Phyto-phospholipid Complexes (Phytosomes): A Novel Option to Enhance the Bioavailability of Plants' Pharmacologically Active Chemical Components

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Abstract: **Phytosomes a little "cell-like structure" which is made up of a molecular complex of phospholipids with phytoconstituents. They serve as a link between traditional and novel formulations. Phytosomes, which are lipid-based nanocarriers, have a crucial function in strengthening the pharmacokinetic and pharmacodynamic properties of herbal-derived polyphenolic compounds, making this nanotechnology a promising tool for the development of novel formulations. Bioavailability is a significant concern in improving bio-efficacy in the transport of dietary phytochemicals. Phospholipids work as emulsifiers by increasing the hydrophilicity and lipophilicity of phytoconstituents. For enhanced absorption and bioavailability of natural phytoconstituents, a balance of hydrophilicity (helps phytoconstituents dissolve in digestive fluids) and lipophilicity (helps phytoconstituents to penetrate lipid-based cell membranes) is essential. The enormous potential of emerging nanotechnology in the delivery of bioactive phytochemicals is examined, with a special focus on phytosomes as a novel lipid-based nanocarrier. The current review represents an overview of the vesicular system and its application, with emphasis on formulation consideration and characterization of the phyto-phospholipid complex.**
Keywords: **Phytosomes, Bioavailability, Phospholipid, Phytoconstituents, Novel Drug Delivery Systems.**

INTRODUCTION

Despite modern medicinal systems, the herbal system of medicine shows more health-promoting benefits to well-established phytochemical and phytopharmacological studies.[1] Herbal pharmaceuticals with nanometric novel drug delivery systems have a promising future in terms of improving activity and resolving problems accompanied with herbal medications.[2] Improved solubility, bioavailability, stability enhancement, sustained delivery, improved tissue macrophage distribution, pharmacological activity enhancement, toxicity protection, and protection from physicochemical and biological degradation are the beneficial aspects of the novel formulations over traditional formulations of herbal extracts and their constituents.[1],[3],[4] The current medication faces the risk of multidrug resistance, and therapeutic efficiency suffers. Multidrug resistance can be reduced using phytochemicals.[5] To address those problems, innovative drug delivery systems are being developed using several nano-formulation methodologies as described in Table (1) to provide homogenous medication targeting at the dynamic location in the required concentration and increased therapeutic efficacy.Indena (Milan, Italy) was the first to develop a phyto-phospholipid complex in the year 1989 by reacting phospholipids with the polyphenolic extract.[6],[7] The Phytosomes are a tiny cell-like structure which protects the essential components of the plant actives from physicochemical and microfloral degradation in the gastrointestinal tract. Phytosomes are framed by standardized extract or polyphenolic components complexed with a stoichiometric amount of phospholipid in a non-polar solvent. The phytosomes are essentially composed of phosphatidylcholine, a bifunctional molecule with a lipophilic phosphatidyl moiety and a hydrophilic choline moiety.[8] As a result, a molecular complex of phospholipids with phytoconstituents produces a phyto-phospholipid complex also known as Phytosomes.

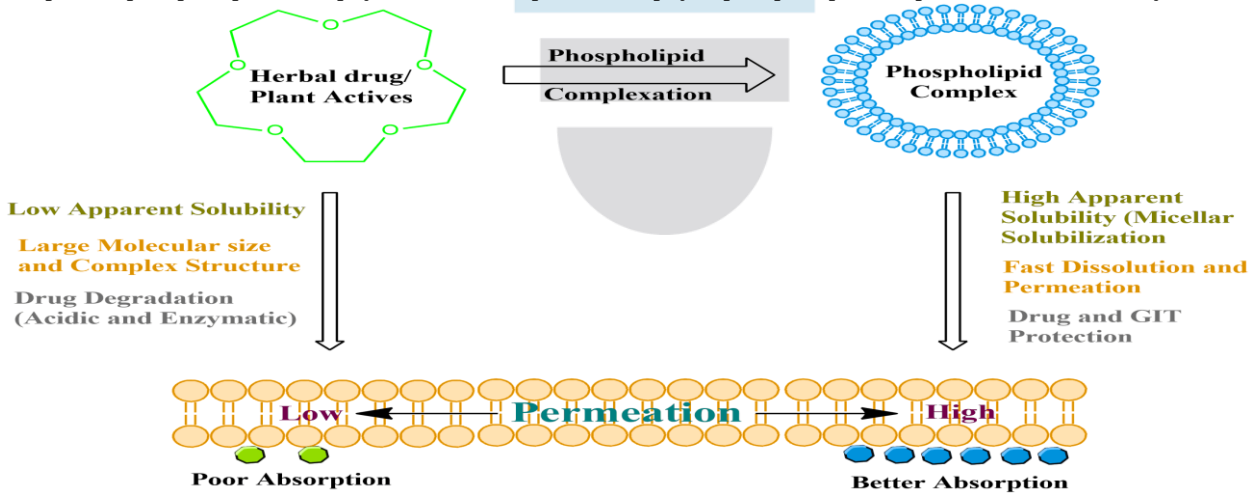

Figure 1: Schematic representation of the rate of permeation of phytosomes over traditional drugs.

HOW DOES PHYTOSOMES ARE SUPERIOR FROM A LIPOSOME?

Liposomes are used to transfer water-soluble components to the skin. A liposome is structured when a water-soluble component is encapsulated within phosphatidylcholine. The water-soluble component may have enclosed by the thousands of phosphatidylcholine molecules without forming a chemical bond. The Phytosome technique, on the other hand, uses a 1:1 or 2:1 stoichiometric ratio of phosphatidylcholine and specific plant components, depending on the chemical nature of the substance. Because of this distinction, Phytosomes absorb significantly better and are more stable than liposomes. Phytosomes perform better in skincare products, which is unsurprising.[1],[9]

Table 1: Emerging 'some' and their application

Vesicular system	Developed by	Skeleton	Carrier for	Application	Reference
Aquasomes	Kossovsky N *et al*. in 1995	Three-layered self-assembled structure	Proteins and peptides	Molecular shielding, specific targeting	[10],[11]
Archaeosomes	-	Bilayer (monopolar archaeol lipids) Monolayer (bipolar caldarchaeol lipids) or a mixture of both	Antigen, vaccines, gene delivery, proteins, and peptides, immunoadjuvants	Stabilized across wide pH, temperature, oxidative degradation, and pressure range; Poor adjuvant activity	[12],[13]
Colloidosomes	Velev *et al.* in 1996	Colloidal particles self-assembled on the emulsion droplet's interface	Both hydrophilic and lipophilic actives	Drug targeting	[14]
Cryptosomes/ Immune-liposomes	Dinesh Kumar *et al.*	Liposomes and Pluronics (Poloxamer molecules) are embedded with delivery agents	Biologically active compound	Ligand-mediated drug delivery system; Sterically well stabilized	[15]
Cubosomes	Larsson *et al.*	Bicontinuous cubic liquid crystalline structures in the form of Colloidal dispersion	Hydrophilic, lipophilic, and amphiphilic drugs	Oral bioavailability improvement and prolongation of drug residence time.	[16], [17]
Discosomes/ Giant niosomes	-	Niosomes are modified to disc-shaped structures by incorporation of non-ionic surfactant Solulan C24 (poly-oxy-ethylene cholesteryl ether)	Ophthalmic drug	Enhanced ocular absorption with reduced or minimal side effects	[18],[19]
Emulsosomes	Amselem S *et al.*	Solid fat core stabilized by a phospholipid bilayer	Poorly soluble drugs, biomicromolecules, and vaccine	Prolongation of drug the systemic circulation	[20],[21],[22]
Enzymosomes	-	Functional lipid vesicles encapsulating an enzyme	Enzymes acting as therapeutic proteins	Enhanced pharmacokinetic effects, active drug targeting, site-specificity	[23]
Erythrosomes	-	A lipid bilayer is coated on the chemically cross-linked human erythrocytes	DNA for gene therapy, Polar drugs, Metabolic enzymes, Erythropoietin, Anti-inflammatory drugs, or steroids	Drug delivery, phototherapy, imaging, detection, sensing and immunomodulation	[24]
Ethosomes	Touitou *et*	A lipid bilayer with	Both hydrophilic	Improved skin delivery	[25]

	al. in 2000	high ethanol concentrations	and lipophilic drugs	and encapsulation efficiency; High deformability, biocompatibility, and stability	
Genosomes/ Lipoplexes	-	Cationic lipid-DNA complexes	Functional gene	Cancer therapy at the genetic level	[26],[27]
Hemosomes	Chang TMS *et al.* in 1957	Encapsulation of heam or hemoglobin within lipid vesicles or liposomes.	Artificial oxygen	Acute brain ischemia, blood transfusion replacement therapy	[28]
Novasomes	Novavax. IGI laboratories	Non-phospholipid paucilamellar vesicles	Both hydrophilic and lipophilic drugs	More encapsulation efficiency and shows better targeting and sustained release	[29]
Niosomes/ Nonionic surfactant vesicles	Handjanivila *et al.*	Bilayer structures that is made mostly of nonionic surfactant and lipid compounds	Protein, Vaccine, and antigen	Oral bioavailability enhancement, Stability improvement, Tumour targeting	[30],[31]
Photosomes	-	Photolyase encapsulated in liposomes	Photoactive enzyme-Photolyase	Photodynamic therapy, skin cancer	[32]
Ufasomes/ Unsaturated fatty acid vesicles	J M Gebicki and M Hicks in 1973	Closed lipid bilayers of fatty acid with their ionized species in the form of colloidal suspensions	Anti-inflammatory, antifungal, antiosteoarthritic, anticancer drugs.	Transdermal delivery	[33],[34]
Vesosomes	Zasadzinski *et al.*	Large lipid bilayer enclosing many smaller liposomes	Colloidal particles, biological macromolecules	Loading of pH sensitive drugs, Steric stabilization, and intrinsic biocompatibility	[35],[36]
Virosomes	-	Spherical, unilamellar vesicles reconstructed from phospholipids of the viral envelope with the removal of nucleocapsid	Hydrophilic and hydrophobic drugs, polymers and peptides, immunogenic substances, and chemotropic agent	Vaccine development	[37]

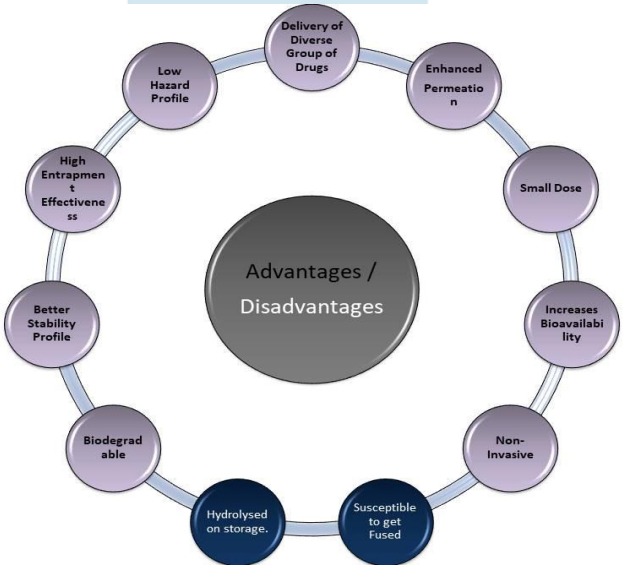

Figure 2: Advantages and Disadvantages of Phytosomes[3]

FORMULATION CONSIDERATION

Based on the literature, we have summarized the essential components involved in phyto-phospholipid complex formation: phyto-active ingredients, phospholipids, the stoichiometric ratio, and solvents.[38]

a) Selection of herbal extract

For the development of a novel drug delivery system, solubility remains a critical parameter. The most appropriate formulation is developed based on the nature of the phytoconstituent, which was either hydrophilic or lipophilic.[9] Some phytochemicals cannot cross the lipid bilayer and some are unable to dissolve in aqueous GI fluids due to their hydrophilic and lipophilic nature respectively. Phyto-phospholipid complexes help to overcome the problem associated with phytochemicals by improving membrane penetrability of hydrophilic and solubility of lipophilic components. In addition, the formation of complexes helps in the protection of phytoactive compounds from the destructive effects of environmental stimuli such as moisture, light, and air which are prone to hydrolysis, photolysis, and oxidation.[38] The key aspects for the selection of plants actives depend on the type of phytochemical (alkaloids, polyphenols, saponins, tannins, and triterpenoids) and pharmacokinetic properties. The complex structure and larger molecular size prevent phytochemicals to be absorbed via simple diffusion. In some instances, natural compounds may lose limited or all of their biological activity during extraction and purification, therefore entire plant extracts are used. While formulating the phyto-phospholipid complex, standardized extracts were taken on a weight basis and active constituents on molar ratios.[39] A drug that carries a reactive hydrogen atom-like, -OH, NH, NH_2, COOH, etc., can form a hydrogen bond linking the drug and quaternary nitrogen of phosphatidylcholine molecules.[39]

b) Selection of phospholipid

The plants and animals are the primary sources of phospholipids, with the most common sources being soya bean, sunflower seeds, rapeseed, cotton, vegetable oils, and animal tissue such as egg yolk and bovine brain. The phospholipids are made up of glycerol molecules with two fatty acids (non-polar chain), and the third site is replaced by a phosphate group (polar part). Phosphatidylcholine, phosphatidylserine, phosphatidylinositol, phosphatidylethanolamine , phosphatidic acid are the major part of the biological membrane that is mostly used in the phytosome preparations.[39] Both Synthetic and natural phospholipids are available for the preparation of phytosomes. Synthetic phospholipid are relatively stable, and purity is relatively high but the price is also relatively high while natural phospholipid has a price relatively low but purity is difficult to control and are relatively unstable.[40] The source should be considered while choosing natural phospholipids. Phosphatidylcholine is a vital part of the biological membrane where they perform a dual function in Phytosomes technology by acting as the best carrier for plant actives and have therapeutic benefits in the treatment of hepatic disease.

Utilization of various phospholipids makes different phytosomes of the same phytochemicals with changes in their properties, as seen in Ginkgo biloba phytosomes, Ginkgoselect is a phytosome complex with standard phosphatidylcholine and Virtiva is complex with standard phosphatidylserine.[7] To date, the phospholipid complexes prepared from phosphatidylinositol (PI), and phosphatidylglycerol (PG) have not yet been reported.

c) Selection of solvents

Aprotic solvents have traditionally been employed to create phytophospholipid complexes, such as methylene chloride, cyclic ethers, aromatic hydrocarbons, ethyl acetate, halogen derivatives, etc. as illustrated in Table 2. that are not food grade solvents[41] so protic solvents such as ethanol have largely superseded them.[6] This issue revolves around the fact that food-grade solvents, such as ethanol, should be used when formulating phytosomes for food applications.[42] In the formulation of phytosomes by supercritical fluids technique, CO_2 is the most widely used solvent. Supercritical CO_2 has advantages over other solvents such as it has a high diffusivity, its innocuity, and its green features make it a perfect candidate for the pharma industry. [43]

Table 2: Comparing several phytosome formulations using phospholipids, solvents and methods involved.

Author	Phytosomes	Phospholipid	Solvents	Ratio (Phospholipid: extract)	Method
Komeil IA *et al*.[44]	Genistein-phytosomes	Lipoid S100, Phosal 53 MCT, and Phosal 75 SA	Dimethyl Sulphoxide	-	Solvent Evaporation Method
Sharma S *et al*.[45]	Abutilon indicum and Piper longum Phytosomes	Soy Phosphatidylcholine	Methylene chloride	1:1	Solvent Evaporation Method
Makhlourf AIA *et al*.[46]	Silymarin phytosomes	Soybean lecithin and egg yolk lecithin	Methanol	1:1 and 0.25:1	Solvent Evaporation Method
Yu F *et al*.[47]	Berberine-phospholipid complex	Soybean phosphatidylcholine LIPOID S-100	Ethanol to dichloromethane	9:1	Rotary Evaporation

Molaveis M *et al*.[48]	Echinacea extract phospholipid phytosome	Phosphatidylcholine	1, 4-dioxane: methanol (14:6)	1:3	Anti-solvent Precipitation Technique
Varadkar M *et al*.[49]	Crocetin from Nyctanthes arbor-tristis phospholipid complex	Phosphatidylcholine	Chloroform	1:1	Lipid Film Hydration Method

d) Preparation method of Phytosomes

1. Anti-solvent precipitation technique

The different molar ratios of herbal extract and phospholipids were taken in a round bottom flask and refluxed with required quantity of an organic solvent such as dichloromethane[50],[51], methanol, acetone[52] at a specified temperature below 60 ^{o}C for minimum of 2 h. The reaction mixture was reduced to a minimum volume of 10 ml and low polarity hydrocarbon n-hexane was added to form precipitate with continuous stirring. The precipitate was pulverized and sieved using #100 mesh size and was kept in vacuum desiccator for overnight.

2. Solvent evaporation technique

The known quantity of phyto actives and phospholipid were dissolved in dichloromethane[47] or tetrahydrofuran and placed in the RBF. This flask of the reaction mixture was assembled on a rotary evaporator with a speed of 180 rpm. To generate a film on the flask wall, the solvent was evaporated at 40 ^{o}C [53]; 60 ± 2 ^{o}C [54] under reduced pressure. At the same temperature, the casted film was dispersed in phosphate buffer saline (pH 6.8[53] ; pH 7.4[54]). Due to the phosphate buffer saline, lipid in the film hydrated and swelled which was peeled off from the wall of the flask. By using the probe sonicator, the resultant phytosomal suspension was sonicated for about 4 mins with 5 s on-off interval and 60% amplitude. Before characterization, all phytosomal suspensions were maintained in the refrigerator for a maximum of 24 h. [54] Using a systematic quality by design approach, Kaliappan Ilango *et al*. developed Vasaka loaded phytosomes using a thin layer hydration technique.[55]

3. Ether-injection technique

The phyto actives and phospholipids were dissolved in an organic solvent to form the complex. The mixture was slowly injected into a heated aqueous media, resulting in the formation of vesicles which is directly proportional to the concentration of amphiphiles. They form a monomer state at the lower concentration, but as the concentration rises, a range of structures, including disc, cubic, spherical, cylindrical, or hexagonal structures, might appear.[56]

4. Supercritical fluids technique (SCF)

Traditional phytophospholipidic complexation methods reported, required multi-stage processing and were time-consuming. SCF approach ensures particle size and particle size distribution control in the micrometric or nanometric regions. Supercritical antisolvent method, Compressed antisolvent process, gas anti-solvent technique, solution enhanced dispersion by supercritical fluids, and the rapid expansion of supercritical solutions are supercritical fluid techniques that are the best approach for improving solubility profiles of phytochemicals which are poorly soluble.

Supercritical antisolvent precipitation (SAS) procedures were used by Li et al. (2007) to prepare the puerarin-phospholipid complex. The researchers compared two techniques: The gas anti-solvent method which produced particles with more precisely controlled morphological properties and solution improved dispersion by supercritical fluids produced particles with a total loss of crystallinity. This demonstrated that the SAS approach superseded the traditional Phytosomes preparation method in terms of particle size and distribution control as well as time savings and process ease.[57]

5. Mechanical dispersion method

A mechanical dispersion approach to making a Marsupsin–Phospholipid complex was firstly reported by Sikarwar et al. In this method, phospholipid components were dissolved in a minimum quantity of a non-polar solvent (e.g. diethyl ether) and sonicated in an ultrasonic bath. The aqueous solution of phyto actives was added drop by drop to phospholipid solution while sonicating for 15 minutes. The phyto-phospholipid complex was formed in the resulting suspension.[58]

6. Co-solvent lyophilization method

Sublimation of ice or even other solvents through the substance as well as eliminating bound water molecules by desorption is known as lyophilization or freeze-drying. Sublimation is the basic principle of the lyophilization technique. Freeze drying is carried out at pressures and temperatures below the triple point, allowing ice to sublimate. The Lyophilization cycle is carried out in three steps namely the freezing stage, primary drying, and secondary drying. Cui *et al*. used an anhydrous co-solvent lyophilization process to prepare the insulin phospholipid complex. The insulin powder and soybean phosphatidylcholine were gently dissolved in dimethyl sulfoxide (DMSO) with 5% glacial acetic acid to obtain a transparent mixture. This mixture was placed in the freeze dryer overnight at a temperature of -40 ^{o}C and a vacuum of 10 Pa. In their investigation, the authors confirm that the insulin phospholipid complex can significantly increase insulin absorption in the intestine.[59]

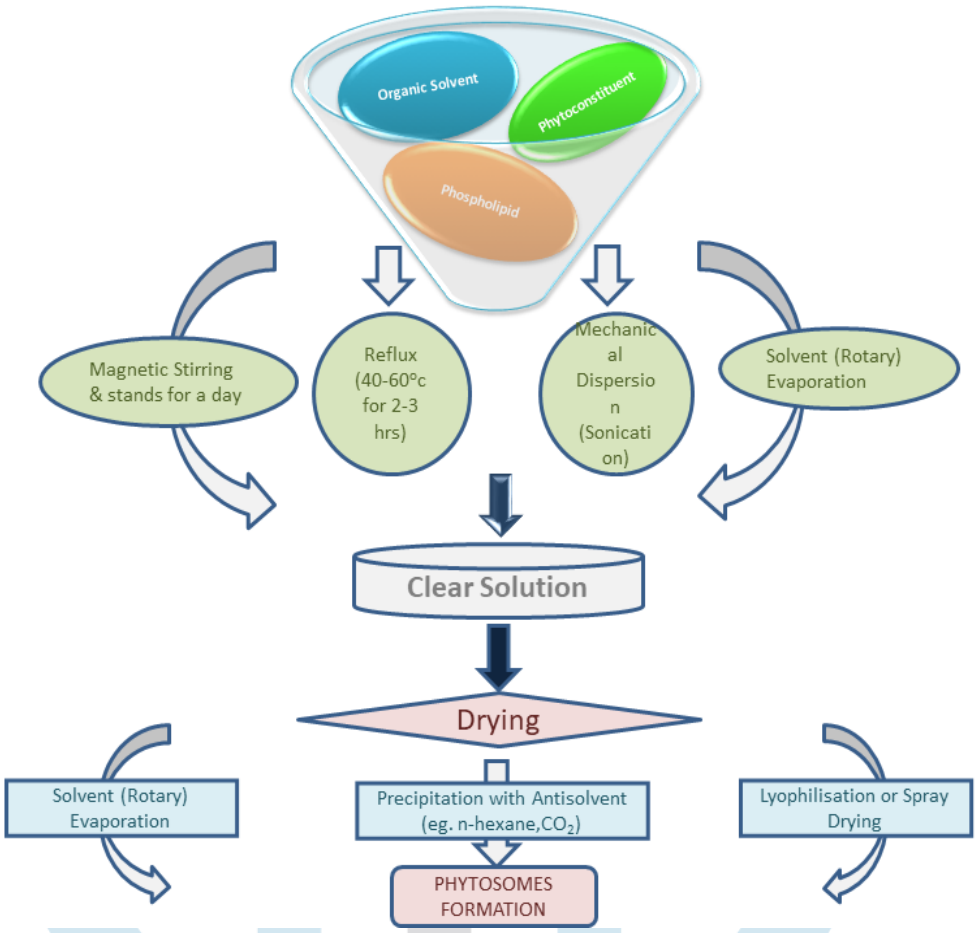

Figure 3: Various methods for phytosome formulation.

e) Selection of appropriate dosage form for phytosome delivery.

An optimal formulation/dosage form for the distribution of phytosomes can be developed, depending on its ability to improve the efficiency and effectiveness of bioactive substances. The intrinsic features of herbal drugs, such as hydrophilic or lipophilic, degree of biodegradability, and tonicity; system surface characteristics, such as permeability and charges, the size of the product required for the final formulation, and release profile must all be considered. The following are some dosage formulations for phytosome delivery that have been suggested.

Oral dosage form

1. **Soft gelatin capsules**

Phytosome complex can be easily encapsulated into the soft gelatin capsules, by dispersing it into the oily vehicles to obtain a suspension. For this purpose vegetable oils or semi-synthetic oils can be utilized. Ahmed N. Allam et al. prepared curcumin phytosomal soft gels. They have seen many benefits of soft gels as compared to hard gelatin capsules. In soft gels, the dose can be increased by two folds as compared to hard gelatin capsules as investigated by the author.[60]

2. **Hard gelatin capsules**

Hard gelatin capsules containing the Phytosome complex are also available. A direct volumetric filling process without precompression can be used for the phytosome complex with a high density. However, using a piston tamp capsule filling procedure, the amount of powder that can be placed in a capsule can be increased, although precompression may impair the disintegration time. The optimal manufacturing process is defined by a preliminary dry granulation procedure.[61]

3. **Tablets**

The dry granulation process can be used to get the best release of phytosomal preparation from solid dosage forms. However, because of the phytosome complex's limited flowability, low apparent density, and significant stickiness, a direct compression procedure should be used for low unitary doses. 60-70 % of diluents can be used to make phytosome complex tablets with the needed properties. In the wet granulation process, basic requirements are water and heat which have unfavorable impacts on the phospholipid complex's stability.[62]

Topical dosage form

The phyto-phospholipid complex can also be applied topically as a cream, gel, and ointment. Taleuzzaman M *et al*. has prepared phytosomal gel of aloe-vera extract for topical delivery and which is a better option for topical use than aloe-vera gel. The Phytosomal gel of Manjistha extract has enhanced permeation and prolonged release when compared to Manjistha extract gel.[63] Purnamasari N D *et al*. prepared Nano-Phytosomes of Myricetin Peel-Off Gel Mask having excellent antioxidant potential.[64]

CHARACTERIZATION AND EVALUATION OF PHYTOSOMES

1. **Entrapment Efficiency (EE)**

   The EE of phytoconstituents loaded with phytosomes can be measured by ultracentrifugation. Ultracentrifugation operated for longer periods of time at lower rpm or shorter period of time at higher rpm. Furthermore, the supernatant should be tested for phytoactive chemicals using UV-Visible spectroscopy or high-performance liquid chromatography.[65]

2. **Particle size and zeta potential**

   The particle size of the vesicular system should be maintained throughout the shelf life. As the concentration of the complex rises, the sizes of the vesicle begin to increase by the physical interactions between vesicles, such as collisions and electrostatic interactions. These interactions cause the particles to move differently, resulting in larger vesicles. The formulation's high lipid content increases the possibility of aggregation, resulting in bigger vesicle sizes.[54] Zeta potential can be the most vital parameter, for the physical stability of phytosomes. The greater the electrostatic repulsion between particles, the more stable the system. The zeta potential of 20 mV indicates that the dispersion is physically stable.[53]

3. **Scanning electron microscopy (SEM) and transmission electron microscopy (TEM)**

   The morphology of phytosomes can be studied using SEM and TEM. The surface morphology of phytosomes is frequently used to detect entrapment mechanisms as well as the presence of possible impurities on the surface.[65] The changes in the structure and shape of phytosomes can be monitored using both SEM and TEM.

4. **Ultraviolet spectra (UV-spectra)**

   The most quantitative study can be done by UV spectroscopy. The drug content, in vitro drug release, and solubility study can be done by this technique.[53]

5. **Differential scanning calorimetry (DSC)**

   DSC is a quick and accurate thermoanalytical technique for gaining insight into solid-state interactions. Elimination of endothermic peaks, change in peak form and its onset, relative peak area or enthalpy, the emergence of new peaks, and peak temperature/melting point are all indicators of successful interaction between phytoconstituents and phospholipids in DSC. The crystalline nutraceutical moiety is represented by a prominent peak at high melting temperatures in DSC thermograms. The appearance of a broad peak is owing to the structure of phytosomes, which has a substantially lower melting point than pure nutraceuticals. The broad peak shows a decrease in the crystallinity of phytoactive compounds.[65]

6. **Fourier transform infrared spectroscopy (FTIR)**

   FTIR is a qualitative structural analysis approach that produces diverse functional groups with distinct location, band number, intensity, and shape parameters. Comparing the spectra of phyto-phospholipid complexes and physical mixtures can be used to verify the formation of Phyto-phospholipid complexes.[38]

7. **X-ray diffraction**

   Due to complexation, the crystallinity of phytoactive chemicals is lost, causing the hydrophilicity and hydrophobicity to be balanced. The most commonly used techniques for evaluating the crystallinity and interaction of phospholipid with phytoconstituents, are DSC and X-ray diffraction (X-RD) studies.[65]

8. **Nuclear magnetic resonance (NMR)**

   The phytosome complex, PC, and pure forms of phytoactive substances can be distinguished by comparing the 1H-NMR and 13C-NMR spectrum. The peaks of fatty acid chains are essentially unchanged, indicating that they enfolded around the phytoactive chemical, resulting in the formation of a lipid-compatible cover that protects the polar component of the phytosome and allows it to be dissolved in low-polarity solvents.[65]

   According to IR and NMR investigations a phytosome is a particular complex between a hydrophilic guest and a lipophilic host characterized by distinct dipolar interactions, instead of being a physical combination of its two elements.[7]

MECHANISM OF ABSORPTION OF PHYTOSOMES

The possibilities by which drugs show low bioavailability are low solubilization, the presence of metabolizing enzymes, P-gp efflux pump, and pH-mediated degradation. Two essential qualitative aspects for the development of novel lipid-based drug delivery systems have been highlighted:

1) Drug solubility by particular interaction within the lipidic system and

2) To promote effective drug absorption, the drug-loaded lipidic system is subjected to physiological processing.[66]

The mechanism of phospholipid-drug complex absorption is similar to that of endogenous phospholipid absorption through enterocytes.
In the phyto-phospholipid complex, phospholipid comprises glycerol with two fatty acid chains (diacylglycerol) and one polar group H-bonded with the drug moiety. In the intestine, drug-diacyl glycerol undergoes hydrolysis in the presence of phospholipase A2, resulting in the release of fatty acids and the formation of drug-monoacyl glycerol.[66] This elevated level of free fatty acids triggers the release of the hormone cholecystokinin (CCK) which aids in bile excretion into the duodenum. Micellar vehicles are generated when drug-monoacyl glycerol is combined with bile salts. Enterocytes take up the micellar vehicles through passive diffusion. [67]
The acidic intestinal unstirred water layer (UWL) protonates long-chain fatty acid (LCFA) in mixed micelles. This reduces the amphiphilic nature and solubility of LCFA in mixed micelles, resulting in increased LCFA thermodynamic activity and further its dissociation from mixed micelles and apical membrane absorption. The lipid absorption affects the solubilization capacity of the drug. Drug supersaturation near absorptive sites, such as enterocytes, improves drug absorption.[68]
Wolfgang Stremmel et al. introduced another phosphatidylcholine transport pathway in which, phosphatidylcholine passes across apical side of the polarized intestinal tumor cell-line CaCo2 through lateral tight junctions. According to Author, the electrochemical gradient induced by the apical accumulation of HCO_3^- and Cl^- through the Cystic fibrosis transmembrane conductance regulator promotes translocation. [69]

Recent research on phytosomes and their activities
Rita Kartika Sari et al. have studied the phytochemical profile of alcoholic extracts of Daemonorps acehensis resin, its phytosomes, their antioxidant activity, and sun protection activity. They concluded that increasing the polarity of the solvent did not enhance the compound's solubility from the resin to solvent while adjusting the solvent ratio for extraction of Daemonorps acehensis resin. The antioxidant capacity and SPF value of the extract prepared using 100 percent ethanol were the maximum. The promising extract and phytosome were selected on the basis of antioxidant capacity and SPF value.[70]
Christian Bergamini et al. have examined the antioxidant effects and bioenergetics of a Coenzyme Q10 phytosome formulation (UBIQSOME, UBQ) in a rat cardio myoblast cell line (H9c2) and a human epithelial intestine cell line (Intestine 407, I407). CoQ10 is the lipophilic antioxidant found in cells; and in its reduced form (CoQH2), it protects circulating lipoproteins and cell membranes from lipid peroxidation. Due to its low bioavailability, it is formulated as Coenzyme Q10 phytosome (UBIQSOME).[71]Beatriz P.P. Oliveira et al. aimed at another approach to improving protection and stability against degradation by coating nano-phytosomes with various natural polymers. With a primary or secondary coating on a phytosome loaded with enriched extract of coffee silverskin (a by-product of the coffee roasting industry), the finished product can also have great efficiency at lower doses, making it appropriate for oral distribution.[72]Heba M.K. Ebada et al. first worked on changing the makeup of traditional phytosomes. They created a hybrid among phytosomes and transfersomes or bilosomes by adding several edge activators (EAs) into the bilayer membrane of Rhein phytosomes, such as Tween 80, sodium deoxycholate, and Span 80. This method appears to be a promising alternative for increasing medication transdermal permeability.[73]

Vivek S. Dave *et al.* prepared the apigenin phytosome and studied its pharmacokinetic and pharmacological activity in carbon tetrachloride-induced oxidative damage in rats. In comparison to pure apigenin, the Apigenin phytosome has shown a 36-fold increase in aqueous solubility. Apigenin phytosome complex enhanced the oral bioavailability by improving the lipophilic property of apigenin was demonstrated by increased Cmax, Tmax, and AUC. The apigenin phytosome complex exerted better hepatoprotective activity in carbon tetrachloride-induced rats. The antioxidant activity was measured by examining its influence on antioxidant marker enzymes Serum Glutamic-Oxaloacetic Transaminase (SGOT), Serum Glutamic-Pyruvic Transaminase (SGPT), Serum Alkaline Phosphatase, and total bilirubin in the liver.[74]

Akram Pezeshki *et al.* have prepared Resveratrol nano-phytosome by thin-layer hydration and sonication. The Resveratrol phytosome have a good antioxidant effect than hydrophobic Resveratrol without nanocarriers. The antioxidants are required for improving shelf life and ultimately the quality of the food matrix. This study aimed to incorporate the Resveratrol nano-phytosomes as antioxidants into the mayonnaise for increasing shelf life and also nutritional properties.[75]

May S. Freag *et al.* have formulated Tripterine Phytosomes having anticancer potential, by solvent evaporation technique. The tripterine phytosomes were functionalized with protamine a mucopenetrating peptide. This mucosal targeted tripterine phytosomes were incorporated into the composite sponges using the lyophilization technique. Ex-vivo permeation tests revealed that composite sponges of tripterine phytosomes had a greater permeation rate while in-vivo pharmacokinetic investigations revealed a considerable rise in AUC and Cmax. The research resulted in a novel buccal mucoadhesive system containing mucopenetrating phytosomes that enabled tripterine transfer via buccal mucosa, with the ultimate goal of increasing its bioavailability.

Sudhir Kumar *et al.* have performed an Ex vivo investigation of the cytotoxic effect based on in vitro antioxidant assay of taxifolin phytosomes on human breast cancer cell lines (MCF7). The in vitro antioxidant assay was estimated by several methods namely DPPH radical scavenging assay, Hydrogen peroxide scavenging activity, Nitric oxide scavenging assay and, Reducing power assay. MTT and Trypan blue assays were used to evaluate ex vivo anticancer activity in MCF7 cell lines. The phytosome formulations can be developed for the treatment of carcinoma caused by cancer mediators and free radicals reducing the incidence of breast cancer significantly. [76]

Jeanetta du Plessis *et al.* have prepared Sinigrin-phytosome complex which is evaluated for In vitro cytotoxic effects and wound healing. On HaCaT cells, the wound healing properties of pure Sinigrin and its phytosome complex were investigated. The Sinigrin-phytosome complex completely healed the wound, but Sinigrin alone only healed it 71%. The Sinigrin has cytotoxic activity on melanoma cells (A-375) but the phytosome complex of Sinigrin has increased the cytotoxic activity.[51]

Arlene McDowell et al. have prepared Rutin Phytosomes a superior nano delivery system for antioxidants. The objective of this study was to compare the structure of rutin liposomes to that of rutin phytosomes.[77]

PHYTOSOMES: CLINICAL TRIAL (www.clinicaltrials.gov) Accessed date 25/03/2022

Several phytosome-based formulations have reached clinical trials to check their safety and efficacy in the human body. In 2020, the first clinical trial of Quercetin Phytosome (QP) was conducted against early-stage COVID-19 infection. QP a safe medication, when administered in conjunction with normal care in the early phase of viral infection, may help to improve early symptoms and reduce the severity of COVID-19 disease.[78] (Identifier: NCT04578158) In a preclinical study, grape seed procyanidin extract was found to have anticancer effects. Grape seed procyanidin extract is also studied in a phase IIa clinical trial to evaluate the potential usefulness against early-stage lung cancer patients when formulated as a phytosome called Leucoselect phytosome(LP).[79] (Identifier: NCT04515004**)** The activity of Artichoke and Bergamot Phytosome as an anti hypercholesterolemic agent was investigated in a Randomized Double-Blind Clinical Trial. The result showed that administered bergamot Phytosome and artichoke dry extract have a synergistic effect which was a beneficial treatment in subjects who did not respond well to bergamot.[80] (Identifier: NCT04697121)

CONCLUSION:

In the fast changing world, peoples need rapid effect of any medicine with minimal or no side effect. This can be achieved by some modification in conventional medicinal system. The delivery of standardized herbal extract need to be explored through some value added novel drug delivery systems. However, more attention should be given to the carrier system in the delivery of phytoactives resulting in the improved activity and decreased toxicity. Using phytoactives of herbal medicine with lipid base called as Phytosomes, can increase bioavailability of active moiety and better therapeutic action. Many plant extract and phytomolecules have a considerably great bioactivity in vitro than that of in vivo due to larger molecular size and inadequate lipid solubility. This technique is enables to overcome this problem. Also desire therapeutic effect can be obtained with same or less dose compared to a traditional plant extract. The study in the field of phytosomes is still at exploratory stage. Many issues in research, development, and application should be solved. Hence there is a great potential in the development of novel drug delivery systems for the plant extracts and actives.

REFERENCES:

[1] Ajazuddin and S. Saraf, "Applications of novel drug delivery system for herbal formulations," *Fitoterapia*, vol. 81, no. 7, pp. 680–689, 2010, doi: 10.1016/j.fitote.2010.05.001.

[2] A. Dhiman, A. Nanda, and S. Ahmad, "Novel Herbal Drug Delivery System (NHDDS): the need of Hour 2 . Types of Novel Herbal Drug Delivery Systems," vol. 49, pp. 171–175, 2012, doi: 10.7763/IPCBEE.

[3] A. Pandita and P. Sharma, "Pharmacosomes: An Emerging Novel Vesicular Drug Delivery System for Poorly Soluble Synthetic and Herbal Drugs," *ISRN Pharm.*, vol. 2013, no. 3, pp. 1–10, 2013, doi: 10.1155/2013/348186.

[4] M. S. Khan and K. Krishnaraj, "Phospholipids : A Novel Adjuvant in Herbal Drug Delivery Systems," vol. 31, no. 5, pp. 407–428, 2014.

[5] S. Wahab, M. Y. Alshahrani, M. F. Ahmad, and H. Abbas, "Current trends and future perspectives of nanomedicine for the management of colon cancer," *Eur. J. Pharmacol.*, vol. 910, no. March, p. 174464, 2021, doi: 10.1016/j.ejphar.2021.174464.

[6] J. Khan, A. Alexander, S. Saraf, and S. Saraf, "Recent advances and future prospects of phyto-phospholipid complexation technique for improving pharmacokinetic pro fi le of plant actives," *J. Control. Release*, vol. 168, no. 1, pp. 50–60, 2013, doi: 10.1016/j.jconrel.2013.02.025.

[7] A. Semalty, M. Semalty, M. Singh, M. Rawat, and F. Franceschi, "Fitoterapia Supramolecular phospholipids – polyphenolics interactions : The PHYTOSOME ® strategy to improve the bioavailability of phytochemicals," *Fitoterapia*, vol. 81, no. 5, pp. 306–314, 2010, doi: 10.1016/j.fitote.2009.11.001.

[8] N. Jain *et al.*, "Phytosome : A Novel Drug Delivery System for Herbal Medicine," *Int. J. Pharm. Sci. Drug Res.*, vol. 2, no. 4, pp. 224–228, 2010.

[9] S. Saraf and C. D. Kaur, "Phytoconstituents as photoprotective novel cosmetic formulations," vol. 4, no. 7, 2010, doi: 10.4103/0973-7847.65319.

[10] S. Banerjee and K. K. Sen, "Aquasomes: A novel nanoparticulate drug carrier," *J. Drug Deliv. Sci. Technol.*, vol. 43, no. November 2017, pp. 446–452, 2018, doi: 10.1016/j.jddst.2017.11.011.

[11] M. S. Umashankar, R. K. Sachdeva, and M. Gulati, "Aquasomes: a promising carrier for peptides and protein delivery," *Nanomedicine Nanotechnology, Biol. Med.*, vol. 6, no. 3, pp. 419–426, 2010, doi: 10.1016/j.nano.2009.11.002.

[12] G. Kaur, T. Garg, G. Rath, and A. K. Goyal, "Archaeosomes: an excellent carrier for drug and cell delivery," *Drug Deliv.*, vol. 23, no. 7, pp. 2497–2512, 2016, doi: 10.3109/10717544.2015.1019653.

[13] R. Ahmad, S. Srivastava, S. Ghosh, and S. K. Khare, "Phytochemical delivery through nanocarriers: a review," *Colloids Surfaces B Biointerfaces*, vol. 197, p. 111389, 2021, doi: 10.1016/j.colsurfb.2020.111389.

[14] F. J. Rossier-Miranda, C. G. P. H. Schroën, and R. M. Boom, "Colloidosomes: Versatile microcapsules in perspective," *Colloids Surfaces A Physicochem. Eng. Asp.*, vol. 343, no. 1–3, pp. 43–49, 2009, doi: 10.1016/j.colsurfa.2009.01.027.

[15] A. V. Vidyapeetham, "Int J App Pharm , Vol 11 , Issue 1 , 2019 , 7-13 Review Article CRYPTOSOMES : A REVOLUTIONARY BREAKTHROUGH IN NOVEL DRUG DELIVERY," vol. 11, no. 1, pp. 7–13, 2019.

[16] S. M., B. HARSHINI, P. V. K. KUMARI, and Y. S. RAO, "Review on Cubosomes," *Int. J. Curr. Pharm. Res.*, vol. 13, no. 6, pp. 37–42, 2021, doi: 10.22159/ijcpr.2021v13i6.1926.

[17] M. Garg, A. Goyal, and S. Kumari, "An Update on the Recent Advances in Cubosome: A Novel Drug Delivery System," *Curr. Drug Metab.*, vol. 22, no. 6, pp. 441–450, 2021, doi: 10.2174/1389200221666210105121532.

[18] A. M. Jose, V. U. Lakshmi, S. Gayathri, and S. C. Nair, "Discosomes: A futuristic upheaval in vesicular drug delivery," *Int. J. Appl. Pharm.*, vol. 13, no. 6, pp. 41–46, 2021, doi: 10.22159/ijap.2021v13i6.42008.

[19] S. K. Sahoo, F. Dilnawaz, and S. Krishnakumar, "Nanotechnology in ocular drug delivery," *Drug Discov. Today*, vol. 13, no. 3–4, pp. 144–151, 2008, doi: 10.1016/j.drudis.2007.10.021.

[20] R. P. Swain, B. B. Subudhi, A. K. Mahapatra, and V. Bolapareddi, "Bridging between disease, prevalence and treatment of diabetes mellitus: A review," *Int. J. PharmTech Res.*, vol. 7, no. 2, pp. 212–228, 2014.

[21] B. Gill, J. Singh, V. Sharma, and S. Hari Kumar, "Emulsomes: An emerging vesicular drug delivery system," *Asian J. Pharm.*, vol. 6, no. 2, pp. 87–94, 2012, doi: 10.4103/0973-8398.102930.

[22] Y. Shiba, "United States Patent (19)," no. 19, 1981.

[23] S. Shefrin, C. S. Sreelaxmi, V. Vijayan, and S. C. Nair, "Enzymosomes: A rising effectual tool for targeted drug delivery system," *Int. J. Appl. Pharm.*, vol. 9, no. 6, 2017, doi: 10.22159/ijap.2017v9i6.22556.

[24] F. Castro, C. Martins, M. J. Silveira, R. P. Moura, C. L. Pereira, and B. Sarmento, "Advances on erythrocyte-mimicking nanovehicles to overcome barriers in biological microenvironments," *Adv. Drug Deliv. Rev.*, vol. 170, pp. 312–339, 2021, doi: 10.1016/j.addr.2020.09.001.

[25] T. Limongi *et al.*, "Lipid-Based Nanovesicular Drug Delivery Systems," 2021.

[26] D. Rafael, F. Andrade, A. Arranja, S. Luís, and M. Videira, "Lipoplexes and Polyplexes: Gene Therapy," *Encycl. Biomed. Polym. Polym. Biomater.*, no. January, pp. 4335–4347, 2015, doi: 10.1081/e-ebpp-120050058.

[27] D. D. Lasic, "Recent developments in medical applications of liposomes: Sterically stabilized liposomes in cancer therapy and gene delivery in vivo," *J. Control. Release*, vol. 48, no. 2–3, pp. 203–222, 1997, doi: 10.1016/S0168-3659(97)00045-X.

[28] N. F. Idris and Y. R. Hundekar, "Development of Hemosomal Drug Delivery System," vol. 1, no. 3, pp. 1–5, 2014.

[29] A. Singh, R. Malviya, and P. K. Sharma, "Novasome-A Breakthrough in Pharmaceutical Technology a Review Article," *Adv. Biol. Res. (Rennes).*, vol. 5, no. 4, pp. 184–189, 2011.

[30] S. Kamboj, V. Saini, N. Magon, S. Bala, and V. Jhawat, "Vesicular drug delivery systems : A novel approach for drug targeting," vol. 5, pp. 121–130, 2013.

[31] M. Gharbavi, J. Amani, H. Kheiri-Manjili, H. Danafar, and A. Sharafi, "Niosome: A Promising Nanocarrier for Natural Drug Delivery through Blood-Brain Barrier," *Adv. Pharmacol. Sci.*, vol. 2018, 2018, doi: 10.1155/2018/6847971.

[32] L. Decome, M. De Méo, A. Geffard, O. Doucet, G. Duménil, and A. Botta, "Evaluation of photolyase (Photosome®) repair activity in human keratinocytes after a single dose of ultraviolet B irradiation using the comet assay," *J. Photochem. Photobiol. B Biol.*, vol. 79, no. 2, pp. 101–108, 2005, doi: 10.1016/j.jphotobiol.2004.11.022.

[33] D. M. Patel, R. H. Jani, and C. N. Patel, "Ufasomes: A vesicular drug delivery," *Syst. Rev. Pharm.*, vol. 2, no. 2, pp. 72–78, 2011, doi: 10.4103/0975-8453.86290.

[34] S. L. V, D. M. R, S. Mathan, and S. S. Dharan, "Ufasomes : A Potential Vesicular Carrier System," vol. 12, no. 10, pp. 1332–1335, 2020.

[35] A. Chime, "Lipid-based drug delivery systems (LDDS): Recent advances and applications of lipids in drug delivery," *African J. Pharm. Pharmacol.*, vol. 7, no. 48, pp. 3034–3059, 2013, doi: 10.5897/ajppx2013.0004.

[36] B. Kapoor, R. Gupta, M. Gulati, S. K. Singh, R. Khursheed, and M. Gupta, *The Why, Where, Who, How, and What of the vesicular delivery systems*, vol. 271. Elsevier B.V, 2019. doi: 10.1016/j.cis.2019.07.006.

[37] K. Asadi and A. Gholami, "Virosome-based nanovaccines; a promising bioinspiration and biomimetic approach for preventing viral diseases: A review," *Int. J. Biol. Macromol.*, vol. 182, pp. 648–658, 2021, doi: 10.1016/j.ijbiomac.2021.04.005.

[38] M. Lu *et al.*, "Phyto-phospholipid complexes (phytosomes): A novel strategy to improve the bioavailability of," *Asian J. Pharm. Sci.*, vol. 14, no. 3, pp. 265–274, 2019, doi: 10.1016/j.ajps.2018.05.011.

[39] K. Gnananath, K. S. Nataraj, and B. G. Rao, "Phospholipid Complex Technique for Superior Bioavailability of Phytoconstituents," *Adv Pharm Bull*, vol. 7, no. 1, pp. 35–42, 2017, doi: 10.15171/apb.2017.005.

[40] J. Li, X. Wang, T. Zhang, C. Wang, and Z. Huang, "ScienceDirect A review on phospholipids and their main applications in drug delivery systems," *Asian J. Pharm. Sci.*, vol. 10, no. 2, pp. 81–98, 2015, doi: 10.1016/j.ajps.2014.09.004.

[41] K. Maiti, K. Mukherjee, A. Gantait, B. P. Saha, and P. K. Mukherjee, "Enhanced therapeutic potential of naringenin-phospholipid complex in rats," *J. Pharm. Pharmacol.*, vol. 58, no. 9, pp. 1227–1233, 2010, doi: 10.1211/jpp.58.9.0009.

[42] B. Ghanbarzadeh, A. Babazadeh, and H. Hamishehkar, "Nano-phytosome as a potential food-grade delivery system," *Food Biosci.*, vol. 15, pp. 126–135, 2016, doi: 10.1016/j.fbio.2016.07.006.

[43] T. Anukiruthika, S. Dutta, J. A. Moses, C. Anandharamakrishnan, C. Modeling, and N. Processing, *Modern Applications of Supercritical Fluids Extraction in Food Toxicology*. Elsevier, 2019. doi: 10.1016/B978-0-08-100596-5.22939-9.

[44] I. A. Komeil *et al.*, "Oral genistein-loaded phytosomes with enhanced hepatic uptake , residence and improved therapeutic efficacy against hepatocellular carcinoma," *Int. J. Pharm.*, vol. 601, no. April, p. 120564, 2021, doi:

10.1016/j.ijpharm.2021.120564.
[45] S. Sharma and A. Sahu, "Development, Characterization, and Evaluation of Hepatoprotective effect of Abutilon indicum and Piper longum Phytosomes," *Pharmacognosy Res.*, vol. 8, no. 1, pp. 29–36, 2016, doi: 10.4103/0974-8490.171102.
[46] A. I. A. Makhlouf, A. M. A. Soelm, and M. A. Mohmoud, "Antioxidant and hepatoprotective effects of silymarin phytosomes compared to milk thistle extract in CCl 4 induced hepatotoxicity in rats," vol. 2048, no. 1, pp. 23–30, 2014, doi: 10.3109/02652048.2013.805836.
[47] F. Yu *et al.*, "Monodisperse microparticles loaded with the self-assembled phytosomes for improving oral bioavailability and enhancing hypoglycemic efficiency," *Eur. J. Pharm. Biopharm.*, 2016, doi: 10.1016/j.ejpb.2016.03.019.
[48] M. Molaveisi, M. Shahidi, K. Parastouei, and R. Ali, "Fate of nano-phytosomes containing bioactive compounds of Echinacea extract in an acidic food beverage," *Food Struct.*, vol. 27, no. July 2020, p. 100177, 2021, doi: 10.1016/j.foostr.2021.100177.
[49] M. Varadkar and C. Gadgoli, "Journal of Traditional and Complementary Medicine Preparation and evaluation of wound healing activity of phytosomes of crocetin from Nyctanthes arbor-tristis in rats," no. xxxx, 2021.
[50] N. A. Alhakamy *et al.*, "Thymoquinone-loaded soy-phospholipid-based phytosomes exhibit anticancer potential against human lung cancer cells," *Pharmaceutics*, vol. 12, no. 8, pp. 1–17, 2020, doi: 10.3390/pharmaceutics12080761.
[51] A. Mazumder, A. Dwivedi, J. L. Preez, and J. Plessis, "In vitro wound healing and cytotoxic effects of sinigrin – phytosome complex," *Int. J. Pharm.*, vol. 498, no. 1–2, pp. 283–293, 2016, doi: 10.1016/j.ijpharm.2015.12.027.
[52] C. Chi, "Phytosome-Nanosuspensions for Silybin-Phospholipid Complex with Increased Bioavailability and Hepatoprotection Efficacy State Key Laboratory of Natural Medicines , Department of Pharmaceutics , China Corresponding authors at State Key Laboratory of Natura," *Eur. J. Pharm. Sci.*, p. 105212, 2020, doi: 10.1016/j.ejps.2020.105212.
[53] K. S. Sachin, A. J. N. J, and T. M. T, "Preparation and Evaluation of Curcumin Phytosomes by Rotary Evaporation Method," no. January 2019, 2020, doi: 10.14445/23942576/IJPBE-V6I1P104.
[54] W. Maryana, H. Rachmawati, and D. Mudhakir, "Symposium on Flexible Organic Electronics Formation of Phytosome Containing Silymarin Using Thin Layer-Hydration Technique Aimed for Oral Delivery," vol. 3, pp. 855–866, 2016, doi: 10.1016/j.matpr.2016.02.019.
[55] N. Sundaresan and I. Kaliappan, "Development and characterization of a nano-drug delivery system containing vasaka phospholipid complex to improve bioavailability using quality by design approach," *Res. Pharm. Sci.*, vol. 16, no. 1, pp. 103–117, 2021, doi: 10.4103/1735-5362.305193.
[56] P. Udapurkar, O. Bhusnure, and S. Kamble, "Phyto-phospholipid complex vesicles for phytoconstituents and herbal extracts : A promising drug delivery system Phyto - phospholipid complex vesicles for phytoconstituents and herbal extracts : A promising drug delivery system," no. April, 2018.
[57] Y. Li, D. Yang, S. Chen, S. Chen, and A. S. Chan, "Process parameters and morphology in puerarin , phospholipids and their complex microparticles generation by supercritical antisolvent precipitation," vol. 359, pp. 35–45, 2008, doi: 10.1016/j.ijpharm.2008.03.022.
[58] M. S. Sikarwar, S. Sharma, A. K. Jain, and S. D. Parial, "Preparation, characterization and evaluation of Marsupsin-phospholipid complex," *AAPS PharmSciTech*, vol. 9, no. 1, pp. 129–137, 2008, doi: 10.1208/s12249-007-9020-x.
[59] F. Cui, K. Shi, L. Zhang, A. Tao, and Y. Kawashima, "Biodegradable nanoparticles loaded with insulin – phospholipid complex for oral delivery : Preparation , in vitro characterization and in vivo evaluation," vol. 114, pp. 242–250, 2006, doi: 10.1016/j.jconrel.2006.05.013.
[60] A. Allam, I. A. Komeil, and O. Y. Abdallah, "Curcumin phytosomal soft gel formulation : Development , optimization and physicochemical characterization Curcumin phytosomal so ft gel formulation : Development , optimization and physicochemical characterization," no. September, 2015, doi: 10.1515/acph-2015-0029.
[61] S. Esmaeili, L. Dayani, A. Taheri, and B. Zolfaghari, "Phytochemical standardization, formulation and evaluation of oral hard gelatin capsules from Pinus eldarica bark extract," *Avicenna J. Phytomedicine*, vol. 11, no. 2, pp. 168–179, 2021, doi: 10.22038/AJP.2020.16716.
[62] N. C. Rompicherla and S. Hebbar, "Phytosomes: A Novel Molecular Nano Complex Between Phytomolecule and Phospholipid as a Value added Herbal Drug Delivery System," no. July, 2018.
[63] M. Taleuzzaman, A. Sartaj, D. K. Gupta, S. J. Gilani, and M. A. Mirza, "Phytosomal gel of Manjistha extract (MJE) formulated and optimized with central composite design of Quality by Design (QbD)," *J. Dispers. Sci. Technol.*, vol. 0, no. 0, pp. 1–9, 2021, doi: 10.1080/01932691.2021.1942036.
[64] N. U. R. Aini, D. Purnamasari, M. Dzakwan, and G. E. K. O. Pramukantoro, "Original Article MYRICETIN NANO-PHYTOSOMES PEEL-OFF GEL MASK FORMULATION AS ANTIOXIDANT," vol. 13, no. 4, pp. 4–7, 2021.
[65] A. Babazadeh, M. Zeinali, and H. Hamishehkar, "Nano-Phytosome: A Developing Platform for Herbal Anti-Cancer Agents in Cancer Therapy," pp. 170–180, 2018, doi: 10.2174/1389450118666170508095250.
[66] K. Thanki, R. P. Gangwal, A. T. Sangamwar, and S. Jain, "Oral delivery of anticancer drugs: Challenges and opportunities," *J. Control. Release*, vol. 170, no. 1, pp. 15–40, 2013, doi: 10.1016/j.jconrel.2013.04.020.
[67] S. Kalepu, M. Manthina, and V. Padavala, "Oral lipid-based drug delivery systems – an overview," *Acta Pharm. Sin. B*, vol. 3, no. 6, pp. 361–372, 2013, doi: 10.1016/j.apsb.2013.10.001.
[68] Y. Y. Yeap, N. L. Trevaskis, and C. J. H. Porter, "Lipid Absorption Triggers Drug Supersaturation at the Intestinal Unstirred Water Layer and Promotes Drug Absorption from Mixed Micelles," no. 1, 2013, doi: 10.1007/s11095-013-1104-6.
[69] W. Stremmel, S. Staffer, H. Gan-schreier, A. Wannhoff, M. Bach, and A. Gauss, "Biochimica et Biophysica Acta

Phosphatidylcholine passes through lateral tight junctions for paracellular transport to the apical side of the polarized intestinal tumor," *BBA - Mol. Cell Biol. Lipids*, vol. 1861, no. 9, pp. 1161–1169, 2016, doi: 10.1016/j.bbalip.2016.06.019.

[70] R. K. Sari, Y. H. Prayogo, S. A. Rozan, M. Rafi, and I. Wientarsih, "Antioxidant Activity, Sun Protection Activity, and Phytochemical Profile of Ethanolic Extracts of Daemonorops acehensis Resin and Its Phytosomes," *Sci. Pharm.*, vol. 90, no. 1, 2022, doi: 10.3390/scipharm90010010.

[71] C. Bergamini and R. Fato, "Coenzyme Q10 Phytosome Formulation Improves CoQ10 Bioavailability and Mitochondrial Functionality in Cultured Cells," 2021.

[72] F. Fathi *et al.*, "Formulation of Nano/Micro-Carriers Loaded with an Enriched Extract of Coffee Silverskin: Physicochemical Properties, In Vitro Release Mechanism and In Silico Molecular Modeling," *Pharmaceutics*, vol. 14, no. 1. 2022. doi: 10.3390/pharmaceutics14010112.

[73] H. M. K. Ebada, M. M. A. Nasra, Y. S. R. Elnaggar, R. A. Nassra, A. A. Solaiman, and O. Y. Abdallah, "Colloids and Surfaces B : Biointerfaces Novel rhein integrate transphytosomes as non-invasive local therapy for osteoarthritis to ameliorate cartilage deterioration in MIA-arthritic rats," *Colloids Surfaces B Biointerfaces*, vol. 202, no. February, p. 111713, 2021, doi: 10.1016/j.colsurfb.2021.111713.

[74] D. R. Telange, A. T. Patil, A. M. Pethe, H. Fegade, S. Anand, and V. S. Dave, "European Journal of Pharmaceutical Sciences Formulation and characterization of an apigenin-phospholipid phytosome (APLC) for improved solubility , in vivo bioavailability , and antioxidant potential," *PHASCI*, 2016, doi: 10.1016/j.ejps.2016.12.009.

[75] M. Rabbani *et al.*, "Phytosomal nanocarriers for encapsulation and delivery of resveratrol- Preparation , characterization , and application in mayonnaise," *LWT*, vol. 151, no. November 2020, p. 112093, 2021, doi: 10.1016/j.lwt.2021.112093.

[76] S. Kumar, A. Baldi, and D. Kumar, "Journal of Drug Delivery Science and Technology In vitro antioxidant assay guided ex vivo investigation of cytotoxic effect of phytosomes assimilating taxifolin rich fraction of Cedrus deodara bark extract on human breast cancer cell lines (MCF7)," *J. Drug Deliv. Sci. Technol.*, vol. 63, no. November 2020, p. 102486, 2021, doi: 10.1016/j.jddst.2021.102486.

[77] H. T. H. Vu, S. M. Hook, S. D. Siqueira, A. Müllertz, and A. Mcdowell, "School of Pharmacy , University of Otago , Dunedin , New Zealand," *Int. J. Pharm.*, 2018, doi: 10.1016/j.ijpharm.2018.06.042.

[78] F. Di Pierro *et al.*, "Possible therapeutic effects of adjuvant quercetin supplementation against early-stage covid-19 infection: A prospective, randomized, controlled, and open-label study," *International Journal of General Medicine*, vol. 14. pp. 2359–2366, 2021. doi: 10.2147/IJGM.S318720.

[79] J. T. Mao *et al.*, "Leucoselect phytosome modulates serum eicosapentaenoic acid, docosahexaenoic acid, and prostaglandin E3 in a Phase I lung cancer chemoprevention study," *Cancer Prevention Research*, vol. 14, no. 6. pp. 619–626, 2021. doi: 10.1158/1940-6207.CAPR-20-0585.

[80] A. Riva *et al.*, "Artichoke and bergamot phytosome alliance: a randomized double blind clinical trial in mild hypercholesterolemia," *Nutrients*, vol. 14, no. 1, pp. 1–13, 2022, doi: 10.3390/nu14010108.