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Herbosome: A New Era of Lipid Based Drug Delivery System

Abhishek Ghosh[1], Piyali Khamkat[2]

[1]Sanaka Education Trusts Group of Institutions, Malandighi, Durgapur, West Bengal -713212, India

[2]Department of Pharmaceutical Technology, Brainware University, 398, Ramkrishnapur Road, Barasat, Kolkata -125, India

*Corresponding author address Email: ghosh.abhishek79@gmail.com

ABSTRACT

Nowadays all the approaches and research in natural products and phytomedicine are targeting to develop lipid based novel drug delivery systems. Herbosome is a lipid based drug delivery system of this type having phospholipids into standardized active ingredients of herbal extracts within it that helps to increase the bioavailability of water-soluble bio-constituents of phytomedicines like Phenolic compounds flavonoids, hydrophilic compounds. These phytoconstituents have ability to exhibit different pharmacological activities with several biological benefits. These phytoconstituents have poor absorption that decreases their bioavailability and this is the main reason for these phytoconstituents do not reach the particular site of action because they degrade before reaching the site. Their multi ring and lipidic in nature of the intestinal wall do not allow them to pass through the small intestine. Herbosome technology can overcome all these difficulties related with the phytoconstituents and are able to show their effectiveness efficiently. Herbosome can be prepared by several methods like rotary evaporation technique, anti-solvent precipitation technique, Solvent evaporation technique etc. This review is based on the recent advances and the concepts, applications and future perspective of herbosome use.

Key words: Herbosomes, Phytomedicine, Lipid based drug delivery system, Phytoconstituent, absorption.

INTRODUCTION

The term “Herbosome” are made up of two words where “Herbo” stands for plant and “some” means cell like. Plant contains biologically active constituents and most of them are polar and water soluble molecules. Most of these water soluble phytoconstituents (flavonoids, tannins, glycosides) are large in molecular size and have poor lipid solubility so that they cannot be absorbed by passive diffusion that finally results in their poor absorption. These

phytoconstituents also have poor bioavailability as they are restricted while crossing lipid rich biological membrane [1]. Different plants and their phytoconstituents have different biological activity such as hepatoprotective activity, antilipidemic activity, immunomodulatory activity etc. Phytoconstituents from plant are mixed with chemical and the mixture is used as phytomedicine to treat diseases since ancient times. Nowadays one third to one half phytomedicines shows their effectiveness to treat a particular disease but the other phytomedicines are unable to show their effectiveness because they are poorly absorbed whenever they are taken by mouth [2]. Africa, China and India have their traditional system of drug formulations of various herbs from which crude drugs are extracted that may show toxic and undesirable effect with the active principle. In case of phyto and analytical chemistry, a single unique or group of same ingredients are extracted and they are examined to manifest their unique therapeutic applications [3]. Partial or total loss of therapeutic activity of the components may sometime takes place by the isolation and purification of single component from the entire herbal extracts and that may finally shows excellent biological effect in in-vitro but not in in-vivo animal models. Herbal extracts have low bioavailability because they have multi- ring structure which stops them to be absorbed by simple passive diffusion into the blood and also as they have more water solubility than lipid solubility, they are unable to cross lipid biomembranes. Moreover, oral intake demolishes the phytoconstituent within the gastric environment which finally decreases their effect [4]. Herbosome is a special approach which shows effective absorption as well as positive in vivo biological effect in the animal models and this herbosome is also known as phytosome.

HISTORY OF HERBOSOME

History proved that different types of herbs are used by human being to treat diseases. From the oldest era people belong to every community had a tradition of use of healthful plant mainly in the Asian region. Use of herbal plants can be found in ancient Chinese and Egyptian Papyrus writings. Researchers found that similar plants around the globe have similar and different components and that is helpful in treating similar as well as different diseases. Therapeutic components of healthful plants can eliminate all bad effects of conventional medical care medicine thus interest in natural medicines are growing day by day in modern era and it looks that these herbal delivery system can improve human health very efficiently. As per world health organization estimates, 80% of concerning 4000 million inhabitants on this planet trust plant merchandise and worldwide ancient drugs markets are rapidly growing annually. Our country exports natural herb medicine which worth 550 INR

crore value. Though in our country we have and numerous biological science resources still there is some lag in export performance considering the worldwide natural herb market value [5].

PRINCIPLE OF PHYTOSOME TECHNOLOGY

The extracts contain phytochemical constituents (flavonoids and terpenoides) which are responsible for the direct complexation with Phosphatidylcholine. Reaction with a certain quantity of the lipid with the standardized extract or polyphenolic constituents using a non-polar solvent results in phytosome. Lipotropic phosphatidyl moiety and the hydrophilic B vitamin moiety help to generate bi-functional Phosphatidylcholine. Phytocomponent is bound to the B vitamin head of phosphatidylcholine molecule binds and the phosphatidyl which is soluble in macromolecule also contains the body and tail that envelops the B vitamin material. Hence, the Phytoconstituents results in a macromolecule like molecular complication with lipid conjointly can be referred as phyto-phospholipid complicated [6,7].

HERBOSOME FORMULATIONS

Herbosome can be formulated in various dosage forms used for both orally and topically. These formulations are convertible also. Various products can be designed in order to obtain the best performances in formulation manageability and to enhance bioavailability various products can be designed in many ways.

Soft gelatin capsules

One of the perfect solutions to formulate herbosome complex is to formulate Soft gelatin capsules. Soft gelatin capsules can be filled with suspension made by the dispersion of phytoconstituents in the oily vehicles. Vegetable or semi-synthetic oils can be used to this purpose. Granulometry of 100% <200 μm is recommended by Indena to be a best perform capsule production. Indena experienced that, behaviour of all the phytosome complexes are not the same when dispersed in oily vehicles a preliminary feasibility trial should run when complexes are dispersed in oily vehicles to select the most suitable vehicle [8].

Hard gelatin capsules

The Phytosome complex can also be formulated in hard gelatin capsules. Sometime apparently Low density of the phytosome complex may exceed the maximum amount of powder that can be filled into a capsule (usually not more than 300 mg for a size 0 capsule), then a direct volumetric filling process (without precompression) can be applied to eliminate

this problem. Excess amount of powder can also be filled in the capusle by piston tamp capsule filling process but according to Indena related parameters should be monitored during precompression as well as the development process because it may affect disintegration time. A preliminary dry granulation can be done to obtain best manufacturing results [9].

Tablets

Dry granulation shows best result in the manufacturing process of tablets with higher unitary doses in terms to obtain best biopharmaceutical properties with suitable technology. For low unitary dose, direct compression process can be applied to overcome limited flowability, potential stickiness and low apparent density of the phytosome complex and phytosome complex should be diluted with 60-70% of excipients whenever the direct compression is applied to achieve best biopharamaceutical properties for low densed phytosome complexes. On the other hand, wet granulation should be avoided due to the negative effect of water and heat (granulation/drying) on the stability of the phospholipid.

HERBOSOME AND LIPOSOME: A COMPARISON

Liposomes can be developed by mixing suitable water-soluble drug constituent in phosphatidylcholine in a particular ratio under suitable conditions. In case of liposome there is no chemical bond formed, the phosphatidylcholine envelops the water-soluble phytoconstituents within it. And thus hundreds of phosphatidylcholine molecules are present surrounding the drug molecule. In herbosomes the plant constituents and phosphatidylcholine are mixed in a particular ratio 1:1 or 1:2 and the phytoconstituents form chemical bonds with phosphatidylcholine whereas liposomes do not form chemical between the phosphatidylcholine molecule and the phytoconstituents as previously discussed. Phytosomes have greater bioavailability and rapid absorption property than the liposomes because of the lesser amount of the phospholipid content [10].

PROPERTIES OF HERBOSOME

Physical Properties-

1. Herbosome is made of lipophilic substances having clear melting point.
2. Herbosome's size ranges from 50 nm to a few hundred μm.
3. Herbosome has more solubility in non-polar solvents, insoluble in water and moderate solubility in fats.
4. Herbosome is treated with water to form miscellar shape like liposome [11].

Chemical properties

Physicochemical and spectroscopic data analysis shown that hydrogen bond is formed between the polar heads of phospholipids (i.e. phosphate and ammonium groups) and the substrate's polar functional groups which finally results in phospholipids-substrate interaction In herbosomes the active principle is the formation of chemical bond between the phosphatidylcholine and the phytoconstituent, becoming an integral part of the membrane [11,12,13].

MERITS OF HERBOSOME

1. Chemical bond between phospholipid molecule and phytoconstituent help herbosome to exhibit better stability(s).

2 More bioavailability of phytoconstituents reduces Dose of phytoconstituents.

3. Enhancement in Duration of action.

4. Ease in manufacturing herbosome.

5. Phytoconstituents complex with phospholipids are more stable in gastric secretion and resist the action of gut bacteria.

6. Permeability of phytoconstituents is also increases across the biological membranes.

7. Lipid insoluble polar phytoconstituents through various routes also shows better absorption.

8. Phosphatidylcholine plays its role as carrier and also it possesses several therapeutic properties to give synergistic effect while it is used in the formation of herbosomes.

9 Herbosome complexes are biodegradable thus drug entrapment is not a problem [14].

DEMERITS OF HERBOSOME

1. Rapid elimination of phytoconstituents.

2. It has a short half-life.

3. Phospholipids used for preparation may face Hydrolysis, fusion, leakage and oxidation.

4. Production cost is high and

5. Herbosomal constituents may sometimes allergic to patient.

5. Targetting various tissues may face difficulty Because of their larger size.

METHODS OF PREPARATION

1. Anti-solvent precipitation technique [15,16]

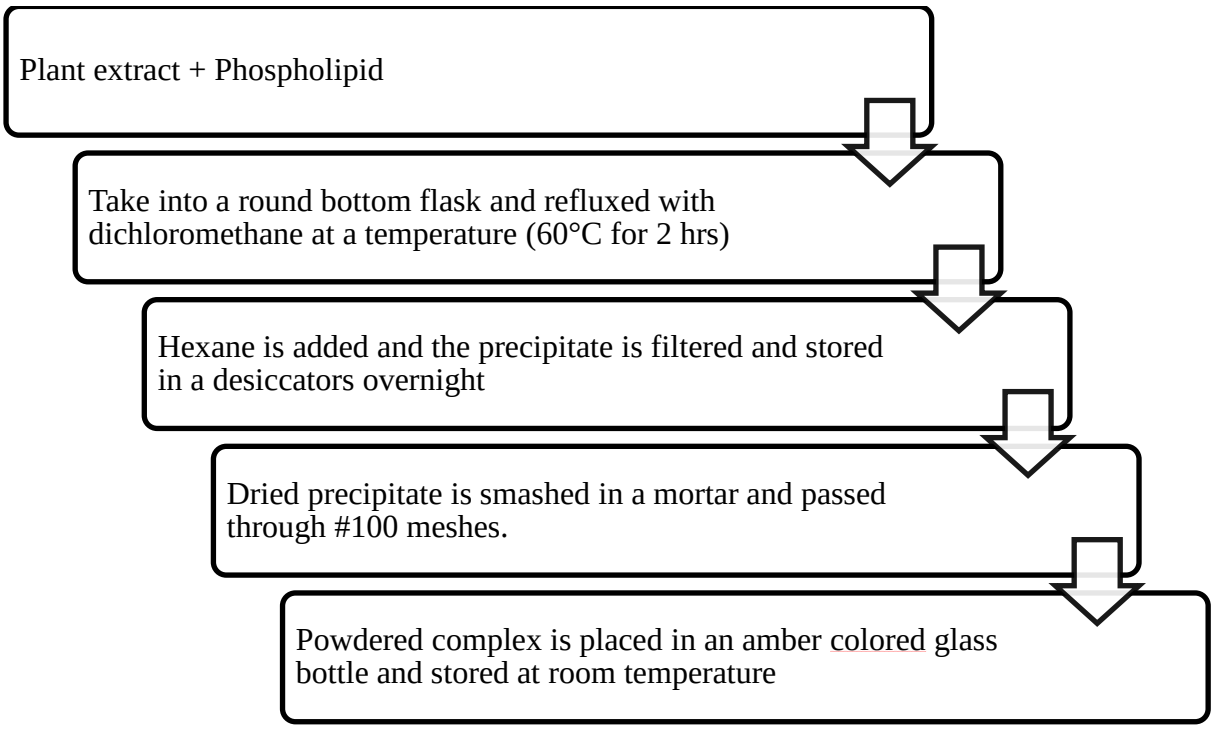

Fig. 1: Preparation of herbosomes by anti solvent precipitation technique

2. Solvent evaporation technique [15,16]

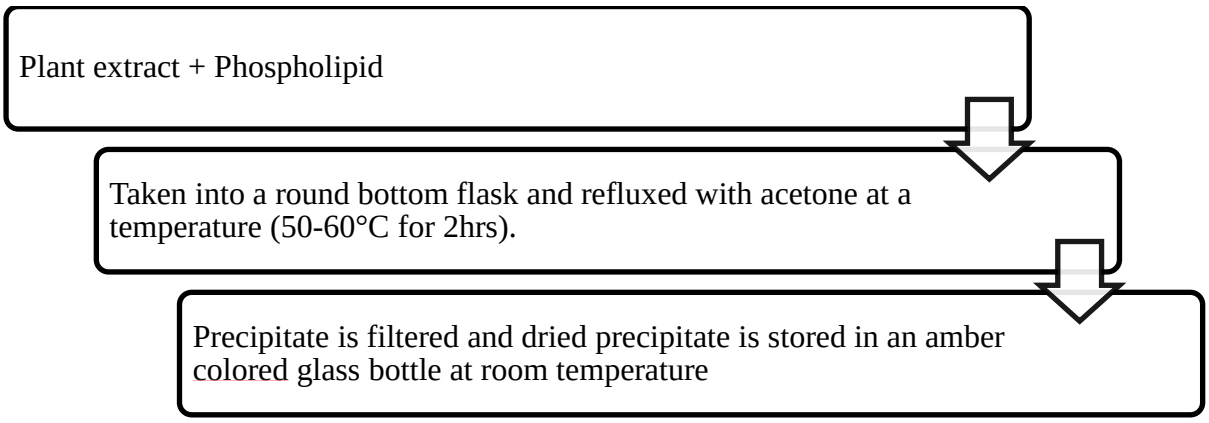

Fig. 2: Preparation of herbosomes by solvent evaporation technique

3. Rotary evaporation technique [15,16]

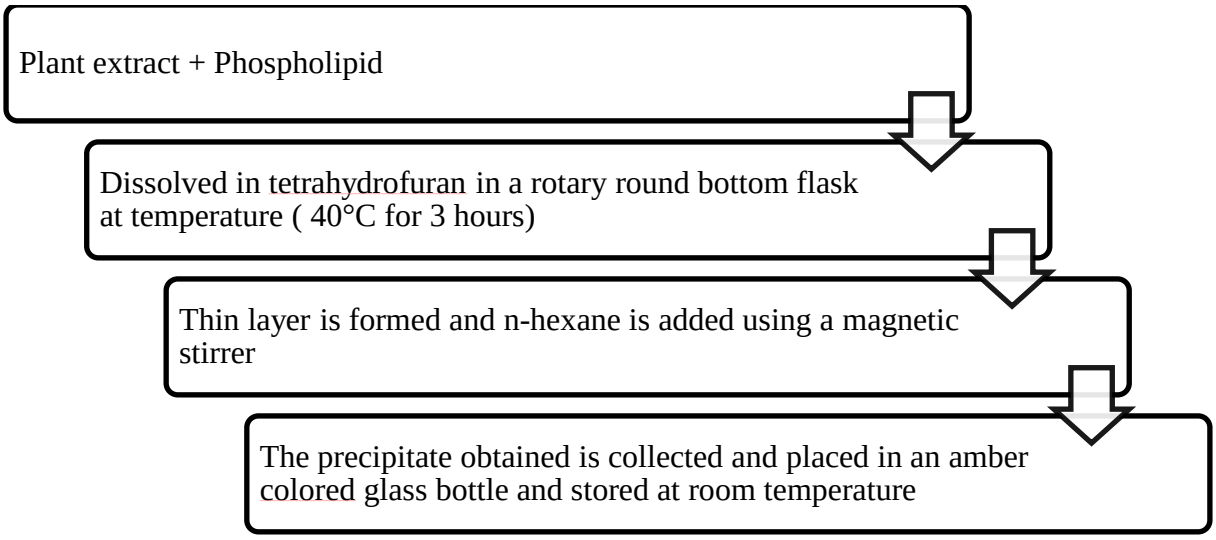

Fig. 3: Preparation of herbosomes by rotary evaporation technique

4. Ether-injection technique [15,16]

In this process, if concentration is less, amphiphiles introduce a monomer state. If concentration is enhanced, different structures may be formed such as hexagon, round, disc, cylindrical, and cubic type

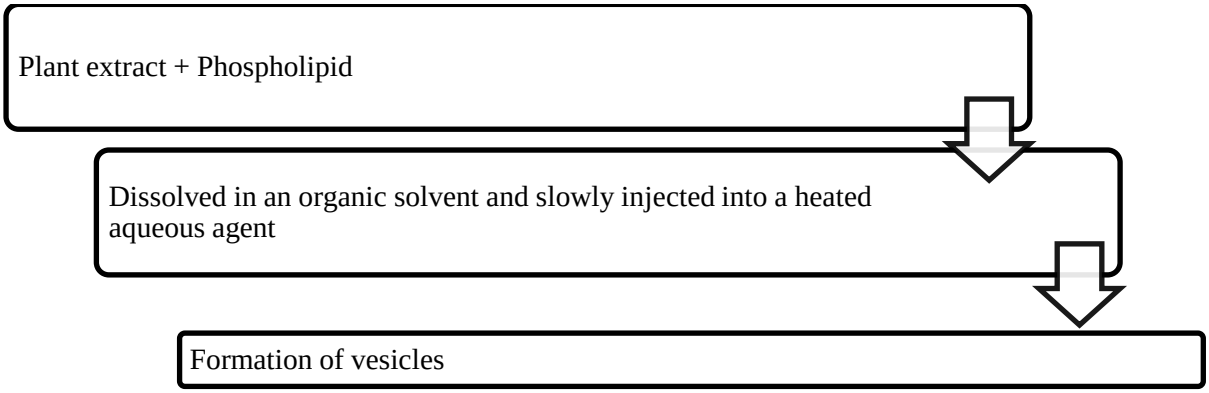

Fig. 4: Preparation of herbosomes by anti ether injection technique

EVALUATION OF HERBOSOME

Structural detection

Internal structure and composition of herbosomes like stress or even magnetic domains, morphology, and crystallization can be detected by transmission electron microscopy (TEM). For better morphological detection, scanning electron microscopy (SEM) can be used [17].

Transition temperature

Differential scanning calorimetry is utilized for detecting transition temperature of herbosomes [18].

Vesicle size and zeta potential

Photon correlation spectroscopy (PCS) and dynamic light scattering (DLS) can be used to detect the particle size and zeta potential of herbosomes. Stability of vesicles can be observed after detecting particle size and structure for longer period [19].

Surface tension activity measurement

Du Nouy ring tensiometer is needed for evaluating surface tension activity of the drug in aqueous solution by ring method [20].

Entrapment efficiency

The drug entrapment capacity or percentage of drug entrapment can be determined by the ultracentrifugation technique [21].

Drug content

High performance liquid chromatographic method or spectroscopic method is used for determining the amount of drug present in herbosomes. Drug content can be detected by the equation [21]:

$$\text{Drug Content (\%)} = \frac{\text{Actual drug content in Phytosomes} \times 100}{\text{Theoretical yield}}$$

Spectroscopic evaluation

To identify the interaction between phytoconstituents and the phospholipid spectroscopic method is used [22].

Nuclear magnetic resonance

If there is any interaction between active phytoconstituents and the phosphatidylcholine molecule can be identified by peak of ^{1}H-NMR and ^{13}C NMR.

Fourier –transform infrared spectroscopy (FTIR)

If there is any complex formation between active phytoconstituents and the phosphatidylcholine molecule can be determined by IR spectroscopy. In this spectroscopy comparison between the spectrums of the complex, the spectrum of the individual components and their mechanical mixtures are detected. It also helps to stabilize herbosome prone to microbial growth [23].

***In vitro* evaluations**

Depending on therapeutic activity *in vitro* evaluations are done for active phytoconstituents of herbosomes.

Preparation of semi permeable membrane

The egg yolk was separated carefully by means of hole on the surface of the egg. After that the egg shell was immersed in HCl for 2 hours with constant stirring followed by the complete separation of egg membrane. The membrane was washed with phosphate buffer pH 7.4 and further used for the experimental work.

Drug release through semi permeable membrane

By using franz diffusion cell *invitro* drug release studies are determined. In this process, herbosomes are poured uniformly on the surface of semi permeable membrane. This is attached with one end of tube so that herbosome must be present inside the tube. Then diffusion cell must be placed into diffusion medium like phosphate buffer having particular pH. This evaluation process in done with the help of water bath and temperature must be maintained at 37±2ºC. The membrane is a barrier between herbosome and phosphate buffer solution. A fixed amount of sample is withdrawn with specific time interval from receptor fluid and replaced by buffer at the same time. The amount of drug release is detected by spectrophotometrically at maximum wavelength of the drug to be used [24].

Release kinetics of *in vitro* drug release study

Drug release kinetics can be detected by mathematical equations of different kinetics model. Zero order (cumulative percentage of drug release versus time), first-order (log cumulative percentage of drug remaining versus time), Korsmeyer- Peppas (log cumulative percentage of drug released versus log time) and Higuchi (cumulative percentage of release versus square root of time) equation models are important for the mechanism of drug release property to be

understood. The equation with the high regression coefficient (R2) for formulation will be the best fit of release data [9].

APPLICATION OF HERBOSOME

Multiple diseases like liver disease and heart disease can be treated by Herbosomes. Herbosome also can be used as a lipolytic, anti-inflammatory, vasokinetic, cicatrizing, trophodermic, anti-oedema, anti-wrinkles, UV protectant, neutraceutical immunomodulator, antioxidant of skin and liver, cardioprotective.

From the Studies better results were found for gingko phytosomes (prepared from the standardized extract of Ginkgo Biloba leaves) than the conventional standardized extract of the plant (GBE, 24% ginkgo flavones glycoside and 6% terpenes lactones). A study of bioavailability in healthy human volunteers, proved that phytosomal GBE has 2-4 times greater plasma concentration than the non phytosomal one and after 3 hours when it is orally administered this GBE constituents (flavonoids and terpenes) stayed for at least 5 hours. Cerebral insufficiency and peripheral vascular disorders are its most vital manisfastation and it can also improve reduced cerebral circulations. It can be used as a ideal gingko product even for long term treatment as it is having good oral bioavailability and good tolerability. Studies in protection of rat isolated hearts against ischemia proved better efficacy of ginkgo phytosomes over the conventional standardized extract [24].

Flavonoid present within the fruit of milk thistle plant has a hepatoprotective effect. Silymarin can be used for treatment of many kinds of liver diseases like alcoholic hepatic steatosis,cirrhosis, inflammation of bile duct, fatty liver and hepatitis. Accumulation of glutathione by the help of silybin acts as a shield in Parenchyma Cells of liver. This helps to repair and replace the cell membrane of parenchyma. These constituents protects liver cell from destruction [25].

Nowadays Phytosomal studies are givng their focus on Silybummarianum (milk thistles) that contains premier liver protectant flavonoids. In 2006 silymarinphytosome was prepared by Yanyu and concentrated on its pharmacokinetics in rats. He found that after oral administration.Development of lipophilic properties of silybin-phospholipid complex in the rat increases bioavailability of silybin which leads to get better biological effect of silybin significantly [26].

Grape seed phytosome made up of Oligomeric polyphenols of different molecular size, complexed with phospholipids. Improvement in total antioxidant capacity and stimulation of physiological antioxidant defences of plasma, safeguard against ischemia/ refusion induced damages in the heart are main properties of procyanidin flavonoids of grape seed, and protection against atherosclerosis improve its cardiovascular protection property [27].

Phytoconstituents of Grape seeds are also used to treat cancer with the help of herbosomal preparations. Rather than that herbosomes can be used as cancer chemo preventive agent and used to treat benign prostate hyperplasia.

Green tea has several properties such as antioxidant, anticarcinogenic, cardioprotective, antimutagenic, antibacterial and antiatherosclerotic. The Green tea polyphenol and herbosomal complexion increases the oral bioavailability of the normal green tea polyphenols [28].

Table 1: Trade Names of Different Herbosomal Formulations of Different Phytoconstituents [29]

Trade name	Scientific name of Plant	Phytoconstituents	Daily dose	Therapeutic activity
Sericoside phytosome	*Terminalia sericea*	Sericoside	120mg	Skin improver, Anti-Wrinkles
Grape seed (Leucoselect) Phytosome	*Vitis vinifera*	Procyanidins	50-300 mg	Antioxidant, Anticancer
Green select phytosome	*Thea sinensis*	Epigallocatechin	50-300mg	Anticancer, Antioxidant
Silybin phytosome	*Silibium marianum*	Silybin	120 mg	Hepatoprotective, Antioxidant
Hawthorn phytosome	Crataegus species	Flavonoids	100 mg	Antihypertensive, Cardioprotective
Echinacea phytosome	Echinacea purpurea	Echinacoside	120 mg	Immunomodulatory
Silyphos milk thistle phytosome	*Silibium marianum*	Silybin	150 mg	Antioxidant, Hepatoprotective
Centellaphytosome	*Centella asitica*	Trepans	60-120 mg	Brain tonic, Vein and Skin Disorder
Ginseng phytosome	*Panax ginseng*	Ginsenosides	150 mg	Immunomodulator
Bilberry(Mertoselet) phytosome	*Vaccinium myritillus*	Anthocyanosides	200 mg	Antioxidant, Improvement of Capillary Tone

Ginko select phytosome	*Ginko biloba*	Flavonoids	120 mg	Anti-aging, Protects Brain & Vascular lining
Palmetto (sabalselect) phytosome	*Serenoa repens*	Fattyacids, alcohols & sterols	160 mg	Anti-oxidant, Benign Prostatic hyperplasia
Olea select phytosome	*Olea europea*	Polyphenols	120 mg	Anti–hyperlipidemic, Anti-inflammatory

CONCLUSION

Herbosome is a novel lipid based drug delivery system that increases bioavailability of natural water soluble phytoconstituents by offering better absorption and that is how they can travel very easily through skin and gastrointestinal tract. Absorption rate as well as penetration power can be enhanced by this system. Herbosomes also shows much better absorption even after oral administration as they have enhanced lipid solubility which allows them to cross the biological membrane easily. In vivo bioavailability of herbal drugs may be improved by herbosome. Periodontal disease can be treated and prevented by using herbal extracts in the form of dentifrice, medicated gel, local drug delivery systems etc. Moreover natural phytoconstituents can be incorporated within the herbosome to prepare different formulations that helps to treat few diseases efficiently. Research is also going on this particular area to make it better and more efficient in treatment of multiple diseases.

Conflict of Interest

None

Authors Contributions

Contribution of each author should be given in the manuscript immediate after acknowledgment/conclusion.

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