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REVIEW ARTICLE

PHYTOSOMES: A NOVEL APPROACH IN HERBAL DRUG DELIVERY SYSTEM

AMRITA I. JADHAV*[1] AMOL A. WADHAVE[2], VILAS A. ARSUL[3,] H. S. SAWARKAR[3]

1. Assistant professor, Department of pharmacognosy, Dr. Vedprakash Patil Pharmacy College, Aurangabad.
2. Assistant professor, Department of pharmaceutics, Dr. Vedprakash Patil Pharmacy College, Aurangabad-431001.
3. Assistant professor, Department of pharmaceutical Chemistry, Dr. Vedprakash Patil Pharmacy College, Aurangabad.

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Abstract:
Phytoconstituents, despite having excellent bioactivity *in vitro*, demonstrate less or no *in vivo* actions due to their poor lipid solubility or improper molecular size or both, resulting in poor absorption and poor bioavailability. Lipid solubility and molecular size are the major limiting factors for molecules to pass the biological membrane and to be absorbed systematically following oral or topical administration. Some phytoconstituents are destroyed in the gastric environment when taken orally. The term "phyto" means plant, while "some" means cell-like. Therefore, phytosomes is a "phytophospholipid complex" resembling a small cell. Phytosomes are produced by a patented process whereby standardized plant extracts or their constituents are bound to phospholipids, mainly phosphatidylcholine, producing a lipid-compatible molecular complex. Phytosomes exhibit a better pharmacokinetic and pharmacodynamics profile than conventional herbal extracts. The phytosomes technology markedly enhances the bioavailability of phytomedicine and has effectively enhanced the bioavailability of many popular herbal extracts, including *Milk thistle, Ginkgo biloba, Grape seed, Hawthorn, Ginseng*.

Keywords: Drug delivery, phosphatidylcholine, phospholipids, phytoconstituents, phytosomes

Introduction

Phytosomes is also called as Phytolipids delivery system which forms a bridge between the convectional delivery system and novel delivery system. It is a newly introduced patented technology developed by incorporate standardized plant extracts or water soluble phytoconstituents into phospholipids to produce lipid compatible molecular complexes, which enhance their absorption and bioavailability[1]. The term “phyto” means plant while “some” means cell-like. The Phytosomes technology produces a little cell, better able to transit from a hydrophilic environment into the lipid-friendly environment of the enterocyte cell membrane and from there into the cell, finally reaching the blood. In such a way it protects the valuable components of the herbal extract 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, finally reaching the blood. When different phytoconstituents such as flavonoids, terpenes & saponins form reversible complexes with phospholipids, they showed that their anti-inflammatory and long lasting than those observed after administration of same amount of substance in free form. This is mainly due to the complexation of active ingredients with phospholipids[2].

An ideal drug delivery system is the one that delivers the drug at a rate dictated by the need of the body, over the period of treatment, and channels the active entity solely to the site of action.[2] for this purpose, a number of carriers have been used, like immunoglobins, erythrocytes, reverse micelles, phytosomes, and pharmacosomes. Phytosomes have improved pharmacokinetic and pharmacological parameters that result in the treatment of acute and chronic liver disease of toxic metabolic or infective origin or of a degenerative nature. These are also widely used in anti-inflammatory activity and pharmaceutical and cosmetic compositions.

Tedesco *et al.* reported that the Silymarin Phytosomes show better anti-hepatotoxic activity than Silymarin alone and can provide protection against the toxic effects of Afflation B1 on the performance of Broiler chicks.

Busby *et al.* reported that the use of a Silymarin phytosomes showed a better fetoprotectant activity from ethanol-induced behavioral deficits than uncompelled Silymarin.

Grange *et al*. conducted a series of studies on the Silymarin Phytosomes containing a standardized extract from the seeds of *Silybum marinum* administered orally to animals and found that it could protect the fetus from maternally ingested ethanol.[3]

Yanyu *et al.* prepared the Silymarin phytosome and studied its pharmacokinetics in rats. In the study, the bioavailability of Silybin in rats was increased remarkably after oral administration of the prepared Silybin-phospholipid complex due to an impressive improvement of the lipophilic property of the Silybin-phospholipid complex and improvement of the biological effect of Silybin.

Mascarella *et al* in one study of 232 patients with chronic hepatitis treated with the Silybin phytosome at a dose of 120 mg either twice daily or thrice daily for up to 120 days, investigated and found that the liver function returned to normal faster in patients taking the Silybin phytosome compared with a group of controls.[4] Grape seed phytosomes is composed of oligomeric polyphenols of varying molecular size complexed with phospholipids. The main properties of the Procyanidine flavonoids of grape seed are in total antioxidant capacity and stimulation of physiological antioxidant defenses of plasma, protection against ischemia reperfusion-induced damages in the heart, protective effects against atherosclerosis thereby offering marked protection for the cardiovascular system and other organs through a network of mechanisms that extend their antioxidant potency.

Maiti *et al.* developed phytosomes of Curcumin and naringenin in two different studies. The antioxidant activity of the complex was significantly higher than pure Curcumin in all dose levels tested in the other study; the naringenin phytosomes produced better antioxidant activity than the free compound with a prolonged duration of action, which may be helpful in reducing the fast elimination of the molecule from the body.[5]

Water-soluble phytoconstituents like flavonoids, tannins, terpenoids, 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 (outer membranes of the enterocytes of the small intestine) biological membranes, resulting in poor bioavailability Phytosomes have improved pharmacokinetic and pharmacological parameters that result in the treatment of acute and chronic liver disease of toxic metabolic or infective origin or of a degenerative nature. These are also widely used in anti-inflammatory activity and pharmaceutical and cosmetic compositions.

History of Phytosomes

The phytosomes process 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[4]. The lipid-phase substances employed to make phytoconstituents lipid compatible are phospholipids from soy, mainly phosphatidylcholine (PC). 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 phytosomes is usually a phytoconstituents molecule linked with at least one PC molecule[6]. PC is not merely a passive "carrier" for the bioactive phytoconstituents 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 the intakes of a phytosomes preparation is sufficient to provide reliable clinical benefit, often leading to provide substantial PC intakes[7]. The phytosomes process has been applied to many popular herbal extracts, including *Milk thistle, Ginkgo biloba, Grape seed, Green tea, Hawthorn, Ginseng* etc[8]. The phytoconstituents lend themselves quite well for the direct binding to PC, 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. This result is a little microsphere or cell being produced.

Properties of Phytosomes

The term phytosomes 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[9]. 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.

3. Phytosomes are advanced forms of herbal products that are better absorbed, utilized and, as a result, produce better results than conventional botanical herbal extracts.[7] The increased bioavailability of the phytosomes over the non-complexed botanical derivatives has been demonstrated by pharmacokinetic studies or by pharmacodynamics tests in experimental animals and in human subjects.

4. Phytosomes 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 micelle shape, forming structures that resemble liposomes exhibiting fundamental differences.

Advantages of Phytosomes

Phytosomes enhance the bioavailability and stability profiles by forming a stable complex with phospholipids, and the drug delivery improves absorption from the site of action in the intestinal tract than when administered as an herbal constituent alone[10, 11, 12, 13].

1. Facilitates liver targeting by increasing the solubility in the bile salts.
2. The required dose is reduced as the absorption of the active phytoconstituents is improved.
3. PC used in the preparation of phytosomes, besides acting as a carrier also acts as a hepatoprotective, gives the synergistic effect.
4. Phytosomes are widely used in cosmetics due to improved skin penetration and high lipid profile.
5. Valuable components of herbal extracts are protected from destruction by digestive secretions and gut bacteria.
6. It assures proper delivery of drug the respective tissues.
7. The nutrient safety of the herbal extracts need not be compromised by conveying the herbal drug as means of phytosomes.
8. Dose requirement has been reduced due to the maximum absorption of chief constituents.
9. Marked enhancement in the bioavailability of drug occurs.
10. Entrapment efficiency is high and more over predetermined because drug itself is in conjugation with lipids in forming vesicles.
11. There is no problem in drug entrapment while formulating phytosomes.
12. Phytosomes show better stability profile due to the formation of chemical bonds between phosphatidylcholine molecules and the phytoconstituents.
13. Phosphatidylcholine used in formulating phytosomes process besides acting as a carrier also nourishes the skin as it is an essential part of a cell membrane.
14. Phytosomes are also superior to liposomes in skin care products.
15. Phytosomes proves to be of significantly greater clinical benefit.
16. Phosphatidylcholine used in preparation of phytosomes; besides acting as a carrier also acts as a hepatoprotective as a result it imparts a synergistic effect.

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, 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[14]. The phytosomes technology meets this challenge. Phytosomes results from the reaction of a stoichiometric amount of the phospholipid (phosphatidylcholine) with the standardized extract or polyphenol constituents (like

simple flavonoids) in a non-polar solvent. Phosphatidylcholine is a functional 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. Hence, the phytoconstituents produce a lipid compatible molecular complex with phospholipids, also called as phyto Phospholipid complex[15]. 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 phytosomes is usually a flavonoid molecule linked with at least one Phosphatidylcholine molecule[13]. The result is a little microsphere or cell is produced.

Technology of Phytosomes

Based on a histochemical observation that certain polyphenols had strong bonding affinity for phospholipids in their intact plant tissue, a group of Italian researchers focused on polyphenol preparations known to be poorly bioavailable when taken orally[16,17,18]. These were typically mixtures of polyphenols extracted from single plant species and their conversion into phytosomes forms markedly increased their bioavailability. To make phytosomes, the polyphenol mix is chemically reacted with a phospholipid preparation, consisting mainly of phosphatidylcholine (PC), which is also the major phospholipid of living tissues. The resulting phytosomes molecular complex is tested for bioavailability and efficacy, usually in direct comparison to its non-phytosomes form. For the four phytosomes preparations under review, the findings from systematic bioavailability comparisons show that when administered orally, phytosomes complexation enhances the blood levels of polyphenol constituents by factors of at least 2-6 times. 3-7 Phytosomes technology has proven to be a breakthrough for the clinical applicability of botanical polyphenols, since improved bioavailability generally results in enhanced efficacy.

Evaluation of Phytosomes

1. Different evaluation techniques used for Phytosomes

a) Visualization

Visualization of phytosomes can be achieved using transmission electron microscopy (TEM) and by scanning electron microscopy (SEM) [20].

b) Vesicle size and Zeta potential

The particle size and zeta potential of phytosomes can be determined by dynamic light scattering which uses a computerized inspection system and photon correlation spectroscopy.

c) Entrapment efficiency

The entrapment efficiency of a Phytosomal formulation can be determined by subjecting the formulation to ultracentrifugation technique

d) Transition temperature

The transition temperature of the vesicular lipid systems can be determined by differential scanning colorimetry.

e) Surface tension activity measurement

The surface tension activity of drug in aqueous solution can be measured by ring method by Du Nouy ring tensiometer.

f) 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.

g) Drug content

The amount of drug can be quantified by a modified high performance liquid chromatographic method or by a suitable spectroscopic method.

2. Spectroscopic evaluations

A) 1H-NMR

The NMR spectra are employed for estimating the complex formation between the active phytoconstituents and the Phosphatidylcholine molecule. The NMR spectra of phytosomes complex had been studied by Bombard Elli. In nonpolar solvents there is a marked change in 1H NMR signal originating from atoms involved in the formation of complex, without any summation of the signal peculiar to individual molecules. The signals from protons belonging to the phytoconstituents are broadened. In phospholipids there is broadening of signals while the singlet corresponding to the N-$(CH3)_3$ of choline undergoes an up field shift.

B) 13C-NMR

In the 13C NMR of the phytoconstituents and the stoichiometric complex with the Phosphatidylcholine when recorded in room temperature all the phytoconstituents carbons are invisible. The signals corresponding to the glycerol and choline portion are broadened and some are shifted, while most of the resonance of the fatty acids chains retains their original sharp line shape.

C) FTIR

The spectroscopic evaluation of the formed complex can be confirmed by FTIR simply by comparing the spectrum of the complex and the individual components and that of the mechanical mixtures. FTIR can also be considered as a valuable tool in confirming the stability of the Phytosomal complex. The stability can be

confirmed by comparing the spectrum of the complex in solid form with that of the spectrum of micro-dispersion in water after lyophilization at different times.

APPLICATIONS

1. **Silymarin Phytosomes**
   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. 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[20].

2. **Curcumin Phytosomes**
   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[21].

3. **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[22].

4. **Phytosomes of grape seed**
   Grape seed phytosomes is composed of oligomeric polyphenols (grape proanthocyanidins or Procyanidine from grape seed extract, *Vitis vinifera*) of varying molecular size complexed with phospholipids. The main properties of Procyanidine flavonoids of grape seed are an increase in total antioxidant capacity and stimulation of physiological defenses of plasma, protection against ischemia/reperfusion induced damages in the heart, protective effects against atherosclerosis thereby offering marked protection against the cardiovascular system and other organs through a network of mechanism that extend beyond their antioxidant effect. In another study, rabbits were fed with a high cholesterol diet for 6 weeks, to markedly elevate their blood cholesterol level and to induce atherosclerotic lesions in their aortas and carotid arteries. One group of rabbit received grape seed phytosomes in their feed for the first 6 weeks, then 4 weeks of high cholesterol diet. These developed significantly less aortic plaque than did the control group which received conventional standardized grape seed extract in similar regimen. In randomized human trial, young healthy volunteers received grape seed phytosomes once daily for 5 days. The blood TRAP (Total Radical-trapping Antioxidant Parameter) was measured at several time intervals during 1st day, then also on 5th day. Already by 30minutes after administration on 1stday, blood TRAP levels were significantly elevated over the control which received conventional standardized grape seed extract.

5. **Phytosomes of Gingko biloba leaves**
   Studies have shown that ginkgo phytosomes (prepared from standardized extract of *Ginkgo biloba* leaves) produced better results compared to the conventional standardized extract from plant (GBE, 24% ginkgo flavones glycoside and 6% terpenes lactones). In a bioavailability study conducted with healthy human volunteers the level of GBE constituents (flavonoids and terpenes) from the Phytosomal form peaked after 3 hours and persisted longer for at least 5 hours after oral administration. It was found that the Phytosomal GBE produced a 2-4 times greater plasma concentration of terpenes than did the non-Phytosomal GBE. Its major indication is cerebral insufficiency and peripheral vascular disorders and it can also ameliorate reduced cerebral circulations. Its improved oral bioavailability and good tolerability makes it the ideal ginkgo product even for long term treatment. Studies with ginkgo phytosomes in patients with peripheral vascular disorders have shown to produce 30-60% greater improvement compared to regular standardized GBE. Studies were also conducted on gingko phytosomes which yielded better result as compared to the conventional form. For conducting the aforesaid studies ginkgo phytosomes was administered for 5 days in guinea pigs, in whom the bronchoconstriction was induced by three different agonists (histamine, PAF and Acetylcholine). The bronchospastic inhibition was measured at the maximum peak, expressed as variations versus the basal values. The result indicated that ginkgo phytosomes can not only counteract direct bronchoconstriction but also it possess the tendency to reduce the TXA2 mediated bronchoconstriction of histamine and PAF as

compared to the conventional forms, thus indicating Phytosomal preparation was done. Antioxidant capacity

the improved efficacy of ginkgo phytosomes in combating the allergen induced bronchospasm. Studies have also proved the improved efficacy of ginkgo phytosomes over the conventional standardized extract in protecting rat isolated hearts against ischemia. The above mentioned results clearly gives an indication about the upper hand that phytosomes possess over the conventional preparations, thus proving it's utility for herbal phytoconstituents.

6. Phytosomes of green tea

Green tea leaves *(Theasinensis)* is characterized by presence of a polyphenolic compound epigallocatechin 3-O-gallate as the key component. These compounds are potent modulators of several biochemical process linked to the breakdown of homeostasis in major chronic-degenerative diseases such as cancer and atherosclerosis. Green tea also furnishes us with a number of beneficial activities such as antioxidant, anticarcinogenic, antimutagenic, hypocholesterolemic, and cardioprotective effects. In spite of such beneficial activities furnished by polyphenols from green tea extract the polyphenols suffer from the problem of poor bioavailability. The complexation of polyphenols derived from green tea with phospholipids strongly improves the oral bioavailability. A study on absorption of Phytosomal preparation was performed in healthy human volunteers along with non complexed green tea extract following oral administration. Over the study period of 6 hours the plasma concentration of total flavonoids was more than doubled when comparison was done between the Phytosomal and the non-was measured as TRAP (Total Radical Trapping Antioxidant Parameter). The peak antioxidant effect was a 20% enhancement and it showed that the phytosomes formulation had about double the total antioxidant effect[23].

Phytosomes products

Phytosomes delivery forms have been developed by Indena starting from the late eighties. In the table below are reported current commercially available products[23].

CONCLUSION

Phytosomal products show their potential in cosmetics as anti-aging agents and for the use of other non-pathogenic skin conditions. Phytosomes can play a vital role in efficient drug delivery of a broad spectrum of hepatoprotective phytoconstituents like flavones, xanthones, terpenes, etc. More recently, these are considered as a value-added drug delivery system. From the literature, it is very evident that several plant extracts possess different significant pharmacological or health-promoting properties. These extracts can be standardized accordingly and may be formulated as phytosomes for systematic investigation of any improved potential and can be used rationally. After screening and selection of potential extracts or constituents from plants, phytosomes can be developed for therapeutic purposes like cardiovascular, anti-inflammatory, immune-modulator, anti-cancer, anti-diabetic, etc. for prophylactic and health purposes as Neutraceutical in due course.

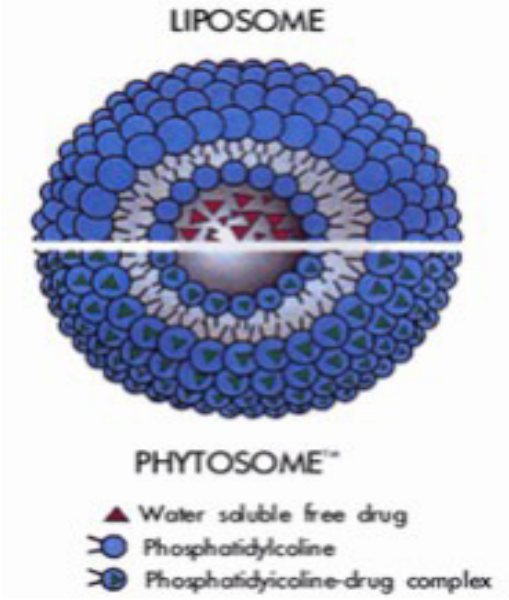

Figure 1- Mechanism of Phytophospholipid Complex Formation

Method of Preparation

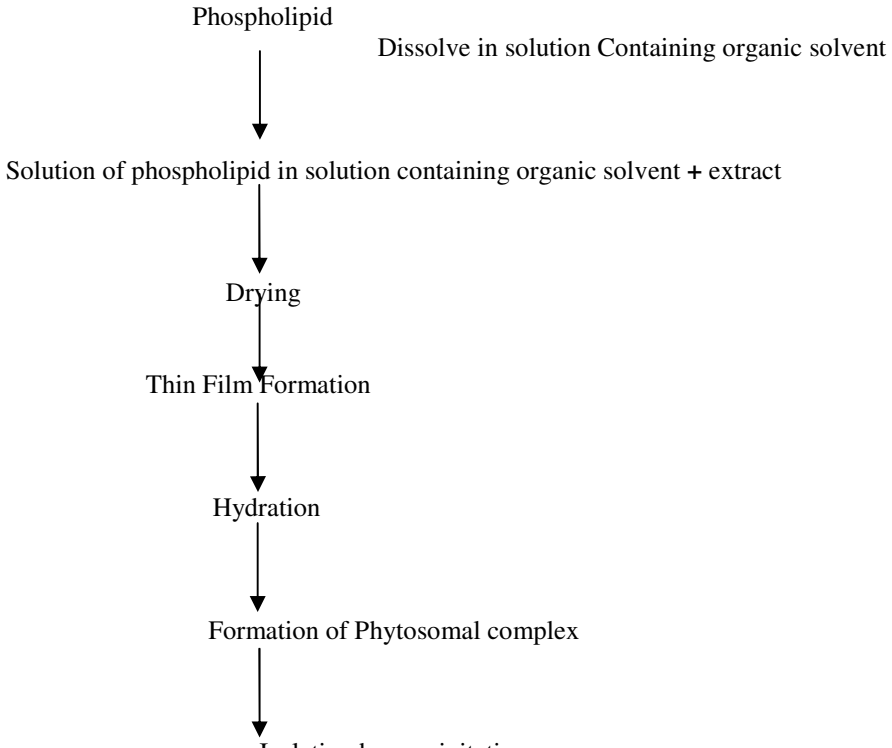

Figure 2- Stags of Preparation of Phytosomes [19]

Table 1: Herbal Drugs and Their Phytosomes[23]

No	Herbal Drug	Phytosome	Phytoconstituents complexed with phosphatidylcholine	Indications
1	Ginkgobiloba	Ginkgoselect Phytosome	(a) Dimeric flavonoids (b) terpenoids (gikgolides and bilobalide)	(a)Vasoactive agent (b)Anti-inflammatory agents
2	Silybum Marianum	Silybin Phytosome	(a)Flavolignan (Silybin) (b)Flavanolignan (Silymarin)	(a)Antioxidant and Hepatoproptective (b)Anti-inflammatory Anti-aging
3	Crataegus oxyacantha	Hawthorne Phytosomes	Flavonoids	Antioxidant, cardioprotective, Food product
4	Camellia sinensis	Greenselect Phytosome	Catechins and their gallate derivatives.	Antioxidant, cardioprotective, Food product
5	Panax ginseng	Ginselect	Saponins]	Anti-aging
6	Terminalia Serica	Sericosides Phytosome	Sericosides	anti-inflammatory.
7	Vaccinium myrtillus	Mirtoselect Phytosome	Antcinocide	Antioxidant
8	Vitis vinifera	Leucoselect Phytosome	Monomeric flavan-3-ols (catechins and epicatechins and their gallate derivatives)	antioxidant.

Table 2: commercially available Phytosomes products

Trade Name	**Active Compounds Formulated With Phytosome Technology**
Boswellia Phytosome	Boswellic acids from *Boswellia serrata*'s resin
Centella Asiatica Selected Triterpenes Phytosome	Selected triterpenes from *Centella asiatica*'s leaf
Escin β-sitosterol Phytosome	Escin and β-sitosterol from *Centella asiatica*'s seed
Ginkgoselect Phytosome	Ginkgoflavonglucosides, ginkgoterpenes, bilobalide and ginkgolides
Ginkgo Biloba Phytosome	from *Ginkgo biloba*'s leaf
Virtiva - Ginkgo Biloba Phosphatitylserine Phytosome	Ginkgoflavonglucosides, ginkgoterpenes and phosphatidyleseine from *Ginkgo biloba*'s leaf
Ginkgo Biloba Dimeric Flavonoids Phytosome	Biflavones from *Ginkgo biloba*'s leaf
Ginkgo Biloba Terpenes Phytosome	Ginkgoterpenes, bilobalide and ginkgolides from *Ginkgo biloba*'s leaf
Ginselect Phytosome	Ginseng typical constituents from *Panax ginseng*'s root
Greenselect Phytosome	Polyphenols from *Camelia sinensis*' young leaf
Hawthorn Phytosome	Vitexin-2''-O-rhamnoside from *Crategus*' flowering top
Leucoselect Phytosome	Proanthocyanidins from *Vitis vinifera*'s seed
Proanthocyanidin Phytosome	Proanthocyanidin A2 from *Aesculus hippocastanum*'s bark
Rexatrol Resveratrol Rhytosome	Resveratrol from *Polygonum cuspidatum*'s rhizome
Sericoside Phytosome	Sericoside from *Terminalia sericea*'s root bark
Silymarin Phytosome	Silybin-like substances from *Silybum marianum*'s fruit
Siliphos Silybin Phytosome	Silybin from *Silybum marianum*'s fruit

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