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PHYTOSOMES: AN OVERVIEW

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Abstract

Phytosome is a patented technology that incorporates standardized plant extracts into phospholipids to create lipid-soluble molecular complexes with improved bioavailability and absorption. These phyto-constituents are increasingly important due to their nutritional and medicinal properties, but their bioavailability remains poor. Phytosome drug delivery is a method developed to enhance their bioavailability and is compatible in-vivo. Preparation methods are easy and can be characterized using techniques like FTIR, PXRD, DSC, SEM, TEM, and HNMR. Phytosomes can be used to augment the bioavailability of plant constituents and treat incurable diseases with less side effects. Phytosomes are formed by reacting a stoichiometric amount of phospholipid with standardized herbal extract or polyphenolic constituents in an aprotic solvent. Phosphatidylcholine molecules in phytosomes have hepatoprotective activity and nutritional value. In this article, we are going to keep an eye on an Phytosomes Overview.

Keywords: Phytosomes, Phytoconstituents, Phospholipid, Bioavailability.

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1. Introduction

The new class of herbal formulations known as phytosomes is made up of the bioactive phytoconstituent(s) of the herb extract complexed with phospholipid to create lipid-compatible molecular complexes that, when dissolved in water, form micellar structures [1]. A revolutionary approach to drug distribution, the innovative drug delivery system overcomes the drawbacks of the conventional drug administration methods. Ayurveda is a wide field of knowledge in our country, and its full potential has only just come to light. However, the herbal medicine's potency has been diminished since the conventional medication delivery method employed to administer it is antiquated. Modern phytopharmaceutical research, however, may address issues with solid dispersions, solid lipid nanoparticles, phytosomes, phytosomes, liposomes, microemulsions, nanoparticles, and more [2].

Due to their safety, effectiveness, cultural acceptance, and low side effects, they have withstood the test of time. The liver, an essential organ, plays a critical role in the metabolism of xenobiotics, which makes it susceptible to a variety of hepatic illnesses. Phytosomes are a unique type of herbal formulation that comprise one or more bioactive phytoconstituents from the herb extract complexed with phospholipid to generate lipid-compatible molecular complexes that form micellar structures when water is added [3]. Phytosome is a recently developed patented method whereby phytomolecules create hydrogen bonds with phospholipids to form complexes. They have the capacity to go from the exterior water phase into the lipid layer of the enterocyte, enter the cell, and ultimately enter the blood. "Some" refers to a structure that resembles a cell, while "Phyto" refers to a plant [4]. Many plants have low oral bioavailability, especially those carrying active principles, researchers and academics are becoming concerned about the bioavailability of plant active principles [5]. A new, patented technology that overcomes the shortcomings of traditional medication delivery methods is called a unique drug delivery system. Although they were once employed as first aid treatments, herbal cures are no longer effective [6]. One way to refer to "phyto-constituents" is as "plant-chemicals." Phyto-constituents are found naturally in plants, have the potential to be both nutritious and therapeutic, and have been shown to improve human health [7].

Phytoconstituents help in preventing diseases by the following ways:

- They trigger the body's immune system to combat harmful bacteria, viruses, and other microorganisms.
- Minimize oxidation to avoid potential cell damage brought on by pollutants and certain free radicals.
- They might slow down the rate at which malignant cells proliferate and help control hormones and also help in DNA repair mechanisms [7].

Phyto-constituentstypes [7,8]

1. Alkaloids: Alkaloids are a diverse family of secondary metabolites that are basic in nature, composed of amino acids with a heterocyclic nitrogen structure. The term 'alkaloid' originates from its alkaline state and is likely associated with a nitrogen-containing base. Their primary uses are as pharmaceuticals, cures, and bitter-tasting ingredients. Their primary purpose is to shield plants from insects, herbivores, and microorganisms because to their inherent toxicity.

2.Phenolics: Plants contain phenolic chemicals that may polymerize into bigger molecules such as lignins and proanthocynadines. It is extensively distributed in many plant species and has been valued since prehistoric times for its ability to protect plants from oxidative stress-related harm.

3.Saponins: They are called "saponins" because they often produce stable soaps in aqueous solutions. The class of substances known as saponins is composed of triterpenoids, steroidal alkaloids, and glycosylated steroids. One might consider saponins to be effective antimicrobial agents.

4. Glycosides: The two components of a glycoside's structure are carbohydrate and non-carbohydrate. Glycone is the non-carbohydrate portion of this, whereas glycone is the portion that contains carbohydrates. They are divided into groups that include aldehyde glycoside, flavonoids, cyanophore, saponin, coumarin and furocoumarin, and anthraquinone.

5. Terpenes/Terpenoids: Because it is a volatile oil derived from pine trees, turpentine is also known as "terpene." Terpenes are polycyclic substances with distinct functional groups on their fundamental carbon skeletons. They are separated into five categories: sesquiterpenes, diterpenes, triterpenes, hemiterpenoids, monoterpenes, and tetraterpenes.

6. Tannins: Tannins have anti-oxidant properties and work by scavenging free radicals, forming transition metal complexes, blocking the enzyme peroxidase, and stopping lipid peroxidation. They are referred to as astringents because of their bitter flavor and polyphenols, which precipitate proteins.

Advantages of Herbal Medicines [2]

1) The absence of adverse effects is the main advantage of using herbal medication.

2) Obesity is an increasing issue that is recognized to have dangerous consequences on a person's health. Herbal therapy successfully addresses the obesity issue with no time and effort required.

3) The cost of herbal medications is significantly lower than that of conventional pharmaceuticals.

Disadvantages of Herbal Medicines

1) Sometimes people go to herbal medication without recognizing that the symptoms can be associated with another illness [2, 3].

2) Herbal remedies typically take longer to cure than conventional medications, despite their ability to treat a wide range of illnesses. When receiving herbal treatment, the patient has to be more patient [2, 3].

3) Because herbal medications are polar in nature, the body absorbs them slowly.

4) The majority of herbal remedies are unsupported by scientific research since no clinical trials have been done on them.

5) The likelihood of drug interactions between natural medications and prescription medications is another drawback [6].

Phytosomes [6, 7, 9-17]

Phytosome is a patented technology that incorporates standardized plant extracts into phospholipids to create lipid-compatible molecular complexes with improved bioavailability and absorption. Phytosomes, also known as herbal drug loadedin vesicles, provide an envelope-like coating around the active constituent of the drug, preventing degradation by digestive secretion and bacteria. They effectively absorb from a water-loving environment into a lipid-loving environment of the cell membrane and reach blood circulation.

Advantages of Phytosomes

- The solubility of bile in herbal components is enhanced by phytosomes [18].
- Because of the establishment of chemical connections between phytoconstituents and phosphatidylcholine molecules, phytosomes exhibit superior stability [19].
- The production of phytosomes shields the active ingredients in herbal extracts from being destroyed by digestion and intestinal fluids [20].
- A little dosage can yield the intended effects since the active component's absorption is enhanced [21].
- The process of creating phytosomes is simple because drug entrapment is not a concern [22].
- Phytosomes provide an improved stability profile [23].
- The phytosomes' duration of action is extended. [24].
- Higher drug entrapment efficiency is demonstrated by phytosomes [25].
- Not only is phosphatidylcholine a carrier, but it also has nutritional value and hepatoprotective properties [26].
- Phytosome formulations enable the topical use of herbal ingredients for cosmetic and other purposes [27].

Disadvantages of Phytosomes

- The primary drawback of phytosomes is their tendency to lixiviate the phytoconstituent off of the "some," resulting in an unstable state when the intended drug concentration is lowered.
- While phytosomes offer many benefits, they also have some deadly drawbacks, such as growth on the MCF-7 breast cancer cell line because to phospholipid (lecithin) [5].
- The active components leave phytosomes quickly [6].

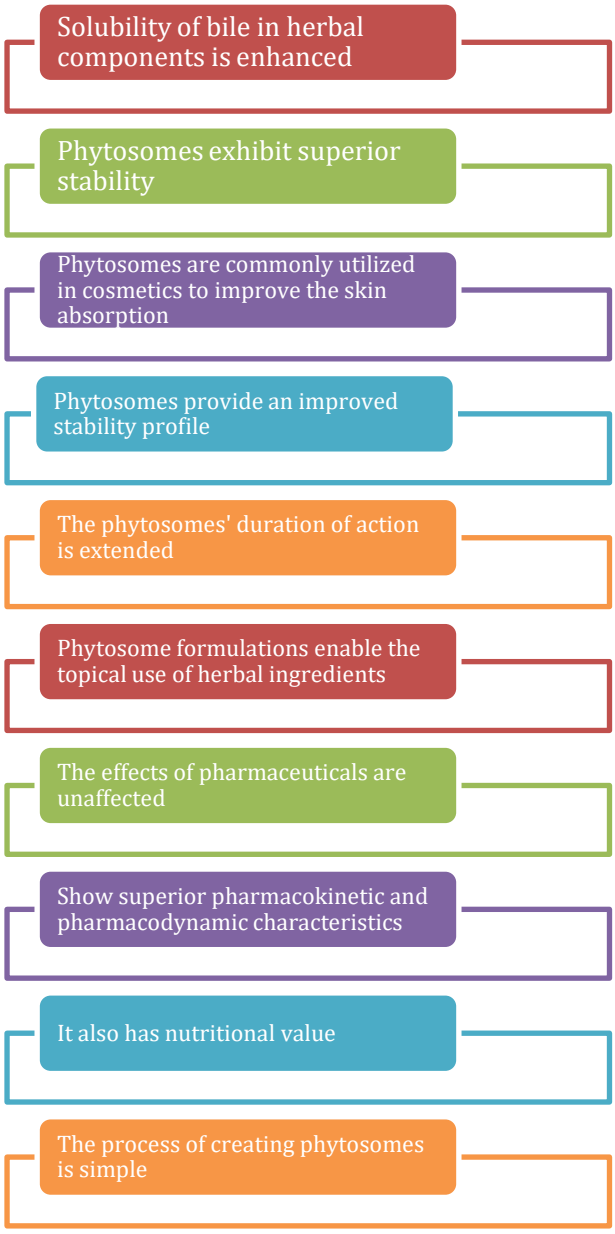

Figure 2: Advantages of Phytosomes

Phospholipids

The structural makeup of phospholipid molecules is composed of an extended hydrocarbon chain of fatty acids, which gives them their lipophilic properties. On the other hand, the hydrophilic choline molecule, which may bind to polar phytoconstituents, gives them their hydrophilic properties. This molecule is referred to as an amphiphilic molecule. Its structure also includes a negatively charged phosphate group [7].

Advantages of Phospholipids [28, 7]

1. Entrapment effectiveness was also seen to be enhanced and stability was increased as a result of the creation of vesicles.
2. Increase in the phyto-constituents' bioavailability by the application of lipid properties to the whole molecule.
3. Phospholipids have extremely little risk for toxicity, therefore using them may enhance patient compliance.

Mechanism of Phytosome Technology

A stoichiometric quantity of phospholipid (phosphatidylcholine) reacts with standardized extract or polyphenolic components (simple flavonoids) in an aprotic solvent to form phytosomes [28]. The phosphatidyl and choline moieties of phosphatidylcholine are hydrophilic and lipophilic. The lipid-soluble phosphatidyl part envelops the choline-bound material while the choline head of the molecule attaches to polyphenolic components. Thus, the phytomolecules and phospholipids combine to form a lipid-soluble molecular complex known as the phytophospholipid complex. The particular spectroscopic methods show that molecules are linked to the hydrophilic head of the phospholipids by chemical bonds [29,30].

According to precise chemical analysis, a flavonoid molecule connected to at least one phosphatidylcholine molecule often makes up the unit phytosome [31,2].

Difference between liposome and phytosome:

Similar to phytosomes, liposomes are created by precisely combining phosphatidylcholine and water in a given ratio under particular circumstances. [6] On the other hand, depending on the chemical bonds within the complex, the phosphatidylcholine and the herbal components within the phytosome really create a 1:1 or 1:2 molecular complex. Additionally, it has been discovered that phytosomes work better than liposomes in topical and skin care products [32]. A liposome is an aggregate of several phospholipid molecules that can encapsulate other phytoactive molecules without necessarily connecting to them, whereas a phytosome is a unit of a few molecules bound together [33, 34].

Preparation techniques for phytosomes:

A. Thin layerrotary evaporator method:
In a 250 ml round-bottom flask, the phytosomal complex was combined with anhydrous ethanol. A rotating evaporator had the flask fastened to it. At around 60˚C, the solvent will evaporate and create a thin coating around the flask. Phosphate buffer at a pH of 6.8 hydrates the film, and the lipid layer peels off to form a suspension of vesicles in the phosphate buffer. Prior to characterisation, the phytosomal solution will be refrigerated for a full day [35].

B. Solvent evaporation method: 5 ml of n-hexane was added to the thin film with stirring after the dichloromethane had evaporated, and it was then placed in a fume hood to ensure that all of the solvent had been removed. Following the total elimination of n-hexane, the thin film was sonicated and hydrated to

produce the required phytosomalcomplex [36].

C. Reflux method

Reflux technique may also be used to prepare phytosomes. Phospholipid and polyphenolic extract were added to a 100 ml round-bottom flask and refluxed in dichloromethane for one hour at a temperature not to exceed 40°C. After evaporating the clear solution, 15 milliliters of n-hexane were added till a precipitate formed. After being extracted, the precipitate was put in a desiccator to dry out [37].

Properties of Phytosomes

1. Embracing the active principle linked to the membrane's polar head, phytosomes enable the membrane to become an integral component. [38].
2. Phosphatidylcholine: Research comparing the complex's nuclear magnetic resonance signals to those of the pure precursors shows that the fatty chain's signals remain unaltered. [39].
3. Phytosomes are sophisticated, more effectively absorbed herbal compounds. Consequently, outperform traditional botanical herbal extracts in terms of outcomes. Pharmacokinetic investigations or pharmacodynamic testing in experimental animals and humans have proven the phytosome's improved bioavailability over the non-complexed botanical derivatives. [40].
4. With a defined melting point, phytosomes are lipophilic materials that are easily soluble in non-polar solvents and very slightly soluble in lipids. [41].
5. When phytosomes are handled with water, they take on the shape of micellar structures, which are fundamentally different from liposomes [42].

Chemical properties:

An intricate interaction between an organic product and an organic phospholipid is called a phytosome. By nature, phytosomes are lipophilic. They are easily soluble in organic solvents, have a high melting point, and are very slightly soluble in lipids. When dissolved in aqueous solvent, phytosomes take on the form of a micellar substance [6].

Biological properties:

- These studies have assessed the phytosomes superior bioavailability compared to the non-complex botanical derivatives
- Pharmacological investigations on humans and experimental animals have been utilized to illustrate the biological characteristics of phytosomes
- Their pharmacokinetic profile is superior than that of a basic herbal extract [6].

Physicochemical properties

- The phytosomes are composed of phospholipids and extract, resulting from the reaction between the main extract ingredient and the phospholipid in a specific solvent.
- Phytosomes have a cellular shape akin to liposomes following interaction between phospholipid and hydrophilic extract equivalents. However, because they are encased in polar heads in phospholipids, the main extract elements become an essential component of the membrane [7].

How to select Herbal extract?

Herbal extracts have various properties, including photo-protection, anti-aging, moisturizing, antioxidant, astringent, anti-irritant, and antimicrobial. Selection of herbal extracts depends on their nature, availability, estimation method, stability, and utility. Solubility is an important criterion for developing novel formulations, with hydrophilic or lipophilic natures determining the best formulation [60].

Here are a few recommended dose formulations for the distribution of phytosomes in Figure 1.:

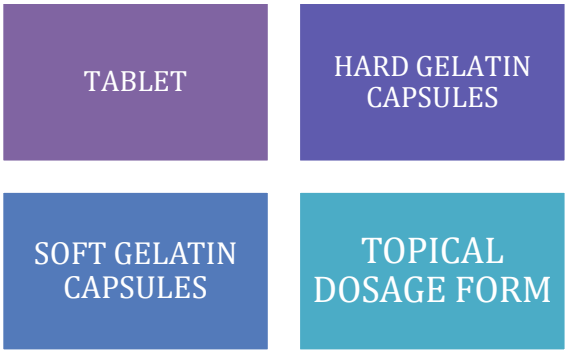

Figure 1. Recommended dose formulation

Characterization of Phytosomes

1. **Surface tension activity measurement:**
   Using a Du Nouy ring tensiometer, the drug's surface tension activity in an aqueous solution is measured using the ring technique..
2. **Entrapment efficiency:**
   The Ultracentrifugation technique may be used to test the drug's entrapment efficiency by phytosomes. [43].
3. **Visualization:**
   Transmission electron microscopy (TEM) and scanning electron microscopy (SEM) are two methods for seeing phytosomes
4. **Vesicle stability:**
   Vesicles' stability can be ascertained by evaluating their size and structure over time. Transmission electron microscopy (TEM) tracks structural changes while differential light scattering (DLS) measures the mean size.[44].
5. **Vesicle size and zeta potential:**
   Using a computerized inspection system and photon correlation spectroscopy (PCS), dynamic light scattering (DLS) may be used to evaluate the particle size and zeta potential of phytosomes.
6. **Transition temperature:**
   The differential scanning calorimeter can figure out the vesicular lipid systems' transition temperature. [45].
7. **Drug content:**
   A appropriate spectroscopic approach or a modified high-performance liquid chromatographic method can be used to quantify the drug's quantity. [46].

Characterization Techniques

1. **Differential scanning calorimetry:**The drug-phospholipid complex, phosphatidylcholine, drug polyphenolic extract, and a physical combination of the drug and phosphatidylcholine were all put in an

aluminum cell and heated to a temperature of 50–250˚C/min in a nitrogen environment, ranging from 0 to 400˚C.[47].

2. **Scanning electron microscopy (SEM):** The particle's appearance and size were assessed using SEM. A gold-coated brass stub from an electron microscope was used to hold a dry sample in an ion sputter. scanning the complex with random speed at 100.
3. **Transitionel ectronmicroscopy (TEM):**Using a 1000x magnification, the size of phytosomal vesicles was measured using TEM.[48].
4. **Fourier transform infrared spectroscopy (FTIR):** The drug's and the phospholipid's structural integrity will be verified using FTIR analysis, which will be performed between 4000-400 cm^{-1} [49].

Selection of Dosage Form [60]

1. **Tablets**
   To create tablets with the right qualities, the phytosome complex has to be diluted with 60–70% of the excipients. Because heat and water have a detrimental influence on the stability of the phyto-phospholipid complex for the delivery of phytosomes, wet granulation should be avoided.
2. **Hard gelatin capsules**
   It appears that the greatest quantity of powder (often no more than 300 mg for each capsule) that may be packed into a capsule is limited by the low density of phytosome complex. We may enhance the amount of powder that is packed into capsules by using a piston pump capsule filling procedure.
3. **Soft gelatin capsules :**
   Soft gelatin capsules can be filled with a suspension of the phytosome by dispersing it in oily media (such as vegetable or semi-synthetic oil).
4. **Topical dosage form**
   The primary lipid solvents used in topical formulation are soluble in the phyto-phospholipid complexes. Emulsion should first be prepared at a low temperature (no more than 40°C), and then the phytosome complex should be added.

Evaluation Techniques [6, 50-53]

1. **Carbon-Nuclear Magnetic Resonance (13C-NMR)**
   Research revealed that neither the stoichiometric compound with phosphatidylcholine nor the 13C-NMR of the phytoconstituents contained any carbons. The bulk of the fatty acid chain resonance has maintained its original crisp line structure, however the signals pertaining to the glycerol and choline sections were expanded and others were displaced.
2. **Determination of entrapment efficiency**
   Using a cooling centrifuge machine, the phytosome complex was diluted one-fold with 10 ml of an appropriate organic solvent and centrifuged at 10,000 rpm for one hour at -4 ˚C. After isolating the supernatant, the quantity of free herbal medication was calculated using UV/Vis spectroscopy at a particular wavelength. The volume was adjusted to 10 ml by diluting 0.1 ml of the phytosome complex in an inorganic solvent in order to calculate the total quantity of herbal medicine.
   The Entrapment efficiency is calculated by using:-
   Entrapment efficiency (%) = (Total drug amount) – (free drugamount) × 100 (Total drugamount)
3. **Determination of particle size**
   Using a particle size analyzer, the phytosome's average diameter was determined. The diameter of the generated vesicles was measured after the precise amount of formulation was diluted with the proper amount of phosphate buffer saline at pH 6.8.
4. **Scanning electron microscopy (SEM)**
   The produced phytosome complexes' size, shape, and surface morphology have all been determined using scanning electron microscopy. The optimized freeze-dried phytosomes are imaged after being examined under a scanning electron microscope.
5. **Determination of drug content**
   By dissolving 100 mg of the phytosome complex in 10 ml of an appropriate organic solvent, such as methanol, the drug concentration of the complex was ascertained. Following an appropriate dilution, the drug concentration was ascertained by measuring the absorbance at a particular wavelength using a UV-Visible Spectrophotometer.
6. **FTIR Spectroscopy**
   The structure and chemical stability of plant medications, phospholipids, and phytosome complex were ascertained using FTIR spectrum data. We used the KBr pellet technique for sampling. The pressure used to create the pellets was 500 kg/cm2. After the produced pellets were exposed to FTIR, the chemical interactions between the medication and the phospholipid were assessed by interpreting the peaks seen in the graphs.
7. **Proton-Nuclear Magnetic Resonance (1H-NMR):**
   Spectroscopic analyses are frequently employed to assess how phytoconstituents and the phospholipid moiety form complexes and to investigate the ensuing relationship. This technique may be used to mimic how the phosphatidylcholine molecule forms a compound with active phytoconstituents.
8. **In vitro drug release study**
   The treated cellophane membrane, which is affixed to one end of the open tube that holds the phytosomes, was used to assess the drug release. After that, the dialysis tube was suspended in a 500 ml beaker containing 250 ml of pH 6.8 phosphate buffer. Using a magnetic stirrer, the solution was agitated at 37+/- 0.5 degrees Celsius. Subsequently, a 1 milliliter sample was extracted at predetermined intervals and mixed with an equivalent volume of fresh PBS. After that, the samples were diluted and filtered. The UV spectrophotometer was used to evaluate the diluted samples. The phytoconstituent and the complex's penetration were contrasted.

Applications of phytosomes

- Silybummarianum (family: Steraceae) was the subject of the first phytosome research because of its fruit, which contains flavonoids with hepatoprotective properties and has demonstrated promising results in treating liver diseases such as cirrhosis, hepatitis, fatty infiltration of the liver, and bile duct inflammation. Three flavonoids make up

silymarin; silybin predominates and is suppressed by silychristin and silydianin. The strongest is silybin, which protects the liver by preserving glutathione in parenchymal cells [54, 55, 2].

- An oral formulation of coated tablets (Monoselect Camellia®) containing highly bioavailable green tea extract (GreenSelect®Phytosome) was studied by Francesco et al. for the analysis of 100 overweight subjects of both genders on a hypocaloric diet. The results showed that there were no adverse effects at all, suggesting that this is a safe and effective weight loss tool.[56,57].
- By creating a complex between hesperetin and hydrogenated phosphatidylcholine, Mukerjee et al. created a new hesperetinphytosome. Antioxidant activity of the complex was assessed, indicating that the phytosomes had a greater relative bioavailability than the active pharmaceutical ingredient [58, 2].

Table: Marketed formulations of Phytosomes [6,11]

S. No.	Phytosome or trade name	Biological activity	Source
1.	Berberine	Antidiabetic	Berberis Vulgaris
2.	Olive Oil	Anti-Inflammatory, Antioxidant, Anti-hyperlipidaemic	Europaea Oil
3.	Ginseng	Immunomodulator	Panax Ginseng
4.	Gingko	Brain and Vascular Protection	Ginkgo Biloba
5.	Centellaphytosomes	Cicatrizing, trophodermic	Centellaasiatica
6.	Sericosidephytosome	Skin improvers	Terminalia sericea
7.	Silymarin	Antihepatotoxic	Silybummarianum

Conclusion

This review discusses phytosomes that enhances the bioavailability of water-soluble herbal constituents through the skin and gastrointestinal tract. Phytosomes, also known as herbsomes, are vesicular drug delivery systems that can be used for phyto-constituents that are better absorbed orally, transdermally, and topically. They have improved pharmacokinetics and pharmacological properties, making them potential targets for targeted drug delivery. The simple, reproducible, and non-conventional preparation methods make phytosomes a promising future for pharmaceutical applications. Thus, phytosomal formulation is a connecting link between conventional drug delivery systems of phytoconstituents and advanced drug delivery systems. Phytosomes have improved pharmacokinetic and pharmacological parameter, which enable them to be used for different therapeutic purposes like cardiovascular, anti-inflammatory, anticancer, immunomodulator, antidiabetic etc. They have many advantages over the conventional formulations. The formulation methodology for phytosomes is simple and can be easily upgraded to a commercial scale. Phytosomes has a great future for use in formulation technology and applications of hydrophilic plant compounds.

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Conflicts of Interests

There are no conflicts of interest.

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