

Phyto-Phospholipid Complexes as Drug Delivery System for Herbal Extracts/Molecules

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The plant active molecules uses in home remedies have been relocated increasingly to the modern treatment. However, some of them have long side chains and high polarity that causes not to be able to pass through lipidic skin or intestine cell membranes by passive diffusion. Novel complexation technique named as ‘phytosome’ plays an important role to facilitate absorption and improve bioavailability. Drug molecules from natural sources and dietary soy phospholipids are complexed and generated cell-like structures. Up till now, the researchers have studied many phyto-phospholipid complexes as drug delivery system carrying out different methods (nonsolvent precipitating, supercritical fluids etc.) and provided pharmacokinetic and pharmacodynamic progresses. A lot of phytosome formulations are still under clinical trials and some of them on market. This presented review includes phytosome’s properties, advantages, preparation methods, dosage forms and marketed products. In this review, introducing the most important points in phytosome and canalizing the researchers to this drug delivery system designed for herbal extracts/molecules are aimed.

Key words:Phyto-phospholipid complexes, Phytosome, Drug delivery system, Herbal extracts/molecules

Bitkisel ekstreler/moleküller için ilaç salım sistemi olarak fito-fosfolipit kompleksleri

Bitkisel kaynaklı etken maddelerin geleneksel tedavide kullanımları giderek modern tedaviye aktarılmaktadır. Fakat bu bitkisel etkin moleküllerin bazıları, uzun yan zincirlere ve yüksek polariteye sahiptir. Bu da deriden veya barsaktan pasif difüzyonla emilime engel teşkil etmektedir. İşte bu noktada, ‘fitozom’ olarak adlandırılan yeni kompleksleştirme tekniği absorpsiyonu kolaylaştırmak ve biyoyararlanımı artırmakta önemli bir rol oynamaktadır. Bitkisel kökenli ilaç molekülleri ve doğal soya fosfolipidlerinin kompleksleştirilmesiyle hücre zarına benzeyen yapılar oluşturulmuştur. Günümüze kadar araştırmacılar birçok bitkisel molekülü veya ekstreyi çeşitli yöntemlerle (çöktürme, süperkritik sıvı kullanma vb.) fitozom formülasyonu haline getirmiş ve farmakokinetik/farmakodinamik iyileşmeler elde etmiştir. Hala birçok formül klinik deneme aşamasındadır, bazıları ise pazara sunulmuştur. Bu derlemede, fitozomların özellikleri, avantajları, hazırlama yöntemleri, üretilen dozaj şekilleri ve pazara çıkan fitozom ürünleri anlatılmıştır. Bu çalışmada, fitozomlar hakkında önemli bilgiler aktararak araştırmacıların bitkisel ekstreler/moleküller için tasarlanan bu ilaç salım sistemine yönlendirilmesi amaçlanmıştır.

Anahtar kelimeler:Fito-fosfolipid kompleksi, Fitozom, İlaç salım sistemi, Bitkisel ekstreler/moleküller

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INTRODUCTION

WHO says that, especially in developing countries, eighty or ninety percent of people preferred nonconventional drugs in first step remedy. Recently, natural products—

exclusively plants- have taken interest in treatment. They must have a hydrophilic-lipophilic balance to dissolve in gastrointestinal environment and cross the lipophilic membranes to reach the effect area like all chemicals. Phytoconstituents generally have good water solubility but not adequate

miscibility for an ideal bioavailability. Eventually, the ability of flavonoids to cross the lipid-rich outer membrane of small intestine enterocytes is severely limited (1,2).

Last few decades, novel drug delivery systems (polymeric nanoparticles, nanocapsules, liposomes, nanoemulsions, microsphere, transfersomes, and ethosomes) have applied on natural extracts to defeat absorption problems. These studies have provided significant advantages such as enhancement in solubility, bioavailability, pharmacological activity, stability, improved tissue macrophages distribution, sustained delivery, and protection from physical and chemical degradation as well as from toxicity (3, 52).

In last quarter century, researchers have been studying a private formulation for phytochemicals, denominated to 'phytosome'. The phytosome is an innovative carrying system what is formulated from solid dispersion of extract in phospholipid matrix for deficiently bioavailable natural products. Firstly, phytosome has been developed by Bombardelli et al.(4) in Milano. It was named as 'phyto-vesicle', 'herbosome' and 'phyto-phospholipid complex' in different publications. Phospholipid (such as phosphatidylcholine, phosphatidylserine etc. derived from soybean oil) was used overcoming the absorption-originated problems of -particularly- flavonoids, terpenoids, tannins and triterpens (4).

So far, many studies have showed different advances of phytosomes. Bombardelli et al. (4) prepared phytosomal silymarin and observed that it was more bioavailable and more stable in the gastric media than the other vesicular systems. In a comparative study in humans, the overall curcuminoid absorption was about 29-fold higher in phytosome form (27.2 for the low dosage, 31.5 for the high dosage) than unformulated curcuminoid mixture. On the other hand a 50 to 60 fold higher absorption has been shown for demethoxycurcumin and bisdemethoxycurcumin. The improved absorption, and possibly a better plasma curcuminoid profile, might underlie the clinical efficacy with phytosome at significantly lower doses than the unformulated curcuminoid mixtures (5). Remarkable results have been also seen

comparing the absorption (-)-epigallocatechin 3-O-gallate (EGCG), the main constituent of phytosome. Twelve healthy male volunteers were randomly divided in two groups. The first group received a single dose of (containing 240 mg) tea catechins. The second group received 1200 mg of phytosome (containing 240 mg of tea catechins). EGCG was chosen as the biomarker for absorption. The peak concentration at 2 hours is more than doubled with phytosome in comparison to the simple form. Further, the plasma levels of EGCG remain considerably higher with phytosome (6). The pharmacokinetic profile of *Ginkgo biloba* terpene lactones phytosome has been defined in experimental animals (7) and in human volunteers (8). Its bioavailability has been compared to *Ginkgo biloba* extract (GBE). Fifteen healthy volunteers were randomly divided into two groups and administered respectively with simple form and phytosome, providing both 9.6 mg of total terpene lactones. The subjects switched formulations after a week of wash out. Blood samples were collected at 30, 60, 120, 180, 240, 300 and 400 min after ingestion. Terpene lactones detection was performed by means of liquid chromatography/atmospheric pressure chemical ionization mass spectrometry. Ginkgolides A, B and bilobalide were absorbed to a higher extent (about three-fold) after administration of phytosome. As an example, the chart below reports plasma concentrations of ginkgolide A which, according to area under curve (AUC), shows a 3.5 fold higher absorption of the phytosome (7). Finally as a further example, the concentration of the six major boswellic acids [11-keto- β -boswellic acid (KBA), acetyl-11-keto- β -boswellic acid (AKBA), β -boswellic acid (β BA), acetyl- β -boswellic acid (A β BA), α -boswellic acid (α BA), and acetyl- α -boswellic acid (A α BA)] was evaluated in the plasma and in a series of rats tissues when administered in the phytosome. Weight equivalent and equimolar oral administration of phytosome provided significantly higher plasma levels (up to 7-fold for KBA, and 3-fold for β BA quantified as area under the plasma concentration time curve, AUC last) compared to the non-formulated extract and this was accompanied by remarkably higher tissue levels providing a further confirmation

of this delivery system also for semi-polar compounds (9).

Once, a short history of phytosomes is declared in this paper. Then, properties and advantages of phytosomes are given basically. Afterwards, preparation techniques are explained exhaustively both conventional and supercritical fluid methods.

Mostly used dosage forms of phyto-phospholipid complexes and GMP procedures of preparing them are discussed concisely. Additionally, phytosome formulations on the market are noticed with a chart. After some assessments, useful advices are given in the final part.

Phytosome's Properties

Chemical properties

Phytosome can be defined as a complex between a natural product and natural phospholipids (Figure 1). 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 aliphatic chains are wrapped around the active principle, producing a lipophilic envelope, which shields the polar head of the phospholipid and the catechin (10).

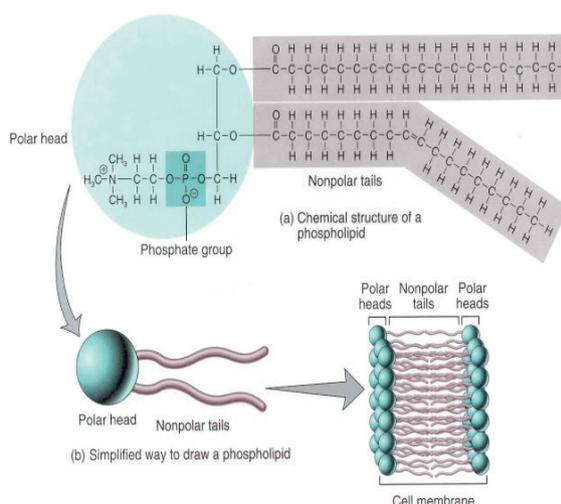


Figure 1. Phospholipid's structure (11)

Such a complex is obtained by reaction of stoichiometric amounts of phospholipid and the substrate in a convenient 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 characteristics of the substrate. When treated with water, phytosomes assume a micellar shape forming liposomal-like structures. In liposomes, the active molecule 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 (Figure 2). For example in the case of the catechindistearylphosphatidylcholine complex (Figure 3), there is the formation of H-bonds between the phenolic hydroxyls of the flavone moiety and the phosphate ion on the phosphatidylcholine side (12).

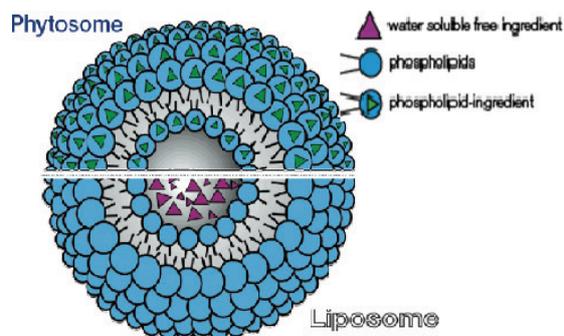


Figure 2. Liposome/phytosome difference (13)

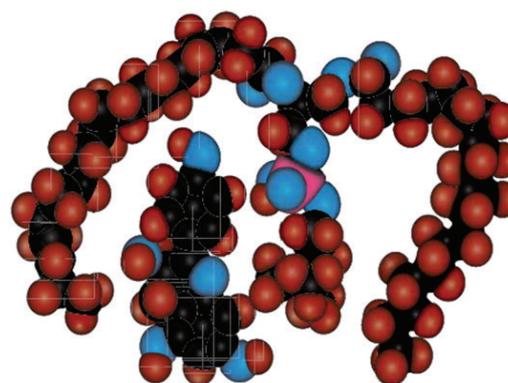


Figure 3. Phyto-phospholipid molecule (14)

Biological properties

Phytosomes are sophisticated forms of herbal products. They are better absorbed, utilized and as a result more bioavailable than conventional herbal extracts. Increased bioavailability of the phytosome over the

noncomplexed botanical derivatives has been demonstrated by pharmacokinetic studies or pharmacodynamic tests in experimental animals and in human subjects (15). The behavior of the phytosome in both physical and biological systems 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, phytosomes are characterized for physical attributes i.e. shape, size, its distribution, percentage drug entrapped volume, percentage drug released and chemical composition (16).

Advantages of Phytosomes

The phyto-phospholipid complex technology has impressed numerous the nutraceutical industry by serving the following benefits. First of all, herbosomes enhance the absorption of lipid insoluble polar phytoconstituents through oral as well as topical route showing better bioavailability, hence significantly greater therapeutic benefit. Then, phospholipid, one of the components of phytosome, has a dualfunction. It acts as a carrier as well as having some health benefits just as hepatoprotective effect. The content of phytosome is safe and the components are approved for pharmaceutical usage. The absorption and bioavailability of water soluble phytoconstituents are increased so better therapeutic effects are obtained. This results less dose to produce desirable effect. Phytosomes have a better stability than liposomes beside of other vesicular systems, because the former consists of chemical bonds while as it is absent in the layer. The process of manufacturing phytosomes is comparatively simple. Phospholipids add to the nutritional value of extracts. The water soluble phytoconstituents are enveloped by phospholipid which prevents them from destruction by digestive enzymes and bacteria of gastrointestinal environment. It helps to proper drug delivery to targeted tissues. Phosphatidylcholine feeds skin besides acting as a carrier because being a part of cell membrane. Phytosomes can be used for systematic drug targeting as they are able to transit from hydrophilic environment into

lipophilic environment of enterocyte cell and from there into cell (17-25).

Preparation Techniques

Phytosomes' structures, combinations of soybean lecithin with standardized extracts containing polyphenolic compounds or phytochemicals, are very similar with body cells. Complexation of extracts or specific active ingredients with dietary phospholipids is generally prepared by solvent evaporation/anti-solvent precipitation techniques using alcoholic or organic solvents but super critical fluids have been used in recent years, as well(26).

Solvent evaporation technique

In solvent evaporation technique, generally the drug and the phospholipids are placed in the same flask containing a suitable solvent/solvent system (i.e. tetrahydrofuran and ethanol). The reaction is allowed to be performed at suitable fixed temperature for a fixed duration of time to get maximum yield and drug entrapment (27,28).

Marsupsin–phospholipid complex has formulated using mechanical dispersion oriented liquid antisolvent precipitation process (29). They dissolved phospholipids in diethyl ether by sonication and marsupsin in double distilled water before drug solution was added dropwise to the phospholipid solution with sonication. The resultant formulation was cooled and on analyzing the complex showed 44% entrapment of marsupsin with 20% cumulative drug release. In another recent work Jain et al. (30) have prepared a rutin–phospholipid complex by an anhydrous co-solvent lyophilization method in which the drug and the phospholipids were dissolved in methanol but in different vessels. Both the solutions were stirred mechanically till all the solvents evaporated out. The photomicrography represented the rutin–phospholipid complex in amorphous state in contrast to rutin which is crystalline. A drug to phospholipid molar ratio of 1:3 provided comparatively superior experimental results. Complexation of a specific plant active molecule or a group of structurally similar plant actives with phospholipids has been performed at different molar ratios ranging from 0.5:1 to 3:1. In most of the research

works a stoichiometric ratio of 1:1 has been considered most suitable for formulating a complex. Yue et al. (31) have optimized the formulation of the oxymatrine–phospholipid complex molar ratio by using a composite design technique and had used drug to phospholipid ratios of 1:1, 1.4:1, 2:1, 2.6:1 and 3:1, respectively. The ratio of 3:1 at 60 °C for 3 h produced the complex with highest yield. Qin et al. (32) optimized the formulation of berberine with phospholipids using a statistical model incorporating polynomial and interactive terms. The optimal formulation was formed with a drug to phospholipid ratio of 0.9 (w/w), drug concentration of 80 g/l and a temperature of 60 °C. The combination percent of the resultant formulation was found to be 100% and drug content in the complex was 45.98%. Pathan and Bhandari(33) prepared an embelin–phosphatidylcholine complex using molar ratios of 1:0.5 to 1:3. The formulation at a ratio of 1:3 indicated the highest entrapment efficiency of 83.4%. They concluded that the entrapment efficiency of embelin which is lipophilic in nature improves with an increase in its aqueous solubility. Different solvents with low dielectric permittivity have been utilized by different researchers as the reaction medium for formulating herbosomes. Aprotic solvents like methylene chloride, ethyl acetate, dioxane etc. have been used for preparing complexes but they have been enormously replaced by protic solvents like ethanol. Yue et al. (34) and Zhang et al. (35) have used tetrahydrofuran as the reaction solution. Maiti et al. (36, 37) and Habbu et al. (38) have used dichloromethane as solvent and n-hexane as the medium for precipitation of the complex. Most of the recent work has been done using absolute ethanol as the reaction medium (39). In addition to the solvent system, different researchers have used phospholipids from different sources. The common criterion for selection was the ratio of phosphatidyl group lied in them. Soy lecithin, phosphatidylserine, and 1,2-distearoyl-sn-glycero-3-phosphatidylcholine are some of the phospholipids used. Phospholipids of the soybean oil have been used because of the higher content of phosphatidylcholine in them, which offers

compatibility and similarity with the mammalian plasma membrane (40, 41).

Utilizing from super critical fluids (SCF)

The super critical fluids (SCF) have emerged as an effective tool for preparing in a large size of particles (5-2000 nm). Different methods of supercritical fluid have been utilized for improving solubility profiles of poorly soluble drug candidates some of which are compressed antisolvent process (PCA), supercritical antisolvent method (SAS), rapid expansion of supercritical solutions (RESS), gas anti-solvent technique (GAS) and solution enhanced dispersion by supercritical fluids (SEDS). Supercritical fluid technique has incorporated for preparing puerarin–phospholipid complex (42, 43). Li et al. (42) have formulated the complex by three different conventional methods, namely, solvent evaporation, lyophilisation and micronized puerarin and compared them qualitatively with the complex prepared by the supercritical antisolvent precipitation technique. GAS and SEDS techniques were used for preparation of complexes. In the GAS technique, a supercritical antisolvent was added to the drug and phospholipid solutions separately until the final pressure was performed. The reaction media was kept for 3 hours without any agitation at a fixed temperature of 38°C with 10 mPa of pressure. In the SEDS technique, the liquid solution and the supercritical antisolvent were continuously added into the precipitation unit. Carbon dioxide gas was allowed to pass through a nozzle of 0.1 mm diameter into the mixture of phospholipid and puerarin in the solvent. The experimental conditions were optimized with temperature of 35 °C, pressure of 10 mPa, 1% mass ratio of drug to phospholipid and a 100 mg/mL concentration of puerarin. The resultant method provided 93% yield. The morphology of the product obtained from the SEDS technique was found to be in the form of aggregated particles with ordered appearance ranging in size of about 1 µm, while those formed by conventional methods were in the form of nubby granules with fused or viscous plates. Surface area of particles formed by the SEDS technique increased from 0.50 to 1.08. The phyto-phospholipid complex prepared by the supercritical techniques

demonstrated rapid dissolution with an increase of 1.91 folds from 2.87 mg/mL of puerarin to 5.49 mg/mL of its phospholipid complex. The product of the supercritical GAS technique has shown to be having more absolutely controlled morphological characteristics while the particles from the SEDS technique represented complete loss of crystallinity. The traditional anti-solvent precipitation technique has also been utilized by incorporating n-hexane as the antisolvent to precipitate out the drug-phospholipid complex from the organic solvent. Murugan et al. (44) have performed a similar method for preparing a phyto-phospholipid complex of andrographolide using dichloromethane as the reaction medium and n-hexane as the anti-solvent for final precipitation of the product. The solution is evaporated off and residue is dried usually under vacuum.

Dosage Forms

Phytosome vesicles have been formulated both orally and topically. Most proper manufacturing methods must be selected in order to enhance bioavailability and provide the convenience of management.

Oral dosage forms

Soft gelatin capsules: Soft gelatin capsule is an ideal material to ferry phytosome complex as it is dispersed in oily vehicles as a suspension. Natural or semi-synthetic oils are used to this purpose. Type of the oily vehicles is the most important critical parameter for this dosage form. Generally, size of the phytosome is smaller than 200 µm exhibit good flowing properties for soft gelatin capsules.

Hard gelatin capsules: Hard gelatin capsules can be used with direct volumetric filling process. That is important filling capsules without tapping in spite of low density so it may cause longer disintegration time. Dry granulation is preferred if it is necessary (much more powder than 300 mg for size 0 capsules).

Tablets: Phyto-phospholipid complex powders have not got good technological properties because of their limited flowability, potential stickiness and low apparent density. When considering the direct compression process, material should be diluted with 60-

70% of excipients to optimize powder characteristics. For higher doses, dry granulation process may be suitable to obtain dose uniformity and convenient bioavailability. All the way, wet granulation process must be avoided owing to the negative effect of water (used for granulation) and heat (for drying) on the stability of the phospholipid complex.

Topical dosage forms

Another option to perform phytosomes is topical route. Primarily, phospholipid complex is dispersed in a small amount of oily phase and then added to already prepared emulsion at less than 40°C degrees temperature. If outer phase is a watery phase, phospholipid complex must be added to watery phase and later added to the final emulsion again under 40°C degrees (13).

GMP and GACP Procedures for Phytosomes

Starting herbal material's quality is an essential precondition, since it may affect all the ensuring phases. Therefore GMPs (Good Manufacturing Practices) are applied already from these early steps to guarantee the characteristics of the final product. At this stage, some measures must be employed like; supplier inspection and qualification, according to GACP (Good Agricultural and Collection Practices), location selection, botanical identification of the plant and part of the plant, processing herbal material (harvesting period, harvesting method, drying conditions, storage), quarantine of the biomass under monitored conditions, microbiological analysis, chemical analysis, control of contaminants (pesticides, aflatoxins, heavy metals, etc.). If there is a non-conformance with any of all these controls, raw material mustn't be released for further processing.

The whole production process must be controlled by strict adherence to GMPs with well defined procedures and analysis at critical steps of production. All raw data must be recorded every critical procedure and parameter must be thoroughly described for workers.

The manufacturing process includes controls on grinding, extraction process parameters (solvent type, extraction conditions),

concentration, purification, drying, packaging/labelling and cleaning.

Final analysis and documentation review is performed to finished product to ensure compliance with specifications. Modern technology and analytical instrumentation are put to use, including HPLC and NMR, master batch record documentation review, analytical controls (content of active principles, content of impurities, heavy metals, pesticides, residual solvents), physical analysis, microbiological analysis of the final product. Furthermore, laboratory equipment qualification and periodical maintenance is assured.

according to suitably validated analytical methods. Qualified analytical reference standards must be used, and all data is summarized in a certificate of analysis. All analytical data is saved for future reference.

The final stage involves quality assurance/quality control review including GACPs including cultivation, growing and harvesting of the plant is very important.

The quality of a product is controlled during all stages of the process by adherence to strict GMPs and extensive testing at every stage of manufacturing. Product quality must be satisfying to enter the market (45).

Table 1. Marketed phytosome formulations (46-54)

Commercial product	Plant origin	Analysis	Biological activity
18 β -GLYCYRRHETINIC ACID PHYTOSOME®	Glycyrrhizaglabra L.- Root	$\geq 27.0\%$ $\leq 31.0\%$ of 18 β -glycyrrhetic acid by HPLC	Mitigative
CASPEROME™ BOSWELLIA PHYTOSOME®	BoswelliaserrataRoxb. exColebr. - Resin	$\geq 25\%$ boswellic acids by HPLC	Anti-inflammatory, Mitigative
CENTELLA ASIATICA TRITERPENE PHYTOSOME®	Centellaasiatica (L.) Urban - Leaf	$\geq 30.0\%$ $\leq 35.0\%$ of selected triterpenes by HPLC	Collagenrepairin, Wrinkle removing
DIMERIC FLAVONOIDS PHYTOSOME®	Ginkgo biloba L. - Leaf	$\geq 10.0\%$ of total biflavones by HPLC	Lipolytic, Vasokinetic, PDE inhibition
ESCIN β -SITOSTEROL PHYTOSOME®	Aesculushippocastanum L. - Seed	$\geq 32.0\%$ $\leq 40.0\%$ of escin by TLC	Capillary creating
FRANKINCENSE PHYTOSOME®	BoswelliaserrataRoxb. exColebr. - Resin	$\geq 25\%$ boswellic acids by HPLC	Mitigative
GINKGOSELECT® PHYTOSOME®	Ginkgo biloba L. - Leaf	$\geq 7.0\%$ of flavonglucosides, $\geq 0.8\%$ of bilobalide by HPLC	Cognition, roaming, increaser, vasokinetic
GREENSELECT® PHYTOSOME®	Camellia sinensis (L.) O. Kuntze - Young leaf	$\geq 19.0\%$ $\leq 25.0\%$ of polyphenols by HPLC	Antioxidant
HAWTHORN PHYTOSOME®	Crataegus spp. - Flowering top	$\geq 3.0\%$ of vitexin-2''-O-rhamnoside by HPLC	Cardiovascular
GINSELECT® PHYTOSOME®	Panax ginseng C.A. Meyer - Root	$\leq 40.0\%$ of ginseng typical constituents by gravimetry	Adaptogen, tonic, Skin tightener
LEUCOSELECT® PHYTOSOME®	Vitisvinifera L. - Seed	$\geq 25\%$ $\leq 30\%$ of pro-anthocyanidins by GPC	UV protectant, Antioxidant
MERIVA® TURMERIC PHYTOSOME®	Curcuma longa L. - Rhizome	$\geq 18.0\%$ $\leq 22.0\%$ of curcuminoids by HPLC	Arthrosis health, Anti-inflammatory
PROANTHOCYANIDIN A2 PHYTOSOME®	Aesculushippocastanum L. - Bark	$\geq 31.0\%$ $\leq 37.0\%$ of proanthocyanidin by HPLC	Skin tightener, UV protectant
RESVERATROL PHYTOSOME®	PolygonumcuspidatumSi eb. eZucc. - Rhizome	$\geq 30\%$ of resveratrol by HPLC	Anti-oksident, Anti-aging
SERICOSIDE PHYTOSOME®	Terminalia sericea Burch. ex. DC. - Root bark	$\geq 25.0\%$ of sericoside by HPLC	Anti-oksident, UV protectant, Mitigative, Redensifier
SILYMARIN PHYTOSOME®	Silybummarianum (L.) Gaertn. - Fruit	$\geq 15.0\%$ $\leq 20.0\%$ of flavolignans by HPLC	UV protectant, Anti-oksident, Liver protectant
SILIPHOS® SILYBIN PHYTOSOME®	Silybummarianum (L.) Gaertn. - Fruit	$\geq 29.7\%$ $\leq 36.3\%$ of silybin by HPLC	Liver protectant
TERPENES PHYTOSOME®	Ginkgo biloba L. - Leaf	$\geq 30.0\%$ of total ginkgo terpenes by HPLC	Anti-allergic, mitigative
VIRTIVA®	Ginkgo biloba L. - Leaf	$\geq 5.0\%$ of flavonglucoside phosphatidylserine by HPLC	Cognition increaser
VISNADEX® VISNADIN PHYTOSOME®	Ammivisnaga (L.) Lam. - Umbel without fruits	$\geq 10.0\%$ $\leq 13.0\%$ of visnadin by TLC	Vasokinetic

Already Phytosome Preparations

A lot of commercial product has marketed after formulation researches and clinical trials that used for personal care and food supplement. About twenty phytosome preparations (extracts or isolated active compounds) are showed in Table 1.

CONCLUSION

The phytosome complexes that had practised for cosmetics at first, have been carried out for serious therapies such as cardiovascular, anti-inflammatory, hepatoprotective and anticancer drug delivery system for last few decades (55). Phyto-phospholipid complexing technique became an important chance/hope for herbal medicines that can't demonstrate a remarkable effect at in vivo tests instead of good in vitro results.

With the phytosome technology, lipidic membrane penetration and drug plasma concentration is upgraded notably. On the other hand, sustained release profile is gained by decelerating eliminate of the drug molecules. Efficacy, quality and targetability of herbal drugs are improved through this new patented technology. Unfortunately, there is not enough stability studies about phytosome formulations. On the other hand, there are virginal herbal molecules which exists a potential to make phytosome formulations especially polyphenolics.

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