Phytosome an advancement technology in Herbal Drug Delivery, a review

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Abstract

Herbal medicine has a longstanding history in traditional and modern healthcare systems, offering bioactive compounds with therapeutic potential. However, the hydrophilic nature of these compounds often limits their absorption and bioavailability, affecting treatment efficacy. Recent advancements in drug delivery systems, particularly phytosomes, offer a promising solution to enhance bioavailability and therapeutic outcomes.

Phytosomes, nano-scale complexes of bioactive plant ingredients enveloped within phospholipids, have emerged as an innovative approach to overcome the challenges of poor solubility and absorption. By encapsulating hydrophilic compounds within lipid-compatible structures, phytosomes protect them from degradation and facilitate passage through lipid-rich membranes, enhancing absorption and systemic circulation. This technology finds applications across pharmaceuticals, nutraceuticals, and cosmeceuticals, offering benefits such as enhanced bioavailability and targeted drug delivery.

Phytosomes are prepared by combining phospholipids, with herbal extracts, forming lipid-bound structures that improve solubility and absorption. Various methods, including film hydration and anti-solvent precipitation, are employed for their preparation, with characterization techniques such as Dynamic Light Scattering (DLS) and Scanning Electron Microscopy (SEM), Transmission Electron Microscopy (TEM), Fourier Transform Infrared Spectroscopy (FTIR), Powder X-ray Diffraction (PXRD) etc used to assess their size, shape, and composition. Additionally, drug entrapment studies quantify the percentage of entrapped drugs within phytosomes, crucial for determining their efficacy.

Phytosomes represent a promising strategy to enhance the bioavailability and efficacy of herbal bioactive compounds. Their lipid-bound structures overcome the limitations of poor solubility, facilitating targeted delivery and improved therapeutic outcomes. With applications spanning pharmaceuticals, nutraceuticals, and cosmetics, phytosomes offer versatile solutions for enhancing the delivery of bioactive constituents, advancing the potential of herbal medicine in healthcare. Continued research and development in phytosome technology hold significant promise for addressing the challenges of herbal medicine delivery and maximizing its therapeutic benefits.

Keywords: *phytosome, nanotechnology, herbal drug technology, improved bioavailability*

1. Introduction

Herbal medicine has a rich historical significance in traditional and modern healthcare systems. Many plants have bioactive compounds such as glycosides and flavonoids, which have huge therapeutic potential in the health care system. However, the bioactive compounds have a hydrophilic nature which often poses a challenge to their absorption, thus affecting their bioavailability. Addressing this challenge has become an important point in the field, as it directly influences the efficacy of herbal product treatments. [1]

Whereas traditional herbal products have contributed significantly to healthcare, recent drug delivery system steps have pushed different advanced techniques to improve the herbal compound bioavailability. This includes advances in drug delivery systems that can precisely and stably deliver the active compounds to specific sites. Compared to herbal medicines, these systems reduce the loss of active substances due to delivery in specific sites. These systems not only reduce the amount of dosage but also reduce unnecessary side effects. [1,2]

The term "Phytosome" is derived from "Phyto" meaning plant and "some" meaning cell-like structure. [3]

An important innovation in addressing different bioavailability challenges is the application of phytosomes. These nano-scale complexes envelop hydrophilic bioactive compounds within phospholipids, thus forming structures compatible with lipid-based environments. Phytosomes provide a shield of the active constituents from degradation by different digestive processes and gut microorganisms. Additionally, The hydrophilic nature of the phospholipid complex helps the passage from the water-based environment to the lipid-rich cell membrane, significantly enhancing the absorption and systemic circulation. [4,5]

Structure of Phytosome:

Phytosome technology is an innovative approach to herbal medicine. They encapsulate bioactive plant ingredients with phospholipids, resulting in the formation of lipid-compatible complexes for better absorption and efficacy. [5]

Phytosomes are produced by combining phospholipids, mostly phosphatidylcholine, with herbal extracts in different solvents. This results in a lipid-bound structure where the bioactive phytoconstituents are encased by lipids. Bioactive Phytoconstituents in herbal

extracts are often water-soluble and struggle to mix with lipids. However, phytosomes overcome this low solubility challenge. They enhance solubility in gastrointestinal fluids and enhance passage through lipid-rich membranes, which causes increasing bioavailability. [3,6]

The structure of a phytosome involves the following components:

The herbal extract: The bioactive compounds that are extracted from plant material are usually water-soluble and lipid-insoluble. These compounds could be different types of flavonoids, polyphenols, terpenoids, or other bioactive molecules that have some potential health benefits. [7]

Phospholipids: Phospholipids are molecules with a hydrophilic (water-attracting) “head” and hydrophobic(water-repelling) “tails”. They are fundamental components of cell membranes and they are naturally found in the body. In preparation for phytosome nano-technology, phospholipids are derived from sources like soy lecithin. [8,9]

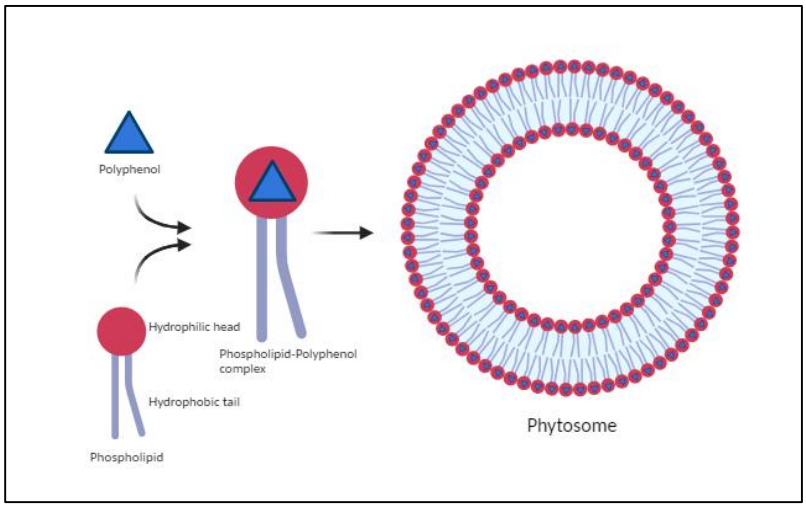


Figure 1. Structure of Phytosome

1.1.Application of Phytosome:

Phytosomes, a delivery system composed of a natural bioactive ingredient and a phospholipid, have various applications in different fields like pharmaceutical, nutraceutical, and cosmeceutical. [10]

❖ **Pharmaceuticals:**

- Enhanced Bioavailability: Phytosome nano-technology helps to enhance the absorption rate of herbal extracts that are poorly soluble. Phospholipid complex enhances the solubility of bioactive compounds, resulting in their absorption in the body. [11]
- Drug Delivery: Phytosomes technology can be used as a carrier for drug delivery of herbal bioactive compounds, ensuring targeted delivery on site and improved therapeutic efficacy of pharmaceutical compounds. [11]

❖ **Nutraceuticals:**

- Herbal Supplements: Phytosomes technology is used as a formulation of herbal supplements to increase the absorption of bioactive constituents. This is mainly beneficial for herbal extracts that have low bioavailability. [12]
- Nutritional Products: Phytosomal technology is also used to improve the delivery of different nutrients and antioxidants, enhancing their absorption and efficacy in the body. [12]

❖ **Cosmetics:**

- Skin Care Products: Phytosomes have various applications in many cosmetic formulations, particularly for skincare products. They are used to deliver plant extracts to the skin, such as antioxidants and anti-inflammatory compounds. [9]
- Topical Formulations: Phytosomal technology is also used to develop topical creams, lotions, and serums for improving the direct skin penetration and precise targeted delivery of bioactive herbal extracts. [9]

1.2.Comparison between phytosomes and liposomes

Phytosomes and liposomes are both types of nanoparticles (NPs) used for targeted drug delivery and enhancement of bioavailability, but both are very different in their structure, function, and application. [8, 13, 14]

Table 1. Comparison between Phytosomes and Liposomes

Feature	Phytosomes	Liposomes
Composition	Bioactive plant extracts and phospholipids	phospholipids and bioactive drugs with an aqueous core
Source	Mainly used for enhancing herbal extract delivery	Widely used for low-soluble drug delivery
Structural Features	Plant extracts bind with the polar part of the phospholipid bilayer	The structure is made up of one or more layers of lipids, with an aqueous core
Applications	Pharmaceuticals, cosmetics, nutraceuticals	Low soluble Drug delivery, nutraceuticals.
Stability	Generally, more stable compared to liposome	Less stable compared to phytosome.
Biocompatibility	Generally well-tolerated and more biocompatible	Biocompatible and it can be modified for targeted drug delivery with reduced toxicity

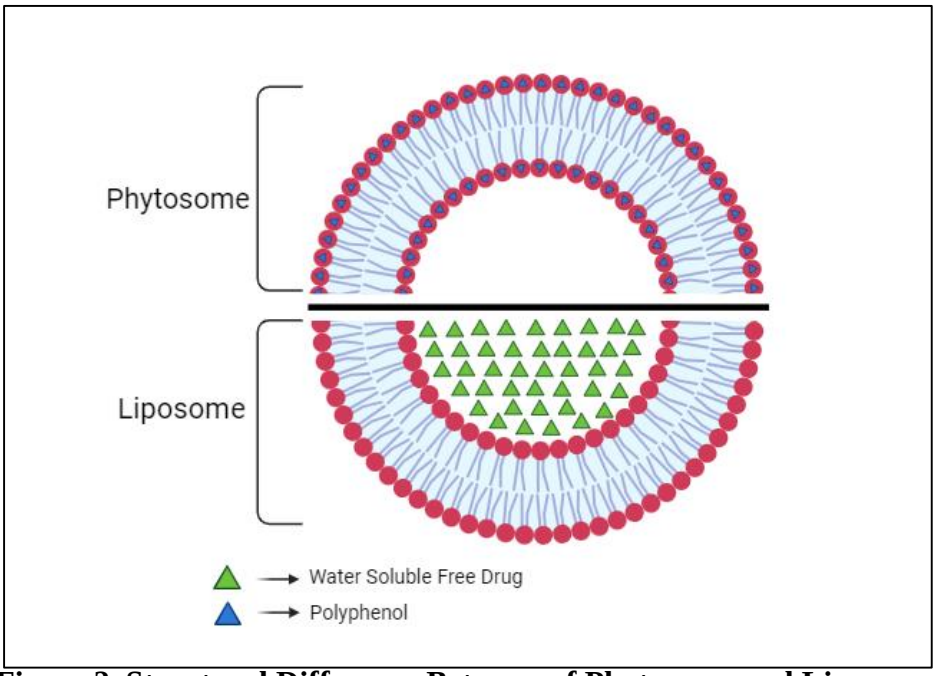


Figure 2. Structural Difference Between of Phytosome and Liposome

1.3. The Phytoconstituents:

Phytoconstituents, non-nutrient bioactive plant chemical compounds, play important roles in both plant protection and human health. Here are some of their applications:

1. Plant Protection: The phytoconstituents help protect plants against many infections, infestations, and predation by different microbes, pests, pathogens, or predators. They can also improve the plant's ability to resist environmental pressures like drought, salinity, and cold. [7]

2. Immunomodulation: Phytoconstituents show immunomodulatory properties, which means they can influence the immune system. This application is of particular interest in the pharmaceutical industry, as immunomodulators can be used to treat various medical conditions. [15]

3. Food Industry: Many phytoconstituents, such as alkaloids, terpenoids, and polyphenols, are responsible for colour, aroma, and other organoleptic properties in the food industry. They also have nutritional and medicinal value, which is why they are used in the food industry. [16]

4. Cosmetics: The bioactive compounds present in phytoconstituents can also be used in the cosmetics industry to protect skin against different conditions. [15]

Phytoconstituents are compounds that occur naturally in plants. These bioactive compounds are responsible for the diverse biological activities exhibited by different plant species. Phytochemicals are compounds found in plants that can interact with living organisms, leading to therapeutic effects. Examples of phytochemicals include phenols, alkaloids, carbohydrates, lipids, terpenoids, and other elements. [17]

Herbal extracts contain a major group of compounds called polyphenols. Polyphenols have shown various health benefits and as well as help in the cure of diseases like obesity, inflammation diabetes mellitus, liver diseases and also in curing cancer. Polyphenols can be mainly categorized into two main types: flavonoids and non-flavonoids. [3]

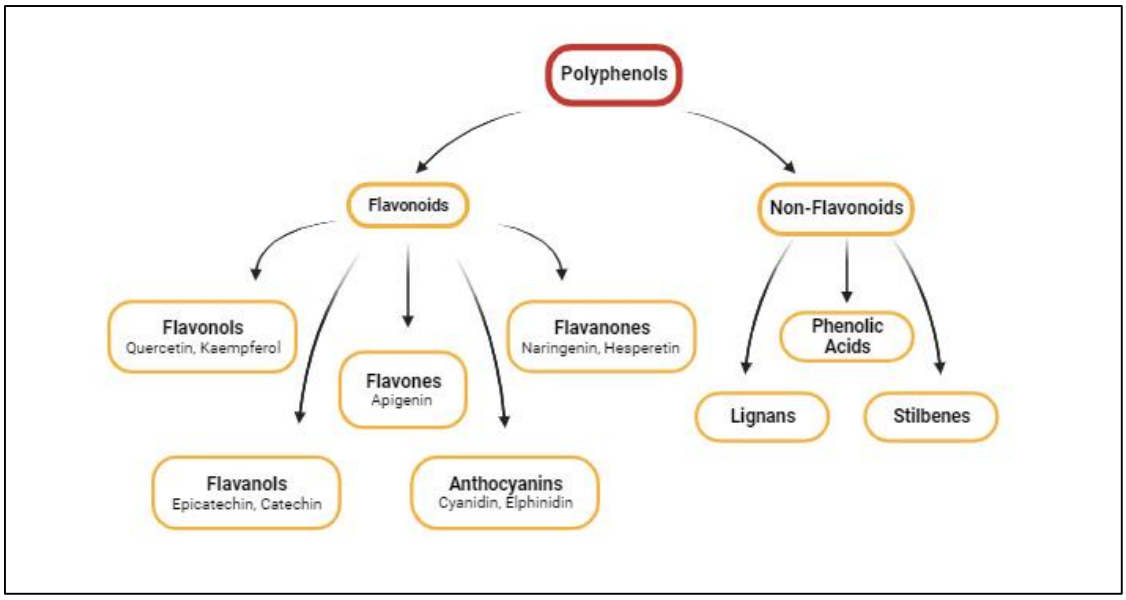


Figure 3. Different types of polyphenols

Flavonoids: Flavonoids are a group of polyphenolic compounds that are found in plants, and they are known for their diversity. They include several subclasses, each subclass with its unique structure and biological activities. They include various subclasses such as:[18]

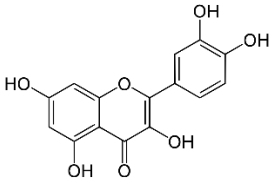
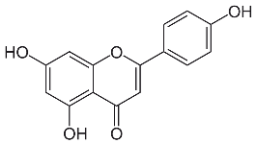
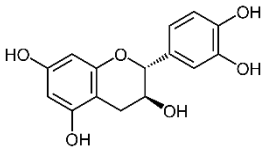
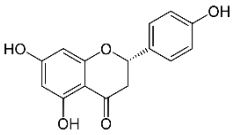
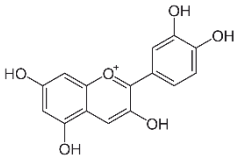
- Flavanols: Flavanols are found in many foods like onions, apples, and berries. Quercetin and kaempferol are common flavanols.[19]
- Flavones: Present in parsley, celery, and chamomile tea. Apigenin is a well-known flavone. [20]
- Flavanones: Flavanones, such as naringenin and hesperetin, are present in citrus fruits like oranges and grapefruits. [21]
- Flavanols: Flavanols, such as epicatechin and catechin, are commonly found in tea, cocoa, and red wine. [22]
- Anthocyanins: It is found in various fruits like grapes, cherries etc. [23]

Non-flavonoid polyphenols are a group of polyphenolic compounds. They are diverse in their structure and are found in many plants. Here are some common types of non-flavonoid polyphenols:

- Phenolic Acids: Phenolic acids are one of the important subclasses of non-flavonoid polyphenols. For example, gallic acid and ellagic acid are found in fruits, nuts, and other foods; Coumaric acid is found in coffee and tea. [24]
- Lignans: Lignans are another important subclass of nonflavonoid polyphenols. They are found in foods such as flaxseeds, sesame seeds, whole grains and some vegetables. Secoisolariciresinol and matairesinol are some common lignans.[25]

- Stilbenes: Resveratrol is a well-known stilbene and it is found mostly in red fruits, red wine and peanuts. It is known for its health benefits. [26]

Table 2. Flavonoids/chief constituents with their molecular structure which are used in the preparation of Phytosomes. (15)

Sl.no	Flavonoid/chief constituents	Plant name	Structure	Reference
1	Quercetin	onions, grapes		(27)
2	Apigenin	parsley, onions, oranges		(28)
3	Catechin	cocoa, tea, and red wine		(29)
4	Naringenin	citrus fruits like oranges		(30)
5	Cyanidin	grapes, bilberry, blackberry		(31)

1.4. Phospholipids:

Phospholipids are a type of lipid molecule that are important components of the structure of cell membranes in living organisms. Phospholipids consist of two fatty acid chains, a glycerol molecule, and a phosphate group. The phospholipid has a unique structure as they have both hydrophobic (water-repelling) and hydrophilic (water-attracting) properties to the molecules, allowing them to form the basic structural framework of cell membranes, which is also known as the lipid bilayer. [5]

Currently, industrially produced phospholipids are used for the preparation of phytosome, and liposomes. The main ingredients of phospholipid are extracted from soya, chicken egg, etc. [32]

1.4. Lecithin:

A phytosome is a delivery system that consists of a natural active ingredient and a phospholipid. Lecithin is the most common phospholipid used for the preparation of phytosomes. [27]

Source: Lecithin is a naturally occurring mixture of many phospholipids, and it is commonly extracted from various sources, including sunflower seeds, soybeans, egg yolks, and some other plant and animal tissues. Soy lecithin is one of the most commonly used sources of lecithin in commercial applications due to its cost-effectiveness and availability.[33]

Lecithin is a complex mixture of phospholipids, and its composition can vary depending on the source. The main phospholipids found in lecithin include:

- **Phosphatidylcholine (PC):** Phosphatidylcholine is a key ingredient in lecithin It is made up of a choline head group, a glycerol backbone, and two fatty acid chains. Phosphatidylcholine is well known for its emulsifying properties. [34]
- **Phosphatidylethanolamine (PE):** Phosphatidylethanolamine, a significant component of lecithin, contains a choline head group, a glycerol backbone, and two fatty acid chains. It contributes to lecithin's overall amphiphilic nature. [33]
- **Phosphatidylinositol (PI):** Phosphatidylinositol is a lipid found in lecithin that contains a glycerol backbone, two fatty acid chains, and an inositol head group. It plays a role in cellular signalling. [35]
- **Other Phospholipids:** Lecithin may also contain many other phospholipids, such as phosphatidic acid and phosphatidylserine, depending on the source. [33]

2. Preparation of Phytosome:

There are several methods are used for the preparation of phytosomes, every process has its own unique set of advantages and limitations. Here are some of the most commonly used processes for preparing phytosomes: [8]

2.1. Thin film hydration method: [10, 32]

- Dissolve both the phospholipids and the bioactive compound (plant extract) in an organic solvent (commonly ethanol, dichloromethane, or chloroform) separately.
- Mix the components to form a homogeneous solution.
- Transfer the solution to a round bottom flask.
- Evaporate the solvent using a rotary evaporator at a controlled temperature (around 50°C-60°C). This process results in the formation of a thin film on the surface of the container.
- Add a phosphate buffer to the container containing the thin film.
- Sonicate the solution for achieving a more uniform particle size distribution and enhancing the stability of the phytosomes.
- Store the phytosomal suspension in the refrigerator.

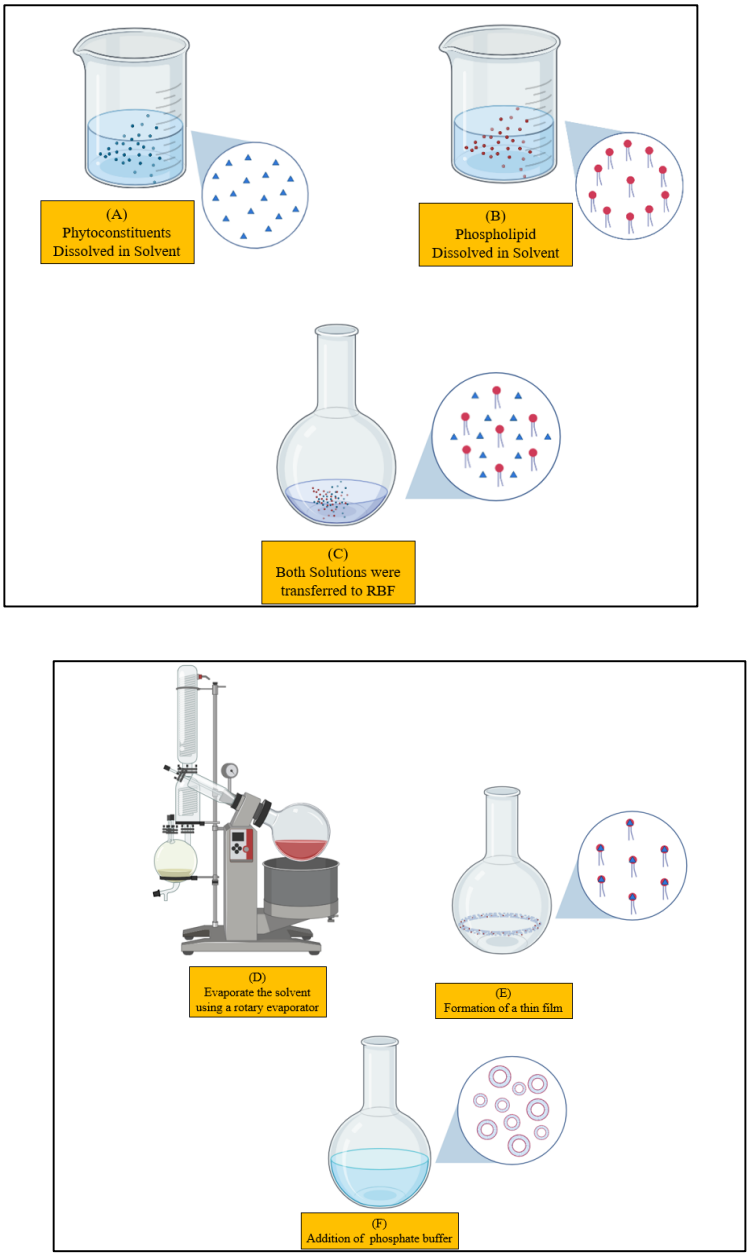


Figure 4. Preparation of phytosome through thin film hydration method. A. Phytoconstituents were dissolved in solvent, B. Phospholipids were dissolved in Solvent, C. Both of the Solutions were transferred to RBF, D. Evaporate the solvent by using a rotary evaporator, E. Formation of a thin film, F. Addition of phosphate buffer

2.2. Anti-solvent precipitation Method: [32, 36]

- Dissolve phospholipids in a suitable organic solvent (e.g., ethanol).
- Dissolve the bioactive compound (plant extract) separately in a solvent (e.g., acetone,chloroform).
- Mix both solutions for the formation of the phytosomes complex.

- After 24-48 hours, Add n-Hexane to the solution which acts as an anti-solvent, causing precipitation and the formation of phytosomal complexes.
- Evaporate any remaining solvents using the vacuum to obtain a dry phytosomal complex.
- Store the phytosomal complex under suitable conditions.

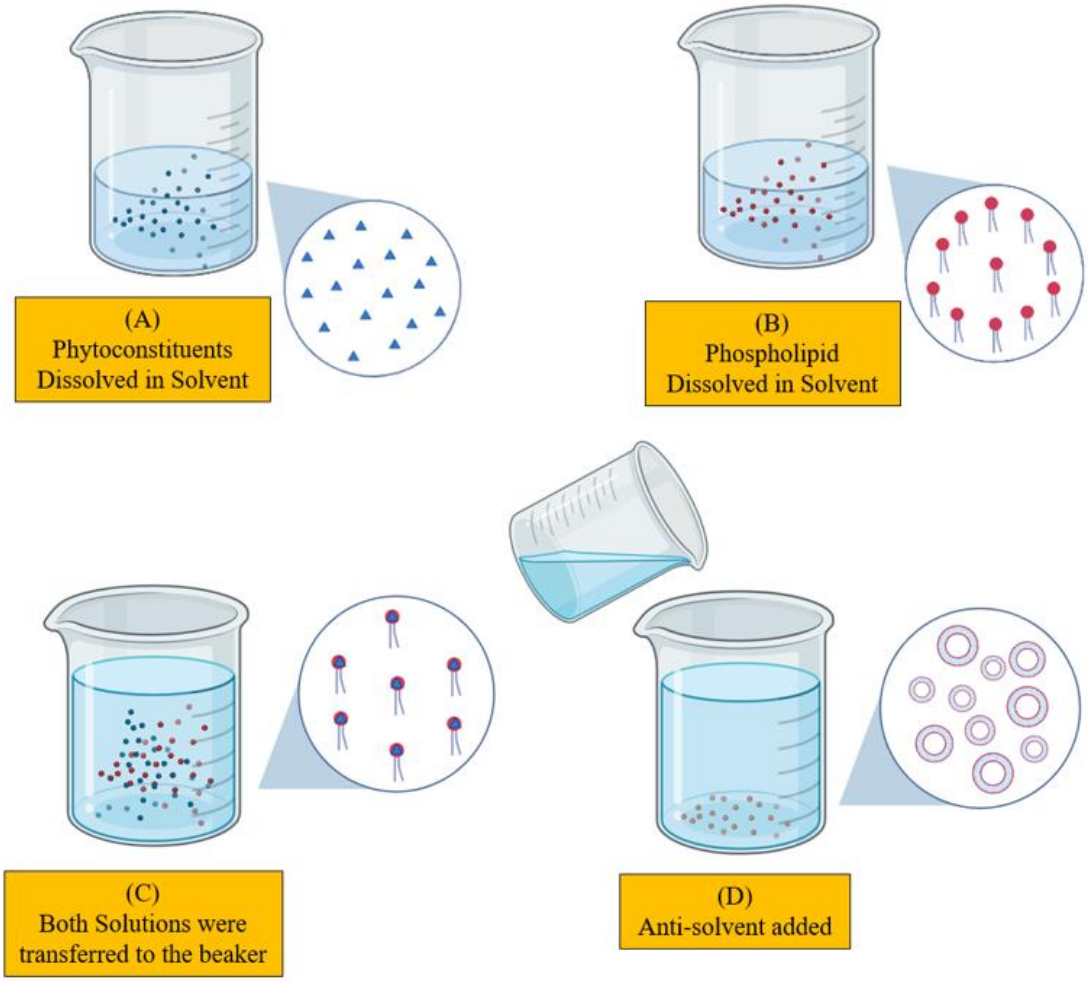


Figure 5. Preparation of phytosome through Anti-solvent precipitation Method

2.3. Characterization of phytosomes:

Several factors affect the behavior of phytosomes, including chemical composition, physical size, membrane permeability, the percentage of entrapped solutes etc. There are several techniques used in the characterization of phytosomes. [8, 36]

Table 3. Characterization of phytosomes

Character	Techniques
Size and shape	Scanning Electron Microscopy (SEM), Dynamic Light Scattering (DLS), Transmission Electron Microscopy (TEM).
Chemical composition	Proton Nuclear Magnetic Resonance spectroscopy (^{1}H NMR), Fourier Transform Infrared Spectroscopy (FTIR), Powder X-ray Diffraction (PXRD).
Encapsulation efficiency	*UV-Vis spectrophotometry,* High-performance liquid chromatography (HPLC).
Transition temperature	Differential scanning calorimetry(DSC)
Release behavior	Dissolution Apparatus, *UV-Vis spectrophotometry.*

2.4. Dynamic Light Scattering (DLS):

Dynamic Light Scattering is used to determine the size distribution of particles in a liquid suspension of phytosome, with exceptional accuracy for particles within the nanometre range. The underlying principle is rooted in the Brownian motion of particles present within a fluid. A laser beam is projected onto the sample, and the scattered light is carefully observed and analysed for fluctuations in its intensity over time. The correlation function obtained from this analysis provides valuable insights into particle motion, and by applying the Stokes-Einstein equation, it is possible to establish a direct relationship between the diffusion coefficient and the hydrodynamic diameter of the particles. [32, 37]

2.5. Scanning Electron Microscopy (SEM):

Scanning Electron Microscopy is an imaging technique that can produce high-resolution three-dimensional images of nano samples. In this technique, a focused beam of electrons scans the sample's surface, generating signals from the interactions between electrons and atoms in the sample. These signals are detected and used to create detailed images. To use SEM, a dry sample is applied to a brass stub, which is ion sputter-coated with gold/platinum before scanning the sample at random speeds of 100. [37, 38]

2.6. Transmission Electron Microscopy (TEM):

TEM is a highly advanced imaging technique that uses a beam of electrons to visualize the internal structure of specimens at a nanoscale level. During this process, electrons pass through thin specimens, and their interactions provide detailed information about the specimen's composition and structure. Recently, TEM was used to determine the size of phytosomal vesicles with a magnification of 1000. (38,39)

2.7. Fourier Transform Infrared Spectroscopy (FTIR):

Infrared spectroscopy is a technique that helps in studying the composition of materials based on their interaction with infrared light. To perform mid-infrared spectroscopy, we used an FTIR spectrophotometer and the KBr disk method. The test samples were completely dried using a sodium lamp and then ground together with KBr powder using an agate mortar. The dry mixture was then pressed into a thin, plate-like sample using a grinding apparatus. The scans were taken in the range of 400 to 4000 cm−1, with a resolution of 2 cm−1. [36, 37]

2.8. Proton Nuclear Magnetic Resonance spectroscopy (^{1}H NMR):

Proton Nuclear Magnetic Resonance spectroscopy, also known as ^{1}H NMR, is a highly effective analytical technique used to study the chemical structure of molecules. The process involves placing the sample in a strong magnetic field and using radiofrequency pulses to disturb the alignment of hydrogen nuclei, or protons. When the protons return to their equilibrium states, they emit signals that are then detected and analyzed. To perform ^{1}H NMR, the sample is first dissolved in a suitable solvent such as deuterated chloroform (CDCl3), deuterated dimethyl sulfoxide (DMSO-d6), or deuterated water (D2O). The sample is then placed in a strong external magnetic field, and the emitted signals are detected by the NMR instrument.[32, 36]

2.9. Powder X-ray Diffraction (PXRD):

Powder X-ray diffraction (PXRD) is an analytical technique that is used to study the crystalline structure of materials in powder form. In this technique, a sample is first ground into a fine powder and then exposed to X-rays. When X-rays pass through the sample, they are diffracted by the crystal lattice, resulting in the formation of a diffraction pattern. This pattern is characterized by the positions and intensities of the diffraction peaks, which provide important information about the crystallographic structure of the material. The X-ray source used in PXRD is based on copper (Cu) with Kα radiation. [36, 40]

2.10. Differential Scanning Calorimetry (DSC):

Differential Scanning Calorimetry is a technique used to analysed the physical and chemical changes or transition temperature of materials as the temperature changes. To conduct this analysis, the samples are sealed in standard aluminum pans, and then heated at a rate of 10°C per minute, from 40°C to 250°C, in an atmosphere of pure nitrogen. [10, 38]

2.11. Drug entrapment:

Drug entrapment is the process of incorporating a drug into a carrier system, such as a phytosome. To measure the percentage of drug entrapment, a phytosomal complex needs to be centrifuged at approximately 10000 rpm for 90 minutes at a temperature of 4°C. After centrifugation, the untrapped drug can be separated from the phytosome by using ultraviolet spectroscopy. It is calculated by using this following formula: [37, 41]

Percentage Drug Entrapment (%) = (Total Amount of Drug Added/ Amount of Entrapped Drug) *100

3. Conclusion:

Phytosome technology represents a promising avenue for overcoming the bioavailability challenges associated with herbal medicine. By encapsulating bioactive plant ingredients within phospholipids, phytosomes enhance the solubility and absorption of herbal compounds, leading to improved therapeutic efficacy. Phytosomes make herbal treatments safer, more effective, and accessible by utilizing natural ingredients and innovative science.

The innovative application of phytosomes extends across pharmaceuticals, nutraceuticals, and cosmeceuticals, offering targeted delivery and enhanced bioavailability of herbal extracts. Further research and development in this field hold the potential to revolutionize the way we harness the therapeutic benefits of traditional herbal medicine in modern healthcare systems.

4. List of abbreviations:

Abbreviation	Definition
DLS	Dynamic Light Scattering
SEM	Scanning Electron Microscopy
TEM	Transmission Electron Microscopy
^{1}H NMR	Proton Nuclear Magnetic Resonance spectroscopy
FTIR	Fourier Transform Infrared Spectroscopy
PXRD	Powder X-ray Diffraction
HPLC	High-performance liquid chromatography
DSC	Differential scanning calorimetry
UV-Vis	Ultraviolet-Visible Spectroscopy

5. Conflict of Interest:

The authors have no conflict of interest.

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