WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.084
Volume 11, Issue 9, 208-220. Review Article ISSN 2277– 7105

PHYTOSOMES: A GOOD STRATERGY FOR FORMULATION OF HERBAL MEDICINES

Isha P. Wakde[1]*, [2]Dr. Dinesh M. Biyani and [3]Dr. Milind J. Umekar

[1]Post Graduate Student of Pharma (Department of Pharmaceutics), Smt. Kishoritai Bhoyar College of Pharmacy, New Kamptee, Dist. Nagpur, Maharashtra, India- 441002.

[2]Professor and Dean Academic of Smt. Kishoritai Bhoyar College of Pharmacy, New Kamptee, Dist. Nagpur, Maharashtra, India- 441002.

[3]Principal of Smt. Kishoritai Bhoyar College of Pharmacy, New Kamptee, Dist. Nagpur, Maharashtra, India- 441002.

Article Received on
05 May 2022,

Revised on 26 May 2022,
Accepted on 15 June 2022

DOI: 10.20959/wjpr20229-24594

***Corresponding Author**
Isha P. Wakde
Post Graduate Student of Pharma (Department of Pharmaceutics), Smt. Kishoritai Bhoyar College of Pharmacy, New Kamptee, Dist. Nagpur, Maharashtra, India- 441002.

ABSTRACT

Drug delivery techniques are being explored to improve the efficacy of medicinal plant. Phytosomes are a type of nanotechnology that involves the incorporation of standardised plant extracts or water-soluble phytoconstituents with phospholipids to create lipid-compatible molecular complexes. This technique aids in the bioavailability of a variety of medicinal plants and is one of the newest methods for preparing therapeutic plant extracts or phytoconstituent. The various methods involved in preparation of phytosomes are solvent evaporation, salting out, Anti-solvent precipitation method, mechanical dispersion, super critical fluids (SCF) techniques.

KEYWORDS: Phytosomes, phospholipids, medicinal plant extract/component, phytophospholid complexes, phytosome properties, method of preparation of phytosomes.

INTRODUCTION

Medicinal plants are the major components in several oriental formulations used in various traditional medical systems around the world. Traditional medicines play an important role in the health-care sector. In several countries, particularly in rural areas, traditional medicines is the primary source of health care, if not the only source of health care.[1] The popularity of traditional medicines is growing in industrialised countries for a variety of reasons, one of

which is that ethnopharmacological research has proven the effectiveness of these traditional medicines.[1]

Plant-derived medicines appear to be growing as their demand in underdeveloped countries is increasing due to their therapeutic efficacy and simplicity of procurement. Plants have been utilised to treat a wide range of ailments in a variety of ways. Pills, powders, semi-liquid extracts, tinctures, decoctions, medicated teas, and solutions are all examples of traditional dosage forms. Tablets, capsules, soluble granules, and ointment are modern herbal dosage forms.There has been a lot of advancement in herbal dosage forms, but still, there are a lot of limitations in modern herbal dosage forms such as delayed therapeutic response, lack of potential for reaching the drug to the target site, requirement of a relatively large quantity of drug, potential for variability in herbals, and drug destruction during its systemic passage from the gastrointestinal tract (GIT) to the liver (e.g. Flavonoids). The limitations can be overcome by increasing the therapeutic performance through increasing bio-availability of existing herbal medications by re-purposing them in a novel dosage form for improved drug delivery.[2]

Indena, a leading supplier of nutraceutical ingredients, developed Phytosome in 1989 to incorporate phospholipids into standardised extracts and thus vastly improve their absorption and utilization.[3] The phrase "phytosome" is a mixture of two words: "PHYTO" denotes plant, and "SOME" implies cell-like. The stoichiometric reaction of phospholipids (phosphatidylcholine, phosphatidylserine, etc.) with standardised extracts or polyphenolic compounds (such as flavonoids, terpenoids, tannins, and xanthones) in a nonpolar solvent produces phytosomes, which are cell-like structures. They are more easily absorbed, used, and produced than traditional herbal extracts.[4] The phospholipid complex-technique, which encapsulates plant actives, can also be used as potent drug delivery mechanism for enhancing therapeutic index. This approach is known as phytosome and pharmacosome, and it can be used for both herbal and conventional dosage forms.[5]

PROPERTIES OF PHYTOSOMES

PHYTOPHOSPHOLIPID COMPLEXES

Structure of phytosomes

Interactions between active components and the polar head of phospholipids form phytosomes. The active ingredient is an integral component of the membrane, as it is made up of molecules that are held together by hydrogen bonds with the polar heads of

phospholipids. Phospholipid complexes are formed as a result of interactions between active ingredients and phospholipids, in which the phospholipids head group is anchored but the two long fatty acid chains do not participate in complex formation. To generate a lipophilic surface, the two long fatty acid chains can migrate and envelop the polar component of complexes. When diluted in water, phytosomes form agglomerates that resemble a tiny cell with some similarities to liposomes.[6]

Steriochemistry of phyto-phospholipid complex

The reaction between stoichiometric amounts of phospholipids and the phytoconstituents leads to the formation of phyto-phospholipid complexes and the spectroscopic data revealed that the phopspholipid – active ingredient interaction is due to the formation of hydrogen bond between the polar head and the polar functionalities of the active ingredient in phyto-phospholipid complexes. The signal of the fatty chain has not changed in both free and complex phospholipids, implying that long aliphatic chains are wrapped around the active principle, providing a lipophilic envelope. Thermal examination in other research has also led to the conclusion that the contact between the two molecules is due to the creation of hydrogen bonds or hydrophobic interactions. A molecular docking investigation of the interaction of the 20(S)-protopanaxadiol phospholipid complexes revealed that a hydrogen bond developed between one of the –OH groups in 20(S)-protopanaxadiol and the —P=O group in the phospholipids. In conclusion, most experts agree that hydrogen bonds, rather than chemical or hybrid bonds, provide intermolecular force when active ingredients interact with phospholipids.[7]

Stoichiometric ratio of active constituents and phospholipids

Normally, phyto-phospholipid complexes are prepared by mixing a synthetic or natural phospholipid with the active ingredients at a molar ratio of 0.5 to 2.0 respectively. A stoichiometric ratio of 1:1, on the other hand, is thought to be the most efficient for forming phospholipid complexes.[7] Maryana et al. formulated silymarin-phospholipid complexes with stoichiometric ratios of 1:5, 1:10, and 1:15 and discovered that the complexes with a stoichiometric ratio of 1:5 had the best physical attributes and the largest loading capacity of 12.18 percent 0.30 percent. For different types of medications, the stoichiometric ratio of active components and phospholipids should be adjusted experimentally for different reasons, such as the highest drug loading.[8]

The factors influencing phyto-phospholipid complexes

The key parameters that determine the formation of phyto-phospholipid complexes are the solvent, stoichiometric ratio of active components, reaction temperature, and reaction duration. Depending on the desired goal, several process parameters may be applied. Saoji et al. used a central composite design to determine the optimal formulation by examining the impacts of process factors such as the phospholipid-to-drug ratio, reaction temperature, and reaction time on yield. According to a recent publication, Telange and his colleagues prepare the highest yield apigenin-phospholipid complexes by altering stoichiometric ratios and reaction temperature.[7]

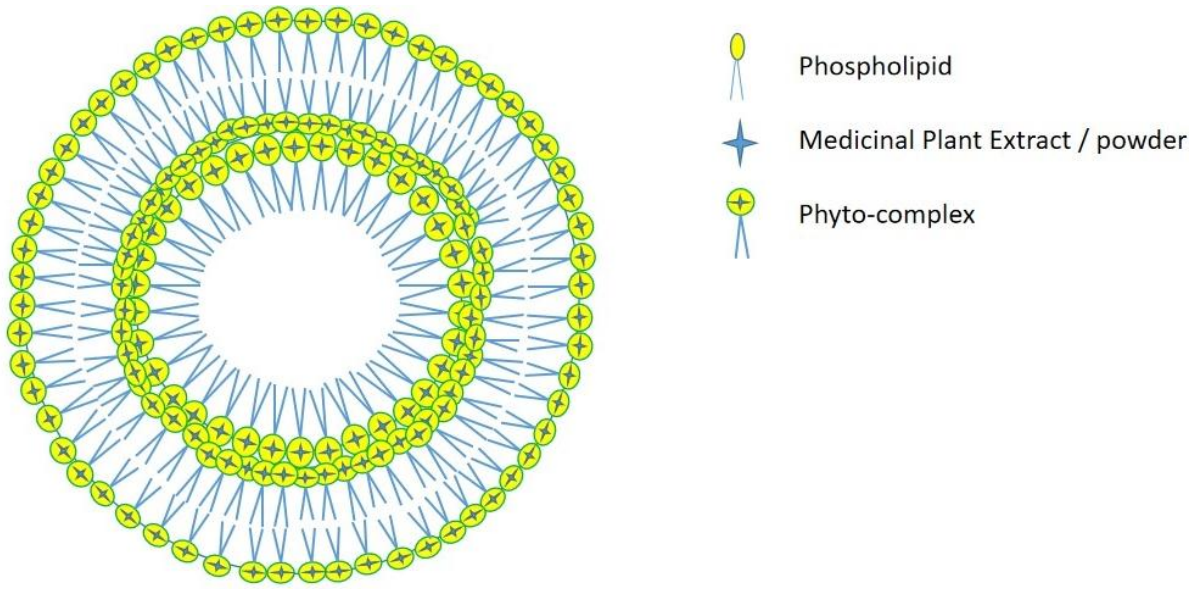

Fig. 1: Structure of phytosome.

BASIC COMPONENT FOR THE PRODUCTION OF PHYTOSOME OF PHYTOPHOSPHOLIPID COMPLEX Phospholipid

1. Plant extract/Active phyto-constituent
2. Phospholipid
3. Solvent

1. Plant extract/Active phyto-constituent

Standardized extract or polyphenolic ingredients such flavonoids, terponoids, tannins, and xanthose are employed in the preparation of phytosomes as active constituents or herbal extracts.[4] Some physiologically active polyphenols, such as hesperidin, are hydrophilic in nature and hence cannot pass through cellular membranes. Crucumin and rutin, for example, have significant lipophilic characteristics and cannot dissolve in aqueous gastrointestinal

fluids.[7] A medicine with an active hydrogen atom, such as –COOH, -OH, -NH_2, -NH etc., that can form a hydrogen bond between the drug and Phophatidylcholine molecules' N-(CH_3) group. Any medication with electrons can be combined with phospholipid molecules to generate various complexes. To increase bioavailability, both hydrophilic and lipophilic actives can be complexed.[5] Other compounds from herbal extracts, such as 20(R)-25-methoxyl-dammarane-3,12,20-triol (25-OCH_3-PPD) , evodiamine (EVO)[9], and siramesine (SRM)[10], can also be produced in complexes with phospholipids. As a result, phyto-phospholipid complexes are no longer restricted to polyphenols, and the approach for generating complexes can theoretically be used to any active chemical.[11]

2. Phospholipid

Phospholipids are found in egg yolks and plant seeds. Industrially manufactured phospholipids are currently accessible.[12] Depending on the backbone, phospholipids are classified as glycerophospholipids or sphingomyelins. Phosphatidylcholine (PC), phosphatidylethanolamine (PE), phosphatidylserine (PS), phosphatidic acid (PA), phosphatidylinositol (PI), and phosphatidylglycerol (PG) are all glycerophospholipids. The principal phospholipids used to create complexes with a hydrophilic head group and two hydrophobic hydrocarbon chains are PC, PE, and PS. PC is the most often used phospholipid in the synthesis of phospholipid complexes. PC has two neutral tail groups and a positive head group with an oxygen atom in the phosphate group that has a strong tendency to gain electrons while nitrogen has a strong tendency to lose electrons, a unique chemical property that causes PC miscible in both water and lipid environments.[7]

PC has two neutral tail groups and a positive head group with an oxygen atom in the phosphate group that has a strong tendency to gain electrons while nitrogen has a strong tendency to lose electrons, a unique chemical property that causes PC miscible in both water and lipid environments.[5] Phospholipids, which are important components of cell membranes, can also be used as a vehicle, making drug delivery systems more adaptable to the body's needs. Phospholipids are biocompatible and provide a number of benefits, including formulation flexibility and the ability to choose from a variety of NDDS depending on the intended usage. Phospholipids are lipids with phosphorus in their structure, as well as a polar and non-polar portion.[5, 13] Phosphotidylcholine's amphipathic characteristics offer it moderate solubility in water and lipid environments, which is one of its advantages.

Furthermore, because PC is a necessary component of cell membranes, it has a high biocompatibility and low toxicity.[7]

PROPERTIES OF PHOSPHOLIPIDS

PHYSICOCHEMICAL PROPERTIES

Phospholipids are amphipathic molecules having considerable solubility in aqueous and oily mediums. They have a polar and a nonpolar portion in their structures. The phospholipids are one among the main components of the mammalian cell wall. In the eukaryotic cell membrane glycerol based lipids are predominantly present which incorporates phosphatidylcholine, phosphatidylinositol, phosphatidylethanolamine, phosphatidylserine and cardiolipin. Phosphatidylcholine possesses a cylindrical shape with highest entropy and is involved in formation of bilayer. It contains one saturated and one unsaturated chain in its structure. Phosphatidylethanolamine is cone shaped and doesn't form bilayer itself.[14]

PHYSIOLOGICAL PROPERTIES

The soya phospholipids are absorbed at a rate greater than 90% in humans and reach peak plasma concentration in about 6 h after oral administration. The maximum plasma concentration reached was found to be 20% of the dose administered.

Apart from a physiologically compatible pharmacokinetic and toxicological profile the dietary phospholipids also possess some medicinally significant properties in human beings. Phospholipids are a decent source of phosphatidylcholine and choline, both of which liquefy the fat dumped inside the liver in case of hepatic steatosis or fatty liver and exhibit other hepatoprotective effects as well. The essential or soya phospholipids have shown to be hepatoprotective in nature and stop liver damage by alcohol, drugs and other toxins. They have also been reported to assist in clearance of serum cholesterol and increase circulating HDL levels in plasma.[14]

Phospholipid structure and chemistry

Phospholipids have a glycerol backbone that would be esterified with fatty acids in positions 1 and 2 and phosphate in position 3. Phospholipid is a type of lipid that is utilized to produce phytosomes. PE and PC are zwitterionic and have a neutral charge at pH values of about 7. Phospholipids generate hydration dispersions with varied colloidal structures depending on the ratio of the polar head group area and the fatty acid portion

area in the molecule.[14] Micelles are created when the polar head group is larger than the carboxylic acid component (example: monoacyl-phosphatidylcholine (i.e. lysolecithin)) and inverted micelles are formed when the polar head group is smaller than the fatty acid part (example DOPE or soybean-PE).[15]

3 Solvent

The choice of solvent in the phospholipid complexation procedure is determined by the solubility of both the medication and the phospholipids. In truth, research proposes using both aprotic and protic solvents for greater solubility, and many others have revealed the usage of a mixture of solvents. Most aprotic solvents, such as diethyl ether, dichloromethane, dioxane, chloroform, and n-hexane, have recently been replaced by ethanol, which is safer than the previous ones.[5] Different studies have used various solvents as the reaction medium for forming phyto-phospholipid complexes. Aprotic solvents such aromatic hydrocarbons, halogen compounds, methylene chloride, ethyl acetate, or cyclic ethers were employed to prepare phyto-phospholipid complexes, but protic solvents like ethanol have completely replaced them. Furthermore, protonic solvents like ethanol and methanol have lately been used to successfully create phospholipid complexes. When the yield of phospholipid complexes is high enough, ethanol can be a useful and popular solvent because it leaves little residue and does not cause damage. Some liposomal drug complexes add the presence of water or a solution, during which the phytosomes interact with a lower dielectric constant solvent.[7]

METHOD OF PREPARATION

Phytosomes are phospholipid complexes of vegetable extracts prepared by refluxing and stirring aqueous extracts with phospholipid solution in a suitable solvent such as ethyl acetate, acetone, or ethanol. Reduced pressure concentrates the resultant suspension into a thick residue that can be dried and pulverised. Purified components of vegetable extracts have also been observed to form complexes with natural, synthetic, or semi-synthetic phospholipids.[4]

The three main procedure for praparation of phytosome (phytosome- phosphoplipid complex) are solvent evaporation, freeze-drying, and anti-solvent precipitation. Mechanical dispersion is also used for the preparation of phytosomes.[7]

Solvent Evaporation Method

Solvent evaporation is a traditional and widely used approach. In this method, both phytoconstituents and PC are added to a flask containing organic solvent. To achieve maximum drug entrapment in the phytosomes generated, this reaction mixture is held at an ideal temperature of 40^0 C for a particular time interval of approximately 1 hr. A rotary evaporator is then used to extract the organic solvent.

Thin film phytosomes are sieved through 100 mesh sieves and kept overnight in desiccators. To achieve stability, the phytosomes are stored in a light-resistant amber-colored glass bottle that has been flushed with nitrogen at room temperature. For example oleanolic acid - phospholipid compexes prepared by Shan and Colleagues.[5,7]

Salting out Anti solvent Precipitation Method

In this technique both the selected phytoconstituents and PC are placed in a flask containing a common organic solvent, and the mixture is refluxed at a certain temperature on a magnetic stirrer for a specific duration of time. The solution is then concentrated, and an anti-solvent such n-hexane is added. A phospholipid complex precipitation occurs, which is filtered and stored in an airtight amber tinted glass container under vacuum. For example allium cepa - phospholipid complexes were prepared by this method for anti- diabetic activity.[5,7]

Mechanical Dispersion Method

The lipids dissolved in an organic solvent are brought into contact with an aqueous phase containing the medication in this approach. PC is first dissolved in diethyl ether, then slowly injected into an aqueous solution containing the phytoconstituents to be encapsulated. The synthesis of phyto-phospholipid complex occurs after the organic solvent is removed under reduced pressure. Supercritical fluids (SCF), which include gas anti-solvent technique (GAS), compressed anti solvent procedure (PCA), and supercritical anti solvent method, are novel ways for the synthesis of phospholipid complexes (SAS).[5]

Use of Super critical fluids (SCF) techniques

Supercritical fluids (SCF) have proven to be an excellent technique for preparing particles of a large size (5-2000 nm). 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 are some of the supercritical fluid methods that have been used to improve the solubility profiles of poorly soluble drug

candidates (SEDS). Supercritical procedures were used to create a phyto-phospholipid complex.[l6]

OPTIMIZATION AND CHARACTERIZATION OF PYTOPHOSPHOLIPID COMPLEX

Phytosome consistency and stability is influenced by many factors like drug to phospholipid ratio, interaction between drug and phospholipid, physical state of drug, experimental duration of time, temperature, rotation per minute RPM (in solvent evaporation method), and type of drying method used. All of these factors are statistically optimized through quality by design. Authenticating and validating the size, structure, and morphology of a phospholipid complex usually necessitates the use of various approaches.[5]

A] Characterization of phyto-phospholipid complexes

Surface Morphology and Visualization

Scanning Electron Microscopy is used to determine the surface morphology and solid state properties that is size and shape of complexes. Active chemicals can be seen in a highly crystalline condition using a scanning electron microscope, but the structured crystals vanish following complexation. The optimized freeze dried phytosomes are subjected for SEM.[17] Scanning Electron Microscopy (SEM) or Transmission Electron Microscopy (TEM) are also used to visualize phospholipid compounds.[5]

Crystalinity and Polymorphism

The most often used procedures for determining crystallinity and polymorphism are differential scanning calorimetry (DSC) and X-ray diffraction (XRD). The disappearance of endothermic peaks, the emergence of additional peaks, changes in peak form and start, peak temperature/melting points, and relative peak area, or enthalpy, are all common DSC interactions in phospholipid complexes. The phospholipid complex, on the other hand, is characterised by the entire lack, disappearance, or reduction in the intensity of major diffraction peaks corresponding to its crystalline drug in XRD.[5] The crystallization and dispersion of phytosomes can also be to studied by TEM. It is difficult to visualize shaped crystal in scanning electron microscopy (SEM) as cyrstals disappear after complexation, thus when phyto-phospholipid complexes are diluted in distilled water and shaken gently, TEM can reveal a vesicle-like structure.[7]

Solubility and partition coefficient

For characterization of active ingredients, active constituent phytophospholipid complexes, and physical mixes requires determining solubility in water or organic solvents, as well as the n-octanol/water partition coefficient (P). Phyto-phospholipid complexes, in general, have higher lipophilicity and hydrophilicity than active ingredients, and they usually have better lipophilicity.[7]

Particle size and Zeta potential

The particle size and zeta potential are important properties of compexes as it affects stability and reproducibility. Particle size and zeta potential are two crucial features of complexes that are linked to their stability and repeatability. The typical particle size of phospholipid complexes ranged from 50 nm to 100 µm.[7] A particle size analyzers used to determine the particle size are Dynamic Light Scattering (DLS),[18] particle size analyzer (Microtrac)[17], scanning electron microscopy (SEM) and transmission electron microscopy (TEM).[7] The most critical metric for phytosome physical stability is zeta potential. The stability increases as the electrostatic repulsion between the particles increases. A zeta potential of less than 20 mV indicates that the dispersion is physically stable. The Microtrac was used to test the zeta potential of the optimised phytosome suspension.[17]

Entrapment Efficiency

The drug entrapment efficiency is determined using an ultracentrifugation technique wherein a specific amount of phyto-phospholipid complex is been weighed and added to phosphate buffer (pH 6.8). The clear liquid is then decanted and centrifuged, the supernatant is then filtered using Whatman filter (0.45) paper, and the absorbance is measured using UV or HPLC. The following formula is used to compute the drug entrapment percentage (percent).[7]

The percentage drug entrapment is calculated by using following formula

$$\text{Entrapment Efficiency} = \frac{\text{Amount of encapsulated drug}}{\text{Amount of drug added}} \times 100$$ [17]

Determination of percentage yield

The yield of active constituents in complex with phospholipids is important and critical factor to determine the dose and effectiveness of the formulation during clinical trials. The amount of active constituent in complex with phospholipids is the weight difference between the initial active constituent and free compounds. The formula is as follows.

$$\text{Yield (\%)} = \frac{(\text{weight of initial active constituent} - \text{weight of free active constituent})}{\text{weight of initial active constituent}} \times 100$$

High performance liquid chromatography (HPLC) or UV spectrophotometry can also be employed to calculate the yield based on the characteristics of the active ingredients. The key parameters that determine the yield of phospholipid complexes are the solvent used, the temperature, the time, the drug concentration, and the stoichiometric ratio of active components to phospholipids.[7]

B] Optimization of phyto-constituent/extract

Preliminary test – Physical identification and detection of chemical nature

The preliminary test of phytoconstituent includes organoleptic characteristics such as color, odour, taste, and a general test, which is a solubility and identification test. Identification tests for herbal drugs are mentioned below.

Identification test

Test for carbohydrates are:- Molisch's test, Benedict's test, Fehling's test and Iodine test.

Test For Protein are:- Milon's test, Biruet test, Test with trichloroacetic acid, Xanthoproetic test and Lead acetate Test.

Test For Amino Acids are:- Ninhydrin Test and Milon's Test.

Test for Fixed Oils And Fats is:- Spot Test.

Test For Alkaloids are :- Mayer's reagent Test, Wager's reagent Test, Drangandorff's Test and Hager's reagent Test.

Test For Glycosides is:- Borntrager's Test

Test For Anthraquinone Glycoside are:- Borntrager's Test and Modified Borntrager's Test.

Test For Cardiac Glycosides are:- Killer Killani test, Raymond's test and Legal's test.

Test For Saponin glycoside are:- Froth Formation Test and Haemolysis Test.

Test For Phenols and Tannins are:- Ferric Chloride test, Phenazone Test, Lead Acetate Test and Potassium Dichromate Test.

Test For Steriods is :- Liebarmann- Bruchard Test and Salwoski Test.

Test For Flavonoides are :- Shinoda Test are, Alkaline reagent Test and Lead acetate Test.

REFERENCES

1. Xu Y, Liang B, Kong C, Sun Z. Traditional Medicinal Plants as a Source of Antituberculosis Drugs: A System Review. Biomed Res Int, 2021 Sep 8; 2021: 9910365. doi: 10.1155/2021/9910365. PMID: 34541000; PMCID: PMC8448615.
2. Sikarwar MS, Patil MB. Antidiabetic activity of Crateva nurvala stem bark extracts in alloxan-induced diabetic rats. J Pharm Bioallied Sci, 2010 Jan; 2(1): 18-21. doi: 10.4103/0975-7406.62700. PMID: 21814425; PMCID: PMC3146085.
3. Ashwini S Dhase, and Shweta S Saboo. "Preparation and Evaluation of Phytosomes Containing Methanolic Extract of Leaves of Aegle Marmelos (Bael)." *International Journal of PharmTech Research*, 0 0 2015, https://sphinxsai.com/2015/ph_vol8_no6/2/(231-240)V8N6PT.pdf.
4. Anupama Singh; Vikas Anand Saharan; Manjeet Singh; Anil Bhandari. "Phytosome: Drug Delivery System for Polyphenolic Phytoconstituents". *Iranian Journal of Pharmaceutical Sciences*, 2011; 7(4): 209-219.
5. Gnananath K, Sri Nataraj K, Ganga Rao B. Phospholipid Complex Technique for Superior Bioavailability of Phytoconstituents. Adv Pharm Bull, 2017 Apr; 7(1): 35-42. doi: 10.15171/apb.2017.005. Epub 2017 Apr 13. PMID: 28507935; PMCID: PMC5426732.
6. Mane, Kavita & Baokar, Shrikrishna & Bhujbal, Atul & Pharande, Swapnali & Patil, Gauri & Patil, Rajendra & Jain, Prabhat & Pandey, Adityanath. (2020). PHYTO-PHOSPHOLIPID COMPLEXES (PHYTOSOMES): A NOVEL APPROACH TO IMPROVE THE BIOAVAILABILITY OF ACTIVE CONSTITUENTS. 68-78.
7. Mei Lu, Qiujun Qiu, Xiang Luo, Xinrong Liu, Jing Sun, Cunyang Wang, Xiangyun Lin, Yihui Deng, Yanzhi Song, Phyto-phospholipid complexes (phytosomes): A novel strategy to improve the bioavailability of active constituents, Asian Journal of Pharmaceutical Sciences, 2019; 14(3): 265-274,
8. Maryana, W. & Rahma, Annisa & Mudhakir, Diky & Rachmawati, Heni. (2015). Phytosome Containing Silymarin for Oral Administration: Formulation and physical evaluation. 25. 54-65. 10.4028/www.scientific.net/JBBBE.25.54.
9. Tan Q, Shan L, Chen X, et al. Design and evaluation of a novel evodiamine-phospholipid complex for improved oral bioavailability. AAPS Pharm Sci Tech, 2012; 13(2): 534–47.
10. Parry MJ, Alakoskela JMI, Khandelia H, et al. High-affinity small molecule−phospholipid complex formation: binding of siramesine to phosphatidic acid. J Am Chem Soc, 2008; 130(39): 12953–60.

11. Kidd PM. Bioavailability and activity of phytosome complexes from botanical polyphenols: the silymarin, curcumin, green tea, and grape seed extracts. Altern Med Rev, 2009; 14(3): 226–46.
12. Ghanbarzadeh B, Babazadeh A, Hamishehkar H. Nano-phytosome as a potential food-grade delivery system. Food Biosci, 2016; 15: 126–35.
13. Constantinides PP, Chaubal MV, Shorr R. Advances in lipid nanodispersions for parenteral drug delivery and targeting. Adv Drug Deliv Rev, 2008; 60(6): 757-67. doi: 10.1016/j.addr.2007.10.013
14. Arun Kumar Singh, Anita Singh. Phyto-Phospholipid Complexes: A Potential Novel Carrier System for Improving Bioavailability of Phytoconstituents. Research J. Pharm. and Tech, 2020; 13(2): 1059-1066. doi: 10.5958/0974-360X.2020.00195.X.
15. van Hoogevest P. Review - An update on the use of oral phospholipid excipients. Eur J Pharm Sci, 2017 Oct 15; 108: 1-12. doi: 10.1016/j.ejps.2017.07.008. Epub 2017 Jul 12. PMID: 28711714.
16. KARATAŞ A, TURHAN F. Phyto-Phospholipid Complexes as Drug Delivery System for Herbal Extracts/Molecules. Turk J Pharm Sci, 2015; 12: 93-102.
17. Sachin K S, Adlin Jino Nesalin J, Tamizh Mani T, *"Preparation and Evaluation of Curcumin Phytosomes by Rotary Evaporation Method"* SSRG International Journal of Pharmacy and Biomedical Engineering, 2019; 6.1: 29-34.
18. Sharma S, Sahu AN. Development, Characterization, and Evaluation of Hepatoprotective Effect of Abutilon indicum and Piper longum Phytosomes. Pharmacognosy Res, 2016 Jan-Mar; 8(1): 29-36. doi: 10.4103/0974-8490.171102. PMID: 26941533; PMCID: PMC4753757.
19. Dr. K.R. Khandelwal, Dr. Vrunda Sethi Practical Pharmacognosy Techniques and Experiments 29th Edition, Nirali Prakashan.