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Review on- Herbosomes, A new arena for drug delivery

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Abstract

The effectiveness of any herbal medication is dependent on the delivery of effective level of the therapeutically active compounds. Herbosomes are recently introduced the herbal formulations that have better bioavailability and actions than the conventional botanical extracts. Herbosomes technology is one of such systems that incorporate phospholipids into standardized active ingredients of herbal extracts, thus effectively enhancing the bioavailability of water soluble bioactive constituents of phytomedicines such as flavonoids, phenolics and hydrophilic compounds. 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. Recent advances in natural products chemistry and phytomedicine research has been aimed at novel lipid based drug delivery systems. 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, Phytomedicines, Phospholipids, Liposomes, Herbosomes complex

1. Introduction

The term "Herbo" means plant while "some" means cell like. 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 [1]. Phytomedicines have been used for the treatment of various ailments since ancient times. Various plants materials have been observed to exhibit a variety of biological activity such as antilipidemic activity, hepatoprotective activity, immunomodulatory activity etc. 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. Currently, as many as one-third to approximately one-half of all the drugs available are derived from plants or other natural sources [2].

The drug formulations of traditional systems of medicine like the African, Chinese and Indian systems usually contain crude extracts of different herbs which incorporate in the undesirable and many times, toxic principles along with the active principles. With the developments in the field of phyto and analytical chemistry, specific ingredients or a group of similar ingredients from plants are being extracted, isolated and tested for their different therapeutic applications [3]. Nevertheless, isolation and purification of individual components from whole herbal extracts often lead to partial or total loss of therapeutic activity. Although having excellent bioactivity *in vitro*, plant extracts often exhibit poor effectiveness *in vivo* or in animal models. The basic reasons for the low bioavailability of herbal extracts are that the bioactive components of these herbs possess multi- ring molecular structures which cannot be absorbed into the blood by simple passive diffusion and the bioactive phytoconstituents are mostly water soluble, hence, their poor lipid solubility limits their ability to pass across lipid biomembranes. Moreover, when it is taken orally bioactive phytoconstituents are destroyed by or lost to the gastric environment or they may be rendered less effective by interaction with other drugs or nutraceuticals [4].

1.1 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 phospholipid like phosphatidylcholine with the standardized extract or polyphenolic constituents like simple flavonoids in aprotic solvent [8]. Phosphatidylcholine is a bifunctional compound and 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.

1.2 Method of Herbosome Preparation

Herbosomes novel complexes which are prepared by reacting from 3-2 moles but preferably with one mole of natural or synthetic phospholipids like phosphatidylcholine, phosphatidylethanolamine or phosphatidylserine with one mole of component like flavolignans, either alone or in the natural mixture in aprotic solvent such as dioxane or acetone. The herbosome complex can be then isolated by precipitation with non-solvent such as aliphatic hydrocarbons or lyophilisation or by spray drying. In the complex formation of herbosomes the ratio between these two moieties is in the range from 0.5-2.0 moles. The most preferable ratio of phospholipids to flavonoids is 1:1.

1.3 Pharmaceutical Approach of Herbosomal Technology

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 liposomes 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 biomembranes quite easily, and the active components of the herbal extracts are well protected from destruction by digestive secretions and gut bacteria. Therefore, with the 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.

1.4 Properties of Herbosomes

1.4.1 Physical Properties-

1. Herbosome has lipophilic substances with a clear melting point.
2. Average size of herbosome range is 50 nm to a few hundred μm .
3. They are easily soluble in non-polar solvents, insoluble in water and moderately soluble in fats.
4. Liposomal like structures of miscellar shape are formed when herbosome are treated with water [5].

1.4.2 Chemical properties

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 [5, 6, 7].

1.5 Cell membrane with hydrophilic and lipophilic phase

A number of drug delivery system is based entirely on phosphatidylcholine such as liposome's, ethosomes, phytosomes, transferosomes, and nanocochelates. Some commonly used synthetic phospholipids are dioleoyl-phosphatidyl-choline (DOPC), dioleoyl-phosphatidyl-ethanolamine (DOPE), distearoyl-phosphatidyl-choline (DSPC), distearoyl-phosphatidyl-ethanolamine (DSPE). 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.

1.5.1 Advantages

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. The vesicular system is passive, non-invasive and is available for immediate commercialization.
4. Their composition is safe and the components are approved for pharmaceutical and cosmetic use.
5. High market attractiveness for products with proprietary technology.

1.6 Merits of Herbosomes

1. Herbosomes show better stability as chemical bond is formed between phospholipid molecule and phytoconstituent (s).
2. Dose of phytoconstituents is reduced due to more bioavailability of phytoconstituents in the complex form.
3. Duration of action is increased.
4. Herbosomes are simple to manufacture.
5. Phytoconstituents complex with phospholipids are more stable in gastric secretion and resist the action of gut bacteria.
6. Enhanced permeability of phytoconstituents across the biological membranes.

- Absorption of lipid insoluble polar phytoconstituents through different routes shows better absorption, hence shows significantly higher therapeutic effects
- Phosphatidylcholine used in the formation of herbosomes, besides acting as a carrier also possess several therapeutic properties and gives the synergistic effect.
- Drug entrapment is not a problem with herbosome as the complex is biodegradable^[8].

1.7 Demerits of herbosomes

- In herbosomes, phytoconstituents are rapidly eliminated.
- It is a short half-life.
- Hydrolysis, fusion, leakage and oxidation is undergone by the phospholipids.
- It has a high cost of production and sometimes occurrence of allergic reactions to the herbosomal constituents may be observed.
- Because of their larger size problems can occur while trying to target to the various tissues.

1.8 Characterization and evaluation of herbosomes

The physical size, membrane permeability, percentage of entrapped solutes, percentage drug released and chemical composition as well as the quantity and purity of the starting material. Herbosomes influence both physical and biological system.

2. Microscopic and Other Technique

- Visualization:** Visualization of herbosomes can be achieved using Transmission Electron Microscopy (TEM) and by Scanning Electron Microscopy (SEM) electron microscopic techniques^[9].
- 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)^[10].
- Entrapment efficiency:** The entrapment efficiency of a drug in herbosomes can be measured by the ultracentrifugation technique.
- Transition temperature:** The transition temperature of the vesicular lipid systems can be determined by differential scanning calorimeter^[11].
- Surface Tension Activity Measurement:** The surface tension activity of the drug in aqueous solution can be measured by the ring method in a Du Nouy ring tensiometer^[12].

6. Vesicle stability: The stability of vesicles can be determined 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^[13].

7. Drug content: The amount of drug can be quantified by a modified high performance liquid chromatographic (HPLC) method or by a suitable spectroscopic method^[14].

H-NMR

The NMR spectra of (+)-catechin and its stoichiometric complex with distearoylphosphatidylcholine in polar solvents, there is a marked change of the ¹H-NMR signal originating from the atoms involved in the formation of the complex, without any summation of the signal peculiar to the individual molecules. The signals from the protons belonging to the flavonoid are to be broadened that the proton cannot be relieved. In the phospholipids, there is broadening of all the signals while the singlet corresponding to the N-(CH₃)₃ of choline undergo an uplift shift. Heating the sample to 60°C results in the appearance of some new broad bands, which correspond mainly to the resonance of the flavonoid moiety.

C¹³NMR

In the ¹³C-NMR spectrum of (+)-catechin and its stoichiometric complex with distearoylphosphatidylcholine, particularly when recorded in C₆D₆ at room temperature, all the flavonoid carbons are clearly invisible. The signals corresponding to the glycerol and choline portion of the lipid (between 60-80ppm) are broadened and some are shifted, while most of the resonance of the fatty acid chain retains 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 phytosomal 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.

2.1 Commercially Marketed Formulation

S. No.	Trade name	Phytoconstituents complex	Daily dose	Indications
1	Silybin phytosome	Silybin from <i>Silibium marianum</i>	120 mg	Hepatoprotective, Antioxidant
2	Silyphos milk thistle	Silybin from <i>Silibium marianum</i>	150 mg	Antioxidant, Hepatoprotective
3	Grape seed (Leucoselect) phytosome	Procyanidins from <i>vitis vinifera</i>	50-300 mg	Antioxidant, Anticancer
4	Ginseng phytosome	Ginsenosides from <i>panax ginseng</i>	150 mg	Immunomodulator
5	Hawthorn phytosome	Flavonoids from <i>crataegus species</i>	100 mg	Antihypertensive, Cardioprotective
6	Sericoside phytosome	Sericoside from <i>Terminalia sericea</i>	-	Skin improver, Anti-Wrinkles
7	Ginkgo select phytosome	Flavonoids from <i>Ginkobiloba</i>	120 mg	Anti-aging, Protects Brain & Vascular lining
8	Olea select phytosome	Polyphenols from <i>Oleauropea</i>	120 mg	Anti-hyperlipidemic, Anti-inflammatory
9	Green select phytosome	Epigallocatechin from <i>Thea sinensis</i>	50-300mg	Anti-cancer, Antioxidant
10	Echinacea phytosome	Echinacosides from <i>Echinacea</i>	-	Immunomodulatory,

		angustifolia		Nutraceuticals.
11	Bilberry(Mertoselet) phytosome	Anthocyanosides from Vaccinium myritillus	-	Antioxidant, Improvement of Capillary Tone
12	Palmetto (sabalselect) phytosome	Fattyacids, alcohols & sterols from Serenoarepens	-	Anti-oxidant, Benign Prostatic hyperplasia
14	Centellaphytosome	Trepans' from Centella asitica	-	Brain tonic, Vein and Skin Disorder

2.2 Application of Herbosome

- Herbosome are used in the treatment of liver diseases including alcoholic hepatic steatosis, drug induced liver damage and hepatitis.
- Herbosomes are used in anti-inflammatory activity as well as in pharmaceutical and cosmetic composition.
- Herbosomes are used to treat acute and chronic liver diseases of toxic metabolic or infective origin or of degenerative nature.
- Herbosomes are used as brain tonic, immunomodulator, skin improver, antiwrinkle, anti-aging etc.
- They are used as anticancer and antioxidant, eg- grape seed.
- They are used in hyperlipidemia, vein and skin disorder.
- Herbosomes are used as cancer chemo preventive agent and used to treat benign prostate hyperplasia.
- They are also used to treat hypertension.

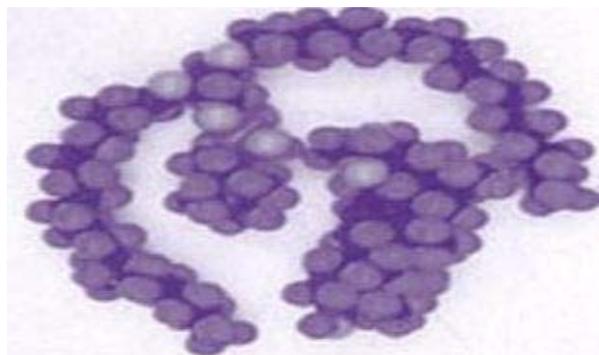


Fig 1: Arrangement of the herbosomal molecular complex. A flavonoid molecule (lower right) is enveloped by a phospholipid molecule

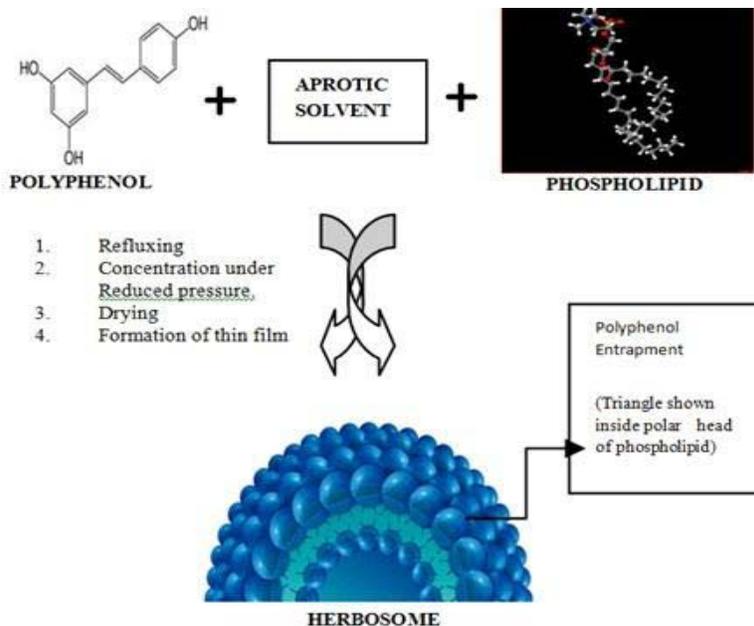


Fig 2: General Diagrammatic Representation of Herbosome Preparation Characterization and Evaluation of Herbosomes

2.3 Benefits of herbal formulations

- Potential enhancement of bioavailability.
- Herbosome process produces a little cell whereby the valuable components of the herbal extracts are protected from destruction by digestive secretions and gut bacteria.
- Pharmacologically Assured delivery to the different biological tissues
- Less dose requirement is due to absorption of chief constituent.
- Drug loading efficiency is so high and more over predetermined because drug itself in conjugation with lipids is forming vesicles.
- Herbosomes shows better stability profile because chemical bonds are formed between phosphatidylcholine molecules and phytoconstituents.
- Phosphatidylcholine used in the herbosome process which acting as a carrier and also nourishes the skin, because it is essential part of cell membrane.
- Herbosome is also superior to liposomes in skin care products.
- Significantly gives greater clinical benefit than liposomes.

3. Conclusion

Herbosomes are novel formulations which offer improved bioavailability of hydrophilic flavonoids and other similar compounds through the skin or gastrointestinal tract. Herbosomes results from the reaction of stoichiometric amount of phospholipid with standardized herbal extract or polyphenolic constituents like (flavonoids, terpenoids, tannins, xanthenes etc.) in nonpolar solvents. Herbosomes shows much better absorption profile following oral administration owing to improve lipid solubility which enables them to cross the biological membrane resulting enhanced bioavailability. Herbosomes improve the *in vivo* bioavailability of herbal drugs, which in spite of positive *in vitro* results fail to deliver a similar response *in vivo*. Use of herbal extracts in the form of dentifrice, medicated gel, local drug delivery systems proved to be efficient in preventing and treating periodontal disease.

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