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Herbosomes drug delivery system for improving the phytochemical bioavailability

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Abstract

Since ancient times, herbal medicines have been the most significant type of medicine used in all societies. There have been numerous plants reports that plant extracts exhibit a variety of biological properties, including immunomodulator activity, hepatoprotective activity, antilipidemic activity, etc. Herbosomes are freshly developed herbal preparations that are absorbed more readily than traditional Phyto molecules or botanical extracts, producing improved bioavailability and effects. The integration of polyphenolic compounds into phospholipid-based self-assembled delivery systems, also referred to as Herbosomes, can improve the less oral bioavailability of these compounds. Numerous products, including those made from Ginkgo biloba, Silybum marianum, and Camellia sinensis, contain phytosomal drug delivery systems.

Keywords: Herbosomes; Phytosomes; Phosphatidylcholine; Phospholipid; Bioavailability

1. Introduction

Herbo refers to a plant, and in some languages, it also denotes resembling a cell. A plant's physiologically active components are primarily polar or water-soluble substances. Flavonoids, tannins, and glycosides are examples of phytoconstituents that are water soluble yet poorly absorbed. Large molecules with poor lipid solubility or passive diffusion absorption are severely constrained in their capacity to traverse lipid-rich biological membranes, leading to less bioavailability**.** Since Before times, phytomedicines have been utilized to cure a variety of diseases. Numerous plant materials have been found to possess a range of biological properties, including antilipidemic, hepatoprotective, and immunomodulatory properties. Phytomedicines, or sophisticated chemical mixtures created from plants, have been used to sustain health since ancient times. However, the ineffective oral absorption of many phytomedicines limits their effectiveness. Currently, between one-third and about half of all medications on the market are made from plants or other natural sources.(1)

Herbal products need to maintain a healthy balance between hydrophilic and lipophilic molecules to increase bioavailability (for absorption into gastrointestinal tract fluid) (to cross lipid bio membrane balance) In both traditional and modern medicine, plant preparations are frequently employed. Traditional researchers have examined the medicinal potential of several plant extracts and their constituent parts through a variety of pharmacological tests. The creation of innovative drug delivery systems for various plant extracts and their active components has advanced significantly during the past year. Innovative drug delivery methods include targeted drug delivery, which delivers the active ingredient directly to the site of action. Such a delivery system could provide focused and sustained drug release,

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allowing for the achievement of pharmacological effect at a lower dose. To treat human illnesses with fewer side effects, the field of herbal medicine began to emerge earlier.(2)

2. Herbosome technology

The Italian company Indena s.p.a. created the phytosome technology, which significantly increases the bioavailability of specific phytomedicines by integrating phospholipids into standardised plant extract, which enhances their absorption and utilisation. Both in water and lipids, the polyphenols have a limited solubility. Spectroscopy reveals a special arrangement formed when the polar functions of the lipophilic guest engage with the charged phosphate head of phospholipids through hydrogen bonding and polar contact. The hydrophilic choline group head attaches to the chemical, and the hydrophobic phosphatidyl group envelops the confined section because phosphatidylcholine is a bifunctional molecule.(3)

The initial phytosome generation was created by mixing selected phospholipids with polyphenolic extract in a non-polar solvent, but more recently, hydroethanolic solvent has been used to create phytosome generations in order to meet the requirements for modern foods.(4)

2.1. Herbosomes have advantages

- It improves the bioavailability of lipid-insoluble polar phytoconstituents through oral and topical routes, leading to a much higher therapeutic benefit.
- Significant drug entrapment.
- As the absorption of the active ingredient(s) improves, so does the dose needed.
- In addition to serving as a carrier, the phosphatidylcholine used in the manufacture of herbosomes also works as a hepatoprotective, creating a synergistic effect when other hepatoprotective compounds are added.
- Phosphatidylcholine and phytoconstituent establish chemical bonds, which improves the stability profile of the herbosomes.
- The uses of herbal constituents in the form of herbosomes enhances their transdermal absorption and serves as a cosmetic ingredient.
- Phospholipids have additional nutritional advantages.
- The herbosome penetrates the non-lipophilic botanical extract to improve intestinal lumen absorption.
- Due to their easy bioavailability, herbosomes have been employed to deliver flavonoids that protect the liver.
- Herbosomes exhibit superior stability profiles than liposomes because chemical linkages are formed between the phosphatidylcholine molecule and phyto constituent.

- Liver targeting can be aided by increasing the bile's solubility in herbal constituents.(5)

2.2. Disadvantage of Herbosome

- Herbosomes quickly remove phytoconstituents and have a high production cost.
- The half-life is extremely brief.
- Hydrolysis, fusion, leakage, and oxidation of phospholipids occur.
- Because of the increased size, focused delivery is challenging.(6)

3. Properties of the herbosome

3.1. Physical Properties

- The lipophilic materials that make up a herbosome have a distinct melting point.
- The size of a herbosome can range from 50 nm to several hundred m.
- The herbosome is less soluble in water, more soluble in non-polar solvents, and only moderately soluble in lipids.
- Water is used to treat herbosome to create a miscellar shape similar to a liposome.

3.2. Chemical properties

The polar heads of phospholipids (phosphate and ammonium groups) create hydrogen bonds with the polar functional groups of the substrate, which leads to phospholipids-substrate interaction, according to physicochemical and

spectroscopic data analysis. The development of a chemical link between the phosphatidylcholine and the phytoconstituent, which becomes a crucial component of the membrane, is the active principle in herbosomes. (1)

3.3. Biological Properties

Phytosomes, advanced botanical innovation, provide increased absorption, enhanced delivery, and Studies comparing the pharmacokinetics or pharmacodynamic properties of herbal extracts and phytosomes to non-complexed botanical derivatives have shown that the latter had a higher bioavailability.(7)

4. Advantages of phytosomes over conventional dosage forms

- Improved absorption
- Cosmetic use
- Protective in nature
- Cost-effective
- As a carrier
- Enhance the entrapment efficiency
- Improve the stability
- Dose reduction
- Low risk profile (8)

5. Difference between phytosomes and liposomes

It is important to differentiate phytosomes from liposomes in order to understand their distinctiveness. A molecular association called a unit phytosome might consist of as few as two molecules (1 pc plus 1 polyphenol). The unit liposome is a spherule formed by the accumulation of hundreds of phospholipid molecules, with additional molecules segregated but not particularly linked. The phytosome is known to significantly improve oral delivery, however the liposome notion is still unproven as a vehicle for oral delivery. (9)

Like phytosomes, liposomes are produced by carefully mixing a water-soluble substance with phosphatidylcholine in a specific ratio under specific conditions. In this case, no chemical linkages are formed since the water-soluble substance is surrounded by phosphatidylcholine molecules. Phosphatidylcholine molecules may number in the hundreds or even thousands surrounding the water-soluble material. Depending on the substance(s) complexes, including chemical bonding, the phosphatidylcholine and plant components actually create a 1:1 or a 2:1 molecular complex during the phytosome process. Because of this difference, phytosomes have a higher bioavailability and are absorbed much more easily than liposomes. Furthermore, it has been found that in topical and skin care products, phytosomes work better than liposomes. (10)

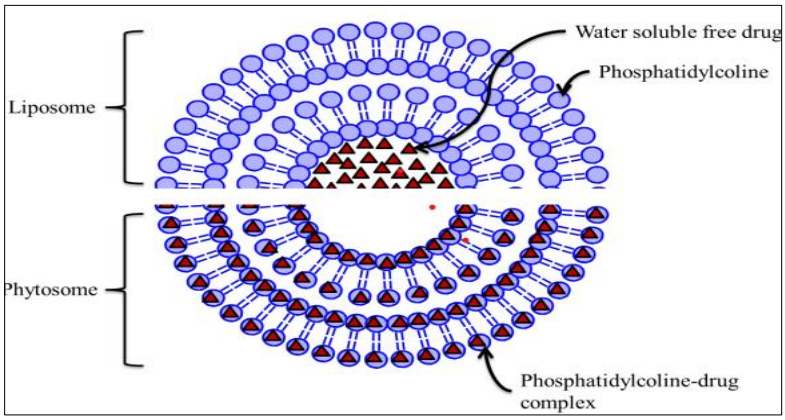

Figure 1 Illustration on comparative account of phytosomes and liposomes.(11)

6. Mechanism of herbosomes formation

Plant extracts' polyphenolic components have a well-established track record of binding directly to phosphatidylcholine. Phospholipids like soya phosphatidylcholine combine with the standard extract or polyphensolic

components to generate herbosomes. Flavonoids in an aprotic solvent are simple. A bifunctional substance, phosphatidylcholine has a hydrophilic choline moiety and a lipophilic phosphatidylcholine moiety. Phosphatidylcholine, specifically the choline head, attaches to these chemicals, and the lipid-soluble phosphatidyl part, which includes the body and tail, envelops the choline-bound material. As a result, the Phyto molecules create a phospholipid and lipid soluble molecular complex known as the phyto-phopholipid complex. Specific spectroscopy techniques can show that Phyto molecules are connected to the polar choline head of phospholipids through chemical interactions. The herbosome unit is typically a flavonoid molecule coupled to at least one phosphatidylcholine molecule, according to the specified chemical analysis.(12, 13)

7. Techniques for making phyto phospholipid complex

A polyphenolic phytoconstituent or a combination of phospholipids are complexed to create a phytosome. Observed mass ratios range from 1:1.5 to 4:1, depending on the product. Depending on the methodology utilized, the ways of preparing the phytosome and the final complex may differ. Phyto phospholipid complexes can be made using three main techniques: anti-solvent precipitation, solvent evaporation, and freeze-drying.(14)

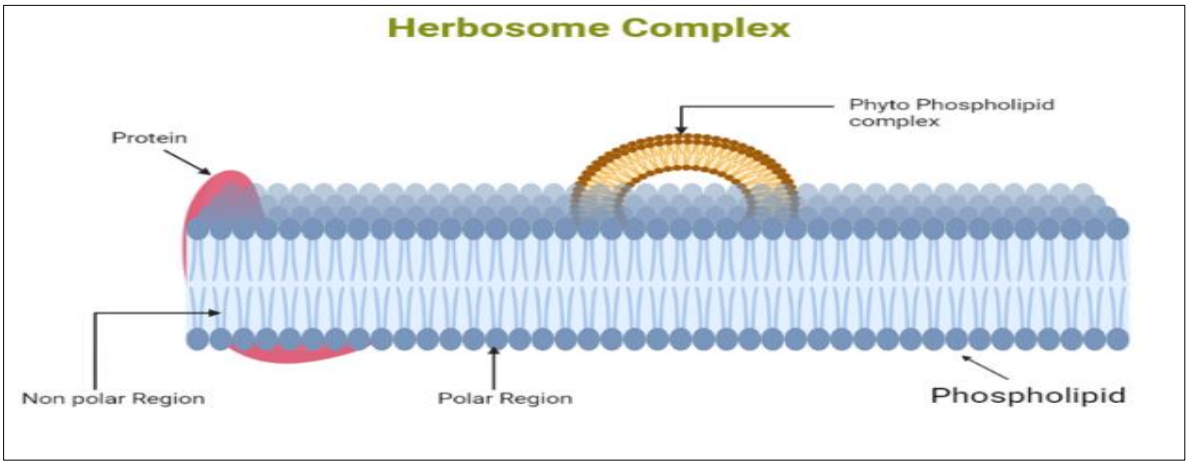

Figure 2 Herbosome complexs

The manufacture of Phyto-phospholipid complexes, also known as phytosomes, involves the use of phospholipids to create a complex between phytoconstituents or extract and phospholipids. Its sophisticated herbal medicine administration technique has described the hazy bioavailability of plant actives that are lipid insoluble. By chemically digesting herbal extracts into phospholipids in a precise ratio, lipid insoluble herbal extracts can be transformed into lipid compatible medicinal candidates. Generated cellular vesicles by using phytosome techniques, you can prevent the gut microbiota and stomach secretion from destroying water-soluble active ingredients. The phytomedicine industry has undergone a revolution as a result of the active constituents complexes with phospholipid, which have a variety of benefits including reduced dose to produce desired therapeutic effect, hepatoprotective action, improved stability due to chemical linkage, and ability to permeate through skin.(15, 16) The limitation of therapeutic efficacy brought on by low solubility and permeability of large size hydrophilic phytoconstituents across biological membranes has been overcome by Phyto-Phospholipid Complexes. The current work emphasises the significance and future directions of phytophospholipid complexes of plant actives.(17)

8. Drug delivery system for plants

Significant progress has been achieved in the last few years in the creation of innovative drug delivery systems for extracts and active ingredients found in plants. Bioactive and plant extracts have been used to create a variety of new herbal formulations, such as polymeric nanoparticles, nanocapsules, liposomes, phytosomes, nanoemulsions, microspheres, transferosomes, and ethosomes. According to reports, the novel formulations of plant actives and extracts have notable advantages over conventional formulations. These advantages include improved solubility, bioavailability, protection from toxicity, pharmacological activity, stability, improved tissue macrophage distribution, sustained delivery, and protection from physical and chemical degradation. The current review highlights the progress being made in the creation of new herbal formulations and provides an overview of their preparation process, active component type, size, entrapment effectiveness, route of administration, biological activity, and potential uses.(18)

8.1. Type of novel drug delivery system for herbal drug

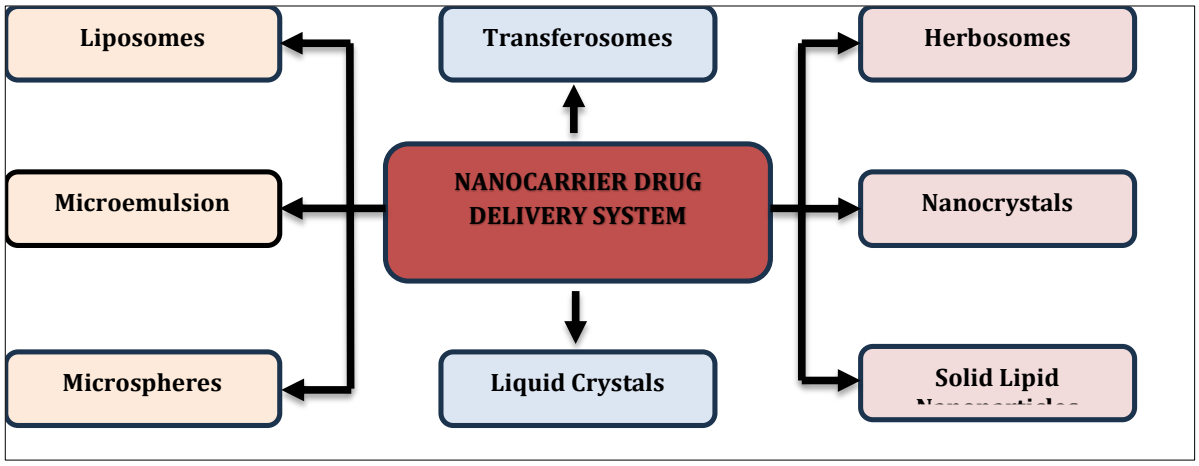

Figure 3 Type of novel drug delivery system for herbal drug (19)

9. Bioavailability of phytosomes:

Numerous studies have shown that when compared to traditional methods, Phytosomes have enhanced absorption and bioavailability. Silybum marianum (milk thistle), whose fruit includes a water-soluble phytoconstituent (flavonoids) known to have a hepatoprotective effect, is the subject of the majority of research studies. But the absorption of these flavonoids is low. Silybin is the main and most effective component of milk thistle. The following is a succinct summary of some of the research studies:

- Silybin phytosomes, which are single oral dosages of silybin directly bonded to phosphatidylcholine, have an absorption rate that is almost seven times higher than that of conventional milk thistle extract (which typically contains 70–80% silymarin concentration).
- He synthesized silymarin phytosomes and demonstrated its pharmacokinetics in rats in a scientific study. Rats received oral administration of the phytosome. The findings indicated that silybin's bioavailability and biological effects had significantly increased.
- Several studies have shown that ginkgo phytosomes, when eaten, have better effects than standard gingko extract. Research on the bioavailability of terpenes and flavonoids in healthy adult volunteers showed that the amounts of (components of GBE) peaked after 3 hours and lasted for a longer duration of 5 hours.

One study demonstrates that certain individuals with intermittent circulation and Reynaud's illness were given ginkgo phytosome, which was demonstrated to induce an improvement of 30–60% above the typical conventional GBE (Ginkgo biloba extract).(20)

10. Commercial herbosome preparation (21)

Table 1 Commercial herbosome preparation

Sr.no.	Phytosome product	Phytoconstituents of plants present in Phytosome	Dose	Indications or uses
1.	Silybin Phytosome	Silybin from Silybummarianum	120mg	Hepatoprotective, antioxidant
2.	Hawthorn Phytosome ™	Flavonoids from Crataegus sp.	100mg	Nutraceutical
3.	Ginseng Phytosome	37.5 % ginsenosides from immunomodulator Panax ginseng	150mg	Nutraceutical And immunomodulator

4.	Green Tea Phytosome	Epigallocatechin from Thea sinensis	50to100 mg	Nutraceutical, systemic antioxidant. Anticancer
5.	Ginkgo biloba Phytosome	24 % Ginkgoflavonglycos Ides from Ginkgo biloba	120 mg	Protects brain and vascular lining, anti-ageing agent.
6.	Grape Seed Phytosome	Procyanidins from Vitis vinifera	50to100 mg	Nutraceutical, systemic Antioxidant, anti-diabetic and protects against heart disease
7.	Bilberry Phytosome	Extract of Bilberry which provides anthocyanoside	-	Improve capillary tone, reduce abnormal blood vessel permeability, potent antioxidant
8.	Super Milk thistle extract	Silybin from Silymarin Food Product	150 mg	Antioxidant for liver and skin

11. Techniques for preparing

- Herbosomes are novel complexes that are created by reacting three and a half moles, but preferably with one mole of a phospholipid, such as phosphatidylcholine, phosphatidylethanolamine, or phosphatidylserine, with one mole of a component, such as flavolignanans, either alone or in the natural mixture, in an aprotic solvent, such as dioxane or acetone. The ratio between these two moieties ranges from 0.5 to 2.0 moles during the intricate development of herbosomes. The ratio of phospholipid to flavonoids that is preferred is 1:1
- Naringenin was combined with an equimolar quantity of phosphatidylcholine to create the naringenin-PC complex (PC). A 100 mL round bottom flask was filled with an equimolar concentration of PC and naringenin, and the mixture was refluxed in dichloromethane for three hours. 30 mL of n-hexane were added after diluting the solution to 5- 10 mL in order to precipitate the complex, which was then removed by filtration. The precipitate was gathered, and vacuum desiccators were used to dry it out.
- The necessary dosages of the medication and phospholipids were added to a 100 ml round-bottom flask and dissolved in anhydrous ethanol. Once the ethanol has been removed under vacuum at 40'c The dried residues were collected, dried overnight in desiccators, then ground in a mortar, and sieved through a 100-mesh screen. After being created, the silybin-phospholipid complex was put into a glass bottle, flushed with nitrogen, and kept at room temperature.(5)

11.1. Common step for preparing Herbosome

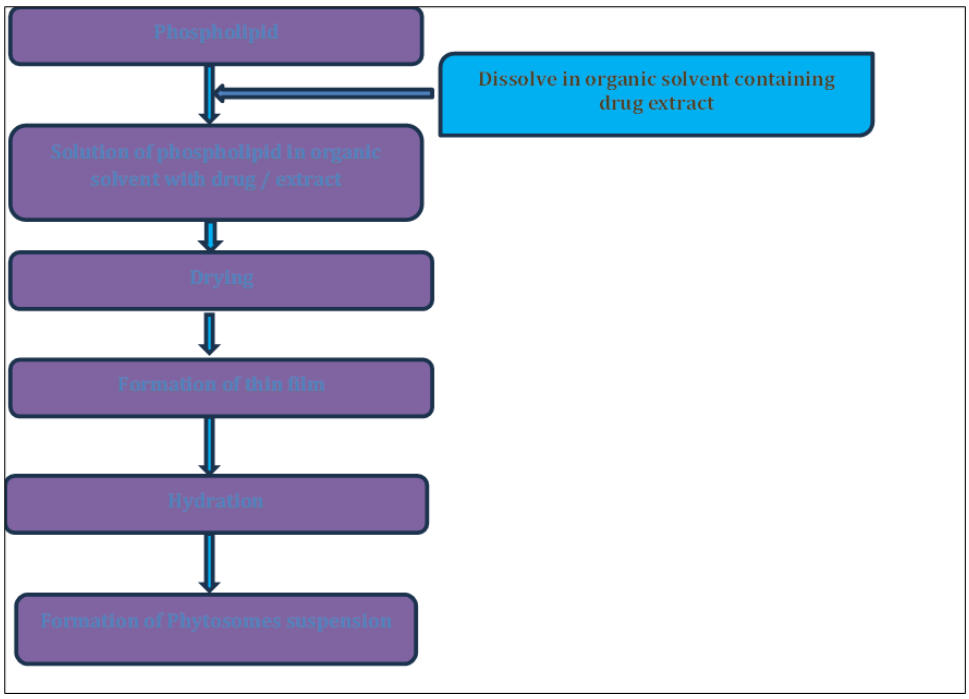

Figure 4 Prepation steps of Herbosomes

12. Methods which are used for the preparation of herbosomes

- Solvent evaporation method
- Super critical fluid (SCF) technique
- Gas anti-solvent method
- Solution enhanced dispersion by supercritical fluids (SEDS)
- Anti-solvent precipitation method

13. Characterization

13.1. Organoleptic assessment

The colour, smell, and transparency of herbosomes are used to determine their organoleptic characteristics. both soluble and organoleptic analysis also determines the drug's wavelength maxima, Ashwagandha extract was discovered to be soluble in dimethylsulphoxide and phosphate buffered saline (both of which have a pH of 7.4), and the standard solution displayed linearity at a maximum wavelength of 226 nm. Mangiferin- soya phosphatidylcholine (MF-SPC) compound was shown by.to be soluble in dichloromethane but insoluble in methanol and hexane.(22)

13.2. Microscopy research

Transmission electron microscopy (TEM) allows for the visualization of many structural aspects of herbosomes, such as morphology, crystallization, stress or magnetic domain, and internal structural network, while scanning electron microscopy (SEM) provides details on the surface texture of the herbosome. By using TEM and digital imaging, discovered that the phytosome (Polyherbal phytosome) extracted from Citrullus colocynthis (L.), Momordica balsamina, and Momordica dioica had a spherical structure without aggregation. With the aid of SEM micrographs (at 20KV for the magnification range of 7500), also discovered a spherical-shaped phytosome carrying a methanolic extract of Allium sativum.(23)

13.3. Size and zeta potential of particles

For the purpose of determining particle size and zeta potential, dynamic light scattering (DLS) in conjunction with computerized inspection systems and photon correlation spectroscopy (PCS) are used, the umbelliferone phytosome's average particle size and zeta potential were discovered to be 1139 nm and respectively, 0.05 mV. With the aid of a particle size analyzer (Horiba Scientific Nanopartica SZ100), it was discovered that the average Ashwagandha phytosome particle size was 98.4 nm. The Ashwagandha phytosome was shown to have good stability by the zeta potential value of (-28.7mV). (24)

13.4. Drug content

Appropriate techniques are adopted to quantify the amount of drug, including UV spectroscopy, HPLC, and GC-MS. By using a UV spectrophotometer at 324 nm, it was discovered that the drug content of an improved umbelliferone phytosome (1:2 stoichiometric molar ratios of umbelliferon and phospholipid 90H) was 97.40%. (25)

13.5. Thermal evaluation

The vesicle-shaped herbosome's transition temperature, onset temperature, and enthalpy are all measured using differential scanning calorimetry (DSC). It is an alternative method for examining drug-excipient compatibility. Anti-diabetic polyherbal extracts and phospholipids showed a similar endothermic melting transition, demonstrating the compatibility of the phytosome formulation. observed the umbelliferone phytosome's exothermic peak and onset temperatures. respectively at 75.17 °C and 63.55 °C. Additionally, a little chemical interaction was picked up by the DSC thermogram.

13.6. Spectroscopic assessment

The spectroscopic investigation confirms the intricacy between the phospholipid's moiety and the bioactive herbal ingredients, which aids in the evaluation of their physical and chemical interactions. (4, 26)

13.7. Vesicle stability

The measurement of the mean size and structural configuration of the herbosome over time by DLS and TEM, respectively, in accordance with ICH criteria, is followed by the stability analysis of the herbosome. Seven ashwagandha

phytosomes were discovered to be stable for three months at both room temperature and in the refrigerator. At a freezing temperature (2-4°C), the herbosome from 15 Aegle marmelos demonstrated greater stability.(27)

14. Applications

14.1. Phytosomes of silymarin

Silybum marianum, sometimes known as milk thistles, is the subject of the majority of phytosomal research because it contains powerful liver-protective flavonoids. Silymarin phytosome was created, and rats were used to study its pharmacokinetics. According to the experiments, silybin's bioavailability in rats rose noticeably after oral administration of silybin phospholipid complex due to the complex's impressively improved lipophilic characteristics and improved biological effects. activity than silymarin alone and can offer defense against the harmful effects of aflatoxin B1 on broiler chicken performance.(28)

14.2. Grape seed phytosomes

The oligomeric polyphenols (grape proanthocyanidins or procyanidine from grape seed extract, Vitis vinifera) in grape seed phytosomes are complexed with phospholipids and have different molecular sizes. The primary benefits of grape seed procyanidine flavonoids include an increase in total antioxidant capacity, stimulation of physiological plasma defences, protection against heart damage caused by ischemia/reperfusion, and protective effects against atherosclerosis, which provide significant protection against the cardiovascular system and other organs through a network of antioxidant pathways. compared to the standard versions, showing that they have additional mechanisms beyond their antioxidant action. In another study, rabbits were fed a high-cholesterol diet for six weeks in order to significantly raise their blood cholesterol levels and to cause atherosclerotic lesions in their carotid and aortic arteries. For the first six weeks, one group of rabbits received grape seed phytosomes in their meal, followed by four weeks on a high-cholesterol diet. Compared to the control group, which received traditional, standardized grape seed extract under similar conditions, these individuals generated considerably less aortic plaque. Young, healthy volunteers were given grape seed phytosomes once daily for five days in a randomized human experiment. On the first day as well as on the fifth day, the blood's TRAP (Total Radical-trapping Antioxidant Parameter) was tested at various intervals. Blood TRAP levels were already considerably higher than the control group, which received conventionally standardized grape seed extract, just 30 minutes after treatment on the first day.(29)

14.3. Curcumin Phytosomes

In two distinct investigations, Curcumin Phytosomes created phytosomes of the flavonoid’s curcumin (from the plant Curcuma longa, or turmeric) and naringenin (from the plant Vitis vinifera, or grape fruit). In every dose level examined, the complex's antioxidant activity was noticeably greater than that of pure curcumin. In the other study, the naringenin phytosome produced better antioxidant activity than the free compound with a longer duration of action, which may be related to a slowing down of the molecule's quick removal from the body

14.4. Quercetin-phospholipid Phytosomes complex

produced the quercetin phospholipid Phytosomes complex using a straightforward, repeatable process, and shown that it had higher therapeutic efficacy than the molecule in treating carbon tetrachloride-induced liver damage in rats. (30)

15. Future perspectives

herbal medicines' bioavailability, which despite encouraging in vitro results fail to produce a comparable reaction in vivo. The hydrophilic components of plants, like as flavonoids and other polyphenolic components, have tremendous therapeutic promise, but their use in the treatment of various diseases and disease situations is limited by their inability to pass lipoidal barriers. This problem was successfully resolved by combining these phytoconstituents with dietary phospholipids, which provided a preparation of herbal medications with enough lipid penetrability, increased concentration, and prolonged therapeutic levels in plasma with a slower rate of elimination

16. Conclusion

In order to maximise the distribution of the active components, it is important to have the right formulations and delivery systems for plant products, especially those that contain flavonoids and other phenolic compounds. Hydrophilic flavonoids and other related chemicals have enhanced bioavailability through the skin or gastrointestinal system thanks to phytosomes, a unique formulation. They differ from other traditional formulas in numerous notable

ways. The phytosome formulation process is straightforward and is easily adaptable to a commercial scale. For this kind of new formulation, the characterization approaches and analytical tools are well established. For novel phytosome formulations, procedures, and applications, numerous patents have previously been approved. In terms of phytosome technology's potential, it has a bright future for application in formulation technology and applications of hydrophilic plant compounds

Compliance with ethical standards

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Disclosure of conflict of interest

No conflict of interest to be disclosed.

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No conflict of interest to be disclosed.

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