HERBOSOMES: A POTENTIAL CARRIERS FOR THE BIOAVAILABILITY ENHANCEMENT OF HERBAL EXTRACTS

G. Monica* and V. Vasu Naik

Department of Pharmaceutics, Hindu college of Pharmacy, Amaravathi road, Guntur, India.

ABSTRACT

The effectiveness of any herbal medication is dependent on the delivery of effective level of the therapeutically active compounds. Herbosomes are recently introduced herbal formulations that are better absorbed and as a result produce better bioavailability and actions than the conventional botanical extracts. Herbal excipients are non-toxic and compatible they have a major role to play in pharmaceutical formulation. There are many herbal extracts having excellent bioactivity in vitro but less in vivo because of their poor lipid solubility and improper size of the molecule or both, which result in poor absorption and bioavailability of herbal extract or constituents from herbal extract and they destroyed in the gastric fluids when taken orally. Herbosome is the novel emerging technique applied to phyto-pharmaceutical for the enhancement of bioavailability of herbal extract for medicinal applications. Herbosomal formulations have enhanced absorption rate, producing better bioavailability than conventional herbal extract. Since they have improved pharmacological and pharmacokinetic parameters. Herbosomes absorption in GIT is greater resulting in increased plasma level than individual component. Herbosome act as bridge between novel delivery system and conventional delivery system. Phospholipids molecule acting as vital carrier made up of water soluble head and two fat soluble tails, due to this nature they possess dual solubility and thus acting as an effective emulsifier.

Keywords: Herbosomes, Phosphatidylcholine, Polyphenol, Liposomes, Herbosome complex.
INTRODUCTION
The term “Herbo” means plant while “some” means cell-like. Over the past centuries phytochemical and phyto-pharmacological sciences established the compositions, biological activities and health promoting benefits of numerous botanical products. Most of the biologically active constituents of plants are polar or water soluble molecules. However, water soluble phytoconstituents (flavonoids, tannins, glycosides) are poorly absorbed either due to their large molecular size which cannot absorb by passive diffusion or due to their poor lipid solubility, severely limiting their ability to pass across the lipid rich biological membrane, resulting poor bioavailability. Phytomedicines, complex chemical mixtures prepared from plants have been used for health maintenance since ancient’s times. But many phytomedicines are limited in their effectiveness because they are poorly absorbed when taken by mouth. The phytosome technologies, developed by IndenaS.P.A. Italy, markedly enhance the bioavailability of selected phytomedicines, by incorporating phospholipids into standardized extracts and vastly improve their absorption and utilization.

APPROACH OF HERBOSOMAL TECHNOLOGY
Herbosomes, complex of natural active ingredients and phospholipids(s), increase absorption of herbal extracts or isolated active ingredients when applied topically or orally. Herbosomes are cell like structures which result from the stoichiometric reaction of the phospholipids (phosphatidylcholine, phosphatidylserine etc.) With the standardized extract or polyphenolic constituents in a non-polar solvent, which are better absorbed, utilized produce better results than conventional herbal extracts. Phospholipids are the main building blocks of life and are one of the major components of cellular membranes. In general, they are considered as natural digestive aid and carriers for both polar and non-polar active substances. Most of phospholipids possess nutritional properties, like phosphatidylserine which acts as a brain cell nutrient, phosphatidylcholine which is important in liver cell regeneration. Soya phospholipids have lipid reducing effect with hydrogenated phospholipids serve as basis for preparation of stable liposome’s because of their amphiphilic character herbosomal formulations enhance the bioavailability of active phytochemical constituents as they are now permeable and can cross the lipid rich bio membranes quite easily, and the active components of the herbal extracts are well protected from destruction by digestive secretions and gut bacteria. Therefore, with help of herbosomal preparations, the amount of standardized herbal extracts or phytoconstituents administered in body through several routes are required in fewer amounts for good therapeutic activity. With the advancements in science, the
herbosomes have gained importance in various fields like pharmaceuticals, cosmeceuticals and nutraceuticals in preparing different formulations such as solutions, emulsions, creams, lotions, gels, etc. Several companies involved in production and marketing of herbosomal products are Indena, Jamieson natural resources, Thorne Research, Natural factors, and Natures herb. Sometimes it is difficult to understand the basic difference between liposome’s and herbosomes.

**HERBOSOME TECHNOLOGY**

The poor absorption of flavonoid nutrients is likely due to two main factors. First, these are multiple-ring molecules not quite small enough to be absorbed from the intestine into the blood by simple diffusion. Nor does the intestinal lining actively absorb them, as occurs with some vitamins and minerals. Second, flavonoid molecules typically have poor miscibility with oils and enterocytes, the cell that line the small intestine. The herbosomes technology meets this challenge. Certain of the water-phase flavonoid molecules can be converted into lipid-compatible molecular complexes, aptly called herbosomes.

These are better able to transition from the water phase external to the enterocyte, into the lipid phase of its outer cell membrane and from there into the cell, finally reaching the blood. The lipid-phase substance employed to form molecular complexes with phospholipids from soya, mainly phosphotidylcholine (PC). Phospholipids are small lipid molecules where glycerol is bonded to two fatty acids, while the third hydroxyl, normally and of the two primary methylenes, bears a phosphate group bound to a biogenic amino or to an amino acid thus making herbosomes different from liposome’s. PC is the principal molecular building block for cell membranes and the molecular properties that suit PC for this role also render it close to ideal for its herbosome role. PC is miscible both in the water phase and in oil/lipid phase, and is excellently absorbed when taken by mouth, and has the potential to act as a chaperon for polyphenolics, shuttling them through biological membranes. Precise chemical analysis indicates the unit herbosome is usually a flavonoid molecule linked with at least one PC molecule. A bond is formed between the two molecules to create a hybrid molecule. This hybrid is highly lipid-miscible, better suited to merge into the lipid phase of the entrocyte’s outer cell membrane. Once there, it can cross the entrocyte and reach the circulating blood. The flavonoid and terpenoid constituents of plant extract lend themselves quite well for the direct binding to phosphatidylcholine. Herbosomes result from the reaction of a stoichiometric amount of the phospholipids (phosphatidylcholine) with the standardized
extract or polyphenolic constituents (like simple flavonoid) in a non polar solvent. The formation of lipid molecular complex results in a formation of a little micro sphere or cell is produced and this can be demonstrated by specific spectroscopic techniques. The herbosome technology produce a little cell, whereby the plant extract or its active constituents is protected from destruction by gastric secretions and gut bacteria owing to the gastroproctective property of phosphatidylcholine.

ORGANIZATION OF THE HERBOSOME MOLECULAR COMPLEX

HERBOSOMES

Herbosome are created when the standardized extract and active ingredients of an herb are bound to the phospholipids on a molecular level. Herbosome structures contain the active ingredients of the herb surrounded by the phospholipids. Herbosome is a patented process developed by Indena, a leading supplier of nutraceutical ingredients, to incorporate phospholipids into standardized extract and so vastly improve their absorption and utilization. Certain of the water-soluble phyto-molecules (mainly flavonoids and other polyphenols) can be converted into lipid-friendly complexes, by reacting herbal extract owing to their enhanced capacity to cross the lipid-rich bio membranes and, finally, reach the blood. They have improved pharmacokinetic and pharmacological parameters which are advantageous in the treatment of acute disease as well as in pharmaceutical and cosmetic compositions. Lipid solubility and molecular size are the major limiting factors for molecules to pass the biological membrane to be absorbed systematically following oral or topical administration. Several plant extracts and phytoconstituents, despite having excellent bio-activity in vitro demonstrate less or no in vivo actions due to their poor lipid solubility or improper molecular size or both, resulting poor absorption and poor bioavailability. Development of herbosomes is at the budding stages in India and abroad.
These drug-phospholipids complexes can be formulated in the form of solution, suspension, emulsion, syrup, lotion gel, cream, aqueous micro dispersion, pill, capsule, powder, granules and chewable tablet phosphatidylcholine resulting in a product that is better absorbed and produces better result than the conventional herbal extracts. Herbosomes also has added dimensions; the proven health giving activity of the phospholipids themselves. The presence of a surfactant i.e. the phospholipids in the molecule allows obtaining a higher adhesion of the product itself to the surface it comes into contact with and a better interaction of various molecules with cell structure. This aspect is of paramount importance in cosmetics and pharmaceutical formulations.

The Herbosome technology enables cost effective delivery and synergistic benefits from the phospholipids nutraceuticals intrinsic to life. The phospholipids mainly employed to make herbosomes, is phosphatidylcholine, derived from soybean (glycine max). Herbosomes are more bioavailable as compared to conventional herbal extract owing to their enhanced capacity to cross the lipoidal biomembrane and finally reaching the systemic circulation. Herbosome has been an emerging trend in delivery of herbal drugs and nutraceuticals.

**Phospholipids**

**For the improvement of nutrient absorption and bioavailability**

Phospholipids (pronounced fos-fo-lip-ids) are complex substance with chemical, biochemical and nutritional characteristics that place them in a unique nutritional category. They are complex lipid molecules indispensable for life and are abundant in all human and the other known forms to make cell membranes. The profound biochemical importance of phospholipids is reflected in their extraordinary clinical benefits as dietary supplements. The phospholipids are readily compatible with the entire range of vitamins, minerals, metabolites, and herbal preparations currently consumed as the dietary phospholipids and omega-3 fatty acid works in functional synergy in cell membranes.

Phosphatidylcholine is a bifunctional compound miscible both in water and in oil environments, and is well absorbed when taken by mouth. Phosphatidylcholine is not merely a passive “carrier” for the bioactive compounds, but is itself a bioactive nutrient with documented clinical efficacy for liver disease, including alcoholic hepatitis. Phosphatidylcholine is present in egg yolk, brain tissue and a wide variety of animal fat and plant oils. It is routinely present in the bile fluid, to help emulsify food ingredient for absorption. It work in concert with the body’s orthomolecular antioxidants (vitamin C & E, alpha-lipoic acid,
glutathione, coenzyme Q10, selenium, zinc, manganese, copper) to protect membranes in the liver and other organs. Also, when phosphatidylcholine and other phospholipids are taken as dietary supplement along with food is better absorbed.

![Structure of Phosphatidylcholine](image)

**STRUCTURE OF PHOSPHATIDYLCHOLINE**

A number of drug delivery system is based entirely on phosphatidylcholine such as liposome’s, ethosomes, phytosomes, transferosomes, and nanocochelates. The hydrophilic and hydrophobic domain/segment within the molecular geometry of amphiphilic lipids orient and self organize in ordered supramolecular structure when confronted with solvent. Some commonly used synthetic phospholipids are dioleoyl-phosphatidyl-choline (DOPC), dioleoyl-phosphatidyl-ethanolamine (DOPE), distearoyl-phosphatidyl-choline (DSPC), distearoyl-phosphatidyl-ethanolamine (DSPE). Among these all phospholipids, phosphatidylcholine classes of phospholipids are very important in the drug delivery technology. The very first and most important advantage of phospholipids based vesicular system is the compatibility of phospholipids with membrane of human either internal...
membrane as well as skin. Advantages of phospholipids based carrier system in comparison to other delivery systems.

1.) These systems show enhanced permeation of drug through skin for transdermal and dermal delivery.

2.) These are platform for the delivery of large and diverse group of drugs (peptides, protein molecules).

3.) Their composition is safe and the components are approved for pharmaceutical and cosmetic use.

4.) Low risk profile- the toxicological profiles of the phospholipids are well documented in the scientific literature.

5.) High market attractiveness for products with proprietary technology. Relatively simple to manufacture with no complicated technical investments required for production of Ethosomes.

6.) The vesicular system is passive, non-invasive and is available for immediate commercialization.

MECHANISM OF HERBOSOME FORMATION

The polyphenolic constituents of plant extracts lend themselves quite well for direct binding to phosphatidylcholine. Herbosomes are formed from the reaction of a stoichiometric amount of the phospholipids like phosphatidylcholine with the standardized extract or polyphenolic constituents like simple flavonoids in aprotic solvent. phosphatidylcholine is a bifunctional compound, the phosphatidyl moiety being lipophilic and the choline moiety being hydrophilic in nature. Specifically the choline head of the phosphatidylcholine binds to these compounds while lipid soluble phosphatidyl portion comprising the body and tail which then envelopes the choline bound material. Hence, the Phytomolecules produce a lipid soluble molecular complex with phospholipids called as phyto-phospholipid complex. Phytomolecules are anchored through chemical bonds to the polar choline head of phospholipids, as can be demonstrated by specific spectroscopic techniques. Often Precise chemical analysis indicates the unit Herbsome is usually a flavonoid molecule linked with at least one phosphatidylcholine molecule. The result is a little microsphere or cell is produced
MERITS OF HERBOSOMES OVER OTHER CONVENTIONAL DOSAGE FORMS

There is a dramatic enhancement of the bioavailability of botanical extract due to their complexation with phospholipids and improved absorption.

- They permeate the non-lipophilic botanical extract to allow better absorption from the intestinal lumen, which is otherwise not possible. The formulation of herbosomes is safe and the component has all been approved for pharmaceutical and cosmetic use.

- They have been used to deliver liver-protecting flavonoid because they can be made easily bioavailable by herbosomes. In addition to this phosphatidylcholine is also hepatoprotective and so provide a synergistic effect for liver protection. This technology offers cost-effective delivery of phytoconstituents and synergistic benefits. They can also be used for enhanced permeation of drug through skin for transdermal and dermal delivery.

- Phosphatidylcholine, an essential part of the membrane used in herbosome technology, act as a carrier and also nourishes the skin. There is no problem with drug entrapment during formulation preparation. Also, the entrapment efficiency is high and more over predetermined, because the drug itself forms vesicle after conjugation with lipid. They offer a better stability profile because chemical bonds are formed between the phosphatidylcholine molecule and phytoconstituents.

- The herbosomal system is passive, non-invasive and can is suitable for immediate commercialization. The dose requirement is reduced due to improved absorption of the main constituent. They can also be given in smaller quantities to achieve the desired result. Relatively simple to manufacture with no
complicated technical investment required for the production of herbosomes.
Herbosomes are also superior to liposomes in skin care products while the liposomes are an aggregate of many phospholipids molecules that can enclose other phytoactive molecules but without specifically bonding to them. Liposomes are tout delivery vesicles but, for dietary supplement, their promise has been fulfilled.
However, in the case of herbosomes products, numerous studies have proved that they are markedly better absorbed and have substantially greater clinical efficacy. Companies have successfully applied this technology to a number of standardized flavonoid preparations.

BENEFITS OF HERBAL FORMULATIONS
1. Potential enhancement of bioavailability.
2. Herbal herbosome process produces a little cell whereby the valuable components of the herbal extracts are protected from destruction by digestive secretions and gut bacteria.
3. Pharmacologically Assured delivery to the different biological tissues.
4. No compromise of nutrient safety.
5. Less dose requirement is due to absorption of chief constituent.
6. Drug loading efficiency is so high and more over predetermined because drug itself in conjugation with lipids is forming vesicles.
7. No problem of drug entrapment.
8. Herbosomes shows better stability profile because chemical bonds are formed between phosphatidylcholine molecules and phytoconstituents.
9. Phosphatidylcholine used in the herbosome process which acting as a carrier and also nourishes the skin, because it is essential part of cell membrane.
10. Herbosome is also superior to liposomes in skin care products.
11. Significantly gives greater clinical benefit than liposomes.
12. The structure of herbosome elicits peculiar properties and advantages in cosmetic application.
13. Significantly Enhanced ability of herbosome to cross cell membranes and enter cells.
14. Their low solubility in aqueous media allows the formation of stable emulsions or creams

PHYSICAL PROPERTIES OF HERBOSOMES
- Herbosome has lipophilic substances with a clear melting point.
- Average size of herbosome range is 50 nm to a few hundred μm.
- They are easily soluble in non-polar solvents, insoluble in water and moderately soluble in fats.
- Liposomal like structures of miscellar shape are formed when herbosome are treated with water.

**CHEMICAL PROPERTIES OF HERBOSOMES:**

On the basis of their physicochemical and spectroscopic data, it has been shown that, the phospholipids-substrate interaction is due to the formation of hydrogen bond between the polar heads of phospholipids (i.e. phosphate and ammonium groups) and the polar functional groups of substrate. In herbosomes the active principle is anchored to the polar head of phospholipids, becoming an integral part of the membrane.

**DIFFERENCE BETWEEN HERBOSOMES AND LIPOSOMES:**

<table>
<thead>
<tr>
<th>Herbosomes</th>
<th>Liposomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>In herbosomes active chemical constituents molecules are anchored through chemical bonds to the polar head of phopholipid.</td>
<td>In liposomes, the active principle is dissolved in the medium of activity or in the layers of the membrane. No chemical bonds are formed.</td>
</tr>
<tr>
<td>In herbosomes, phosphatidylcholine and the individual plant compound form a 1:1 or 2:1 complex depending on the substance.</td>
<td>In liposomes, hundreds and thousands of phosphatidylcholine molecules surround the water soluble molecule.</td>
</tr>
</tbody>
</table>
PREPARATION METHODS

Herbosomes are formulated by patented processes in which the standardized extract (having a standardized content of active principles) and/or active ingredients of herbs (like flavoliganans and terpenoids) are bound to the phospholipids like phosphatidylcholine (PC) through a polar end. The herbosomes process produces small cells which protect the valuable components of the herbal extracts are well suited to direct binding to phosphatidylcholine from soy. PC is also the principle molecular building block of cell membranes and is miscible with both water and oil/lipid mixtures, and is well absorbed orally. Herbosomes are also considered as a phytolipid delivery system. Herbosomes are prepared by reacting 3-2 moles (Preferably with one mole) of a natural or synthetic phospholipids, such as phosphatidylcholine, phosphatidylethanolamine or phytoco constituent is 1:1. The complex thus formed can be isolated by precipitation with an aliphatic hydrocarbon or lyophilisation or spray drying.

Mareno and lampertico (1991) Jiang et al (2001), Maiti et al (2006), Maiti et al (2006), have described the methods used for herbosome preparation. Jiang et al. have optimized the preparation conditions using a uniform design and step regression and have prepared herbal Epimedi total flavonoid phytosomes (EFP) by means of solvent evaporation and investigated the cumulative dissolution of different ratios of EFP-PVP precipitates by means of dissolution release. The optimized preparation conditions are as follows: solvent- tetrahydrofuran, lecithin to PVP ratio-2.5, temperature-40°C and reaction time-3 hrs. The oil/water apparent partition coefficient of icariin was enhanced more than 4-fold by phospholipids. The cumulative dissolution of Herbal Epimedi flavonoid of the EFP-PVP precipitate was significantly higher than that of its physical mixture and an Herbal Epimedi extract tablet. Yanyu et al prepared a silybin-phospholipids complex using ethanol as a reaction medium. Silybin and phospholipids were resolved into the medium, after the organic solvent was removed under vacuum condition, and a silybin-phospholipids complex was formed. Naringenin-PC complex was prepared by taking naringenin with an equimolar concentration of phosphatidylcholine (PC). The equimolar concentration of PC and naringenin were placed in a 100 ml round bottom flask and refluxed in dichloromethane for 3h. on concentrating the solution to 5-10 ml, 30 ml of n-hexane was added to get the complex as a precipitate followed by filtration. The precipitate was collected and placed in vacuum desiccators. The required amount of the drug and phospholipids were placed in a 100 ml round-bottom flask and dissolved in anhydrous ethanol. After ethanol was evaporated off
under vacuum at 40°C, the dried residues were gathered and placed in desiccators overnight, then crushed in the mortar and sieved with a 100 mesh. The resultant silybin-phospholipids complex was transferred into a glass bottle, flushed with nitrogen and stored in the room temperature.

**Preparation methodology**

![Diagram of preparation methodology](image)

Common stages for preparation of Herbosome

\[
\text{Phospholipids} \xrightarrow{\text{Dissolved in organic solvent containing drug/extract}} \text{Hydration} \xrightarrow{\text{Solution of phospholipids in organic solvent with drug/extract}} \text{Drying} \xrightarrow{\text{Formation of thin film}} \text{Formation of planterosomal suspension}
\]

**CHARACTERIZATION OF HERBOSOME**: Herbosome are characterized for physical attributes, i.e. shape, size, its distribution, percentage drug capture, entrapped volume,
percentage drug release, and chemical composition. Hence, behaviour of herbosome in both physical and biological systems is governed by the following factors:

1. Physical size
2. Membrane permeability
3. Percent entrapped solutes
4. Chemical composition
5. Quantity and purity of the starting materials

EVALUATION OF HERBOSOME

I. Characterization technique

1. Visualization: Visualization of herbosome can be measured by transmission electron microscopy (TEM) and by scanning electron microscopy (SEM). Visualization of planterosomes can be achieved using Transmission Electron Microscopy (TEM) and by Scanning Electron Microscopy (SEM) electron microscopic techniques used to assess liposome shape and size are mainly negative-stain transmission microscopy and scanning electron microscopy. The later technique requires dehydration of the sample prior to examination and is less preferred. Negative stain electron microscopy visualizes relatively electron transparent liposomes or herbosomes as bright area against a dark background (hence termed as negative stain). Liposome like structure is embedded in this method in a thin film of electron-dence heavy metal (salt) stain. The use of negative stain electron microscopy facilitates estimation of the liposome size range at the lower end of the frequency distribution. Irregular or ellipsoid shape can be treated mathematically to correct for perimeter irregularities thus estimations of original spherical diameter can be calculated.

2. Vesicle size and Zeta Potential: The particle size and zeta potential can be determined by dynamic light scattering (DLS) using a computerized inspection system and photon correlation spectroscopy (PCS).
3. **Entrapment efficiency**: The entrapment efficiency of herbal formulations of drug by herbosome can be measured by the ultracentrifugation technique.

4. **Transition temperature**: The transition temperature of the vesicular lipid systems can be measured by differential scanning calorimetry.

5. **Surface tension property measurement**: The surface tension property of the drug in aqueous solution can be measured by the ring method in a DuNouy ring tensiometer.

6. **Vesicle stability**: The stability of vesicles can be measured by assessing the size and structure of the vesicles over time. The mean size is measured by DLS and structural changes are monitored by TEM.

7. **Drug content**: The amount of drug can be measured by a modified high performance liquid chromatographic method or by a suitable spectroscopic method. There are various factors such as the physical size, membrane permeability, percentage of entrapped solutes, and chemical composition of the preparing materials which play a vital role in determining the behaviour of herbosome in physical and biological system. The spectroscopic evaluations are widely employed in order to confirm the formation of complex between phyto-constituents and the phospholipids moiety as well as to study the corresponding interaction between the two. The widely employed methods are:

**HNMR**

The NMR spectra are employed for determining the complex formation between the active phytoconstituents and the phosphatidylcholine molecule. The NMR spectra of herbosome complex had been studied by Bombardelli. In nonpolar solvents there is a marked change in 1H NMR signal originating from atoms involved in the formation of complex, without any summation of the signal peculiar to individual molecules. The signals from protons belonging to the phyto-constituents are broadened. In phospholipids there is broadening of signals while the singlet corresponding to the N-(CH3)3 of choline undergoes an up field shift.

**CNMR**

The 13C NMR of phyto-constituents and stoichiometric complex with phosphatidylcholine, recorded in C6D6 at room temperature all the phytoconstituents carbons where invisible. The signals corresponding to the glycerol and choline portion are broadened and some are shifted, while most of the resonances of the fatty acids chains retain their original sharp line shape.
FTIR
The spectroscopic evaluation of the formed complex can be confirmed by FTIR simply by comparing the spectrum of the complex and the individual components and that of the mechanical mixtures. FTIR can also be considered as a valuable tool in confirming the stability of the herbosomal complex. The stability can be confirmed by comparing the spectrum of the complex in solid form with that of the spectrum of micro-dispersion in water after lyophilisation at different times.

COMMERCIAL APPLICATIONS OF HERBOSOME
The current research shows enhanced absorption and bioavailability with herbosome as compared to the conventional means. Most of the Commercial Preparations of herbosome are available

COMMERCIALY AVAILABLE HERBOSOME PREPARATIONS

<table>
<thead>
<tr>
<th>Commercial phytosome preparation. S/N</th>
<th>Herbosome</th>
<th>Phytoconstituents complex with phosphatidylcholine</th>
<th>Doses(mg)</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>01</td>
<td>Curcumin phytosome</td>
<td>Curcumin Curcuma longa</td>
<td></td>
<td>Antioxidant, antinflamatory</td>
</tr>
<tr>
<td>02</td>
<td>18ß-glycyrrhetinic acid phytosome</td>
<td>18ß-glycyrrhetinic acid from licorice rhizome</td>
<td></td>
<td>Soothing</td>
</tr>
<tr>
<td>03</td>
<td>Centella phytosome®</td>
<td>Triterpenes from Centella asiatica leaf</td>
<td></td>
<td>Cicatrizing, trophodermic</td>
</tr>
<tr>
<td>04</td>
<td>Crataegus phytosome®</td>
<td>Vitexin-2“-Orhamnoside From hawthorn flower</td>
<td></td>
<td>Antioxidant</td>
</tr>
<tr>
<td>05</td>
<td>Escin β-sitosterol phytosome®</td>
<td>Escin β-sitosterol from horse chestnut fruit</td>
<td></td>
<td>Anti-oedema</td>
</tr>
<tr>
<td>Page</td>
<td>Entry</td>
<td>Description</td>
<td>Functionality</td>
<td></td>
</tr>
<tr>
<td>------</td>
<td>-------</td>
<td>-------------</td>
<td>---------------</td>
<td></td>
</tr>
<tr>
<td>06</td>
<td>Ginkgo biloba Terpenes phytosome®</td>
<td>Ginkgolides and bilobalide from Ginkgo biloba leaf</td>
<td>Soothing</td>
<td></td>
</tr>
<tr>
<td>07</td>
<td>Ginkgo biloba Dimeric Flavonoids phytosome®</td>
<td>Dimeric flavonoids from Ginkgo biloba leaf</td>
<td>Lipolytic, vasokinetic</td>
<td></td>
</tr>
<tr>
<td>08</td>
<td>PA2 phytosome®</td>
<td>Proanthocyanidin A2 from horse chestnut bark</td>
<td>Anti-wrinkles, UV protectant</td>
<td></td>
</tr>
<tr>
<td>09</td>
<td>Sericoside phytosome®</td>
<td>Sericoside from Terminalia sericea bark root</td>
<td>Anti-wrinkles</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>Silymarin phytosome®</td>
<td>Silymarin from milk thistle seed</td>
<td>Antihepatotoxic</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>Virtiva®</td>
<td>Ginkgo flavonglycosides, ginkgolides, bilobalide from Ginkgo biloba leaf</td>
<td>Vasokinetic</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>Visnadex®</td>
<td>Visnadin from Amni visnaga umbel</td>
<td>Vasokinetic</td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>Silybin phytosome TM</td>
<td>Silybin from Silybum marianum</td>
<td>Food product, hepatoprotective, antioxidant for skin and liver</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ginkgo phytosome TM</td>
<td>Protect brain and vascular lining, antiageing agent</td>
<td></td>
</tr>
<tr>
<td>14</td>
<td></td>
<td>24% Ginkgo flavonglycosides from Ginkgo biloba</td>
<td>120</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ginseng phytosome TM</td>
<td>Food product, neutraceutical immunomodulator</td>
<td></td>
</tr>
<tr>
<td>15</td>
<td></td>
<td>37.5% Ginsenoside from panax ginseng</td>
<td>120</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Green tea phytosome TM</td>
<td>Neutraceutical, systemic antioxidant, anticancer</td>
<td></td>
</tr>
<tr>
<td>16</td>
<td></td>
<td>Epigallocatechin3-O-gallate from Camelia sinesis</td>
<td>150</td>
<td></td>
</tr>
</tbody>
</table>
Recent Research on Improved Bioavailability with Phyto-Phospholipid Complexation:

**P. Mukherjee & Co-associates (2009)** enhanced Oral Bioavailability and Antioxidant Profile of Ellagic Acid by Phospholipids. In the research they studied that Ellagic acid (EA) is potent antioxidant with several nutritional benefits but reported to have rapid elimination from the body. To overcome this limitation they developed novel dietary formulation of EA with phospholipids. To investigate the effect of this complex on carbon tetrachloride induced liver damage in rats. The antioxidant activity of complex and free EA was evaluated by measuring various enzymes in oxidative stress condition. The complex significantly protected the liver by restoring the activity of superoxide dismutase, catalase and liver glutathione, and thiobarbituric acid reactive substances with respect to carbon tetrachloride treated group. The complex provides better protection to rat liver than free EA at same dose. The serum concentration of EA obtained from complex was higher than of pure EA and complex maintained effective concentration for longer time in serum. Result shows better hepatoprotective activity of EA complex.

**Sharma A. & Co-associates (2010)** were studied the Complexation with phosphatidyl choline (PC) as a strategy for absorption enhancement of boswellic acid (BA). Boswellic acid
oleo gun resin of *Boswellia serrata* were reported to be effective as anti-inflammatory, hypolipidemic, immunomodulatory, and anti-tumor. Pharmacokinetic studies of boswellic acid reveal its poor absorption through the intestine. The objective of their study was to enhance bioavailability of boswellic acid by its complexation with phosphatidylcholine. They characterize the boswellic acid-phosphatidylcholine (BA-PC) complex and studied the ex-vivo drug absorption of (BA-PC) complex and plain BA. Anti-inflammatory activity of the complex was compared with boswellic acid in carrageenan-induced paw oedema in rats. Hypolipidemic activity was also evaluated in Triton-induced hyperlipidemia. The complex was also converted into vesicles (phytosomes) and compared with other vesicular systems (liposome’s and niosome) by evaluating its anti-inflammatory effect. The results of ex-vivo study show that BA-PC complex has significantly increased absorption compared with boswellic acid, when given in equimolar doses. The complex showed better anti-inflammatory and hypolipidemic activity as compared to BA. Among all vesicular systems phytosomes showed maximum anti-inflammatory activity. Enhanced bioavailability of the BA-PC complex may be due to the amphiphilic nature of the complex, which greatly enhance the water and lipid solubility of the boswellic acid. The present study clearly indicates the superiority of complex over boswellic acid, in terms of better absorption, enhanced bioavailability and improved pharmacokinetics.

**R. Pathan & Co-associates (2011)** prepared an embelin–phospholipid complex (EPC) formulation in an attempt to enhance the water solubility and characterize the new developed formulation. Embelin, due to water insolubility causes poor bioavailability by oral route. To improve the bioavailability and prolong its duration in body system, its phospholipids complexes were prepared by a simple and reproducible method. EPC was formulated by mechanical dispersion method using ethanol as a reaction medium. The complex formation was confirmed by carrying out FTIR, 1H-NMR, XRD, DSC and microscopical studies. Solubility and in vitro studies were carried out to ascertain the solubility and dissolution pattern of free and complexed embelin. Water solubility of embelin was improved from 3-42 1g/mL in the prepared complex. n-Octanol solubility were also altered for free embelin and EPC from 2.3 to 391g/mL Unlike the free embelin, which showed a total of only 19% drug release at the end of 120 min, EPC showed 99.80% release at the end of 120 min of dissolution study in distilled water.
N. Gupta & Co-associates (2011) were enhancing the absorption of grape seed polyphenols by complexation with phosphatidyl choline (PC). Grape seed polyphenols (GPP) are reported to have various biological effects along with strong antioxidant potential. Pharmacokinetic studies of GPP reveal its poor absorption through the intestine. Complex of GPP was prepared and characterize on the basis of solubility, melting point, DSC, and IR. Everted intestine sac technique was used to study *ex vivo* drug absorption of GPP-PC complex and plain GPP. Pharmacokinetic studies were performed in rats and the hepatoprotective activity of GPP-PC complex was also compared with GPP and GPP-PC physical mixture in isolated rat hepatocytes. And the results of *ex vivo* study show that the GPP-PC complex has significantly increased absorption compared with GPP, when given in equimolar doses. The complex showed enhanced bioavailability, improved pharmacokinetics, and increased hepatoprotective activity as compared to GPP or GPP-PC physical mixtures. Enhanced bioavailability of GPP-PC complex may be due to the amphiphilic nature of the complex, which greatly enhance the lipid miscibility of GPP.

Kusumawati & Co-associates (2011) prepared the phospholipids complex of *Kaempferia galangal* rhizome extract using phosphatidylcholine was intend to improve the bioavailability of its constituents. Characteristics and analgesic activity of the extract and its marker compound, ethyl *p*-methoxycinnamate (EPMS), were compared to their phospholipids complex (F. Extract and F.EPMS). Characteristics of the free form and their complexes were analyzed by DTA and SEM. Their analgesic activity was determined using writhing test. The complex showed a better analgesic activity compared to the free form of both extract and EPMS at an equivalent dosage.

R. Kuamwat & Co-associates (2012) studied that Gallic acid and its derivatives are a group of naturally occurring polyphenols antioxidants which have recently been shown to have potential health effects but when administered orally it shows poor absorption because of less lipophilicity. To overcome this limitation, they developed gallic acid- phospholipids complex in different ratio to improve the lipophilic properties of Gallic acid. The physicochemical properties of the complex were analyzed by ultraviolet-visible spectrometry (UV), infrared spectrometry (IR) and differential scanning calorimetry (DSC), solubility, dissolution, etc. the result showed that Gallic and phospholipids in Gallic-phospholipids complex were joined by non-covalent bond and did not form a new compound and observed that complex was an effective scavenger of DPPH radicals and showed the strong antioxidant activity.
U. Bhandari & Co-associates (2012) studied the anti-apoptotic effect of gymnemic-acid phospholipids complex (GPC) pretreatment in wistar rats with experimental cardiomyopathy. They studied that cardiomyocyte apoptosis is one recent cause in heart failure and also investigate the potential cardioprotective effect of GPC on myocardial apoptosis and cardiac function in doxorubicin (DOX)-induced cardiomyopathy model in rats. They observed that pre-treatment with GPC significantly reduce DOX-induced cardiac toxicity including improvement of hemodynamic variables and heart weight loss to body weight ratio, decreased serum Ca²⁺ level and LDH level, myocardial caspase -3 level, increased Na⁺/K⁺ ATPase level, decreased myocardial TBARS levels and elevated antioxidant enzyme levels were compared to pathogenic control group, further the anti-apoptotic effect of GPC by was studied by prevention internucleosomal DNA laddering & attenuation of histopathological perturbation by DOX. The observation demonstrates that GPC might serves as a cardioprotective formulation.

S. Sandhya & Co-associates (2012) Performed Preclinical studies of a novel polyherbal phyto-complex hair growth promoting cream which was incorporated with the aq. extracts of *Trichosanthes cucumerica* (T. cucumerica) Linn and *Abrus precatorius* (A. precatorius) Linn. In the experimental study, extraction of both plants, chemical testing of both extract, then extract were made into phyto-phosphatidylcholine complex, finally preparation of formulation and then evaluation of cream containing polyherbalphyto-complex. Preclinical studies showed that formulated 2% polyherbalphytocomplex hair growth promoting cream was an effective hair growth promoter as the results were analogous to that of minoxidil 2%. it was observed that percentage of hair follicles in the anagen phase increased considerably which predicts that the formulation can be used in alopecia.

Francesco & co-associates (2009): studied on a recently developed oral formulation in the form of coated tablets (Monoselect Camellia®) (MonCam) containing highly bioavailable green tea extract (GreenSelect® phytosomes) was tested in obese subjects (n=100) of both gender on a hypocaloric diet. Fifty subjects were assigned to the green tea extract plus hypocaloric diet, while the others 50 subjects followed the hypocaloric diet only. After 90 days of treatment, significant weight loss and decreased body mass index (BMI) were observed in the group taking the herbal extract (14 kg loss in the green tea group compared to a 5 kg loss in the diet-only group); waistline was reduced only in male subjects. Besides the effect on weight and BMI, biochemical parameters (LDL, HDL, and total cholesterol,
triglycerides, growth hormone, insulin like growth factor-1, insulin, and cortisol) were improved in both groups. Leptin, not tested in the diet-only group, was reduced in patients taking Mon Cam. Taking into consideration the high safety profile of the product and the total absence of adverse effects observed during and after the trial, Mon Cam appears to be a safe and effective tool for weight loss.

Mukerjee & co-associates (2008): Hesperetin is a potent phytomolecule abundant in citrus fruits, such as grapefruit and oranges. In spite of several therapeutic benefits viz. antioxidant, lipid-lowering, anti-carcinogenic activities their shorter half life and lower clearance from the body restricts its use. To overcome this limitation, recently Mukerjee et al. developed a novel hesperetin phytosome by complexing hesperitin with hydrogenated phosphatidyl choline. This complex was then evaluated for antioxidant activity in CCl4 intoxicated rats along with pharmacokinetic study revealed that the phytosome had higher relative bioavailability than that of parent molecule at the same dose level.

Yanyu & co-associates (2006): prepared the silymarin phytosome and studied its pharmacokinetics in rats. In the study the bioavailability of silybin in rats was increased remarkably after oral administration of prepared silybin-phospholipids complex due to an impressive improvement of the lipophilic property of silybin-phospholipids complex and improvement of the biological effect of silybin.

Maiti & co-associates (2006): developed the phytosomes of curcumin (flavonoid from turmeric, curcuma longa) and naringenin (a flavonoid from grape fruit, vitis vinifera) in two different studies.

Maiti & co-associates (2005): developed the quercetin phospholipids phytosomal complex by a simple and reproducible method and also showed that the formulation exerted better therapeutic efficacy than the molecules in rat liver injury induced by carbon tetrachloride.

Ravarotto & co-associate (2004): reported silymarin phytosomes show better anti-hepatotoxic activity than silymarin alone and can provide protection against the toxic effects of aflatoxi B1 on performance of broiler chicks.

Tedesco & co-associate (2004): reported silymarin phytosome show better anti-hepatotoxic activity than silymarin alone and can provide protection against the toxic effects of aflatoxin B1 on performance of broiler chicks. Busby et al., reported that the use of a silymarin
Monica et al.

World Journal of Pharmacy and Pharmaceutical Sciences

Monica et al. showed a better fetoprotectant activity from ethanol-induced behavioural deficits than uncomplexed silymarin.

Grange & co-associate (1999): conducted a series of studies on silymarin phytosome, containing a standardized extract from the seeds of S. marianum, administered orally and found that it could protect the fetus from maternally ingested ethanol grape seed phytosome is composed of oligomeric polyphenols (grape proanthocyanidins or procyanidins from grape seed extract, vitis vinifera) of varying molecular size, complexed with phospholipids. The main properties of procyanidin flavonoid of grape seed are an increase in total antioxidant capacity and stimulation of physiological antioxidant defences of plasma, protection against atherosclerosis thereby offering marked protection for the cardiovascular system and other organs through a network of mechanisms that extends beyond their great antioxidant potency.

Moscarella & co-associates (1993): investigated in one study of 232 patients with chronic hepatitis (viral, alcohol or drug induced) treated with silybin phytosome at a dose of 120 mg either twice daily or thrice daily for up to 120 days, liver functions returned to normal faster in patients taking silybin phytosomes compared to a group of controls (49 treated with commercially available silymarin, 117 untreated or given placebo).

Bombardelli & co-associate (1991): reported silymarin phytosomes, in which silymarin (a standardized mixture of flavanolignans extracted from the fruits of S. marianum) was complexed with phospholipids. Phytosomes showed much higher specific activity and a longer lasting action than the single constituents, with respect to percent reduction of oedema, inhibition of myeloperoxidase activity, antioxidant and free radical scavenging properties. In the human subjects silybin from phytosomes effectively reaches the intended target organ, the liver.

Barzaghi & co-associate (1990): conducted a human study designed to assess the absorption of silybin when directly bound to phosphatadylcholine. Plasma silybin levels were determined after administration of single oral doses of silybin phytosome and a similar amount of silybin from milk thistle in healthy volunteers. The results indicated that the absorption of silybin from silybin phytosome is approximately seven times greater compared to the absorption of silybin from regular milk thistle extract (70-80 % silymarin content).
Schandalik & co-associate: used nine volunteer patients who had earlier undergone surgical gall bladder removal necessitated by gallstones. They received single oral doses of 120 mg silybin as silybin phytosomes, and bile was accessed for silybin levels. Silybin appeared in the bile after 48 hours accounted for 11 percent of the total dose. In the case of silymarin, approximately 3 percent of the silybin was recovered.

These data demonstrates a four times greater passage through the liver for phytosomal silybin studies have approximately 3 percent of the silybin was recovered. These data demonstrate a four times greater passage through the liver for phytosomal silybin studies have shown ginkgo phytosome (prepared from the standardized extract of ginkgo biloba leaves) produced better results compared to the conventional standardized extract from plant (GBE, 24% ginkgo flavones glycoside and 6% terpene lactones).

In a bioavailability study conducted with healthy human volunteers the levels of GBE constituents (flavonoid and terpenes) from the phytosomal form peaked after 3 hours and persisted longer for at least 5 hours after oral administration. It was found that the phytosomal GBE produced 2-4 times greater plasma concentration of terpenes than did the non phytosomal GBE. Their major indications are cerebral insufficiency and peripheral vascular disorder, and it also can ameliorate reduced cerebral circulation. Its improved oral bioavailability and good tolerability makes it the ideal ginkgo product even for long term treatment. In studies with ginkgo phytosomes in patients with peripheral vascular disease (e.g., Raynaud’s disease and intermittent circulation) it was shown to produce a 30-60% greater improvement compared to regular standardized GBE 90.

Green tea extract generally contains a totally standardized polyphenolic fraction (not less than 66.5%, containing epigallocatechin and its derivatives) obtained from green tea leaves (Thea sinensis) and mainly characterized by the presence of epigallocatechin 3-O-gallate, the key compound. These compounds are potent modulators of several biochemical processes linked to the breakdown of homeostasis. Green tea has got several long beneficial activities such as antioxidants anticarcinogenic, antimutagenic, antiatherosclerotic, hypochle-sterolemic, cardioprotective, and antibacterial and anticariogenic effects.

Despite such potential actions green tea polyphenols have very poor oral bioavailability from conventional extracts. The complexation of green tea polyphenols with phospholipids strongly improves their poor oral bioavailability. A study on absorption of phytosomal
preparations was performed in healthy human volunteers along with non complexed green tea extract following oral administration. Over the study period of 6 hours the plasma concentration of total flavonoid was more than doubled when coming from the phytosomal versus the non-phytosomal extract.

Antioxidant capacity was measured as TRAP (Total Radical-trapping Antioxidant Parameter). The peak antioxidant effect was a 20% enhancement and it showed that the phytosome formulation had about double the total antioxidant effect.

In another study, rabbits were fed with a high cholesterol diet for 6 weeks, to markedly elevate their blood cholesterol and induce atherosclerotic lesions in their feed for the first 6 weeks, than 4weeks of the high-cholesterol diet. These developed significantly less aortic plaque than did the control groups which received conventional standardized grape seed extract in similar regimen. In a randomized human trial, young healthy volunteers received grape seed phytosomes once daily for 5 days. The blood TRAP (Total Radical-trapping Antioxidant Parameter) was measured at several time intervals during 1st day, then also on 5th day. Already by 30 minutes after administration on 1st day, blood TRAP levels were significantly elevated over the control which received conventional standardized grape seed extract.

**PHARMACEUTICAL SCOPE OF HERBOSOMES:**

1. It enhances the absorption of lipid insoluble polar phytoconstituents through oral as well as topical route showing better bioavailability, hence significantly greater therapeutic benefit.
2. Appreciable drug entrapment.
3. As the absorption of active constituent(s) is improved, its dose requirement is also reduced.
4. Phosphatidylcholine used in preparation of herbosomes, besides acting as a carrier also acts as a hepatoprotective, hence giving the synergistic effect when hepatoprotective substances are employed.
5. Chemical bonds are formed between phosphatidylcholine molecule and phytoconstituent, so the herbosomes show better stability profile.
6. Application of phytoconstituents in form of herbosome improves their percutaneous absorption and act as functional cosmetics.
CONCLUSION

Herbosomes are novel formulations which offer improved bioavailability of hydrophilic flavonoids and other similar compounds through the skin or gastrointestinal tract. They have many distinctive advantages over other conventional formulations. As far as the potential of herbosome technology is concerned, it has a great future for use in formulation technology and applications of hydrophilic plant compounds.

Standardized plant extracts or mainly polar phytoconstituents like flavonoids, terpenoids, tannins, xanthones when complexed with phospholipids like phosphatidylcholine give rise to a new drug delivery technology called herbosome showing much better absorption profile following oral administration owing to improved lipid solubility which enables them to cross the biological membrane, resulting enhanced bioavailability i.e. more amount of active principle in the systemic circulation. This means more amount of active constituent becomes present at the site of action (liver, brain, heart, kidney etc) at similar or less dose as compared to the conventional plant extract. Hence, the therapeutic action becomes enhanced more detectable and prolonged. Several excellent phytoconstituents have been successfully delivered in this way exhibiting remarkable therapeutic efficacy in animal as well as in human models.

Recently Mukherjee & co associates have regarded herbosomes as a value added drug delivery system. Thorough study of literature reveals that several plant extracts (crude, partially purified or fractionated) are reported to possess different significant pharmacological or health promoting properties. These extracts can be standardized accordingly and may be formulated as Herbosomes for systematic investigation for any improved potential to be used rationally. In this way after screening and selection of potential extracts or constituents from plants, herbosomes can be developed for different therapeutic purposes like cardiovascular, anti-inflammatory, immunomodulator, anticancer, antidiabetic etc or for prophylactic and health purposes as nutraceuticals,inducecourse.

REFERENCES


