e-ISSN: 2320-4230, p-ISSN: 2961-6085

Journal of Drug Discovery and Therapeutics

Available Online at www.jddt.in

CODEN: - JDDTBP (Source: - American Chemical Society)

Volume 12, Issue 02; 2024, 187-211

Phytosome: A Comprehensive Review

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Received: 19-02-2024 / Revised: 09-03-2024 / Accepted: 10-04-2024
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Conflict of interest: No conflict of interest.

Abstract:

Phytoconstituents with minimal unwanted effects provide phytomedicine a viable therapeutic alternative. Reduced bioavailability due to substantial molecular size, inadequate lipid solubility, and instability of bioactive components impedes its efficacy. Various techniques have been used to develop phytochemical carrier systems that enhance bioavailability. Phytosomes have lately emerged as appealing lipid-based carriers for botanical pharmaceuticals and nutraceuticals. A novel pharmaceutical delivery system known as phytosome wraps bioactive compounds inside phospholipid molecules, primarily phosphatidylcholine. Phytosomes, as phyto-phospholipid complexes, enhance targeted drug delivery, bioavailability, stability, pharmacological efficacy, and the protection of bioactive molecules against chemical and physical degradation. Phytosomes are extensively used and recognized by the scientific community for their efficacy and manufacturing simplicity. This study examines phytosome technology, including its structural components, formulation techniques, optimization, characterization, and advantages and disadvantages. Recent studies and commercially available phytosome-based products are also examined. In summary, phytosome technology significantly enhances the bioavailability of plant extracts and phytochemicals using established processing and testing methodologies.

Keywords: Phytomedicine; Innovative drug delivery system; Phytosome; Liposome; Bioavailability; Phytochemicals; Phosphatidylcholine; Thin layer hydration method; Biodegradable; Supercritical anti-solvent precipitation.

Introduction

Phytotherapy with medicinal plants is a crucial component of the healthcare system owing to its safety, efficacy, low cost, accessibility, and little or absent side effects (Jahangir et al., 2020; Mishra, 2022). Since antiquity, phytomedicines have assisted humanity in curing incurable diseases and are used globally. Phytomedicines have attracted worldwide attention in recent years due to their therapeutic benefits and enhanced patient adherence (Dongare et al., 2021). Plant-derived bioactive substances, such as phenolic compounds, lignans, and alkaloids, have many therapeutic benefits, including antibacterial, anti-allergic, antioxidant, anticancer, anti-diabetic, and anti-inflammatory properties (Tran et al., 2020). Conventional herbal medication dosage forms exhibit inadequate absorption, diminished biological membrane penetration, and lowered bioavailability due to their elevated molecular size and lipophilicity, hence limiting their use (Singh et al., 2020).

Conventional dosage forms are inadequate for directing medicine to the intended site. The transport of medicine to non-target areas may need a therapeutic drug dose that surpasses the requirements of the target site, resulting in significant adverse effects (Singh et al., 2021).

The systematic incorporation of plant-based drugs into appropriate dosage forms may enhance their effectiveness (Dongare et al., 2021). Consequently, the investigation of nano-carrier-based drug delivery is essential to address conventional dose limitations and enhance bioavailability for enhanced efficacy, targeted medicine administration, and patient adherence (Shirsath and Goswami, 2019).

Innovative pharmaceutical administration techniques

Drug delivery systems provide therapeutic agents to specific bodily targets (Sivadasan et al., 2023). Innovative drug delivery systems (NDDSs) for herbal extracts and bioactive compounds are advancing (Singh et al., 2014). Recent decades have seen significant advancements in novel drug delivery strategies using phytoconstituent encapsulation (Rahman et al., 2020). Innovative drug distribution technique alleviates conventional limitations. This technique enhances the solubility, bioavailability, and stability of herbal medication and phytoconstituents (Kattyar et al., 2022).

An optimal medication delivery system delivers a specified quantity of medicine to a target spot at the right pace and timing for the body's physiological demands. Consequently, novel drug delivery techniques regulate drug dosage within a clinically significant range, direct drug content to a specific target area, and exhibit prolonged duration (Singh et al., 2021). Pre-designed controlled medication release guarantees effective drug delivery at the target site, mitigating adverse side effects and enhancing therapeutic benefits (Sivadasan et al., 2023).

New nano-carriers have been developed by diverse approaches for the bioavailability of phytoconstituents (Barani et al., 2021). Nanocarriers for phytoconstituents are typically vesicular drug delivery systems containing active phytochemicals inside spheres (Supraja and Mulangi, 2019). Phytosomes, transferosomes, ethosomes, liposomes, colloidosomes, and other carriers have been developed to deliver medications to target areas without undergoing metabolism or degradation (Chivte et al., 2017).

Table 1. Vesicular novel drug delivery systems (Barani et al., 2021; Abdul R. et al., 2022; Sivadasan et al., 2023)

Novel drug delivery system	Development	Composition	Administration
Liposomes	Discovered in 1961 by a British scientist Dr. Alec Bangham	Phospholipid and cholesterol	Parenteral topical, oral and transdermal
Niosomes	L'Oreal generated and patented first niosome formulation in 1975	Nonionic surfactant and cholesterol	Oral, transdermal, and parenteral topical
Cubosomes	1980	Amphiphilic lipids in the presence of a suitable stabilizer	Oral, transdermal, ocular and chemotherapeutic administration

Phytosomes	An Italian pharmaceutical company, Indena developed phytosomes in 1989.	Phospholipid and polyphenolic phytoconstituents	Oral, transdermal, and parenteral topical
Transfersomes	Transfersomes were developed in 1990s by Idea, Munich, Germany.	Phospholipid and surfactant	Topical and transdermal
Ethosomes	1996	Phospholipid, polyglycol, alcohol, and water	Topical and transdermal

Phytosome technology

Herbosomes, also known as phytosomes, are a novel phyto-constituent that exhibits enhanced absorption via topical, oral, and transdermal routes (Gaurav et al., 2021). In 1989, the Italian nutraceutical and pharmaceutical company Indena developed phytosome, a technology for phospholipid complexation (Lu et al., 2019). "Phyto" denotes plant, whereas "some" signifies cell-like (Kattyar et al., 2022). Ghanbarzadeh et al. (2016) 'Phyto' refers to the bioactive portion of a phytosomal complex derived from plants, while 'some' indicates that the complex structure resembles a cell. Hydrogen bonding connects phytoconstituents to phospholipids, often phosphatidylcholine (PC), in phytosomes (Gaurav et al., 2021). Standardized plant extracts or hydrophilic phytoconstituents are incorporated into phospholipid molecules to produce lipid-compatible vesicles in a phytosomal complex (Singh et al., 2014).

In contrast to herbal extracts and bioactive compounds, phytosomes represent a unique composition with several benefits. Phytosome technology enhances the bioavailability of bioactive chemicals, lipid solubility, and gastrointestinal solubility. Vasicine alleviates asthma and bronchitis and may induce bronchodilation. The bioavailability of Vasicine is limited by its poor solubility and gastrointestinal absorption. Phytosome technology enhanced the solubility and absorption of vasicine, hence enhancing its bioavailability (Kattyar et al., 2022). Advantages include enhanced cell membrane permeability, stability, extended administration duration, and safeguarding against toxicity and chemical or physical degradation (Singh et al., 2014). Research indicates that phytosomes provide superior efficacy in dosage reduction and pharmacological potential (Barani et al., 2021). Plantosomes enhance transdermal drug administration and have several cosmetic applications (Gaurav et al., 2021).

Hedyotis corymbosa, Nicotiana tabacum var. Virginia, Moringa oleifera, Punica granatum L., Geophila repens, Vaccinium macrocarpon, and Intsia In summary, phyto-phospholipid technology enhances the absorption of poorly assimilated phytochemicals and herbal extracts (Anjana et al., 2017).

Phytosome Structure

Phytosomes chemically mimic cellular membranes (Ghanbarzadeh et al., 2016). Their formation results from phospholipid polar heads and active phytoconstituents (Khan et al., 2013). The interactions between phytoconstituents and phospholipids produce phyto-phospholipid complexes characterized by polar phospholipid heads and the absence of two elongated fatty acid chains. Fatty acid chains traverse and envelop the polar surfaces

of phytosomes to form lipid-soluble interfaces (Ghanbarzadeh et al., 2016).

Phytosomes are distinct from liposomes.

Diluted phytosomal complexes form cell-like aggregates in water, akin to liposomes. Distinguishing phytosomes from liposomes elucidates their uniqueness (Table 2). The bioactive component in phytosomes is integrated inside the membrane, whereas the active ingredient in liposomes is located between the membrane layers or within the aqueous cavity. A phytosomal unit is formed by the hydrogen bonding of one phospholipid molecule and one polyphenol molecule. This associates bioactive phytochemicals with the polar component of phospholipids, integral to the cell membrane.

In a liposome unit, many phospholipids aggregate to create a spherical structure containing additional bioactive chemicals that are compartmentalized but unconnected. Phytosomes have greater stability, absorbency, and bioavailability than liposomes due to robust hydrogen bonding. The optimal molar ratios of phytoactive compounds to phospholipids for phytosomes are 1:1 or 1:2. In liposomes, phospholipid molecules exceed phytoactive substances by a factor of ten. The efficacy of oral transport via liposomes remains ambiguous, but phytosomes enhance this process (Kidd, 2009; Ghanbarzadeh et al., 2016; Lu et al., 2019).

Table 2. Difference between phytosome and liposome

Property	Phytosome	Liposome
Structure	Bioactive compound is a part of the membrane itself	Active ingredient is located between layers of the membranes or within the water-soluble cavity
Nature of bond	Hydrogen bonding	No chemical bonding
Phospholipid: Bioactive components	1:1 or 1:2	Phospholipid molecules are usually ten times more than bioactive compound
Stability	High	Lower than phytosome
Bioavailability	High	Lower than phytosome

Components of Phyto-phospholipid complex

Bioactive phytoconstituents

Researchers commonly classify plant extract bioactive chemicals by their greater in vitro biological activities than in vivo activities. Most bioactive chemicals are polyphenols (Lu et al., 2019). Herbal polyphenolic chemicals that are hydrophilic cannot pass cell membranes. Rutin and curcumin are lipid-soluble and cannot dissolve in aqueous gastro-intestinal fluid. Phytosomes promote membrane penetrability of water-soluble agents and polar phase solubility of lipid-soluble substances. Phytosomes also protect polyphenolic chemicals against hydrolysis, oxidation, and photolysis (Kidd, 2009).

Besides polyphenols, phospholipids may encapsulate several physiologically active plant extract components, including piperine, allicin, and evodiamine (Lu et al., 2019). Thus, phytosome technology works for all bioactive substances, not only polyphenols (Kidd, 2009).

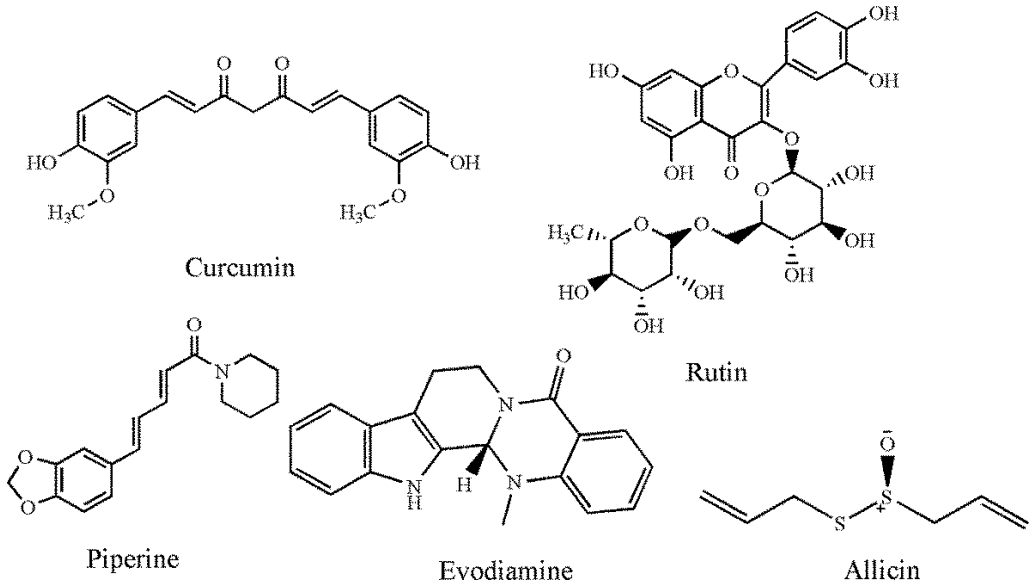

Figure 1. Structure of bioactive phytoconstituents

Phospholipids

Amphiphilic and biocompatible phospholipids are exceptional. Due to their unique properties, phospholipids are ideal pharmacological agents and have several drug delivery uses. The molecular structure of phospholipids is polar, phosphorus, and non-polar. Phospholipids have hydrophilic and hydrophobic acyl chains linked to alcohol. Phospholipids vary greatly according to polar head part, alcohols, and aliphatic chains. The backbone divides phospholipids into glycerophospholipids and sphingomyelins. Glycerophospholipids include PG, PI, PA, PS, PE, and PC. Main phospholipids used to make phytosomal complexes with two non-polar hydrocarbon chains and a polar part include PC, PS, and PE (Li et al., 2015).

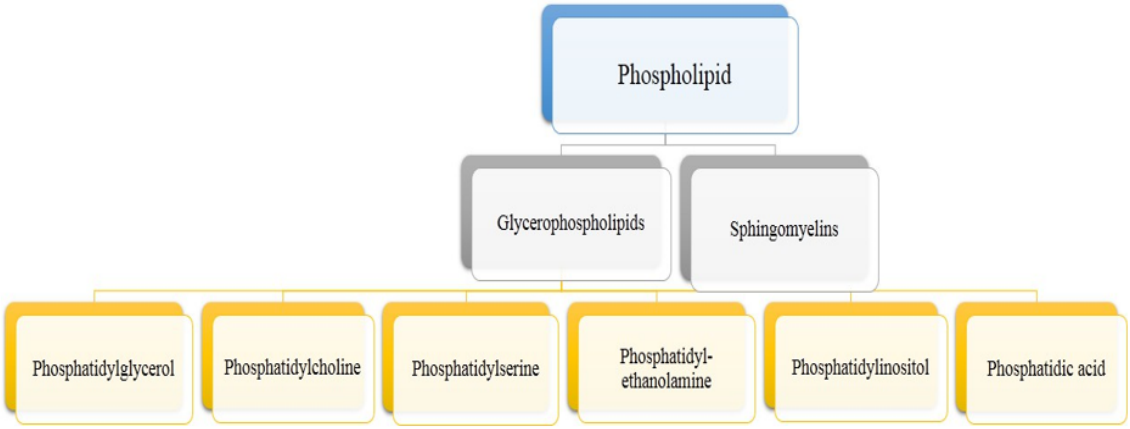

Figure 2. Classification of phospholipids (Li et al., 2015)

Phytosomes are predominantly made from phosphatidylcholine (Lu et al., 2019). Choline is hydrophilic and phosphatidyl is lipophilic in phosphatidylcholine (Agrawal et

al., 2012). Its amphilic properties make it moderately soluble in aqueous and lipid solutions. It is biocompatible, low-toxicity, and essential to biological membranes. It protects the liver and treats fatty liver and hepatitis (Lu et al., 2019).

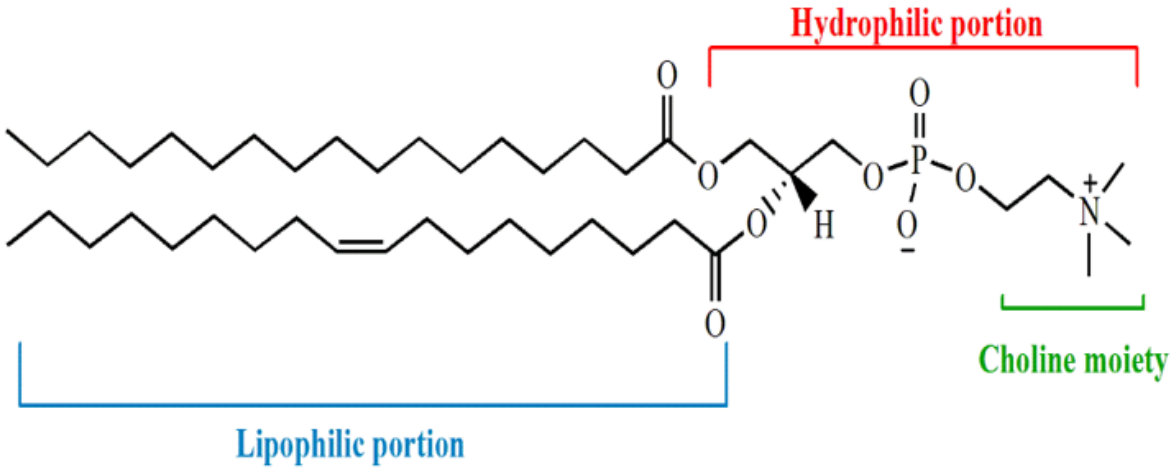

Figure 3. Structure of Phosphatidylcholine

Solvent system

Diverse solvents have been used to synthesize phytosomes (Khan et al., 2013). Phytosomes are often produced in polar aprotic solvents to promote hydrogen bond formation (Telange et al., 2017; Vu et al., 2018). In aprotic solvents, hydrogen atoms are incapable of forming hydrogen bonds with electronegative atoms. Conventional solvents for phytosomes include methylene chloride, aromatic hydrocarbons, cyclic ethers, and ethyl acetate (Khan et al., 2013). Nonetheless, protic solvents such as methanol and ethanol have replaced them (Lu et al., 2019).

In protic solvents such as ethanol and methanol, a hydrogen atom is directly attached to an electronegative atom (Patel et al., 2009). Hydrogen interactions between active chemicals and phospholipid molecules enhance stability, trapping efficiency, and cell membrane permeability, hence augmenting bioavailability and effectiveness (Permana et al., 2020). Hammam et al. (2017) identified hydrogen bonding in methanol. Ethanol is an effective solvent owing to its substantial phytosome yield and negligible residues (Patel et al., 2009). Numerous research use ethanol to produce phytosomes from Nicotiana tabacum var. Virginia leaf extract (Chittasupho et al., 2023), naringenin-loaded dipalmitoylphosphatidylcholine (Yu et al., 2020), and berberine-phospholipid complexes.

Although the majority of industrial techniques use a single solvent, the utilization of mixed solvents has been recorded. Research indicates that phospholipid molecules and extracts are solubilized in two solvents within mixed solvent systems. Mixed solvent systems include methanol and dichloromethane, diethyl ether and water, as well as ethanol and dichloromethane (Barani et al., 2021). Certain pharmacological liposomal complexes function in aqueous solutions or buffers due to the restricted solvent interaction with phytosomal complexes (Patel et al., 2009).

Recent study has used supercritical fluid (SCF) to modify the shape, size, and other morphological characteristics of micronic and submicronic particles. Supercritical anti-solvent technique employs a supercritical fluid, often CO2, to diminish solute solubility in the solvent. It has potential for generating particles with controlled size distribution (Semalty, 2014). Puerarin-loaded phospholipid complexes were produced using supercritical anti-solvent precipitation (Li et al., 2008).

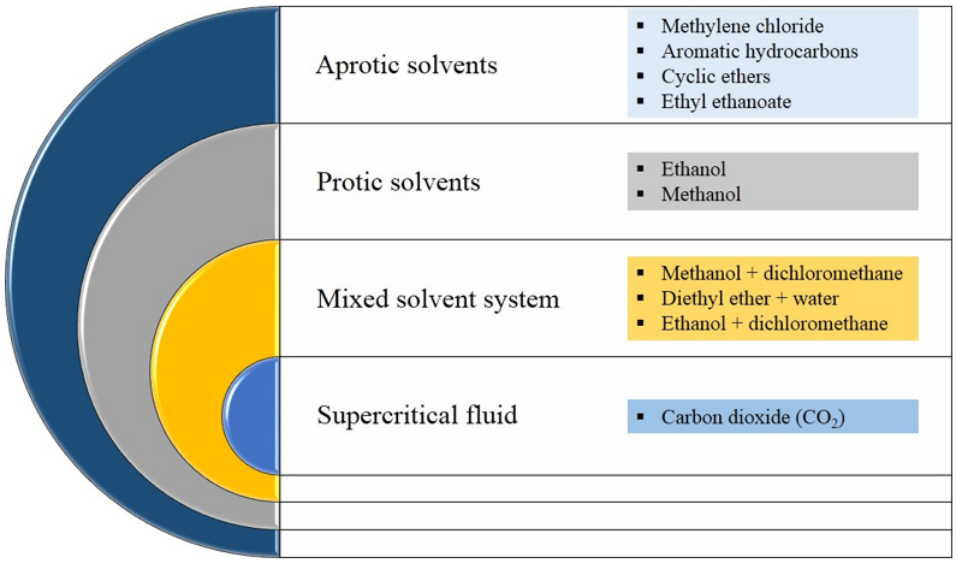

Figure 4. Solvent systems for phytosome formulation (Khan et al., 2013; Semalty, 2014; Lu et al., 2019; Barani et al., 2021)

Methods of formulation of phytosomes

Plant extract is converted into phospholipids, primarily phosphatidylcholine, to make phytosomes (Kattyar et al., 2022). Solvent evaporation, thin layer hydration, anti-solvent precipitation, co-solvent lyophilization, and salting-out are phytosome formulation methods (Anjana et al., 2017; Barani et al., 2021).

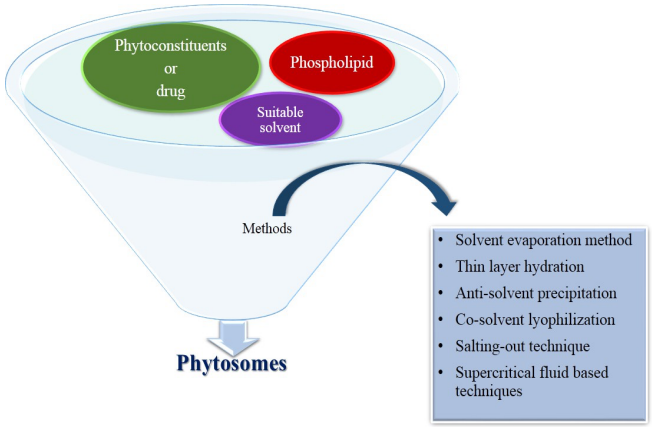

Figure 5. Fabrication of phytosomes (Anjana et al., 2017; Barani et al., 2021)

Solvent evaporation method

Solvent evaporation is a conventional technique for synthesizing phytosomes. In a flask, active phytoconstituents and phosphatidylcholine are heated at a constant ideal temperature for a specified duration to achieve dispersion in an appropriate solvent, maintaining a specific stoichiometric ratio. Phytosomes are produced by evaporating the solvent under vacuum (Lu et al., 2019). Solvent evaporation resulted in the formation of evodiamine-phospholipid complexes (Liu, 2012). Phytosomes were developed using solvent evaporation and self-aggregation to provide an effective berberine delivery mechanism (Yu et al., 2016). Solvent evaporation yielded phytosome-encapsulated methanolic leaf extract of Aegle marmelos (bael) (Dhase and Saboo, 2015).

Anti-solvent precipitation

In anti-solvent precipitation, phospholipid and medicine are refluxed in a suitable solvent. Following the concentration of the mixture, more solvent is introduced during agitation to induce precipitation. Filtered and collected precipitates are kept overnight in desiccators (Anjana et al., 2017). Antisolvent precipitation yielded Allium cepa phospholipid complexes (Habbu et al., 2015), scorpion venom-standardized quercetin-loaded phytosomal complexes (Alhakamy, 2022), and icariin phytosomes (Alhakamy, 2020).

Co-solvent lyophilization methodology

Phospholipid and drug are refluxed separately in a solvent for the co-solvent lyophilization of phytosomes. The two components are meticulously amalgamated until a transparent result is achieved. The continued use of the homogeneous mixture necessitates freeze-drying and storage in an airtight container (Anjana et al., 2017). Lyophilization yielded kaempferol-loaded phytosomes (Telange et al., 2016).

Method of Thin Layer Hydration

A thin layer of hydration combines phytochemicals, phospholipids, and cholesterol in methanol and dichloromethane. A rotary evaporator vaporizes the mixture into a dry, thin film. Nitrogen gas is often run across a thin sheet to effectively eliminate organic solvents. Subsequently, vacuum drying completely eliminates organic solvents. The film is moistened with distilled water (Anjana et al., 2017). Thin layer hydration was used to generate phytosomes from Vitis vinifera L. seed extract (Surini et al., 2018).

Salting-out Technique

Diosmin phytosomes were created by salting. Following salting out, diosmin and soy phosphatidylcholine phospholipid were amalgamated in 35 ml of dehydrated ethanol, dimethyl sulfoxide, and chloroform in a 2:2:3 ratio. An overnight magnetic stirrer was used to agitate the mixture, and 75 ml of n-hexane was added until precipitates emerged (Freag et al., 2013). The salting-out method yielded piperine phytosomes (Islam et al., 2022).

Techniques Utilizing Supercritical Fluids

Supercritical fluid is used for the production of particles ranging from 5 to 2000 nm. The gas anti-solvent technique, fast expansion of supercritical solutions, supercritical anti-solvent method, compressed anti-solvent approach, and solution improved dispersion by supercritical fluids have been used to increase the solubility of poorly soluble pharmaceutical compounds (Karataş and Turhan, 2015). Puerarin-loaded phospholipid complexes were synthesized using supercritical anti-solvent precipitation, demonstrating superiority over conventional procedures for drug-loaded phytosomes (Li et al., 2008).

Optimization

The Container– Behnken experimental design or a comparable methodology optimizes phytosomes. An experimental approach using three factors was used to produce Icariin phytosomes. The molecular ratio of icariin to phospholipid, temperature, and reflux length were independent factors, whereas vesicle size was the dependent variable. The Design-Expert program produced 15 experimental experiments. Adjusted calculated precision ratios and predicted coefficients of determination were used to choose a response model. We also identified the optimal model equation. ANOVA was used to assess observed responses and determine significance at $p < 0.05$. Three-dimensional and interaction plots were generated to analyze parameter interactions (Alhakamy et al., 2020).

Advantages of phytosome technology

- Phytosomes exhibits an excellent feature such as better absorption which leads to better bioavailability than simple plant extracts (Bhise et al., 2019). An improved absorption leads to a lower dosage of phytoconstituents required for a biological effect (Barani et al., 2021).
- Phytosomes are cell-like where all the important constituents of plant extract are prevented from the degradation by gut bacteria and digestive secretions (Nagar, 2019). Formation of phytosomal complexes can also prevent phytochemicals from degradation by the external conditions such as hydrolysis, oxidation, and photolysis (Kidd, 2009).
- Phytosomes exhibit better drug entrapment efficiency and stability because of chemical bonds between the bioactive compounds and phospholipid molecules. It makes sure proper drug delivery to the target tissues (Nagar, 2019).
- Phytosomes also exhibit nutritional benefits of the phospholipids (Karimi et al., 2015). Apart from serving as a carrier, the phosphatidylcholine employed in fabrication of phytosomes also serves as a hepato-protective agent leading to a synergistic effect when hepato-protective drugs are utilized. Phosphatidylcholine also nourishes the skin (Nagar, 2019).
- Phytosomes solubility in an aqueous medium is relatively less that ensures the formulation of stable creams or emulsions (Nagar, 2019).
- Du to enhanced absorption of bioactive phytochemicals across the skin, Phyto-phospholipid complexes are extensively employed in cosmetics due to their higher lipid profile and better skin penetration (Karimi et al., 2015).
- Phytosomes have higher rate drug complexation and also fabrication of phytosomes is not a complex process (Karimi et al., 2015). The methods of phytosomes preparation are simple, non-conventional and reproducible (Gaurav et al., 2021).
- Phytosomal complexation prolong the duration of drug. Frequent administration of the Naringenin is required due to its shorter half-time and rapid removal from the body. Phospholipid complexes of Naringenin were fabricated with motive to enhance its duration in blood circulatory system (Semalty et al., 2010). In another study, half-life of andrographolide–phospholipid complexes was incremented 3.34 times than that of pure andrographolide (Maiti et al., 2010).
- As the phytosomal complexes are biodegradable, drug entrapment is not an issue (Karimi et al., 2015).

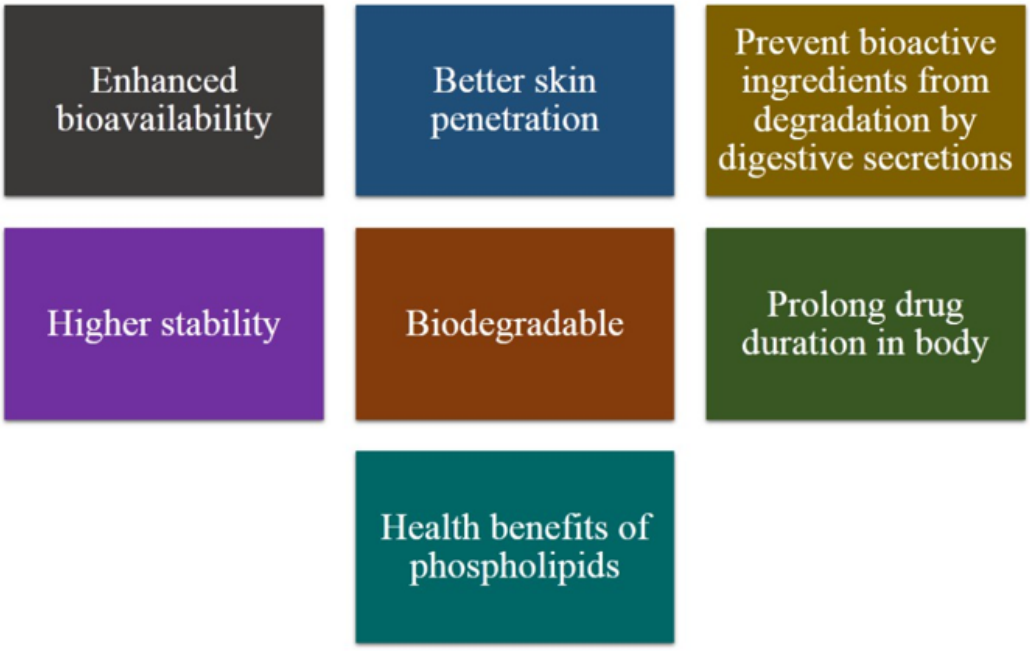

Figure 6. Advantages of phytosome technology

Marketed phytosomal products

Permana et al. (2020) found phytosomes to be effective nano-carrier drug delivery devices. Pharmaceutical companies have investigated phytosomes' biological activity, phytoconstituent bioavailability, and benefits (Barani et al., 2021). Table 2 lists commercialized phytosomes and their biological uses. However, many phytochemicals with the potential to treat life-threatening diseases have not been integrated into phytosomes (Gaurav et al., 2021). Milan-based Indena S.p.A. owns Phytosome® and all other trademarks (Karimi et al., 2015).

Table 3. Phytosomes available in market (Patel et al., 2009; Karimi et al., 2015; Lu et al., 2019)

Sr. #	Trade name	Phytoconstituent complexed with phospholipid	Plant source	
1.	Greenselect® phytosomes	Epigallocatechin 3-O-gallate	Green tea	An anticancer and antioxidant agent
2.	Leucoselect® phytosomes	Procyanidolic oligomers	Grape seeds	Anti-oxidant and anticancer
3.	OleaselectTM phytosome	Polyphenolic compounds from essential oil of olives	Olea europaea L.	Prevent toxic oxidative reaction of low-density lipoprotein cholesterol
4.	CasperomeTM	gum resin	Banksia serrata	Improve tissue distribution of boswellic acids

5.	Hawthorn phytosomeTM	Flavonoids	Crataegus species	Antihypertensive and cardiotonic
6.	Curcumin (Merinoselect) phytosomes	Polyphenol	Curcuma longa	Anticancer and improve bioavailability of curcuminoids
7.	Sericoside phytosome	Sericoside	Terminalia Sericea	Anti-wrinkles and soothing effects
8.	Ginkgoselect®	24 % flavono-glycosides	Ginkgo biloba	Provide protection to vascular lining and brain.
9.	Mirtoselect® phytosome	Anthocyanosides	Bilberry	Decrease abnormal permeability of blood vessel and improve capillary tone. These have high potential in managing venous insufficiency and retinal blood vessel issues.
10.	Sabalselect® (Palmetto) phytosome	Saw palmetto berries extract	Serenoa repens	Helpful for prostate normal functioning
11.	PolinaceaTM phytosome	Echinacosides	Echinacea angustifolia	It improves function of immune system in response to some toxic condition
12.	LymphaselectTM phytosome	Melilotus officinalis standardized extract	Melilotus officinalis	It is suggested for venous diseases
13.	Panax ginseng phytosome	Ginsenosides	Panax ginseng roots	Utilized as a food product
14.	Zanthalene phytosome	Zanthalene	Zanthoxylum bungeanum	Anti-itching, anti-irritant, and soothing effects

Recent advanced research in phyto - phospholipids complexation

Pharmaceutical companies and academics studied phytosome compositions' originality, biological activity, and polar phytochemical bioavailability. The evidence supporting these formulations encourages researchers to continue their work. Clinical studies showing that standardized products are more effective than unformulated extracts or phytochemicals will help promote these technologies (Barani et al., 2021). Due to their biological benefits, silymarin, grape seed extract, quercetin, curcumin, ginkgo biloba extract, and others are gaining attention. The success of this method and the huge demand for herbal medications for illness treatment have led to additional study. Since phytosome technology was developed, several phytosomal compositions using medicinal plants and phytochemicals have been documented. Table 3 lists recent phytosomal formulations and their literature.

Table 4. Literature view of previous reported phytosomal formulations

Sr. #	Phytosomal formulations	Method employed for fabrication	Biological applications	References
1.	Quercetin loaded nano-phytosome	Thin layer hydration method	Anti-leishmania and antimalarial effects	(Hanif *et al.,* 2023)
2.	Bergamot essential oil with spironolactone containing phytosomes	Thin film hydration technique	Treatment of acne vulgaris	(Albash *et al.,* 2023)
3.	Nicotiana tabacum var. Virginia leaves extract loaded phytosomes	Solvent displacement method	Antioxidant and antiinflammatory activities	(Chittasupho *et al.,* 2023)
4.	Hedyotis corymbosa L. extract loaded phytosomes	Phospholipid encapsulation	Enhanced delivery of extract for the efficient relief from neuropathic pain	(Kumar *et al.,* 2023)
5.	Phytosomes containing carotenoids of Nyctanthes arbor-tristis and Tagetes patula	Lipid film hydration technique	Protect skin aging induced due to D-galactose	(Naik *et al.,* 2023)
6.	Phytosomes of Parthenolide	Solvent evaporation method	Parthenolide containing phytosomes attenuate the renal dysfunction and also structural damage by decreasing inflammation, oxidative stress, and apoptosis in kidney.	(Albalawi *et al.,* 2023)
7.	Genistein phytosome	Solvent evaporation method	Breast cancer treatment	(Komeil *et al.,* 2022)
8.	Scorpion venom-standardized quercetin loaded phytosomal complexes	Anti-solvent precipitation	Anticancer activity against MCF-7 Cells in breast cancer management	(Alhakamy *et al.,* 2022)
9.	Silybin loaded phytosome	Solvent evaporation method	Neuro-protective activity and attenuates cerebral ischemia-reperfusion injury	(Pasala *et al.,* 2022)
10.	Polyphenols from Moringa oleifera leaf loaded phytosome	Nano-precipitation method	Treatment against cell lines of breast cancer	(Wanjiru *et al.,* 2022)
11.	Geophila repens phytosome loaded intranasal gel formulation	Co-solvency method	Efficient treatment of Alzheimer's disease	(Rajamma *et al.,* 2022)

12	Phytosome of Punica granatum L. peel extract	Thin film hydration method	Anti-infective, antimicrobial, anti-oxidative, antidiarrheal, hepato-protection, anti-atherogenicity and anti-inflammation therapy	(Kazemi *et al.,* 2022)
13.	Novel diammonium glycyrrhizinate containing phytosome	Solvent evaporation technique	Induce nasal immune responses	(Chen *et al.,* 2022)
14.	Intsia bijuga heartwood extract loaded phytosome	Solvent evaporation technique	Serve as an antioxidant, tyrosinase inhibitor and sun protector	(Sari *et al.,* 2021)
15.	Phytosomes of Aloe vera extract	Phospholipid encapsulation	Anticancer activity	(Murugesan *et al.,* 2021)
16.	Leucoselect phytosome containing grape seed procyanidin extract	Phospholipid complexation	Antineoplastic and anti-inflammatory activity	(Mao *et al.,* 2021)
17.	Phytosome loading allicin-rich extract	Solvent evaporation technique	Extensive pharmacological activities including antihypertensive, antioxidant,	(Nining *et al.,* 2021)
			cardioprotective, antimicrobial, antidiabetic, nephroprotective, anti-carcinogenic and a cytochrome activity.	
18.	Centella asiatica L. phytosomes	Phytosome complexation	Antioxidant and anti-inflammatory activity; Promoting Bdnf expression leading to improvement of cognitive action	(Sbrini *et al.,* 2020)
19.	Trigonella foenum-graecum phytosomes	Thin film hydration technique	Anti-Inflammatory and anti-arthritic activity	(Sharma *et al.,* 2020)
20.	Naringenin-loaded Dipalmitoylphosphatidylcholine phytosomes	Solvent evaporation and a freeze-drying method	Utilized in the inhaled treatment of mild lung damage	(Yu *et al.,* 2020)
21.	Icariin containing phytosomes	Anti-solvent precipitation	Incremented cytotoxicity against ovarian cancer cells	(Alhakamy *et al.,* 2020)
22.	Thymoquinone loaded phytosomes	Refluxing in combination with anti-solvent precipitation	Anticancer effects against human cells of lung cancer	(Alhakamy *et al.,* 2020)
23.	Selenium-deposited tripterine phytosomes	In situ reduction technique or melting-hydration	Boost the anti-arthritic effectiveness a synergistic sensitization	(Zhu *et al.,* 2020)

24.	Cocoa pod husk containing phytosomes	Thin-layer method	Antioxidant and tyrosinase inhibitory effects	(Priani *et al.,* 2019)
25.	Phytosomes containing ethanolic extract of Bombax ceiba leaves	Anti-solvent precipitation technique	Hepato-protective activity	(Karole and Gupta, 2019)
26.	Chrysin-loaded phytosomes	Solvent evaporation method	Enhanced solubility and improved glucose uptake in C2-C12 muscle cells.	(Kim *et al.,* 2019)
27.	Diospyros kaki L. extract containing phytosomes	Phytosomal complexation	Helpful in reducing oxidative degradation caused due to the reactive oxygen species	(Direito *et al.,* 2019)
28.	Diosgenin derivative loaded phytosomes	Thin-film rehydration method	Anticancer action against lung cancer cells	(Xu *et al.,* 2019)
29.	Phytosomes loading aqueous extract of Annona muricata L.	Phytosome complexation	In vivo depression treatment	(Mancini *et al.,* 2018)
30.	Vitis vinifera L. seed extract Phytosome	Thin layer hydration method	Improved drug penetration of in serum dosage form	(Surini *et al.,* 2018)
31.	Curcumin loaded phytosomes	Solvent evaporation method	Helpful in the treatment against human diseases including cancer, retinopathy, diabetic microangiopathy osteoarthritis, and inflammatory diseases	(Mirzaei *et al.,* 2017) (Allam *et al.,* 2015)
32.	Phytosomes containing methanolic extract of Aegle marmelos leaves	Solvent evaporation method	Antioxidant, anti-proliferative and anticancer effects	(Dhase and Saboo, 2015)

Concluding Remarks

The novel phytosome technique is used to produce plant-derived pharmaceuticals using phytochemicals from plant extracts encapsulated in phospholipids. The majority of bioactive constituents in herbal medicine are water-soluble, such as flavonoids. Phytosomes, owing to their lipid-soluble outer layer, exhibit enhanced absorption compared to conventional herbal extracts, hence increasing bioavailability. Furthermore, the employed phospholipids provide therapeutic benefits. There are straightforward, unconventional, and reproducible procedures for formulating phytosomes. A multitude of patents and commercial formulations of phytosomes have been approved for specific applications and purposes. A multitude of phytochemicals have been encapsulated as phytosomes, and more compounds may benefit from analogous formulations. Future research may reveal synergistic benefits when phytosomes are combined with supplementary phytochemicals or pharmaceuticals in nano-vesicles. Future study may benefit from

phytosomes encapsulated with supplementary phytoconstituents or a pharmaceutical agent and phytochemical inside a nano-vesicle.

Prospective Outlook

Phytosome nanotechnology has the potential to transform the delivery of topical bioactive phytochemicals. Phytosomes, lipid-based nanocarriers, enhance the pharmacokinetic and pharmacodynamic properties of plant-derived polyphenolic chemicals, making this nanotechnology compelling for novel topical formulations. This nanoscale delivery technique may enhance phytochemical bioavailability by traversing biological barriers owing to its distinctive physicochemical properties (Alharbi et al., 2021).

Initially used in cosmetics, phytosomes are currently applied in the treatment of cancer, tumors, inflammation, cardiovascular illnesses, and hepatic disorders. Through this novel formulation approach, Phytosomes has reaffirmed the significance of herbal remedies in contemporary therapeutic targeting. Phyto-phospholipid complexes may facilitate active and passive targeting by binding certain ligands and antigens to cellular locations. Consequently, phyto-phospholipid complexes may treat osteoarthritis, cancer, and rheumatism. Advanced techniques include supercritical fluid systems, but pressure, temperature, and other parameters may limit product dimensions. Products will more efficiently target tumors and inflammation owing to enhanced penetration, retention, and size. Statistical methodologies such as Box–Behnken design and factorial design may optimize variables, including phytoactive or drug with phospholipid molar ratios and temperature, to get optimal drug release profiles and entrapment efficiency (Khan et al., 2013).

Phospholipids have much greater bioavailability compared to chemically analogous non-complexed forms. The pharmaceutical uses of the phyto-phospholipid complex are promising with the endorsement of physicians and researchers (Lu et al., 2019). This may facilitate the use of this approach for other medicinal purposes. Encapsulating phytochemicals such as curcumin with efficient drug delivery systems may provide environmentally sustainable and safe treatments for prevalent human ailments. Investigations are required about the consumption of complete curcumin nano-phytosomes for the purpose of targeted organ delivery, particularly in cancer (Ipar et al., 2019).

Numerous nano-technology-based cancer therapeutics delivery systems have received FDA approval. Lipid-based nano-vesicles, an innovative nanocarrier with an extensive research background, provide several benefits over traditional drug carriers in terms of bioavailability, biocompatibility, cost-effectiveness, biodegradability, and availability of raw materials. The incorporation of natural and synthetic anti-cancer agents into nano-phytosomes will enhance cancer therapy delivery methods. Hydrophilic phytochemicals used in cancer treatment may transform phytosome technology in nutraceuticals (Babazadeh et al., 2018).

Phytosome technology offers several benefits compared to other dosing options. A multitude of pharmaceutical phytosomes are patented. This research indicates that Phytosomes® have created new opportunities for pharmacological investigation and advancement (Agarwal et al., 2012). Phytosome technology has considerable potential for formulation technology and applications using hydrophilic plant compounds.

References

1. Abdul Rasool, B.K., N. Al Mahri, N. Alburaimi, F. Abdallah & A.S.B. Shamma (2022). A narrative review of the potential roles of lipid-based vesicles (vesiculosomes) in burn management. Scientia Pharmaceutica, 90: 39. https://doi.org/10.3390/scipharm90030039.
2. Agarwal, A., P. Chakraborty, D.D. Chakraborty & V.A. Saharan (2012). Phytosomes: complexation, utilisation and commerical status. Journal of Biologically Active Products from Nature, 2: 65-77. https://doi.org/10.1080/22311866.2012.10719111.
3. Agarwal, A., M. Wahajuddin, S. Chaturvedi, S.K. Singh, M. Rashid, R. Garg, D. Chauhan, N. Sultana & J.R. Gayen (2023). Formulation and characterization of phytosomes as drug delivery system of formononetin: an effective anti-osteoporotic agent. Current Drug Delivery. https://doi.org/10.2174/1567201820666230124114906.
4. Albalawi, R.S., L.S. Binmahfouz, R.H. Hareeri, R.A. Shaik & A.M. Bagher (2023). Parthenolide phytosomes attenuated gentamicin-induced nephrotoxicity in rats via activation of Sirt-1, Nrf2, OH-1, and NQO1 Axis. Molecules, 28: 2741. https://doi.org/10.3390/molecules28062741.
5. Albash, R., N.M. Badawi, M.I. Hamed, M.H. Ragaie, S.S. Mohammed, R.M. Elbesh, K.M. Darwish, M.O. Lashkar, S.S. Elhady & S. Mosallam (2023). Exploring the synergistic effect of bergamot essential oil with spironolactone loaded nano-phytosomes for treatment of acne vulgaris: In vitro optimization, in silico studies, and clinical evaluation. Pharmaceuticals, 16: 128. https://doi.org/10.3390/ph16010128.
6. Alhakamy, N.A., U.A. Fahmy, S.M. Badr-Eldin, O.A. Ahmed, H.Z. Asfour, H.M. Aldawsari, M.M. Algandaby, B.G. Eid, A.B. Abdel-Naim & Z.A. Awan (2020). Optimized icariin phytosomes exhibit enhanced cytotoxicity and apoptosis-inducing activities in ovarian cancer cells. Pharmaceutics, 12: 346. https://doi.org/10.3390/pharmaceutics12040346.
7. Alhakamy, N.A., S.M. Badr-Eldin, U.A. Fahmy, N.K. Alruwaili, Z.A. Awan, G. Caruso, M.A. Alfaleh, A.L. Alaofi, F.O. Arif & O.A. Ahmed (2020). Thymoquinone-loaded soy-phospholipid-based phytosomes exhibit anticancer potential against human lung cancer cells. Pharmaceutics, 12: 761. https://doi.org/10.3390/pharmaceutics12080761.
8. Alhakamy, N.A., U.A. Fahmy, S.M.B. Eldin, O.A.Ahmed, H.M. Aldawsari, S.Z. Okbazghi, M.A. Alfaleh, W.H. Abdulaal, A.J. Alamoudi & F.M. Mady (2022). Scorpion venom-functionalized quercetin phytosomes for breast cancer management: in vitro response surface optimization and anticancer activity against MCF-7 cells. Polymers, 14: 93. https://doi.org/10.3390/polym14010093.
9. Alharbi, W.S., F.A. Almughem, A.M. Almehmady, S.J. Jarallah, W.K. Alsharif, N.M. Alzahrani & A.A. Alshehri (2021). Phytosomes as an emerging nanotechnology platform for the topical delivery of bioactive phytochemicals. Pharmaceutics, 13: 1475. https://doi.org/10.3390/pharmaceutics13091475.
10. Allam, A.N., I.A. Komeil & O.Y. Abdallah (2015). Curcumin phytosomal softgel formulation: Development, optimization and physicochemical

characterization. Acta Pharmaceutica, 65: 285-297. https://doi.org/10.1515/acph-2015-0029.

11. Angelico, R., A. Ceglie, P. Sacco, G. Colafemmina, M. Ripoli & A. Mangia (2014). Phyto-liposomes as nanoshuttles for water-insoluble silybin–phospholipid complex. International Journal of Pharmaceutics, 471: 173-181. https://doi.org/10.1016/j.ijpharm.2014.05.026.
12. Anjana, R., S. Kumar, H. Sharma & R. Khar (2017). Phytosome drug delivery of natural products: A promising technique for enhancing bioavailability. International Journal of Drug Delivery Technology, 7: 157-165.
13. Babazadeh, A., M. Zeinali & H. Hamishehkar (2018). Nano-phytosome: a developing platform for herbal anti-cancer agents in cancer therapy. Current Drug Targets, 19: 170-180. https://doi.org/10.2174/1389450118666170 508095250.
14. Barani, M., E. Sangiovanni, M. Angarano, M.A. Rajizadeh, M. Mehrabani, S. Piazza, H.V. Gangadharappa, A. Pardakhty, M. Mehrbani & M. Dell'Agli (2021). Phytosomes as innovative delivery systems for phytochemicals: A comprehensive review of literature. International Journal of Nanomedicine, Pages 6983-7022. https://doi.org/10.2147/IJN.S318416.
15. Bhise, J.J., O.G. Bhusnure, S.R. Jagtap, S.B. Gholve & R.R. Wale (2019). Phytosomes: a novel drug delivery for herbal extracts. Journal of Drug Delivery and Therapeutics, 9: 924-930. https://doi.org/10.22270/jddt.v9i3-s.2863.
16. Bresciani, L., G. Di Pede, C. Favari, L. Calani, V. Francinelli, A. Riva, G. Petrangolini, P. Allegrini, P. Mena & D. Del Rio (2021). In vitro (poly) phenol catabolism of unformulated-and phytosome-formulated cranberry (Vaccinium macrocarpon) extracts. Food Research International, 141: 110137. https://doi.org/10.1016/j.foodres.2021.110137.
17. Cai, X., Y. Luan, Y. Jiang, A. Song, W. Shao, Z. Li & Z. Zhao (2012). Huperzine A-phospholipid complex-loaded biodegradable thermosensitive polymer gel for controlled drug release. International Journal of Pharmaceutics, 433: 102-111. https://doi.org/10.1016/j.ijpharm.2012.05.009.
18. Carignani, E., M. Geppi, M. Lovati, E. de Combarieu & S. Borsacchi (2020). Solid State NMR study of the mixing degree between Ginkgo biloba extract and a soy-lecithin-phosphatidylserine in a composite prepared by the phytosome® method. Chemistry Africa, 3: 717-725. https://link.springer.com/article/10.1007/s42250-020- 00165-0.
19. Chauhan, N.S., R. Gowtham & B. Gopalkrishna (2009). Phytosomes: a potential phyto-phospholipid carriers for herbal drug delivery. J Pharm Res, 2: 1267-1270. https://citeseerx.ist.psu.edu/document?repid=rep1&type=pdf&doi=4bffd703d68aa66f42d48117dfe4d056c665e790.
20. Chen, X., X. Fan & F. Li (2022). Development and Evaluation of a Novel Diammonium Glycyrrhizinate Phytosome for Nasal Vaccination. Pharmaceutics, 14: 2000. https://doi.org/10.3390/pharmaceutics14102000.
21. Chittasupho, C., K. Chaobankrang, A. Sarawungkad, W. Samee, S. Singh, K. Hemsuwimon, S. Okonogi, K. Kheawfu, K. Kiattisin & W. Chaiyana (2023). Antioxidant, anti-inflammatory and

attenuating intracellular reactive oxygen species activities of Nicotiana tabacum var. Virginia Leaf extract phytosomes and shape memory gel formulation. Gels, 9: 78. https://doi.org/10.3390/gels9020078.

22. Chivte, P.S., V.S. Pardhi, V.A. Joshi & A. Rani (2017). A review on therapeutic applications of phytosomes. Journal of Drug Delivery and Therapeutics, 7: 17-21. https://doi.org/10.22270/jddt.v7i5.1513.
23. Das, M.K. & B. Kalita (2014). Design and evaluation of phyto-phospholipid complexes (phytosomes) of rutin for transdermal application. Journal of Applied Pharmaceutical Science, 4: 051-057. http://dx.doi.org/10.7324/JAPS.2014.401010.
24. Dewan, N., D. Dasgupta, S. Pandit & P. Ahmed (2016). Review on-Herbosomes, A new arena for drug delivery. Journal of Pharmacognosy and Phytochemistry, 5: 104. https://www.phytojournal.com/archives/2016.v5.i4.902/ review-on-herbosomes-a-new-arena-for-drug-delivery.
25. Dhase, A.S., & S.S. Saboo (2015). Preparation and evaluation of phytosomes containing methanolic extract of leaves of Aegle marmelos (bael). International Journal of Pharm Tech Research, 8: 231-240. http://www.sphinxsai.com/2015/ph_vol8_no6/2/(231-240)V8N6PT.pdf.
26. Direito, R., C. Reis, L. Roque, M. Gonçalves, A. Sanches-Silva, M.M. Gaspar, R. Pinto, J. Rocha, B. Sepodes & M. Rosário Bronze (2019). Phytosomes with persimmon (Diospyros kaki L.) extract: Preparation and preliminary demonstration of in vivo tolerability. Pharmaceutics, 11: 296. https://doi.org/10.3390/pharmaceutics11060296.
27. Dongare, P.N., A.S. Motule, M.R. Dubey, M.P. More, P.A. Patinge, R.L. Bakal & J.V. Manwar (2021). Recent development in novel drug delivery systems for delivery of herbal drugs: An updates. GSC Advanced Research and Reviews, 8: 008-018. https://doi.org/10.30574/gscarr.2021.8.2.0158.
28. Freag, M.S., Y.S. Elnaggar & O.Y. Abdallah (2013). Lyophilized phytosomal nanocarriers as platforms for enhanced diosmin delivery: optimization and ex vivo permeation. International Journal of Nanomedicine, Pages 2385-2397. https://doi.org/10.2147/IJN.S45231.
29. Gándola, Y.B., S.E. Pérez, P.E. Irene, A.I. Sotelo, J.G. Miquet, G.R. Corradi, A.M. Carlucci & L. Gonzalez (2014). Mitogenic effects of phosphatidylcholine nanoparticles on MCF-7 breast cancer cells. BioMed Research International. https://doi.org/10.1155/2014/687037.
30. Gaurav, V., S. Paliwal, A. Singh, S. Pandey & M. Aqil (2021). Phytosomes: Preparation, evaluation and application. Int J Res Eng Sci, 9: 35-39.
31. Ghanbarzadeh, B., A. Babazadeh & H. Hamishehkar (2016). Nano-phytosome as a potential food-grade delivery system. Food bioscience, 15: 126-135. https://doi.org/10.1016/j.fbio.2016.07.006.
32. Habbu, P., S. Madagundi, R. Shastry, R. Vanakudri & V. Kulkarni (2015). Preparation and evaluation of antidiabetic activity of Allium cepa-phospholipid complex (phytosome) in streptozotocin induced diabetic rats. RGUHS J Pharm Sci, 5: 132-141.
33. Hammam, E., J. Basahi, I. Ismail, I. Hassan & T. Almeelbi (2017). The role of hydrogen bonding in the fluorescence quenching of 2, 6-bis ((E)-2-(benzoxazol-2-yl) vinyl) naphthalene

(BBVN) in methanol. Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy, 173: 681-686. https://doi.org/10.1016/j.saa.2016.10.018.

34. Hanif, H., V. Abdollahi, F. Javani Jouni, M. Nikoukar, B. Rahimi Esboei & E. Shams (2023). Quercetin nano phytosome: as a novel anti-leishmania and anti-malarial natural product. Journal of Parasitic Diseases, Pages 1-8. https://link.springer.com/article/10.1007/s12639-022-01561-8.
35. Hou, Z., Y. Li, Y. Huang, C. Zhou, J. Lin, Y. Wang, F. Cui, S. Zhou, M. Jia & S. Ye (2013). Phytosomes loaded with mitomycin C–soybean phosphatidylcholine complex developed for drug delivery. Molecular pharmaceutics, 10: 90-101. https://doi.org/10.1021/mp300489p.
36. Ipar, V.S., A. Dsouza & P.V. Devarajan (2019). Enhancing curcumin oral bioavailability through nano formulations. European Journal of Drug Metabolism and Pharmacokinetics, 44: 459-480. https://link.springer.com/article/10.1007/s13318-019-00545-z.
37. Islam, N., M. Irfan, T. Hussain, M. Mushtaq, I.U. Khan, A.M. Yousaf, M.U. Ghori & Y. Shahzad (2022). Piperine phytosomes for bioavailability enhancement of domperidone. Journal of Liposome Research, 32: 172-180. https://doi.org/10.1080/08982104.2021.1918153
38. Jahangir, M.A., C. Anand, A. Muheem, S.J. Gilani, M. Taleuzzaman, A. Zafar, M. Jafar, S. Verma & M. Barkat (2020). Nano phytomedicine based delivery system for CNS disease. Current Drug Metabolism, 21: 661-673. https://doi.org/10.2174/1389200221666200523161003.
39. Karataş, A., & F. Turhan (2015). Phyto-phospholipid complexes as drug delivery system for herbal extracts/ molecules. Turkish Journal of Pharmaceutical Sciences, 12: 93-102.
40. Karimi, N., B. Ghanbarzadeh, H. Hamishehkar, F. Keyvani, A. Pezeshki & M.M. Gholian (2015). Phytosome and liposome: the beneficial encapsulation systems in drug delivery and food application. https://www.sid.ir/en/VEWSSID/J_pdf/50003520150306.pdf.
41. Karole, S., & G. Gupta (2019). Preparation and evaluation of phytosomes containing ethanolic extract of leaves of Bombax ceiba for hepatoprotective activity. Evaluation, 6: 1-5.
42. Kattyar, S.L., P.S. Patil, S.V. Patil & S.S. Kadam (2022). Phytosomes and recent research on phytosomal drugs. Asian Journal of Pharmaceutical Analysis, 12: 61-69. http://dx.doi.org/10.52711/2231-5675.2022.00012.
43. Kazemi, D., S.N. Ebrahimi & R.M. Kouchaksaraee (2022). Fabrication and optimization of physicochemical properties of nano-phytosome from Punica granatum L. peel enriched polyphenol extract. Journal of Medicinal Plants, 21: 50-61. https://jmp.ir/article-1-3385-fa.pdf.
44. Khan, J., A. Alexander, S. Saraf & S. Saraf (2013). Recent advances and future prospects of phyto-phospholipid complexation technique for improving pharmacokinetic profile of plant actives. Journal of Controlled Release, 168: 50-60. https://doi.org/10.1016/j.jconrel.2013.02.025.
45. Kidd, P.M. (2009). Bioavailability and activity of phytosome complexes from botanical polyphenols: the silymarin, curcumin, green tea, and grape seed extracts. Altern Med Rev, 14: 226-246.
46. Kim, S.-M., J.-I. Jung, C. Chai & J.-Y. Imm (2019). Characteristics and glucose

uptake promoting effect of chrysin-loaded phytosomes prepared with different phospholipid matrices. Nutrients, 11: 2549. https://doi.org/10.3390/nu11102549.

47. Komeil, I.A., O.Y. Abdallah & W.M. El-Refaie (2022). Surface modified genistein phytosome for breast cancer treatment: In-vitro appraisal, pharmacokinetics, and in-vivo antitumor efficacy. European Journal of Pharmaceutical Sciences, 179: 106297. https://doi.org/10.1016/j.ejps.2022.106297.
48. Kumar, M., M. Ahuja & S.K. Sharma (2008). Hepatoprotective study of curcumin-soya lecithin complex. Scientia Pharmaceutica, 76: 761-774. https://doi.org/10.3797/scipharm.0808-09.
49. Kumar, N., R. Goel, M. Singh, N.K. Sharma, P.K. Gaur & P.K. Sharma (2023). Development and evaluation of Hedyotis corymbosa (L.) extract containing Phytosomes: A preclinical approach for treatment of neuropathic pain in Rodent model. Journal of Microencapsulation, Pages 1-16. https://doi.org/10.1080/02652048.2023.2188938.
50. Li, J., X. Wang, T. Zhang, C. Wang, Z. Huang, X. Luo & Y. Deng (2015). A review on phospholipids and their main applications in drug delivery systems. Asian Journal of Pharmaceutical Sciences, 10: 81-98. https://doi.org/10.1016/j.ajps.2014.09.004.
51. Li, Y., D.-J. Yang, S.-L. Chen, S.-B. Chen & A.S.-C. Chan (2008). Process parameters and morphology in puerarin, phospholipids and their complex microparticles generation by supercritical antisolvent precipitation. International Journal of Pharmaceutics, 359: 35-45. https://doi.org/10.1016/j.ijpharm.2008.03.022.
52. Lu, M., Q. Qiu, X. Luo, X. Liu, J. Sun, C. Wang, X. Lin, Y. Deng & Y. Song (2019). Phyto-phospholipid complexes (phytosomes): A novel strategy to improve the bioavailability of active constituents. Asian Journal of Pharmaceutical Sciences, 14: 265-274. https://doi.org/10.1016/j.ajps.2018.05.011.
53. Maiti, K., K. Mukherjee, V. Murugan, B.P. Saha & P.K. Mukherjee (2010). Enhancing bioavailability and hepatoprotective activity of andrographolide from Andrographis paniculata, a well-known medicinal food, through its herbosome. Journal of the Science of Food and Agriculture, 90: 43-51. https://doi.org/10.1002/jsfa.3777.
54. Mancini, S., L. Nardo, M. Gregori, I. Ribeiro, F. Mantegazza, C. Delerue-Matos, M. Masserini & C. Grosso (2018). Functionalized liposomes and phytosomes loading Annona muricata L. aqueous extract: Potential nanoshuttles for brain-delivery of phenolic compounds. Phytomedicine, 42: 233-244. https://doi.org/10.1016/j.phymed.2018.03.053.
55. Mao, J.T., B. Xue, S. Fan, P. Neis, C. Qualls, L. Massie & O. Fiehn (2021). Leucoselect phytosome modulates serum eicosapentaenoic acid, docosahexaenoic acid, and prostaglandin E3 in a phase i lung cancer chemoprevention study effects of grape seed extract on complex lipid metabolomics. Cancer Prevention Research, 14: 619-626. https://doi.org/10.1158/1940-6207.CAPR-20-0585.
56. Maryana, W., H. Rachmawati & D. Mudhakir (2016). Formation of phytosome containing silymarin using thin layer-hydration technique aimed for

oral delivery. Materials Today: Proceedings, 3: 855-866. https://doi.org/10. 1016/j.matpr.2016.02.019.

57. Mazumder, A., A. Dwivedi, J.L. Du Preez & J. Du Plessis (2016). In vitro wound healing and cytotoxic effects of sinigrin–phytosome complex. International Journal of Pharmaceutics, 498: 283-293. https://doi.org/10.1016/j. ijpharm.2015.12.027.
58. Metkari, V., R. Shah, N. Salunkhe & S. Gurav (2023). QBD approach for the design, optimization, development, and characterization of Naringenin-loaded phytosomes to enhance solubility and oral bioavailability. Journal of Pharmaceutical Innovation, Pages 1-15. https://link.springer.com/article/10.1007/ s12247-023-09775-w.
59. Mirzaei, H., A. Shakeri, B. Rashidi, A. Jalili, Z. Banikazemi & A. Sahebkar (2017). Phytosomal curcumin: A review of pharmacokinetic, experimental and clinical studies. Biomedicine & Pharmacotherapy, 85: 102-112. https://doi.org/10.1016/j.biopha.2016.11. 098.
60. Mishra, Y., H.I.M. Amin, V. Mishra, M. Vyas, P.K. Prabhakar, M. Gupta, R. Kanday, K. Sudhakar, S. Saini & A. Hromić-Jahjefendić (2022). Application of nanotechnology to herbal antioxidants as improved phytomedicine: An expanding horizon. Biomedicine & Pharmacotherapy, 153: 113413. https://doi.org/10.1016/j.biopha.2022.11 3413.
61. Murugesan, M.P., M.V. Ratnam, Y. Mengitsu & K. Kandasamy (2021). Evaluation of anti-cancer activity of phytosomes formulated from Aloe vera extract. Materials Today: Proceedings, 42: 631-636. https://doi.org/10. 1016/j.matpr.2020.11.047.
62. Nagar, G. (2019). Phytosomes: a novel drug delivery for herbal extracts. Int J Pharm Sci Res., Pages 949-959. http://www.rjlbpcs.com/article-pdf-downloads/2019/26/610.pdf.
63. Naik, A.A., C.H. Gadgoli & A.B. Naik (2023). Formulation containing phytosomes of carotenoids from Nyctanthes arbor-tristis and Tagetes patula protect D-galactose Induced skin aging in mice. Clinical Complementary Medicine and Pharmacology, 3: 100070. https://doi.org/10.1016/j.ccmp.2022.100 070.
64. Naik, G.G., M.B. Alam, V. Pandey, P.K. Dubey, A.S. Parmar & A.N. Sahu (2020). Pink fluorescent carbon dots derived from the phytomedicine for breast cancer cell imaging. ChemistrySelect, 5: 6954-6960. https://doi.org/ 10.1002/slct.202001613.
65. Nashaat, D., M. Elsabahy, K.M. Hassanein, G.A. El-Gindy & E.H. Ibrahim (2023). Development and in vivo evaluation of therapeutic phytosomes for alleviation of rheumatoid arthritis. International Journal of Pharmaceutics, 644: 123332. https://doi.org/10.1016/j.ijpharm.2023.12 3332.
66. Nazari, M., H. Majdi, M. Milani, S. Abbaspour-Ravasjani, H. Hamishehkar & L.-T. Lim (2019). Cinnamon nanophytosomes embedded electrospun nanofiber: Its effects on microbial quality and shelf-life of shrimp as a novel packaging. Food Packaging and Shelf Life, 21: 100349. https://doi.org/10.1016/j.fpsl.2019.10034 9.
67. Pasala, P.K., R.K. Uppara, et al. (2022). Silybin phytosome attenuates cerebral ischemia-reperfusion injury in rats by suppressing oxidative stress and reducing inflammatory response: In vivo and in silico approaches. Journal of

Biochemical and Molecular Toxicology, 36: e23073. https://doi.org/10.1002/jbt.23073.

68. Patel, J., R. Patel, K. Khambholja & N. Patel (2009). An overview of phytosomes as an advanced herbal drug delivery system. Asian J Pharm Sci, 4: 363-371.
69. Pathan, R.A., & U. Bhandari (2011). Preparation & characterization of embelin–phospholipid complex as effective drug delivery tool. Journal of Inclusion Phenomena and Macrocyclic Chemistry, 69: 139-147. https://link.springer. com/article/10.1007/s10847-010-9824-2.
70. Permana, A.D., R.N. Utami, A.J. Courtenay, M.A. Manggau, R.F. Donnelly & L. Rahman (2020). Phytosomal nanocarriers as platforms for improved delivery of natural antioxidant and photoprotective compounds in propolis: An approach for enhanced both dissolution behaviour in biorelevant media and skin retention profiles. Journal of Photochemistry and Photobiology B: Biology, 205: 111846. https://doi.org/10.1016/j.jphotobiol.2020. 111846.
71. Priani, S.E., S. Aprilia, R. Aryani & L. Purwanti (2019). Antioxidant and tyrosinase inhibitory activity of face serum containing cocoa pod husk phytosome (Theobroma cacao L.). Journal of Applied Pharmaceutical Science, 9: 110-115. http://dx.doi.org/10.7324/JAPS.2019.910 15.
72. Rahman, H.S., H.H. Othman, N.I. Hammadi, S.K. Yeap, K.M. Amin, N. Abdul Samad & N.B. Alitheen (2020). Novel drug delivery systems for loading of natural plant extracts and their biomedical applications. International Journal of Nanomedicine, Pages 2439-2483. https://doi.org/10.2147/IJN.S227805.
73. Rahman, S.H. (2021). Formulation and evaluation of Cassia auriculata flower extract-loaded phytosomal cream to enhance the topical bioavailability. International Journal of Green Pharmacy (IJGP), Page 15.
74. Rajamma, S.S., V. Krishnaswami, S.L. Prabu & R. Kandasamy (2022). Geophila repens phytosome-loaded intranasal gel with improved nasal permeation for the effective treatment of Alzheimer's disease. Journal of Drug Delivery Science and Technology, 69: 103087. https://doi.org/10.1016/j.jddst.2021.1030 87.
75. Sari, R.K., Y.H. Prayogo, R.A.L. Sari, N. Asidah, M. Rafi, I. Wientarsih & W. Darmawan (2021). Intsia bijuga Heartwood Extract and Its Phytosome as Tyrosinase Inhibitor, Antioxidant, and Sun Protector. Forests, 12: 1792. https://doi.org/10.3390/f12121792.
76. Sbrini, G., P. Brivio, M. Fumagalli, F. Giavarini, D. Caruso, G. Racagni, M. Dell'Agli, E. Sangiovanni & F. Calabres (2020). Centella asiatica L. Phytosome improves cognitive performance by promoting BDNF expression in rat prefrontal cortex. Nutrients, 12: 355. https://doi.org/10.3390/nu12020355.
77. Semalty, A. (2014). Cyclodextrin and phospholipid complexation in solubility and dissolution enhancement: a critical and meta-analysis. Expert Opinion on Drug Delivery, 11: 1255-1272. https://doi.org/10.1517/17425247. 2014.916271.
78. Semalty, A., M. Semalty, D. Singh & M. Rawat (2010). Preparation and characterization of phospholipid complexes of naringenin for effective drug delivery. Journal of Inclusion Phenomena and Macrocyclic Chemistry,

67: 253-260. https://link.springer.com/article/10.1007/s10847-009-9705-8.

79. Semalty, A., M. Semalty, D. Singh & M. Rawat (2012). Phyto-phospholipid complex of catechin in value added herbal drug delivery. Journal of Inclusion Phenomena and Macrocyclic Chemistry, 73: 377-386. https://link.springer.com/article/10.1007/s10847-011-0074-8.
80. Sharma, N., S. Singh, N. Laller & S. Arora (2020). Application of central composite design for statistical optimization of Trigonella foenum-graecum phytosome-based cream. Research Journal of Pharmacy and Technology, 13: 1627-1632.
81. Sharma, S., & A.N. Sahu (2016). Development, characterization, and evaluation of hepatoprotective effect of Abutilon indicum and Piper longum phytosomes. Pharmacognosy Research, 8: 29. https://doi.org/10.4103%2F0 974-8490.171102.
82. Shende, M.A., M.S. More & R.P. Marathe (2018). Development and evaluation of Terminalia Arjuna loaded phytosome for bioavailability enhancement. International Journal of Pharmaceutical Sciences and Nanotechnology, 11: 4012-4020. https://doi.org/10.37285/ijpsn.2018.11.2.2.
83. Shirsath, N.R., & A.K. Goswami (2019). Nanocarriers based novel drug delivery as effective drug delivery: A review. Current Nanomaterials, 4: 71-83. https://doi.org/10.2174/2405461504666190527101436.
84. Shriram, R.G., A. Moin, H.F. Alotaibi, E.-S. Khafagy, A. Al Saqr, A.S. Abu Lila & R.N. Charyulu (2022). Phytosomes as a plausible nano-delivery system for enhanced oral bioavailability and improved hepatoprotective activity of silymarin. Pharmaceuticals, 15: 790. https://doi.org/10.3390/ph15070790.
85. Singh, A., A. Ray, R. Mishra, P.K. Biswal, R. Yadav & S.K. Ghatuary (2020). Phyto-Phospholipid complexes: Innovative approach to enhance the bioavailability and therapeutic efficacy of herbal extract. Pharmaceutical and Biosciences Journal, Pages 01-09. https://doi.org/10.20510/ukjpb/8/i4/159352 1611.
86. Singh, A.N., B. Mahanti & K. Bera (2021). Novel drug delivery system & it's future: an overview. International Journal of Pharmacy and Engineering, 9: 1070-1088. http://www.abhipublications.org/journal/G_191_I.pdf.
87. Singh, R., S. Parpani, R. Narke & R. Chavan (2014). Phytosome: Recent advance research for novel drug delivery system. Asian Journal of Pharmaceutical Research and Development, Pages 15-29. http://www.ajprd.com/index.php/journal/article/view/185.
88. Sivadasan, D., M.H. Sultan, S.S. Alqahtani & S. Javed (2023). Cubosomes in drug delivery—A comprehensive review on its structural components, preparation techniques and therapeutic applications. Biomedicines, 11: 1114. https://doi.org/10.3390/biomedicines11041114.
89. Supraja, B., & S. Mulangi (2019). An updated review on pharmacosomes, a vesicular drug delivery system. Journal of Drug Delivery and Therapeutics, 9: 393-402. https://doi.org/10.22270/jddt.v9i1-s.2234.
90. Surini, S., H. Mubarak & D. Ramadon (2018). Cosmetic serum containing grape (Vitis vinifera L.) seed extract phytosome: Formulation and in vitro

penetration study. Journal of Young Pharmacists, 10: S51.

91. Tan, Q., S. Liu, X. Chen, M. Wu, H. Wang, H. Yin, D. He, H. Xiong & J. Zhang (2012). Design and evaluation of a novel evodiamine-phospholipid complex for improved oral bioavailability. Aaps Pharmscitech, 13: 534-547. https://link.springer.com/article/10.1208/s12249-012-9772-9.
92. Telange, D.R., A.T. Patil, A.M. Pethe, H. Fegade, S. Anand & V.S. Dave (2017). Formulation and characterization of an apigenin-phospholipid phytosome (APLC) for improved solubility, in vivo bioavailability, and antioxidant potential. European Journal of Pharmaceutical Sciences, 108: 36-49. https://doi.org/10.1016/j.ejps.2016.12.009.
93. Telange, D.R., A.T. Patil, A.M. Pethe, A.A. Tatode, S. Anand & V.S. Dave (2016). Kaempferol-phospholipid complex: formulation, and evaluation of improved solubility, in vivo bioavailability, and antioxidant potential of kaempferol. Journal of Excipients and Food Chemicals, 7: 1174. https://fisherpub.sjf.edu/pharmacy_facpub/128/.
94. Tran, N., B. Pham & L. Le (2020). Bioactive compounds in anti-diabetic plants: From herbal medicine to modern drug discovery. Biology, 9: 252. https://doi.org/10.3390/biology9090252.
95. Tripathy, S., D.K. Patel, L. Barob & S.K. Naira (2013). A review on phytosomes, their characterization, advancement & potential for transdermal application. Journal of Drug Delivery and Therapeutics, 3: 147-152. https://doi.org/10.22270/jddt.v3i3.508.
96. Vu, H.T., S.M. Hook, S.D. Siqueira, A. Müllertz, T. Rades & A. Mc Dowell (2018). Are phytosomes a superior nanodelivery system for the antioxidant rutin? International Journal of Pharmaceutics, 548: 82-91.
97. Wanjiru, J., J. Gathirwa, E. Sauli & H.S. Swai (2022). Formulation, optimization, and evaluation of moringa oleifera leaf polyphenol-loaded phytosome delivery system against breast cancer cell lines. Molecules, 27: 4430. https://doi.org/10.3390/molecules27144430.
98. Xu, K., B. Liu, Y. Ma, J. Du, G. Li, H. Gao, Y. Zhang & Z. Ning (2009). Physicochemical properties and antioxidant activities of luteolin-phospholipid complex. Molecules, 14: 3486-3493. https://doi.org/10.3390/molecules14093486.
99. Xu, L., D. Xu, Z. Li, Y. Gao & H. Chen (2019). Synthesis and potent cytotoxic activity of a novel diosgenin derivative and its phytosomes against lung cancer cells. Beilstein Journal of Nanotechnology, 10: 1933-1942. https://doi.org/10.3762/bxiv.2019.61.v1.
100. Yu, F., Y. Li, Q. Chen, Y. He, H. Wang, L. Yang, S. Guo, Z. Meng, J. Cui & M. Xue (2016). Monodisperse microparticles loaded with the self-assembled berberine-phospholipid complex-based phytosomes for improving oral bioavailability and enhancing hypoglycemic efficiency. European Journal of Pharmaceutics and Biopharmaceutics, 103: 136-148. https://doi.org/10.1016/j.ejpb.2016.03.019.
101. Yu, Z., X. Liu, H. Chen & L. Zhu (2020). Naringenin-loaded dipalmitoylphosphatidylcholine phytosome dry powders for inhaled treatment of acute lung injury. Journal of Aerosol Medicine and Pulmonary Drug Delivery, 33: 194-204. https://doi.org/10.1089/jamp.2019.1569.

102. Yue, P.-F., W.-J. Zhang, H.-L. Yuan, M. Yang, W.-F. Zhu, P.-L. Cai & X.-H. Xiao (2008). Process optimization, characterization and pharmacokinetic evaluation in rats of ursodeoxycholic acid–phospholipid complex. AAPS Pharm Sci Tech, 9: 322-329. https://link.springer.com/article/10.1208/s12249-008-9040-1.
103. Zhang, K., M. Zhang, Z. Liu, Y. Zhang, L. Gu, G. Hu, X. Chen & J. Jia (2016). Development of quercetin- phospholipid complex to improve the bioavailability and protection effects against carbon tetrachloride-induced hepatotoxicity in SD rats. Fitoterapia, 113: 102-109. https://doi.org/10.1016/j.fitote.2016.07.008.
104. Zhu, S., C. Luo, W. Feng, Y. Li, M. Zhu, S. Sun & X. Zhang (2020). Selenium-deposited tripterine phytosomes ameliorate the antiarthritic efficacy of the phytomedicine via a synergistic sensitization. International Journal of Pharmaceutics, 578: 119104. https://doi.org/10.1016/j.ijpharm.2020.119104.