of the substrate.

1. Phytosomes can accommodate the active principle that is anchored to the polar head of the phospholipids, becoming an integral part of the membrane. For example, in case of the catechin distearoyl PC complex, there is formation of H-bonds between the phenolic hydroxyls of the flavones moiety and the phosphate ion on the PC side.

2. PC: Study of comparisons of nuclear magnetic resonance of the complex with those of the pure precursors indicates that the signals of the fatty chain are almost unchanged. Such evidences inferred that the two long aliphatic chains are wrapped around the active principle, producing a lipophilic envelope that shields the polar head of the phospholipid and the catechin [12].

3. They are advanced forms of herbal products that are better absorbed, utilized and, as a result, produce better results than conventional botanical herbal extracts. The increased bioavailability of the hover the non-complexed botanical derivatives has been demonstrated by pharmacokinetic studies or by pharmacodynamic tests in experimental animals and in human subjects.

4. They are lipophilic substances with a definite melting point, freely soluble in non-polar solvents, and moderately soluble in fats.

5. When treated with water, they assume a micellar shape, forming structures that resemble liposomes exhibiting fundamental differences.

1.5. ADVANTAGES OF PHYTOSOMES [14, 15, 16]

1. It enhances the absorption of lipid insoluble polar phytoconstituents through oral as well as topical route showing better bioavailability, hence significantly greater therapeutic benefit.

2. Appreciable drug entrapment.

3. As the absorption of active constituent(s) is improved, its dose requirement is also reduced.

4. Phosphatidylcholine used in preparation of phytosomes, besides acting as a carrier also acts as a hepatoprotective, hence giving the synergistic effect when hepatoprotective substances are employed.

5. Application of phytoconstituents in form of phytosome improves their percutaneous absorption and act as functional cosmetics.

6. Added nutritional benefit of phospholipids.

7. They permeate the non-lipophilic botanical extract to be better absorbed in intestinal lumen.

8. Phytosomes have been used to give liver protectant flavonoids because they were easily bioavailable.

9. By improving the solubility of bile to herbal constituent, liver targeting can be facilitated.

10. Unlike liposome, chemical bonds are formed between phosphatidylcholine molecule and phytoconstituent, so the phytosomes show better stability profile.

1.6. DISADVANTAGES

1. Phytoconstituent is rapidly eliminated from phytosomes.

1.7. CHARACTERIZATION OF PHYTOSOMES [17, 18]

Phytosomes are characterized for physical attributes, i.e. shape, size, its distribution, percentage drug capture, entrapped volume, percentage drug release, and chemical composition. Hence, behaviour of phytosomes in both physical and biological systems is governed by the following factors:

1. Physical size

1. Membrane permeability

2. Percent entrapped solutes

3. Chemical composition

4. Quantity and purity of the starting materials

1.8. EVALUATION OF PHYTOSOMES:

I. Characterization technique

1. Visualization: Visualization of phytosomes can be achieved using transmission electron microscopy (TEM) and by scanning electron microscopy (SEM) [19].

2. Entrapment efficiency: The entrapment efficiency of a drug by phytosomes can be measured by the ultracentrifugation technique [20].

3. Transition temperature: The transition temperature of the vesicular lipid systems can be determined by differential scanning calorimetry [21].

4. Surface tension activity measurement: The surface tension activity of the drug in aqueous solution can be measured by the ring method in a Du Nouy ring tensiometer [22].

5. Vesicle stability: The stability of vesicles can be determined by assessing the size and structure of the vesicles over time. The mean size is measured by DLS and structural changes are monitored by TEM [23].

6. Drug content: The amount of drug can be quantified by a modified high performance liquid chromatographic method or by a suitable spectroscopic method [24].

II. Spectroscopic evaluations

To confirm the formation of a complex or to study the reciprocal interaction between the phytoconstituent and the phospholipids, the following spectroscopic methods are used [25].

1.1HNMR

2. 13CNMR

3. FTIR

III. In vitro and in vivo evaluations

Models of in-vitro and in-vivo evaluations are selected on the basis of the expected therapeutic activity of biologically active phytoconstituents present in the phytosomes [25]. For example, invitro antihepatotoxic activity can be assessed by the antioxidant and free radical scavenging activity of the herbosomes. For assessing antihepatotoxic activity in-vivo, the effect of prepared phytosomes on animals against thioacetamide, paracetamolor alcohol-induced hepatoxicity can be examined [26, 27]. Skin sensitization and tolerability studies of glycyrrhetinic acid-Phytosome® ointment, a commercial product, describe the in vivo safety evaluation methodology [28].

2. APPLICATIONS OF PHYTOSOMES: (Table.1)

Silymarin Phytosome

Most of the phytosomal studies are focused on Silybum marianum (milk thistles) which contains premier liver protectant flavonoids.

Yanyu et al. (2006) prepared silymarin phytosome and studied its pharmacokinetic in rats. In the studies, the bioavailability of silybin in rat was increased remarkably after oral administration of silybin-phospholipid complex due to an impressive improvement of the lipophilic properties of silybin-phospholipid complex and improvement of biological effect of silybin [29].

Tedesco et al. (2004) reported silymarin phytosome show better anti-hepatotoxic activity than silymarin alone and can provide protection against the toxic effects of aflatoxin B1 on performance of broiler chicks [28].

Curcumin Phytosome

Maiti et al. (2006) developed the phytosomes of curcumin (flavonoid from Curcuma longa, turmeric) and naringenin (flavonoid from grape fruit, Vitis vinifera) in two different studies. The antioxidant activity of the complex was significantly higher than pure curcumin in all dose level tested. In the other study the developed phytosome of naringenin produced better antioxidant activity than the free compound with a prolonged duration of action, which may due to decrease in the rapid elimination of the molecule from body [30, 31].

Quercetin-phospholipid phytosomal complex

Maiti et al. (2005) developed the quercetin-phospholipid phytosomal complex by a simple and reproducible method and also showed that the formulation exerted better therapeutic efficacy than the molecule in rat liver injury induced by carbon tetrachloride [32].

3. CONCLUSION

Phytosomes are advanced form of herbal extract that are better absorbed which results better than conventional herbal extract. The article thus reviews the benefits, physical characteristics, chemical properties and method of preparation of the phytosomes. The formulation methodology for phytosome is simple and can be easily upgraded to a commercial scale. These are novel complexes showing much better absorption profile following oral administration owing to improved lipid solubility which enables them to cross the biological membrane, resulting in enhanced bioavailability i.e. more amount of active principle in the systemic circulation. Also, phytosomes are superior to liposomes due to much better absorption and stability profile. As mentioned in the literature, phytosomes have been therapeutically used for hepatoprotective and liver diseases. After screening and selection for phytoconstituents for therapeutics use, phytosomal drug delivery systems can be developed for various categories like anticancer, cardiovascular and anti-inflammatory activities.

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