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A REVIEW ON PHYTOSOME

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ABSTRACT

Plants are referred to as "phyto," and "some" denotes a covering for a structure. Generally, one or two moles of phospholipid and polyphenolic phytoconstituents are reacted to create a phytosome. "Some" refers to a cell, while "Phyto" implies a plant. It is also called as herbosomes, a novel, patented technology in which phospholipids and standardised plant extracts or water-soluble phytoconstituents combine to form lipid-compatible molecular complexes that significantly improve absorption and bioavailability. This review article discusses the physicochemical, pharmacological, and structural characteristics of phytosomes. several herbal medications for which phytosomes have been utilised as a carrier, commercial availability, and applications are included in this review.Pharmacological potential of liposomal and conventional drug delivery systems is contrasted with that of phytosomes. Examined is the scientific relevance of a list of significant phytosomes patented technologies of different plant extracts that are sold commercially. Many items in the market utilizes phytosome vascular drug delivery system that includes Ginkgo biloba, Silybum marianum, and Camellia sinensis, feature phytosomal drug delivery systems.

➢ KEYWORDS

Phytosomes: Plant,phospholipid,Novel drug delivery system,Bioavalibility.

❖ INTRODUCTION

The majority of plant elements that are physiologically active are polar or water soluble; nevertheless, limited absorption leads to restricted utilisation of these chemicals, ultimately lowering their bioavailability. Herbal products need to have the right balance between hydrophilic (for absorption into gastrointestinal tract fluid) and lipophilic (to pass lipid biomembrane balance) in order to increase bioavailability [1]. The pharmacological action and eventual therapeutic utility of several active ingredients found in medicinal plants, such as flavonoids, tannins, and terpenoids, are restricted due to their limited oral absorption. There are two reasons why active phytochemicals are not well absorbed: The multi-ring architectures of polyphenols make them too big to be absorbed passively or non-actively, while the restricted water or lipid solubility of active chemicals makes them incapable of passing tailored drug delivery, which delivers the active ingredient straight to the site of action, and such a delivery method could provide prolonged and targeted drug release, allowing pharmacological passage across the outer membrane of gastrointestinal cells[2]. At smaller doses, novel medication delivery methods like effect might be realised. Herbal therapy has advanced earlier in order to treat illnes herbosomes.[3] This is a novel, patented technology that produces lipid-compatible molecular complexes by complexing phospholipids with standardised plant extracts or water-soluble phytoconstituents. This greatly increases absorption and bioavailability. Among the phospholipids used are phosphatidylcholine, phosphatidylserine, phosphatidylethanolamine, and phosphatidylinositol; however, phosphatidylcholine is most frequently utilised due to its potential therapeutic benefit in cases of alcoholic liver disease and liver illness. The words "some" and "phyto" refer to plants and cells, respectively. It's also called steatosis, hepatitis, and drug-induced liver damage. Additionally, phospholipids are used as natural digestive aids and as carriers of nutrients that are both water and fat miscible. Phytosomes are easily able to pass through the stratum

corneum layer of skin and the lipophilic route of enterohepatic cell membranes [4]. ses in people with less adverse consequences

Because of their efficiency both chemically and physically, phytosomes are produced when particular plant components interact with phospholipids, either natural or synthetic, in the presence of an appropriate solvent. Phytosomes have become a promising drug delivery method because they enhance the therapeutic efficacy, efficiency, and targetability of active ingredients. Because of its targeted delivery property, phytosome technology has improved the in-vivo performance of herbal extracts. Additionally, because of its nano size, large hydrophilic phytoconstituents' poor permeability across biological membranes has been overcome, and its improved pharmacokinetic profile and increased rate of absorption and dissolution correlate to better therapeutic effect at lower doses, making it useful in the pharmaceutical, nutraceutical, and cosmetic industries [5].

❖ HISTORY

The latest research indicates that phytosome technology is a novel approach to enhance the absorption and bioavailability of plant extracts while reducing the dose level. Numerous studies are being conducted in this area. Ezio Bombardelli and Gian F. Patriot of Italy's Indena Inc., a well-known manufacturer of nutraceutical components, created the phytosome process in 1989. They found that compared to normal silybin, the silybin phytosome complex showed a noticeably higher absorption rate.

Schandalik [6] examined the hepatoprotective effects of silymarin on nine human volunteers and found that the phytosomal form of silybin passed through the liver four times more quickly. A similar study was carried out on 232 patients with chronic hepatitis. Additionally, he asserted that silymarin phytosomes have a higher bioavailability than their uncomplex form [7]. Researchers found that the silymarin phytosomal form of the compound had superior fetoprotectant action (increased pup birth weight and lower neonate mortality rate) in a series of studies on silymarin phytosomes in ethanol-induced foetal alcohol syndrome [8].

❖ PROPERTIES OF PHYTOSOME

1.Physicochemical properties

The phytosome vesicle after the phyto-phospholipid complex forms is 50 nm to several hundred nm in size, based on transmission electron microscopy or photon correlation spectroscopy data. Phytosomes have a spherical shape, rough surface morphology, and strong flowability, as shown by their surface features. Particle size is important when administering medications transdermally. Because of the formulation's high lipid content, agglomerates formed more readily, producing larger particles [9].

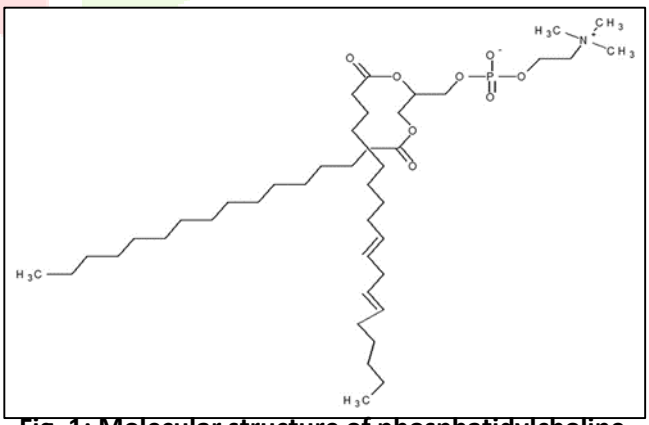


Fig. 1: Molecular structure of phosphatidylcholine

These complexes are produced when phospholipids and herbal extracts or molecules react in a stoichiometric ratio of 1:1 or 2:1. The stability of the phytosome is increased by hydrogen bonds that form between the polar heads of phospholipids (PO4 & NH3) and the polar section of the substrate [10]. . Phytosomes are soluble in non-polar liquids and have a medium solubility in lipids ("Phyto-lipid delivery technique"). When they come into contact with a polar solvent (water), they take on a micellar form (liposomial-like structure00.[11]

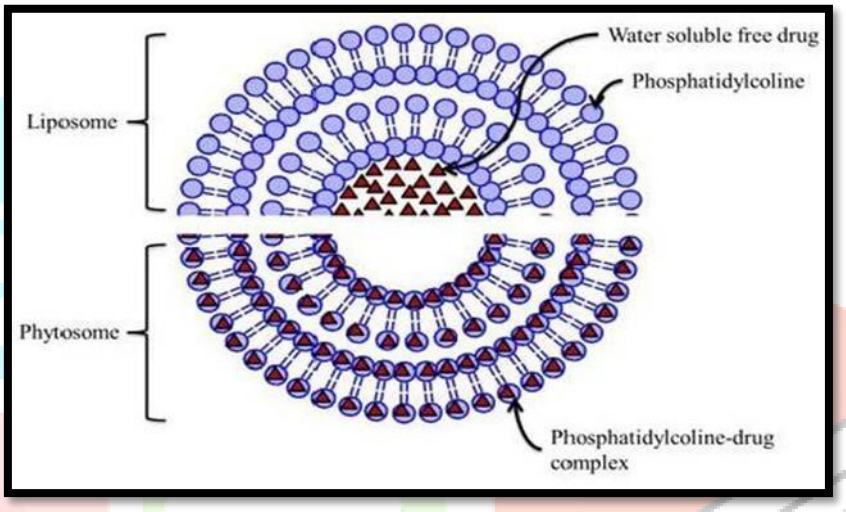
2.Pharmacological Properties

Pharmacokinetic and pharmacodynamic studies in humans and experimental animals have demonstrated the biological behaviour of phytosomes, including improved absorption and utilisation that results in better bioavailability. Dihydromyricetin phytosomes have an enhanced pharmacokinetic profile with decreased clearance rate and volume of distribution, as well as increased bioavailability because of higher Cmax and AUC values [12].

3.Biological characteristics

Pharmacokinetic studies and pharmacodynamic testing in both human subjects and experimental animals have shown that phytosomes are novel complexes that are better absorbed and utilised than conventional herbal extracts or non-complexed extracts, producing more bioavailability and better results.

These days, liposomes are mostly used for cosmetic applications and can entrap several hundred phospholipid molecules. Rather, the phytosomes entail the interplay between one to four phospholipid molecules and the chemically anchored phytoconstituents. In terms of membrane stability and permeability, numerous studies have demonstrated that phytosomes are a superior substitute for liposomes [13].



Figures 2 Illustration on comparative account of phytosomes and liposomes

- **STRUCTURE OF PHYTOSOMES**

By docking the active polar moiety to a phospholipid, which is an essential component of the membrane, molecules can be stabilised through hydrogen bonding. Phosphatidylcholine, which is utilised in phytosomes, has a micellar structure similar to the cell membrane [14].

- **Components of Formulation**:

Plant-derived active substances can react with phospholipids to form phyto-phospholipid complexes. Phospholipids, phyto-active compounds, solvents, and the ratio quantitative relationship involved in the formation of phytosomes are the four elements required for the production of phytosomes [15].

1. Triglycerides

Plant seeds and egg yolks are the two most common natural sources of phospholipid. Commercial phospholipids are those made in an industrial setting. Based on the structure of their backbone, phospholipids are categorised as either sphingomyelins or glycerophospholipids. The main phospholipids used to create complexes are phosphatidylcholine, phosphatidylethanolamine, phosphatidylserine, and phosphatidic acid. Furthermore, phosphatidyl choline has a low toxicity and high biocompatibility due to its essential role in cell membranes. Phosphatidyl choline molecules have been shown to have hepatoprotective properties and to produce positive clinical outcomes when used to treat liver diseases like hepatitis, fatty liver, and hepatocirrhosis. Phospholipids are a component that creates a vehicle in the formation of phytosomes [16].

2. Phyto-active constituents

Researchers typically choose phyto-active constituents not so much for their in vivo activities as for their notable in vitro pharmacological effects. Most of these compounds are flavonoids. Water-soluble flavonoids, such as quercetin, cathechin, and silibinin, are found in plants and prefer the aqueous phase where they cannot pass through biological membranes. As lipophilic flavonoids, rutin and curcumin won't dissolve in aqueous gastrointestinal fluids. Phytosome complexes improve the water solubility of hydrophilic flavonoids and the membrane penetrability of lipophilic flavonoids in the aqueous phase. Furthermore, by assembling into complexes, flavonoids can be shielded from outside influences like hydrolysis, photolysis, and oxidation [17].

3. Solvents

distinct solvents serving as the medium of reaction. Protonic solvents such as ethanol have largely replaced the aromatic hydrocarbons, halogen derivatives, methylene chloride, ethyl acetate, and cyclic ethers that were previously used to create phytophospholipid complexes. In fact, phospholipid complexes have been successfully formed recently using protonic solvents like ethanol and methanol. Phospholipids and polyphenols can rationally interact with these solvents [23]. One of the SCF technologies, the supercritical antisolvent technique (SAS), is becoming more and more popular as a viable way to produce micronic and submicronic particles with regulated sizes and size distributions. In order to decrease the solute's solubility in the solvent, an anti-solvent (often CO2) is used [18].

4. Stoichiometric ratio of active constituents and phospholipids

In most cases, a synthetic or natural phospholipid reacts with the active ingredients in a molar ratio of 0.5 to 2.0 to form phyto-phospholipid complexes. On the other hand, a stoichiometric ratio of 1:1 is thought to be the most effective for forming phytosome complexes because it permits greater interaction between the two elements because the same quantity of phospholipid and active substrate are present, increasing its solubility [25]. All phospholipid complexes cannot always be synthesised with a 1:1 stoichiometric ratio. The ratio can be chosen based on the combination rate of active entity to phospholipid, which indicated a gradual increase in combination rate up to a 1:1 ratio, after that no further increment is visible [19].

5. Upkeep of pH

Buffering agent is used to keep the preparation's pH constant. Saline phosphate buffer (7 percent v/v) and ethanol tris buffer (pH 6.5) are two commonly used buffering agents. Buffer is used to maintain the phytosomes' hydration.

- **Mechanism of Phytosome formation :-**

Phosphatidylcholine is a bifunctional chemical that is also referred to as phosphatidylserine. Nature contains both the hydrophilic choline (serine) moiety and the lipophilic phosphatidyl moiety. The phospholipid is a good emulsifier due to its dual solubility. The lipid-soluble phosphatidyl portion of the phosphatidyl molecule, which has the body and tail, envelops the choline-bound material, while the choline head of the phosphatidylcholine molecule binds to these substances. Thus, as shown in the diagram [20], the phytoconstituents and phospholipids form a lipid-compatible molecular complex known as the phytophospholipid complex.

The following steps are part of the phytosome production mechanism: Step 1: Phospholipids and plant compounds (like acetone and dioxane) are present in aprotic media; Step 2: Hydrogen bond formation Step 2: Encircling the polar complex with the non-polar tail [21].

❖ METHOD OF PREPARATION

Conventional methods

There are mainly three methods available for preparation of phytosome:

1) Solvent evaporation method 2) Rotary evaporation method 3) Anti-solvent precipitation method

1.**Solvent evaporation method**:
Solvent evaporation is one method that can be used to synthesise the phytosome. Phosphatidylcholine is dissolved in 100 mL of a non-polar solvent, such as chloroform, using magnetic stirring at 40°C. Before adding the active phytoconstituent to the phosphatidylcholine chloroform solution, it is dissolved in 20 millilitres of a non-polar solvent, such as methanol. After two hours of stirring, the clear solution is dried under vacuum at 60 °C. It is then moved to a vacuum at 40 °C and left there for an entire night. The residue is then gathered, ground into a powder, and sealed. A phytophospholipid complex is obtained by collecting the resulting light-yellow powder [22].

2.**Anti-solvent preparation (Salting out method)**

To create phytosomes, anti-solvent precipitation is employed. The phospholipid and the bioactive molecule dissolve in an organic solvent. At reduced pressure and temperature, an orbiting vacuum evaporator is employed to completely extract the organic solvent. A thin layer consisting of a conjugated mixture of bioactive material and phospholipid would form in the round-bottom flask. Hexane is used to completely remove the solvents from the thin layer, producing a precipitate that is filtered, gathered, and kept in vacuum desiccators for a full day. In a mortar, crushed dried precipitate is sieved through #100 meshes. Until testing, the powdered substance was kept at room temperature in an amber-colored glass bottle [23].

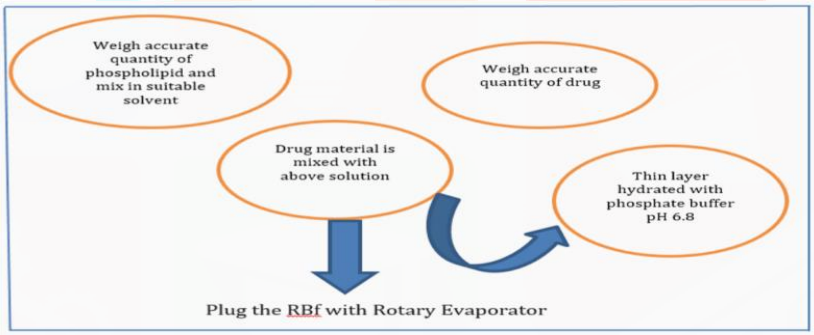


Figure 3 General Preparation of Phytosomes

➢ NOVEL METHODS

1)Gas anti-solvents technique (GAS): Supercritical CO2 gas use as an antisolvent is not necessary. To achieve uniform mixing, it is injected into the solution in a closed chamber, preferably from the bottom. Solutes precipitate because of the decreased solubilization power of the organic solvent brought on by the dissolution of CO2 gas. To get rid of any remaining solvent, the particles are rinsed with more antisolvent. If not, the solutes might resolubilize during the depressurization step, endangering the stability of the product. When scaled up to industrial levels, the gas antisolvent technique outperforms the solvent antisolvent technique in terms of results.[24]

2)Supercritical antisolvent precipitation (SAS): Submicrometer-sized particles with a narrow size distribution are produced by removing the solvent from the gas phase by lowering the pressure in the SAS. The supercritical condition of CO2 is a requirement. Both the solution and the CO2 are pumped from the top into a closed chamber. In contrast to GAS, this tactic has a track record of widespread success. [25]

➢ EVALUATION ATTRIBUTES OF PHYTOSOME

Physical attributes like shape, size, distribution, drug entrapment effectiveness, drug release, and chemical composition can all be used to characterise phytosomes. They are characterised by NMR spectroscopy, differential scanning calorimetry (DSC), percentage drug entrapment, photon correlation spectroscopy (PCS), x-ray diffraction analysis (XRD), and visualisation [26].

1. Visualization

Transmission electron microscopy (TEM) and scanning electron microscopy (SEM) can both be used to visualise phytosomes. The TEM image of a soybean phytosome showed spherical, rough-surface vesicles free of any indications of particle aggregation. TEM analysis can provide information about the drug's internal environment and distribution within the phospholipid mesh. With a 1000x magnification, TEM can be used to measure the size of phytosomal vesicles [27]. When phytosomes were examined using scanning electron microscopy (SEM), no crystalline particles or contaminants were found. The spherical bulging on the surface of the phytosomes confirms their spherical shape. SEM is used to characterise the samples' surface morphologies. According to its description, dihydromyricetin-DMY is a small, prism-like crystal with a smooth surface and regular shape. It has been reported that the surface of hydrogenated soybean phosphatidylcholine, or HSPC, is unevenly and roughly structured. The crystal structure of DMY in the DMY-HSPC complex is hardly discernible, and the particle size was smaller than both DMY and HSPC's. Nonetheless, it is demonstrated that HSPC is only affixed to the crystal surface of DMY in the DMY-HSPC physical mixture. These changes in particle shape suggest that during the complex formation, the DMY was distributed in an amorphous state in the HSPC carrier [28].

1.Vesicle size and zeta potential

Using dynamic light scattering (DLS) with a computerised inspection system and photon correlation spectroscopy (PCS), one can measure particle size and zeta potential [29]. Two crucial properties of complexes that affect their stability and repeatability are their particle size and zeta potential. Particle sizes of phospholipid complexes range from 50 nm to 100m.Particle size distribution is measured by the polydispersity index (PDI), a crucial statistic for nanoparticles. The term "monodisperse" refers to particles whose PDI is less than 0.1. The phytosome particles were found to be fairly homogenous in one study involving curcumin-phytosomes, with an average size of 131.8 nm and a PDI of 0.191.

If the particles' absolute zeta potential is higher than 30 mV, the particle system will be extremely stable and able to stop the particles from aggregating. In the range of 20-30 mV, the particle system is considered relatively stable if the zeta potential values are observed. One measure of the stability of a particle system is the zeta potential value. With a zeta potential of -44.5 mV, the curcumin-phytosome system in the previously mentioned study is comparatively stable [30].

2.Entrapment efficiency

The phytosome entrapment efficiency of a medicine can be determined by the ultracentrifugation method, which demonstrates the amount of the drug that is trapped within the phospholipid mesh. Nearly all phytosomes formulations include the entire medication. The results indicate a uniform binding between rutin and phosphatidylcholine [31].

3.Drug content

To determine the amount of drug, a modified high performance liquid chromatographic methodology or a suitable spectroscopic method can be utilised [32].

4. Partition coefficient determination

The partition coefficient may be considered an important feature in TDDS for anticipating skin permeability from an aqueous environment to the lipophilic stratum corneum. For transdermal absorption, the permeant should have a (octanol water) partition coefficient of -1.0 to 4.0. The best phytosome partition coefficient value, with a value of roughly 3, indicating easy penetration from the aqueous environment [33].

A method for calculating apparent partition coefficients is the shake-flask method. In separate volumetric flasks, equal volumes of water and n-octanol containing pure drug and phospholipid complex are mixed and allowed to equilibrate for 24 hours at 37°C with constant shaking. Prior to using this method, the two phases are mutually saturated [34].

❖ ADVANTAGES OF USE OF PHYTOSOME

The following points outline phytosome's potential for use in medicine. [36]

• It has a wide range of therapeutic benefits because it improves the absorption of lipid-insoluble polar phytoconstituents when applied topically and orally, demonstrating improved bioavailability.

• Phytosomes extend the duration of action and significantly increase drug entrapment.

• Phytosomes lower dosage requirements and enhance the absorption of active ingredients.

• In addition to serving as a carrier, phosphatidylcholine, which is used in the production of phytosomes, also has hepatoprotective prope Phosphatidylcholine and phytoconstituents form chemical bonds, which improve the stability of the phytosome.

❖ APPLICATION OF PHYTOSOME

1.In Nervous system

Research has demonstrated that phytosomes are more effective than traditional standardised extracts at treating the nervous system. In one study, Ginkgo biloba phytosome treatment resulted in a marked increase in spontaneous locomotor motor activity, suggesting increased central nervous system stimulation/excitation. supports their therapeutic usage in Alzheimer's illness [37].

2.In Cardiovascular system

Numerous studies on grape seed phytosomes have shown an increase in the total antioxidant capacity, stimulation of plasma's physiological defences, protection against heart damage caused by ischemia or reperfusion, and protective effects against atherosclerosis, which provide pronounced cardiovascular system protection [38].

3.Inflammation

Numerous studies found that phytosomes had superior anti-inflammatory properties than pure herbal extracts. According to a study on rutin phytosome skin absorption, rutin phytosomes can pass through the extremely impermeable stratum corneum more easily than free rutin. Retaining this increased amount of rutin will allow for a prolonged anti-inflammatory effect and a slow passage through the viable dermis [39,40].

In a study on the effects of pthalic anhydride (PA) on inflammation in mice, inflammatory symptoms such as erythema, oedema, and erosion on the mice's back and ears were significantly reduced when Centella asiatica phytosome therapy was administered in comparison to the control and PA treatment groups [41].

4.Oxidative stress

According to studies, phytosomes exhibit better antihepatotoxic activity than standardised plant-based herbal extract. In one study, phytosomes containing silymarin demonstrated greater specific activity and a longer duration of action compared to pure silymarin in terms of oedema reduction, myeloperoxidase activity inhibition, antioxidant activity, and free radical scavenging activity [43].

5.Diabetes Momordica dioica phytosomes at a lower dose demonstrated a more notable blood glucose lowering effect than the standard total methanolic extract group in a streptozotocin-nicotinamide induced diabetic study in rats. This is comparable to the standard metformin group, an anti-diabetic medication [44,45].

6. In Cancer

When compared to a regular plant extract, several researchers found that the phytosome formulation had a stronger anti-tumor effect. According to a study on phytosome targeting tumour therapy, phytosomes with a molecular weight of more than 40 kDa and a Because of their enhanced penetration and retention impact, tumour cells are actively targeted by the nanometric size range of 100–1200 nm. While passive targeting increases the drugs' bioavailability, active targeting precisely delivers the medications to the site of action. To deliver the bioactive ingredients, the two are combined in phytosomes [46].

7. fungus-related illness

It has been reported that phytosomal complexes exhibit higher anti-fungal activity when compared to simple plant-based herbal extract. The maximum zone of inhibition [47] illustrates how the phytosome complex of lawsone exhibited superior antifungal activity in comparison to both the plant medicine lawsone and plain ketoconazole.

• CONCLUSION

Phytosomes enhance complex chemical absorption, which benefits the drug's pharmacokinetic profile . Denaturation and bioavailability are significant properties of herbal products. There are a tone of cutting-edge methods available in Novel technology form. Despite these methods, the most effective novel approaches for herbal medications to solve this kind of issue are liposomes and phytosomes. The pharmacotherapeutics and pharmacokinetics of herbal medications have been enhanced with the help of phytosome drug delivery system. This type of delivery systems is also applied in the nutraceutical and cosmoceutical fields to enhance skin permeability and therapeutic effect. The process of creating phytosomes is straight forward and repeatable, and the phospholipids utilised to prepare them have positive physiological effects of their own.

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Conflict of interest disclosure.

We affirm that there is no conflict of interest between us.

• REFERANCE

1) Kumar A., Kumar B., Singh S.K., Kaur B., Singh S., “A review on phytosomes: Novel approach for herbal phytochemicals” Asian Journal of Pharmaceutical and Clinical Research 2007, 10(10), 42.

2) Bhattacharya S. Phytosomes: the new technology for enhancement of bioavailability of botanicals and nutraceuticals. Int. J. Health Res. 2009;2(3):225-232

3) Gandhi A, Dutta A, Pal A, Bakshi P. Recent trend of phytosomes for delivering herbal extract with improved bioavailability. J Pharmacogn Phytochem 2012;1(4):6.

4) Jadhav I.A., Wadhave A.A., Arsul V.A., Sawarkar H.S., “Phytosome a novel approach in herbal drug” Int J Pharm Anal 2014, 2(5), 478.

5) Kamel R, Basha M. Preparation and in vitro evaluation of rutin nanostructured liquisolid delivery system. Bull. Fac. Pharm. 2013; 51(2):261-27

6) Schandalik R, Gatti G, Perucca E. Pharmacokinetics of silybin in bile following administration of silipide and silymarin in cholecystectomy patients. Arzneimittel-Forschung. 1992;42(7):964-968.

7) Moscarella S, Giusti A, Marra F, Marena C, Lampertico M, Relli P, Gentilini P, Buzzelli G. Therapeutic and antilipoperoxidant effects of silybin-phosphatidylcholine complex in chronic liver disease: preliminary results. Curr. Ther. Res. 1993;53(1):98-102.

8) La Grange L, Wang M, Watkins R, Ortiz D, Sanchez ME, Konst J, Lee C, Reyes E. Protective effects of the flavonoid mixture, silymarin, on fetal rat brain and liver. J. Ethnopharmacol. 1999;65(1):53-61

9) Surini S, Mubarak H, Ramadon D. Cosmetic serum containing grape (Vitis vinifera) seed extract phytosome: Formulation and in vitro penetration study. J. Young Pharm. 2018;10(2):51-55.

10) Semalty A, Semalty M, Rawat MSM, Franceschi F. Supramolecular phospholipids–polyphenolics interactions: The phytosome strategy to improve the bioavailability of phytochemicals. Fitoterapia. 2010;81(5):306-314 18. HA, Bhangale BD. Phytosome as a novel Pawar biomedicine: a microencapsulated drug delivery system. J. Bioanal. Biomed. 2015;7(1):6-12.

11 HA, Bhangale BD. Phytosome as a novel Pawar biomedicine: a microencapsulated drug delivery system. J. Bioanal. Biomed. 2015;7(1):6-12.

12 Zhao X, Shi C, Zhou X, Lin T, Gong Y, Yin M, Fang J. Preparation of a nanoscale dihydromyricetin-phospholipid complex to improve the bioavailability: in vitro and in vivo evaluations. Eur. J. Pharm. Sci. 2019;138:104-113.

13 Manach C., Scalbert A., Morand C., "Polyphenols, food sources and bioavailability" The American Journal of clinical Nutrition, 2004, 79, 727-47.

14 Hou Z, Wei H, Wang Q, Sun Q, Zhou C, Zhan C, Zhang Q. New method to prepare mitomycin C loaded nanoparticles with high drug entrapment efficiency. Nanoscale Res. Lett. 2009;4(7):732737

15 Tripathy S, Patel DK, Barob L, Naira SK. A review on phytosomes, their characterization, advancement & potential for transdermal application. J. drug deliv. ther. 2013;3(3):147-152 22.

16 Singh RP, Gangadharappa HV, Mruthunjaya K. Phytosome loaded novel herbal drug delivery system: A review

17 Singh RP, Gangadharappa HV, Mruthunjaya K. Phytosome loaded novel herbal drug delivery system: A review

18 Singh RP, Gangadharappa HV, Mruthunjaya K. Phytosome loaded novel herbal drug delivery system: A review

19 Zhao X, Shi C, Zhou X, Lin T, Gong Y, Yin M, Fang J. Preparation of a nanoscale dihydromyricetin-phospholipid complex to improve the bioavailability: in vitro and in vivo evaluations. Eur. J. Pharm. Sci. 2019;138:104-113.

20 Bhattacharya S. Phytosomes: the new technology for enhancement of bioavailability of botanicals and nutraceuticals. Int. J. Health Res. 2009;2(3):225-232.

21 Prasad SB, Bhatia S, Singh S. Phytosome: Phytoconstituent based lipid derived drug delivery system. J. chem. pharm. res. 2016;8(5):664-667.

22 Singh RP, Gangadharappa HV, Mruthunjaya K. Phytosome loaded novel herbal drug delivery system: A review

23 Azeez NA, Deepa VS, Sivapriya V. Phytosomes: emergent promising nano vesicular drug delivery system for targeted tumor therapy. Adv. Nat. Sci.: Nanosci. Nanotechnol. 2018;9(3):33-37.

24 28. Li J, Wang X, Zhang T, Wang C, Huang Z, Luo X, Deng Y. A review on phospholipids and their main applications in drug delivery systems. Asian J. Pharm. Sci. 2015;10(2):81-98.

25 Sheth P, Sandhu H. Amorphous solid dispersion using supercritical fluid technology. In: Shah N, Sandhu H, Choi DS, Chokshi H, Malick AW, editor. Amorphous Solid Dispersions. New York: Springer; 2014.

26 Saroha K, Waliyan P, Pahwa R, Pal S, Singh I, Kumar M. Phytosomes: A Promising Strategy for Enhanced Therapeutic Benefits of Phytochemicals. Int. j. res. pharm. 2020; 11(1): 31573163.

27 El-Menshawe SF, Ali AA, Rabeh MA, Khalil NM. Nanosized soy phytosome-based thermogel as topical anti-obesity formulation: an approach for acceptable level of evidence of an effective novel herbal weight loss product. Int. J. Nanomed. 2018; 13(1):307-310

28 Zhao X, Shi C, Zhou X, Lin T, Gong Y, Yin M, Fang J. Preparation of a nanoscale dihydromyricetin-phospholipid complex to improve the bioavailability: in vitro and in vivo evaluations. Eur. J. Pharm. Sci. 2019;138:104-113.

29 Fry DW, White JC, Goldman ID. Rapid separation of low molecular weight solutes from liposomes without dilution. Anal. Biochem. 1978; 90(2):809-815.

30 Tung BT, Hai NT, Son PK. Hepatoprotective effect of phytosome curcumin against paracetamol-induced liver toxicity in mice. Braz. J. Pharm. Sci. 2017; 53.

31 Das MK, Kalita B. Design and evaluation of phyto-phospholipid complexes (phytosomes) of rutin for transdermal application. J. App. Pharm. Sci. 2014; 4(10):51-70.

32 Patel J, Patel R, Khambholja K, Patel N. An overview of phytosomes as an advanced herbal drug delivery system. Asian J. Pharm. Sci. 2009;4(6):363-371.

33 Das MK, Kalita B. Design and evaluation of phyto-phospholipid complexes (phytosomes) of rutin for transdermal application. J. App. Pharm. Sci. 2014; 4(10):51-70.

34 Ghanbarzadeh B, Babazadeh A, Hamishehkar H. Nanophytosome as a potential food-grade delivery system. Food

Biosci. 2016;15:126-135.

35 Semalty A, Semalty M, Rawat MSM, Franceschi F. Supramolecular phospholipids–polyphenolics interactions: The phytosome strategy to improve the bioavailability of phytochemicals. Fitoterapia. 2010;81(5):306-314

35 Angelico R, Ceglie A, Sacco P, Colafemmina G, Ripoli M, Mangia A. Phyto-liposomes as nanoshuttles for water- insoluble silybin–phospholipid complex. Int. J. Pharm. 2014;471(2):173181.

36 Naik SR, Pilgaonkar VW, Panda VS. Neuropharmacological evaluation of Ginkgo biloba phytosomes in rodents. Phytother. Res. 2006; 20(10):901-905.

37 Naik SR, Pilgaonkar VW, Panda VS. Neuropharmacological evaluation of Ginkgo biloba phytosomes in rodents. Phytother. Res. 2006; 20(10):901-905.

38 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.

39 Das MK, Kalita B. Design and evaluation of phyto-phospholipid complexes (phytosomes) of rutin for transdermal application. J. App. Pharm. Sci. 2014; 4(10):51-70.

40 Kalita B, Das MK. Rutin–phospholipid complex in polymer matrix for long-term delivery of rutin via skin for the treatment of inflammatory diseases. Artif. Cells Nanomed. Biotechnol. 2015;46(1):41-56.

41 Ho PJ, Sung JJ, Cheon KK, Tae HJ. Anti-inflammatory effect of Centella asiatica phytosome in a mouse model of phthalic anhydride-induced atopic dermatitis. Phytomedicine. 2018;43:110-119.

42 Rajput RPS, Chakravarty C, Bhardwaj S. Preparation and evaluation of phytosome of herbal plant of Lawsonia inermis for topical Application. J. innov. pharm. sci. 2019;3(2):9-11.

43 Bombardelli E, Magistretti MJ. inventors. Pharmaceutical Compositions containing flavanolignans and phospholipids as active principles. 1987;EP0209037.

44 Telange DR, Patil AT, Pethe AM, Fegade H, Anand S, Dave VS. Formulation and characterization of an apigenin-phospholipid phytosome (APLC) for improved solubility, in vivo bioavailability, and antioxidant potential. Eur. J. Pharm. Sci. 2017;108:36-49.

45 Rathee S, Kamboj A. Optimization and development of antidiabetic phytosomes by the Box–Behnken design. J. Liposome Res. 2018;28(2):161-172.

46 Azeez NA, Deepa VS, Sivapriya V. Phytosomes: emergent promising nano vesicular drug delivery system for targeted tumor therapy. Adv. Nat. Sci.: Nanosci. Nanotechnol. 2018;9(3):33-37.

47 Rajput RPS, Chakravarty C, Bhardwaj S. Preparation and evaluation of phytosome of herbal plant of Lawsonia inermis for topical Application. J. innov. pharm. sci. 2019;3(2):9-11.