Section A-Review paper

REVIEW ON PHYTOSOMES: A NOVEL DRUG DELIVERY SYSTEM

Satyanarayan Sen[1], Reenu Yadav*[1], Jyotiram Sawale[1], Gaurav Jain[1], Sonam Kushwaha[1], Monam Kushwaha[1], Shipra[1], Jitendra Malviya[2]

Article History: **Received:** 12.02.2023 **Revised:** 20.03.2023 **Accepted:** 22.04.2023

Abstract

As dietary supplements for the homeostatic management of inflammation, toxins, malignancies, weight reduction, and other chronic or acute degenerative illnesses, plant-derived products or plant extracts are gaining more and more attention. However, issues with stability and bioavailability are common with these medications. After being isolated, plant compounds become unstable and may therefore be unable to penetrate the bio membrane. The phytosome method significantly decreases these tasks. The phytosome or herbosome approach improves the lipophilicity of hydrophilic phytoconstituents sufficiently to pass biological membranes and increases the hydrophilicity of highly lipophilic drugs, making them appropriate for drug delivery. It is asserted that phytosome promotes the oral and topically applied absorption of "conventional herbal extracts" or isolated active ingredients. Due to the high demand for and use of plants or medications based on herbs, phytosomes are becoming more and more popular as prospective drug delivery systems. This study emphasises phospholipid chemistry, production, characterization, structural verification, benefits, contemporary research, & their use to increase the bioavailability of active herbal phytoconstituents. It also discusses the special feature of phospholipids in medication delivery. Prospectuses for novel drug regimens can suggest fresh avenues and boundless frontiers using phytosome technology.

Keywords: Phytosome, Novel drug delivery system, Review, Application

[1] IES Institute of Pharmacy, IES University, Bhopal

[2]Department of Life Sciences and Biological Sciences, IES University, Bhopal

*Corresponding Author
* yadavreenu@gmail.com
*

DOI: 10.31838/ecb/2023.12.s2.2272023.26/04/2023

Introduction:

The limitations of the conventional drug delivery methods are addressed by the innovative drug delivery system, which is a novel method of drug administration. Our nation possesses a wealth of Ayurvedic knowledge, but only recently has its full potential been recognised. Any herbal medication's efficacy depends on the therapeutically active component being delivered at an effective dosage. When given topically or orally, their bioavailability is severely constrained. The clinically and pharmacologically tested bioactive group of substances, such as alkaloids, flavonoids, and polyphenolic components, are utilised at random for the efficient management of various illnesses, either in their natural state or as part of formulations. It is true that developing a phytoformulation requires a lot of work because there are problems with the solubility and compatibility of the active ingredients with other formulation factors.[1] Flavonoids, tannins, and other water-soluble phytoconstituents, however, are poorly absorbed either because of their large molecular size, which prevents passive diffusion, or because of their poor lipid solubility, which severely restricts their ability to pass across the lipid-rich biological membranes, leading to poor bioavailability. [2]

The bioavailability can be increased by using several cutting-edge delivery systems, including as liposomes, niosomes, and phytosomes, which can accelerate the rate of release and increase their ability to pass lipid biomembranes. The potency and acceptance of phytosome among vesicular systems are substantially higher. Phytosomes are brand-new medication delivery devices that combine phospholipids with water-soluble herbal components and resemble liposomes in structure. They are micelles that have bioactive substances obtained from plants that conjugate the proteins on their surface. Due to their improved penetration and retention abilities, phytosomes—which fall within the nanometric size range of 100–1,200 nm—are capable of efficiently targeting tumour cells. Standardized plant extract or its bioactive components are coupled to phospholipids, specifically phosphatidylcholine, to create phytosomes, which are then enclosed in a lipid-compatible complex. [3-6]

Both "Phyto" and "some" are Greek words for plants. The term "herbosomes" is sometimes used. This is a brand- new, patented process that produces lipid compatible molecular complexes by complexing standardised plant extracts or water-soluble phytoconstituents with phospholipids. This significantly increases absorption and bioavailability. The phospholipids used are phosphatidylcholine, phosphatidylserine, phosphatidylethanolamine, and phosphatidylinositol, but phosphatidylcholine is the most commonly used one due to its proven therapeutic value for treating liver diseases like alcoholic steatosis, drug-induced liver damage, and hepatitis. Additionally, phospholipids are used as natural digestion aids and as transporters for nutrients that are water- and fat-soluble. Phytosomes can easily pass through the stratum corneum layer of the epidermis and the lipophilic pathway of enterohepatic cell membranes. [7]

Principle behind construction of phytosomes

A bifunctional substance, phosphatidylcholine (or phosphatidylserine) has two functions. Choline (serine) is a hydrophilic compound, whereas the phosphatidyl moiety is lipophilic. The phospholipid's twofold solubility makes it a powerful emulsifier. As a result, the phosphatidylcholine molecule's choline head bonds

to these substances, and the lipid-soluble phosphatidyl part, which includes the body and tail, surrounds the choline-bound material. As a result, the phytoconstituents create the phyto-phospholipid complex, a lipid compatible molecular compound with phospholipids. [8-11]

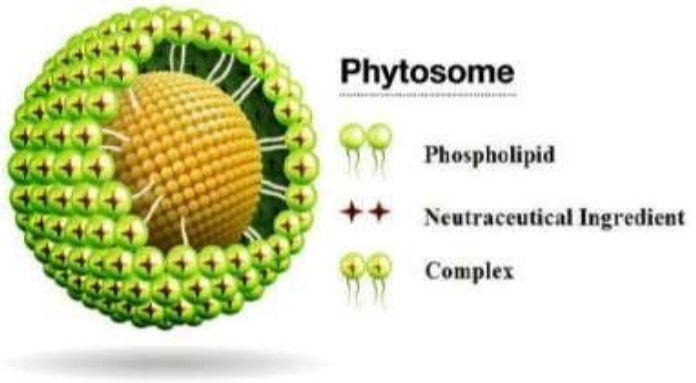

Image Source-Semantic scholar

Difference between liposome & phytosomes

Liposome	Phytosomes
A liposome is a collection of many phospholipid molecules that has the ability to surround other phytoactive molecules without directly connecting to them.	A group of molecules that are linked together form a phytosome.
In liposomes, the cavity's middle is where the active ingredients are dissolved. without a chance for molecular interaction between the surrounding lipid and hydrophilic substance	The phytosome complex can be likened to a crucial component of the lipid membrane. where the polar head of a phospholipid interacts via hydrogen bonding with the polar functions of a lipophilic guest (i.e. phosphate and ammonium groups). forming a distinctive pattern that can be identified using spectroscopy
No chemical bonds are created in liposomes. The water-soluble chemical is surrounded by phosphtidylcholine molecules. The water-soluble substance may be surrounded by hundreds or even thousands of phosphtidylcholine molecules.	Depending on the chemicals complexed, the phosphatidylcholine and plant components really create a 1:1 or a 2:1 molecular complex during phytosome processing. comprised of chemical bonds. They therefore showed greater bioavailability and better absorption.
Water or a buffer solution is necessary for the formation of the liposomal drug complex.	Acetone, Dioxane, Metyhlenechloride, Hexane, and other solvents with a low dielectric constant, among others, are used by phytosomes in their reaction.

[12-14]

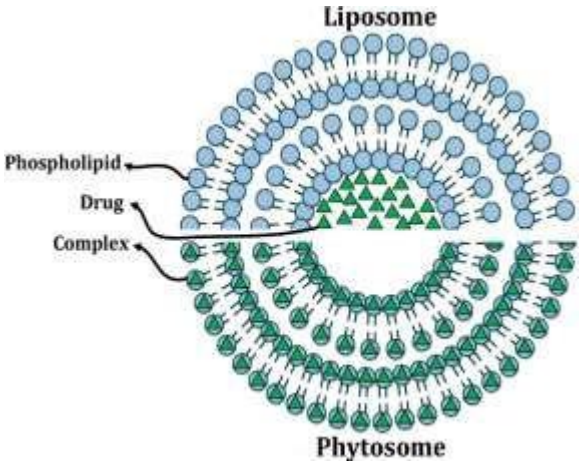

Image source-Semantic scholar

Properties of phytosome

1. Physiochemical properties

- It has been demonstrated using spectroscopic data that the primary interaction between phospholipids and their substrate is caused by the creation of hydrogen bonds between the polar head of phospholipids (phosphate and ammonium groups) and the polar functionality of the substrate. [15]
- When exposed to water, phytosomes take on a micellar shape and produce structures resembling liposomes. [16]
- The active ingredient in phytosomes is fixed to the polar head of phospholipids and turns into a fundamental component of the membrane. For instance, the phosphate ion on the phosphatidylcholine moiety forms an H-bond with the phenolic hydroxyl ends of the flavone's moiety in the case of the catechindistearoylphosphatidylcholine complex.[17]
- Long aliphatic chains are wrapped around the active principle to produce a lipophilic envelope, as seen by the H1 NMR and C13 NMR data, which show that the fatty chain yields unchanged signals both in free phospholipid and in the complex [18].
- The complexes are frequently insoluble in water, mildly soluble in lipids, and easily soluble in aprotic solvents. They are also generally unstable in alcohol. However, upon complexation with phospholipid, the phytosomes of some lipophilic phytoconstituents, such as curcumin, have demonstrated an increase in water solubility. [19]

Biological properties

• In comparison to traditional herbal extract, phytosome is a more advanced form of herbal product that is more absorbed, used, and generates better effects. Several pharmacokinetics and pharmacodynamic experiments on experimental animal models and human volunteers have been used to explain and verify the improved bioavailability of the phytosome over the non-complexed botanical derivatives. [20]

Different methods of Preparation of phytosome

1. Rotatory evaporation method

A specific weight of herbal extract and phospholipids were combined in a glass round-bottom container with 30 ml of water-miscible organic solvent, such as acetone, and stirred for two hours at a temperature below 50°C in a rota evaporator. After continuous swirling with a stirrer, a thin coating can be produced that can be treated with an antisolvent like n-hexane. Precipitate of phytosomes so obtained can be maintained in amber tinted glass container at controlled temperature with prescribed humidity. [21]

2. Solvent evaporation technique

Alcoholic or organic solvents are typically used as the reaction medium to create the complex of plant extracts or particular active principles with dietary phospholipids. The medication and the phospholipids are placed in the same flask that contains an appropriate solvent system, such as tetrahydrofuran or ethanol, in the more popular solvent evaporation approach. To get the highest yield and drug trapping, the reaction must be conducted at a suitable fixed temperature for a predetermined amount of time. By using a mechanical dispersion orientated liquid anti-solvent precipitation approach, Sikarwar et al. created a marsupsin-phospholipid complex. To do this, they dissolved marsupsin in double-distilled water and soy lecithin in diethyl ether using a sonicator. The phospholipid solution was then sonicated while the drug solution was added drop by drop. When the finished formulation was analysed, it revealed a 44% marsupsin entrapment with a 20% cumulative drug release. [22]

3. Anti-solvent precipitation

A precise quantity of herbal extract and soy lecithin were added to a 100 ml round bottom flask, and the mixture was refluxed for two hours at a temperature of no higher than 60 oC with 20 ml of dichloromethane. In 5–10 ml, the mixture is concentrated. To obtain the precipitate, hexane (20 ml) was carefully added with constant stirring. The precipitate was then collected, filtered, and overnight stored in vacuum desiccators.

The synthesis of the andrographolide phyto-phospholipid complex utilising dichloromethane as the reaction medium and n-hexane as the final precipitation anti-solvent is the subject of research based on a patented similar approach. Following the solution's evaporation, the leftover material is typically dried. Vacuum-based. [23-24]

4. Dispersion method

This method involves dissolving phospholipid in a suitable solvent and adding the active component drop by drop while sonicating the solution. They also detailed the process for making curcumin phytosomes. The process of making curcumin phospholipid complexes involves stirring and adding the phospholipid to an ethanol solution of an HCl extract of the turmeric rhizome. By using nonsolvent precipitation, lyophilization, spray reagent, or vacuum drying, the produced complex can be separated. [25]

Characterization of Phytosomes

The physical size, membrane permeability, proportion of entrapped solutes, and chemical composition of the preparation materials are only a few of the variables that are crucial in defining how phytosomes behave in physical and biological systems. These characterisation methods are used to describe the physical characteristics of phytosomes.

1. Entrapment efficiency

Centrifugation can be used to determine how well a herbal extract is entrapped. You can centrifuge a solution containing weighed amounts of phytophospholipid complexes equivalent to the amount of herbal extract that is capsuled for 30 minutes at 5000 rpm. One to two hours are given for stirred contents to stay undisturbed before the absorbance of supernatant liquid obtained through decantation is calculated using UV or HPLC. [26-27].

The drug entrapment percentage (%) is calculated as: Drug entrapment (%) = Actual amount determined/Theoretical amount present.

1. Vesicle stability

Analyzing the evolution of vesicle size and structure provides insight into the stability of vesicles. DLS measures the mean size, and TEM tracks structural changes. [28]

2. In vitro drug release

At room temperature, the dialysis method can be used to monitor drug release. An aliquot of each formulation (0.1 mL) is placed in a dialysis tube (molecular weight cutoff dialysis membrane: 12,000–14,000 Mw), which is tightly sealed, after the freeze-dried formulation has been reconstituted in distilled water/PBS. To maintain sink condition, the tube is submerged in 200 mL of PBS (pH 7.4) release medium and swirled at 300 rpm on a magnetic stirrer. For 24 hours, samples (0.5 mL) are collected at regular intervals and refilled with an equivalent volume of new medium. After the required dilution with acetonitrile, the drug concentration is measured by HPLC or UV without further processing. [29]

3. Differential scanning electron microscopy

Drug phospholipid complex, drug polyphenolic extract, drug phosphatidylcholine, a physical mixture of drug extract and phosphatidylcholine, and drug were all placed in an aluminium cell and heated at a rate of 50–250 °C/min from 0 to 400 °C in a nitrogen atmosphere. [30-31]

4. NMR

1H-NMR - The NMR spectrum is used to calculate the amount of phosphatidylcholine that forms a compound with the active ingredients. The 1H-NMR signal clearly changes in nonpolar liquids, starting with the atoms involved in the complex formation. Proton signals are amplified in range. In contrast to the singlet correlating to the N-(CH3)3 of choline, which results in an upfield shift, signals in phospholipids are broadened.

13C-NMR -When recorded in C6D6 at room temperature for the 13C-NMR of phytosomes, none of the carbons from the phytoconstituents are visible. While certain signals are shifted and much of the resonance of the fatty acids chains

maintains its original sharp lines, the signals equivalent to the choline and glycerol sections are expanded. [32-34]

Applications of phytosomes

- In a 2009 study by Francesco et al., obese patients (n=100) of both sexes on a hypocaloric diet were evaluated with a recently developed oral formulation in the form of coated tablets (Monoselect Camellia®) (MonCam) containing highly accessible green tea extract (GreenSelect® Phytosome). While the other 50 individuals merely followed the hypocaloric diet, 50 were assigned to the green tea extract and hypocaloric diet. After 90 days of treatment, the group consuming the herbal extract experienced considerable weight loss and a decreased body mass index (BMI) (14 kg reduction in the green tea group compared to a 5 kg loss in the diet-only group); the waistline was only reduced in male patients. In addition to the impact on weight and BMI, both groups' biochemical indicators (growth hormone, insulin-like growth factor-1, LDL, HDL, and total cholesterol, triglycerides, insulin, and cortisol) improved. Leptin was decreased in patients taking MonCam but was not examined in the diet-only group. MonCam appears to be a safe and efficient weight reduction solution when taking into account the exceptional safety profile of the product and the complete absence of adverse effects recorded during and after the study. [35]
- Silymarin phytosome, a standardised extract from the seeds of S. marianum, was the subject of several experiments by Grange et al. in 1999. They discovered that it might shield the foetus from ethanol consumed by the mother. [29] The oligomeric polyphenols (grape proanthocyanidins or procyanidins from grape seed extract, Vitis vinifera) in grape seed phytosomes are complexed with phospholipids and have different molecular sizes. The main characteristics of grape seed procyanidin flavonoids include an increase in total antioxidant capacity and stimulation of physiological antioxidant defences in plasma, protection against heart damage caused by ischemia/reperfusion, and protective effects against atherosclerosis, providing significant protection for the cardiovascular system and other organs through a network of mechanisms that go beyond their significant antioxidant potency. [36]
- In two distinct investigations, Maiti et al. created phytosomes of the flavonoids curcumin (from the turmeric plant, Curcuma longa linn) and naringenin (from the grape plant, Vitis vinifera). In every dose level examined, complex had much more antioxidant activity than pure curcumin. In the other study, the naringenin phytosome produced better antioxidant activity than the free compound with a longer half-life, which may be related to a slowing down of the molecule's quick removal from the body. [37-38]
- Yanyu et al. synthesised a phytosome of silymarin and investigated its

pharmacokinetics in rats. Due to the sizable improvement in the silybin-phospholipid combination's lipophilic property, which resulted in an improved biological effect of silybin, the bioavailability of silybin in rats was significantly raised after oral administration of the complex. According to Tedesco et al., silymarin phytosome has superior anti- hepatotoxic action to silymarin alone and can be extremely effective in preventing the negative effects of aflatoxin B1 on the performance of broiler chicks. [39]

-
- Giorgi et al. examined in 180 patients with carpal tunnel syndrome the clinical efficacy of oral supplementation with a combination product combining alpha-lipoic acid, curcumin phytosome, and B group vitamins (CTS). High levels of patient satisfaction and strong adherence to the regimen imply potential clinical utility of this supplementation prior to and following surgery in CTS patients scheduled for surgical decompression of the median nerve. [40]

Other diverse applications

1. Phytosomes in Diabetes

Rathee and Kamboj used a three stage, three factor Box-Behnken design to create the anti-diabetic phytosomes that contained extracts of *Mamordicabalsamina*, *Citrullus colocynthi*s, and *Mamordicadioica*. Entrapment efficiency (%EE), particle size, drug content, zeta potential, and in vitro dissolution were used to describe the synthetic phytosomes. The phytosomes' spherical, enclosed structure and high stability are shown by TEM examination. The anti-diabetic effect of prepared phytosomes was comparable to metformin at low doses. [41]

The antihyperlipidemic and anti-diabetic activity of the *Casuarina equisetifolia* extract loaded phytosomes was tested in wistar rats by Rani and colleagues. The antisolvent precipitation method was used to create the phytosomes. The measured values for zeta potential, mean particle size, span value, and %EE were 82.43 1.65%, 295 0.53 nm, 0.34 0.14, and 19.35 mV, respectively. The results of in vitro drug release investigations showed that the Korsmeyer-Peppas model is followed by drug release. When compared to a crude extract of a phyto-active medication, the authors' findings revealed that synthetic phytosomes have improved antihyperlipidemic and antidiabetic potential. [42]

2. Phytosomes in wound healing

To assess the *Ginkgo biloba*phytosomes' antioxidant activity in rat brains, Naik and colleagues created them. Wistar rats were given prepared phytosomes, and sodium nitrile was used to cause chemical

hypoxia. The striatum, hippocampus, cerebral cortex, and cerebellum were then separated and homogenised after

the animals were sacrificed. In the supernatant, measurements of superoxide dismutase, glutathione peroxidase, glutathione reductase, and catalase were made. When compared to those who received sodium nitrile, phytosome therapy improved the activities of superoxide dismutase, glutathione peroxidase, glutathione reductase, and catalase in all regions of the brain. [43]

3. Phytosoomes in cancer treatment

In order to supplement gemcitabine's safety and effectiveness in treating pancreatic cancer, Pastorelli*et al*. created the phytosome complex of curcumin. In this trial, the subjects received curcumin- phytosome complex together with Gemcitabine. Response rate served as the study's primary goal, with tolerability, progression-free survival, and quality of life serving as secondary endpoints. The authors recorded a response rate of 27.3% and 34.1% of cases with stable disease, totalling a 61.4% disease control rate.10.2 months and 8.4 months, respectively, were spent in overall and free survival. After the first round of treatment, CD40L levels improved and were associated with a poorer prognosis. The quality of life did not significantly change following therapy, according to the authors. Finally, authors concluded that gemcitabine and phytosomal complex of curcumin together offered improved efficacy and safety in the treatment of advanced pancreatic cancer. [44]

4. Phytosomes in brain delivery

The phytosomes and liposomes containing the aqueous extract of *A.muricata* were created by Mancini *et al.*to administer phenolic substances. To support the extract from *A.muricata* from GIT biotransformation and to improve its penetration via the blood–brain barrier, liposomes and phytosomes containing peptide ligand were created. Fluorescence, spectrophotometric, DLS, and HPLC techniques were used to assess the prepared nanoformulations. Utilizing an in vitro trans well model of the blood brain barrier made up of human immortalised microvascular endothelial cells, permeability and cytotoxicity assessment were explored. Despite liposomes being seen as more stable and demonstrating gradual extract release over time, the results revealed that phytosomes had a more significant ability to encapsulate aqueous extract. Comparing phytosomes to liposomes generally resulted in lower toxicity in human immortalised microvascular endothelial cells, and penetrability across the cell monolayer was also improved. [45]

5. Phytosome in liver disorders

The phytosomal curcumin was created by Tung and colleagues, who also examined its hepatoprotective potential against paracetamol-induced liver injury in mice. Rats received both pure and phytosomal curcumin

for seven days. Animals were euthanized after the treatments, and liver homogenate was used to estimate hepatic antioxidants, liver function indicators, and lipid peroxidation. Results found by the authors showed that phytosomal curcumin, as opposed to pure curcumin, has a powerful hepatoprotective effect. Treatment with phytosomal curcumin significantly decreased paracetamol-induced liver damage in mice by lowering the degree of lipid peroxidation and increasing the antioxidant activity of catalase, superoxide dismutase, and glutathione peroxidase. [46]

Conclusion

Herbal medicines contain a variety of phytoconstituents, particularly the flavonoidal and terpenoidal fractions, which have a variety of uses. Its application is restricted by the poor bioavailability and poor absorption linked to the polar phytoconstituents. By creating a suitable medication delivery system, these obstacles can be overcome. In comparison to other phospholipid-based drug delivery systems, phytosome are one of the phospholipid-based drug delivery systems with a better absorption and stability profile. This article aims to provide a succinct overview of phytosomes as a delivery method. Phytosomes are a more sophisticated type of plant extract that is more readily absorbed than traditional herbal extracts. For this kind of new formulation, the characterisation approaches and analytical tools are well established. For novel phytosome formulations, procedures, and applications, numerous patents have previously been approved. Initially employed in cosmetics, phytosome complexes are now widely used in treatments for cancer, heart disease, inflammation, tumours, and other diseases that affect the liver. With the help of doctors and other researchers, phytosomes' potential for therapeutic applications has a promising future. Phytosomes has re-explained the importance of herbals in contemporary medication targeting approaches with this newly developed formulation tool.

References

1. Jain N, Gupta P, Thakur N, Jain R, Banweer J, Jain KDet al.IntJ PharmSci Drug Res.2010;2(4):224-8.
2. Manach C, Scalbert A, Morand C, Rémésy C, Jiménez L. Polyphenols: foodsources and bioavailability. Am J Clin Nutr.2004;79(5):727-47. doi: 10.1093/ajcn/79.5.727, PMID 15113710.
3. SahaS, SarmaA, SaikiaP, ChakrabartyT. Phytosome: A briefoverview. Scholars Acad. JPharmacol. 2013;2(1):12-20.
4. Semalty A, Semalty M, Rawat MS, Franceschi F. Supramolecular phospholipids-Polyphenolics interactions: thePhytosome® strategy to improve the bioavailability of phytochemicals. Fitoterapia. 2010;81(5):306-14. doi: 10.1016/j.fitote.2009.11.001, PMID 19919847.
5. Kalita B, Das KM, Sharma KA.Novel phytosome formulation making herbal extract more effective.J Pharm Technol.2013;6(11):1295.
6. Bombardelli E, Spelta M.Phospholipid-polyphenol complexes: A new concept in skin care ingredients, Cosm and Toil.1991;106:69-76.
7. Jadhav IA, Wadhave AA, Arsul VA, Sawarkar HS.Phytosome a novel approach in herbal drug.Int J Pharm Anal.2014;2(5):478.
8. Bombardelli E.Phytosome: New cosmeticdeliverysystem. Boll Chim Farm.1991;130(11):431-38. PMID 1809296.
9. Bombardelli E, Spelta M. Phospholipid-polyphenolcomplexes: A newconcept in skincareingredients. CosmToil. 1991;106:69-76.
10. Murray D. Phytosomes- increase the absorption of herbalextract[online];2008[citedSep282008]. Available from.Available from: http://www.doctormurray.com/articles/silybin.htm.
11. Phytosomes.A technicalrevolution in phytomedicine[online];2010[citedMar222010].
12. Phytosomes.A technicalrevolution in phytomedicine[online];2010[citedMar222010].
13. Jose MM, Bombardelli E.Pharmaceutical Composition Containing Flavanolignans and Phospholipida Active Principles. U.S.Patent EPO 2090371987.
14. Bombardelli E, Mustich G. Bilobalide phospholipidcomplex, theiruses and formulationcontainingthem. U.S.PatentEPO275005;1991.
15. Tripathy S, PatelDK, Barob L, NairaSK. A review on phytosomes, their characterization, advancement and potential for transdermal application.J Drug Deliv Ther. 2013;3(3):147-52. doi: 10.22270/jddt.v3i3.508.
16. 18, Patel A, Tanwar Y, Rakesh S, Patel P. Phytosome: phytolipid drugdeliverysystem for improvingbioavailability of herbaldrug. J PharmSci Bio SciRes. 2013;3:51-7.
17. 19. JainNK2005.Liposomes as drug carriers, controlled and novel drug delivery.1sted.CBS publisher321-6.

18.Dayan N, Touitou E. Carriers for skin delivery of trihexyphenidyl HCl: ethosomes vs. liposomes.Biomaterials. 2000;21(18):1879-85. doi: 10.1016/s0142-9612(00)00063-6, PMID 10919691.

19.21, Maffei Facino R, Carini M, Aldini G, Bombardelli E, Morazzoni P, Morelli R. Free radicals scavenging action and anti-enzyme activities of procyanidines from Vitis vinifera. A mechanism for their capillary protective action. Arzneimittel-Forschung. 1994;44(5):592-601. PMID 8024628.

20. Gao L, Liu G, Wang X, Liu F, Xu Y, Ma J. Preparation of achemicallys table quercetin formulation using nanosuspension technology.IntJ Pharm. 2011;1(2):231-27.

21. Singh RP, Parpani S, Narke R, Chavan R. Phytosome: recent advance research for novel drug delivery system. Asian J Pharm Res Dev.2014;2(3):15-29.

22. SikarwarMS, SharmaS, JainAK, Parial SD.Preparation, characterization and evaluation of marsupsin–phospholipid complex. AAPS PharmSciTech.2008;9(1):129-37. doi: 10.1208/s12249-007-9020-x, PMID 18446473.

23.MuruganV, MukherjeeK, MaitiK, MukherjeePK.Enhanced oral bioavailability and antioxidant profile of ellagic acid by phospholipids. J Agric FoodChem.2009;57(11):4559-65. doi: 10.1021/jf8037105, PMID 19449806.

24. FranceschiF, GioriA.Phospholipid complexes of olive fruits or leaves extracts having improved bioavailability. GooglePatents2007.

25. Vangapelli S,Laxmaiah C, Sankar G. B,P.Naveen ,B. ChiranjeebS.Ganda, Phytosomy system for improvement of bioavailability of herbal medicine : A Novel drug delievery, International J. of Pharmaceutical Research & Development2011;3(6):175-84.

26. Varde N, Mehta N, Thakor N, Shah V, Upadhyay U. Phytosomes: A potential phospholipid nanoparticulate carrier for the bioavailability enhancement of herbal extracts. Int JCompreh Pharm.2012;10:1-7.

27. Maghraby GMM. E, WilliamsAC, BarryBW: Oestrodiol Skin Delivery from Ultra deformable liposomes: refinement of Surfactant Concentration.Int J Pharm.2000;196:63-74.

28. Dr.ShahMB, ShahAJ, ShahR. An overviewofethosomeasadvancedherbaldrugdeliverysystem. IntJ Res Rev Pharm ApplSci;2(1):1-14.

29. Kumari P, Singh N, Cheriyan BP, Neelam P.A Novalapproachforphytomedicine. IntJ InstPharm Life Sci.2011;1(2):89-100.

30. Saumya PD.Phytosome: A novel entity in herbal delivery system: a review. IJPRD.2010;2:153-64. 31.PatelaJagruti PR, KapilK, NiravP.An overview of phytosomes as an advanced herbal drug delivery system. An overview of phytosomes/Asian.J PharmSci.2009;4(6):363-71.

32. Dwivedi C, Kesharwani S, Tiwari SP, Satapathy T, Roy A. Phytosomes: A promising system of herbal drug delivery.World J Pharm Res.2014;3(2):3443-61.

33. AniketA, KumariP, KumariSS, Khurana L, Rathore KS. Phytosomes: A promising system of herbal drug delivery. Indian J PharmPharmacol.2015;2(2):105-12.

34. Suryawanshi JA.Phytosomes: A promising system of herbal drug delivery.JMedGenetGenom.2011;3(6):109-14.

35.Di Pierro F, Menghi AB, Barreca A, Lucarelli M, Calandrelli A. Green selectphytosome as an adjunct to a low-caloriediet for treatment of obesity: A clinicaltrial. Altern Med Rev.2009;14(2):154-60. PMID 19594224.

36.Schwitters B, Masquelier J. OPC in practice: Biflavanals and theirapplication. Alfa.Rome, Italy: Omega1993.

37.Maiti K, Mukherjee K, Gantait A, Saha BP, Mukherjee PK.Enhanced therapeuticpotential of naringenin-phospholipidcomplex in rats.J Pharm Pharmacol.2006;58(9):1227-33. 48. doi: 10.1211/jpp.58.9.0009, PMID 16945181.

38. Maiti K, Mukherjee K, Gantait A, Saha BP, Mukherjee PK.Curcumin-phospholipidcomplex: preparation, therapeuticevaluation and pharmacokineticsstudy in rats.Int J Pharm.2007;330(1-2):155-63. doi: 10.1016/j.ijpharm.2006.09.025, PMID 17112692.
39. Tedesco D, Steidler S, Galletti S, Tameni M, Sonzogni O, Ravarotto L.Efficacy of silymarin- phospholipidcomplex in reducing the toxicity of aflatoxin b1 in broilerchicks.Poult Sci.2004;83(11):1839-43. doi: 10.1093/ps/83.11.1839, PMID 15554059.
40. Giorgio P, Paola B, Veronica P, Chaira N. Clinical usefulness of oral supplementation with alpha-lipoic acid, curcumin phytosome&Bgroup vitamins inpatient with carpel tunnel syndrome undergoing surgical treatment. EvidBasedComplement AlternatMed:1-7.
41. RatheeS, KambojA.Optimization and development of antidiabetic phytosomes by the Box–Behnken design. J Liposome Res. 2018;28(2):161-72. doi: 10.1080/08982104.2017.1311913, PMID 28337938.
42. RaniA, KumarS, KharRK.Casuarina equisetifoliaextractloadedphytosomes: optimization, characterization and in vivo evaluation of antidiabetic and antihyperlipidemicactivities in Wistar rats. Drug DelivLett. 2019;9(2):116-33. doi: 10.2174/2210303109666190118162157.
43. NaikSR, PilgaonkarVW, PandaVS.Evaluation of antioxidant activity of Ginkgo biloba phytosomes in rat brain. PhytotherRes. 2006;20(11):1013-6. doi: 10.1002/ptr.1976, PMID 16909446.
44. PastorelliD, FabricioASC, GiovanisP, D'IppolitoS, FiduccíaP, SoldàCet al.Phytosome complex of curcumin as complementary therapy of advanced pancreatic cancer improves safety and efficacy of gemcitabine: results of a prospective phase II trial. PharmacolRes. 2018;132:72-9. doi: 10.1016/j.phrs.2018.03.013, PMID 29614381.
45. ManciniS, NardoL, GregoriM, RibeiroI, MantegazzaF, Delerue-MatosCet al.Functionalized liposomes and phytosomes loading Annona muricataL. aqueous extract: potential nanoshuttles for brain-delivery of phenolic compounds. Phytomedicine. 2018;42:233-44. doi: 10.1016/j.phymed.2018.03.053, PMID 29655691.
46. TungBT, HaiNT, SonPK.Hepatoprotective effect of Phytosome curcumin against paracetamol-induced liver toxicity in mice. BrazJPharmSci. 2017;53(1):e16136. doi: 10.1590/s2175-97902017000116136.