



# HERBOSOME: THE MOST RECENT NOVEL DRUG DELIVERY SYSTEM

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## ABSTRACT

Since ancient times, herbal remedies have been the most important type of medicine in all societies. Various plant extracts have been found to exhibit a wide range of biological activity, including immunomodulator activity, hepatoprotective activity, antilipidemic action, and so on. Plant extracts have high in vitro bioactivity but low in vivo in animal models. The primary reasons for the poor bioactivity of herbal extracts are that the bioactive components of these herbs have multiring molecular structures that cannot be permeated into the blood by simple passive diffusion, and the bioactive phytoconstituents are mostly water soluble, resulting in their lack of lipid dissolubility. To address this issue, pharmaceutical researchers devised a unique lipid-based drug delivery system that is favourable in delivering the herbal medication at the site of action, reducing adverse effects while increasing absorption and bioavailability. The integration of standardised herbal extracts into phospholipids to generate a lipidfriendly complex called a herbosome is one delivery technique proposed to increase the in vivo solubility and thus bioavailability of ineffectively dissolvable herbal medications. The current study's goal is to accumulate all herbosome-related data that will be useful to academics.

## Keywords

Phytoconstituents, Herbosome, Lipid friendly Complex, Hepatoprotective, Passive Diffusion, Poor Bioactivity.

## Introduction

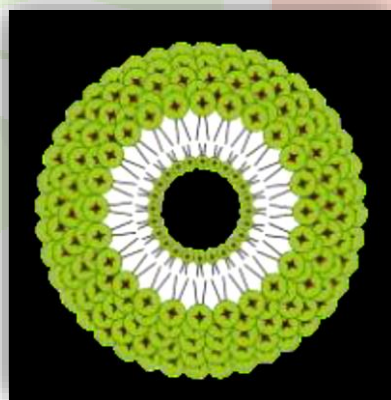
Novel drug delivery system is a novel technique to medication delivery that tackles the limits of the current drug delivery systems. India is a country has a rich knowledge base of Ayurveda whose potential is only being recognised inside the recent years. <sup>[1]</sup> Since ancient times, preparations of plants or parts of them have been widely utilised in traditional medicine, and the majority of people in the world still use phytomedicines today. The goal of the most recent development in herbal medication technology is to increase the bioavailability of polar bioactive components such phenolics, glycosides, flavonoids, etc. In the field of herbal drug delivery systems, a number of strategies have been adopted to increase bioavailability and therapeutic indices of drugs, achieving better results than conventional herbal extracts.

These strategies include ensnaring the lipophilic carrier, incorporation of solubility enhancers, physical/chemical or structural modification.<sup>[2]</sup>

The phyto-phospholipid complex (herbosome) is a novel drug delivery system that is advantageous in delivering the herbal drug at a predetermined rate, delivering the drug to the site of action, minimising adverse effects, increasing the bioavailability of the medication, and controlling the distribution of the drug by incorporating the drug in a carrier system or by altering the molecular structure of the drug. Herbal drugs have become more common in recent years. Three herbosomes are lipid-compatible phospholipid complexes that include phospholipid-bound plant extracts<sup>[2]</sup>. It is a vesicular drug delivery system made up of lipid and phytoconstituents. Herbosome raises the bioavailability of phytoconstituents by increasing their absorption through the GIT.

### Structure of Herbosomes.

A Herbo and some are two words found in the herbosome. The term "herbo" describes the bioactive component of the herbosome complex that comes from plants. Some depict the complex's ultimate form as having characteristics comparable to those of cell membranes. Herbosome complexes are proven to be compatible with both hydrophilic and lipophilic media. Chemically speaking, they resemble cell membranes and serve as a method for delivering phyto-lipids. Phospholipids and polyphenols interact properly in nonpolar solvents, which are employed in the synthesis of Herbosomes. Hydrogen bonds (H-bonds), the primary interaction between the polar portions of phospholipids (i.e., phosphate groups) and the bioactive material that occurs in phytosomal structures, provide the basis for Herbosome production. It was stated that the production of H-bonds between the phosphate group of the phosphatidylcholines and the hydroxyl part of the catechin in this case was the primary interaction occurring in catechin-loaded Herbosomes. When exposed to water, Herbosomes generally have a structure similar to liposomes.<sup>[3]</sup>



Structure of Herbosome

### Mechanism of herbosomes formation

Plant extract polyphenolic constituents are well established for direct binding to phosphatidylcholine. Herbosomes are formed in an aprotic solvent by the reaction of phospholipids such as soy phosphatidylcholine with the standard extract or polyphenolic constituents such as simple flavonoids. Phosphatidylcholine is a bifunctional compound with a lipophilic phosphatidyl moiety and a hydrophilic choline moiety. The phosphatidylcholine choline head specifically binds to these compounds, while the lipid soluble phosphatidyl portion comprising the body and tail then envelopes the choline bound material. As a result, the phytomolecules form a lipid-soluble molecular complex with phospholipids known as the phyto-phospholipid complex. Phytomolecules are chemically bound to the polar choline

head of phospholipids, as demonstrated by spectroscopic techniques. The chemical analysis indicates, however, that the herbosome unit is typically a flavonoid molecule linked to at least one phosphatidylcholine molecule<sup>[5]</sup>

## Merits of herbosomes over Conventional Drug Delivery System

- It improves the absorption of lipid-insoluble polar phytoconstituents via oral and topical administration, demonstrating improved bioavailability and thus a fundamentally more prominent remedial advantage.
- Increased bioavailability due to phospholipid complex.
- Because high lipophilicity leads to high penetrability, it is used in beauty care products instead of liposomes.
- Herbosomes have been used to deliver liver-protecting flavonoid because this technology makes them easily bioavailable.
- The herbosomal system is non-invasive and passive, making it suitable for immediate commercialization. Because of improved absorption of the main constituent, the dose requirement is reduced.
- Because chemical bonds are formed between the phosphatidylcholine atom and the phytoconstituent of the herb, herbosomes have a higher stability profile.
- The required dose is reduced.
- Improved entrapment efficiency
- Herbosomes ensured drug delivery to the tissue; and
- Herbosomes outperformed liposomes in skin care products.
- Due to the low solubility of herbosomes in aqueous media, stable emulsions and creams can be formed.

## Properties of Herbosomes:

### 1. Physico Chemical properties:

Herbosomes are a combination of a natural product and natural phospholipids, such as soy phospholipids. A complex of this type is formed by reacting stoichiometric amounts of phospholipids and substrate in an appropriate solvent. The formation of hydrogen bonds between the polar head of phospholipids (i.e. phosphate and ammonium groups) and the polar functionalities of the substrate has been shown to be the main phospholipids substrate interaction based on spectroscopic data. When exposed to water, Herbosomes take on a micellar shape and form liposomal like structures. While the active ingredient in liposomes is dissolved in the internal pocket or floats in the layer membrane, the ingredient in Herbosomes is tethered to the polar head of phospholipids and becomes a structural component of the membrane. H-bonds are formed, for instance, between the phenolic hydroxyl terminals of the flavones moiety and the phosphate ion on the phosphatidylcholine moiety in the case of the catechindistearoyl phosphatidyl choline complex. Phosphatidyl choline can be deduced by comparing the complex's 1-HNMR and 13C-NMR spectra to those of the pure precursors. The fatty chain signals are nearly unchanged. According to this evidence, the excessively long aliphatic chains wrap around the active principle, forming a lipophilic envelope that protects the polar head of the phospholipid and flavonoid molecule and allows the complex to dissolve in low polarity solvents<sup>[9]</sup>.

### 2. Biological properties:

Herbosomes are more advanced herbal products than typical herbal extracts and are better absorbed, used, and consequently offer better effects. Pharmacokinetic investigations or pharmacodynamic tests on experimental animals and humans have shown that the Herbosome has a higher bioavailability than non-complexed botanical derivatives.<sup>[10]</sup>

## Advantages of Herbosome Vesicles

- They quickly pass through the cell membrane and enter the cell.
- There has been a noticeable rise in the drug's bioavailability.
- Herbosomes ensure that herbal medicines can be taken for an extended period of time.
- Herbosomes improve the bioavailability of hydrophilic polar phytoconstituents by enhancing their absorption through nasal, topical, and other routes.
- A type of tiny cell known as a Herbosome shields the medicinal elements in plant extracts from gastrointestinal secretions and bacteria.
- Herbosomes promote the proper tissue delivery of medications.
- By classifying herbal medications as Herbosomes, the nutritional value of the herbal extracts need not be compromised.
- Because of the primary components' maximum absorption, the dosage needed has lowered.
- They reduce dosage requirements while enhancing the absorption of physiologically active components.
- The phosphatidylcholine molecule interacts chemically with phytoconstituents, demonstrating the high stability profile of Herbosomes.
- Herbosomes are often used in cosmetics to increase phytoconstituent transdermal absorption due to their improved skin penetration and high lipid profile.
- The highest absorption of phytoconstituents in Herbosomes occurs when they pass quickly through the tissue walls of the gut.
- There is no chance of a medication being entrapped because the Herbosome complex is biodegradable.
- Herbosomes are appropriate for the administration of medications because they increase the impact of herbal ingredients by enhancing absorption, enhancing biological activity, and delivering to the target location.
- Because the chemical is linked with lipids during vesicle formation, entrapment efficacy is high.
- Drug entrapment does not pose a difficulty while creating Herbosomes.
- Phosphatidylcholine, a component of the cell membrane that is used to make Herbosomes, not only functions as a messenger but also feeds the skin.
- In skincare products, Herbosomes outperform liposomes.
- It has been demonstrated that Herbosomes have a significant therapeutic advantage.
- Phosphatidylcholine, which is used in the synthesis of Herbosomes and functions as a transporter as well as a hepatoprotective, has a synergistic impact when combined with hepatoprotective substances.
- They can be turned into a potent semisolid dosage form due to their low water solubility.

## DIFFERENT ADDITIVES USED IN HERBOSOME FORMULATION:

**Lipids:** Phospholipid like Soya phosphatidylcholine, Egg phosphatidylcholine, Dipalmitoyl phosphatidylcholine, Distearyl phosphatidylcholine. Utilised as a vesicle-creating element.

**Solvent:**

**Aprotic Solvent:** Dioxane, acetone, methylene chloride. Used as a solvent.

**Non-solvent:** n-hexane and non- solvent i.e. aliphatic hydrocarbon. used as a solvent for complicated precipitations.

**Alcohol:** Methanol and ethanol. As a solvent, use

**Buffering agent:** Saline phosphate buffer (pH 6.5) 7 % v/v Ethanol Tris buffer ((pH 6.5). used as a hydrating agent.<sup>[8]</sup>

**The following techniques are employed in the creation of herbosomes:**

- A. Method of solvent evaporation
- B. The use of supercritical fluids (SCF)
- C. Gas anti-solvent technique
- D. Solution enhanced dispersion by supercritical fluids (SEDS)
- E. Technique for anti-solvent precipitation

### **A. Method of solvent evaporation**

A 100 mL circular bottom flask is filled with the necessary amount of plant material and phospholipids, 20 mL acetone, and is then refluxed for two hours at 50–60°C. The precipitate was filtered off after the mixture was condensed to 5–10 mL. The dried precipitate Herbosome complex was kept at room temperature in an amber-colored glass container<sup>[5]</sup>

### **B. The use of supercritical fluids (SCF)**

For the purpose of creating particles with a size range of 5 to 2000 nm, the super critical fluids (SCF) procedures have proven to be an efficient tool. For example, the compressed antisolvent process (PCA), supercritical antisolvent method (SAS), rapid expansion of supercritical solutions (RESS), gas antisolvent technique (GAS), and solution enhanced dispersion by supercritical fluids have all been used to improve the solubility profiles of poorly soluble drug candidates (SEDS).

For the creation of complexes, GAS and SEDS, two SCF techniques, were frequently employed.<sup>[6]</sup>

### **C. Gas anti-solvent technique**

The drug and phospholipids solutions are each added a supercritical antisolvent separately in the GAS method until the desired final pressure is obtained. The reaction vessel was then maintained at a constant temperature of 38 °C and 10 mPa pressure for 3 hours without any agitation.<sup>[1]</sup>

### **D. Solution enhanced dispersion by supercritical fluids(SEDS)**

This process involves continually adding liquid solution and supercritical antisolvent to the precipitation unit. A 0.1 mm diameter nozzle is used to introduce carbon dioxide gas into the solvent-containing combination of phospholipids and puerarin. The ideal experimental parameters are 35 °C, 10 mPa pressure, 1% mass ratio of medication to phospholipids, and 100 mg/ml puerarin concentration.<sup>[10]</sup>

### **E. Technique for anti-solvent precipitation**

20 mL of dichloromethane was added to the necessary amount of plant extract and phospholipid in a 100 mL round bottom flask. The mixture was then refluxed for two hours at a temperature of no higher than 60°C. 5–10 mL of the mixture are condensed. The precipitate was carefully added 20 mL of hexane while stirring continuously, then filtered, collected, and placed in desiccators for the night. The dry precipitate is crushed and sieved into #100 meshes in a mortar. The powdered substance was kept at room temperature in an amber-colored glass container.<sup>[5]</sup>

## **Evaluation of Herbosomes**

### **I. Characterization technique:**

#### **1. Visualization:**

Transmission electron microscopy (TEM) and scanning electron microscopy (SEM) can both be used to visualise Herbosomes.

#### **2. Entrapment efficiency:**

The ultracentrifugation method can be used to assess how well a medication is captured by Herbosomes.

#### **3. Vesicle size and zeta potential:**

Using a computerised inspection system and photon correlation spectroscopy, dynamic light scattering (DLS) can be used to evaluate the particle size and zeta potential (PCS).

#### **4. Surface tension activity measurement:**

The ring method in a Du Nouy ring tensiometer can be used to assess the drug's surface tension activity in aqueous solution.

#### **5. Transition temperature:**

Differential scanning calorimetry can be used to find the vesicular lipid systems' transition temperature.

#### **6. Surface tension activity measurement:**

The ring method in a Du Nouy ring tensiometer can be used to assess the drug's surface tension activity in aqueous solution.



### 7. Vesicle stability:

Analyzing the evolution of vesicle size and structure provides insight into the stability of vesicles. DLS measures the mean size, and TEM tracks structural changes.

### 8. Drug content:

A customised high performance liquid chromatographic approach or an appropriate spectroscopic technique can be used to quantify the drug's quantity.<sup>[12]</sup>

## II. Spectroscopic evaluations:

The following spectroscopic techniques are utilised to confirm the development of a complex or to research the reciprocal interaction between the phytoconstituent and the phospholipids.

### 1. <sup>1</sup>H NMR:

Bombardelli et al., 26, examined the NMR spectra of (+) catechin and its stoichiometric combination with distearoylphosphatidyl choline. The <sup>1</sup>H-NMR signal from the atoms involved in the complex's creation changes noticeably in non-polar solvents without any summarization of the signal specific to each particular molecule. To prevent the proton from being released, the flavonoid protons' signals must be strengthened. All of the signals in phospholipids expand, but the singlet corresponding to the choline's N(CH<sub>3</sub>)<sub>3</sub> experiences an upward shift. When the sample is heated to 60, some new broad bands start to show up. These bands primarily correspond to the flavonoid moiety's resonance.

### 2. <sup>13</sup>C NMR:

All the flavonoid carbons are visibly absent in the <sup>13</sup>C-NMR spectra of (+)-catechin and its stoichiometric combination with distearoyl phosphatidylcholine, especially when recorded in C<sub>6</sub>D<sub>6</sub> at ambient temperature. While most of the resonances of the fatty acid chains maintain their original sharp line shape, the signals corresponding to the glycerol and choline portion of the lipid (between 60 and 80 ppm) are broadened and some are displaced. All of the flavonoid moieties' signals reappeared after heating to 60°, however they were still very broad and somewhat overlapped.

### 3. FTIR:

IR spectroscopy can also confirm complex formation by comparing the spectrum of the complex to the spectrum of the individual components and their mechanical mixtures. FTIR spectroscopy can also be used to control the stability of Herbosomes when they are microdispersed in water or incorporated into very simple cosmetic gels. Practically speaking, the stability can be verified by contrasting the spectra of the complex in solid form (Herbosomes) with those of its microdispersion in water following lyophilization, at various times. For simple formulations, it is required to subtract the cosmetic form's spectrum at various points and then contrast the resulting spectrum of the complex as a whole.

## III. *In vitro* and *in vivo* evaluations:

On the basis of the anticipated therapeutic action of physiologically active phytoconstituents included in the Herbosomes, models of *in vitro* and *in vivo* evaluations are chosen. For instance, the antioxidant and free radical scavenging activities of the Herbosomes can be used to measure *in-vitro* antihepatotoxic activity. The effect of produced Herbosomes on animals against thioacetamide paracetamol, alcohol-induced hepatotoxicity, can be investigated for determining antihepatotoxic efficacy *in vivo*. The *in vivo* safety evaluation procedure is described in skin sensitization and tolerability tests of glycyrrhetic acid Herbosome® ointment, a commercial product.<sup>[13]</sup>

## Herbosomes' Pharmaceutical Applications

- Herbosomes improve the oral and topical absorption of lipid-insoluble polar phytoconstituents and demonstrate increased bioavailability, leading to noticeably higher therapeutic efficacy.
- The effectiveness of drug entrapment is improved using herbosomal technology.
- Because the active ingredients are better absorbed, the dosage requirement is decreased.
- Soy phosphatidylcholine, which is a component of herbosome preparation and also has hepatoprotective properties, enhances the effects of other hepatoprotective compounds.
- The percutaneous absorption of phytoconstituents is enhanced by e. herbosomes.

## Choosing a dosage form for delivering herbosomes:

### Soft gelatin Capsules:

Soft gelatin capsules are an excellent way to formulate herbosome.

To obtain a suspension suitable for filling soft gelatin capsules, the herbosome can be dispersed in oily vehicles such as vegetable or semi-synthetic oil.

### Hard gelatin capsules:

The herbosomes complex can also be made into hard gelatin capsules. Even though the apparent low density of the herbosomes complex appears to limit the maximum amount of powder that can be filled into a capsule, a direct volumetric filling process (without precompression) can be used (usually not more than 300 mg for a size 0 capsule). However, with a piston tamp capsule filling process, the amount of powder that can be filled in a capsule can be increased, but precompression may affect the disintegration time.

### Tablets:

The herbosomes complex can be made into tablets. Because of limitations such as flow ability, stickiness, and the low apparent density of the herbosome complex, a direct compression process can only be used for lower unitary doses. To obtain tablets with appropriate properties, the herbosome complex should be diluted with 60-70% excipients. Wet granulation should be avoided due to the negative effects of water and heat on phyto-phospholipid stability.

### Topical dosage form:

To prepare a topical dosage form, first prepare an emulsion at a low temperature (no higher than 40°C), then incorporate the herbosomes complex into it. The phyto-phospholipid complexes dissolve in the lipid solvents commonly used in topical formulation.<sup>[8]</sup>

### Conclusions:

Herbosomes serve as a link between the conventional and novel delivery systems. Herbosomes are a more advanced form of herbal extract that is better absorbed and produces better results than traditional herbal extract. Herbosomes have improved pharmacokinetic and pharmacological parameters, allowing them to be used more effectively in a variety of diseases. Nutraceutical products based on Herbosome technology are present at the site of action (liver, kidney, brain, and heart) at comparable or lower doses than conventional plant extracts.<sup>[15]</sup> Herbosomes have a wide range of applications in cosmetology, and many of them will be revealed in the future in the context of pharmaceutical applications.<sup>[14]</sup>

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