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Review article

Herbosomes: A current concept of herbal drug technology An overview

Ajay shukla*, Vikas Pandey, Rajesh Shukla, Punit Bhatnagar, Suchit Jain

Guru Ramdas Khalsa Institute of Science and Technology (Pharmacy) Jabalpur, Madhya Pradesh, India

Corresponding author: Ajay shukla, ✉ ashukla1007@gmail.com,

Guru Ramdas Khalsa Institute of Science and Technology (Pharmacy) Jabalpur, Madhya Pradesh, India

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ABSTRACT

Herbosome is a current concept in herbal drug technology that removes the limitations of the traditional drug delivery systems. Herbal medicines have been widely used all over the world since ancient times and by physicians and patients for their better therapeutic value as they have no or less side effects as compared with modern medicines. The Herbosome structures contain the active ingredients of the herb bounded to phospholipids. The molecular structure of phospholipid includes a water-soluble head and two fat-soluble tails. Because of this dual solubility, the phospholipid acts as an effective emulsifier. By combining the emulsifying action of the phospholipids with the standardized botanical extracts, the herbosome form provides dramatically enhanced bioavailability for lipid soluble drugs explained by faster and improved absorption in the intestinal tract. Herbosome technology has been effectively used to enhance the bioavailability of many popular herbal extracts and phytoconstituents including Ginkgo biloba, milk thistle, grape seed, green tea, hawthorn, ginseng etc. and can be developed for various therapeutic uses or dietary supplements. This method can enhance the rate and the extent of drug absorption across the lipoid bio-membrane, which has been found promising for effective and appropriate systematic delivery of drug.

Keywords: Herbosomes, Phosphatidylcholine, Polyphenol, Liposomes, Herbosome complex.

INTRODUCTION

Herbal medicines, complex chemical mixtures prepared from plants, was use for health maintenance in ancient times. But many phytomedicines are limited in their effectiveness because they are poorly absorbed when taken by mouth. The Phytosome (Herbosome) technology, developed by Indena S.P.A. of Italy, markedly enhances the bioavailability of select phytomedicines, by incorporating phospholipids into standardized extracts and thus significantly improving their absorption and utilization.They are cell membrane building blocks, making up the matrix into which fit a large variety of proteins that are enzymes, transport proteins, receptors, and other biological energy converters. In humans and other higher animals, the phospholipids are also employed as natural digestive aids and as carriers for both fat-miscible and water miscible nutrients [1].

The lipid phase substances employed to make phytoconstituents lipid compatible are phospholipids from soy mainly phosphatidylcholine is the principal molecular building block of the cell membranes, miscible both in water and in oil environments, and is well absorbed when taken orally. Chemical analysis indicates that herbosome is usually a phytoconstituents molecule linked with at least one phosphatidylcholine molecule. It is not merely a passive carrier for the bioactive phytoconstituents of the herbosomes but is itself a bioactive nutrient with documented clinical efficacy for liver disease, Including alcoholic hepatic steatosis, drug-induced liver damage, and hepatitis [2].

The intake of herbosome preparations is sufficient to provide reliable clinical benefit. The herbosome process, applied to many popular herbal extracts, including phytoconstituents, lends these molecules for direct binding to phosphatidylcholine quite well, this

means that the choline head binds to phytoconstituents while the fat soluble phosphatidyl portion comprising the body and tail then envelopes the choline bound material the result is a little microsphere or cell. The herbosome process has been applied to many popular herbal extracts including Ginkgo biloba, grape seed, hawthorn, milkthistle, green tea, and ginseng

Different strategies to improve bioavailability

Various strategies are being followed in the pharmaceutical sector to achieve this goal [3].

The first strategies the medicinal chemistry based: by the chemical derivatization of the chemical product, the aim is to obtain compounds which showing an improved bioavailability.

The second strategies based on the generate number of chemical analogues that require to be appropriately screened. An alternative strategy that is also being pursued is the combination of the active molecules with other compounds as adjuvant promoting the active molecule's absorption.

Third strategies involve in formulation and research of structures which make stabilizingnatural molecules and promoting their intestinal absorption. The formulate research comprises the formation of liposomes, micelles, nanoparticles, nanoemulsions, microsphere or other complexes. The herbosomes approach has the improved pharmacokinetic profile is obtained without resorting to pharmacological adjuvant or structural modification of the ingredients

HERBOSOME vs. LIPOSOME: (Similarities and Differences)

A liposome is prepared by mixing a water soluble substance with phosphatidylcholine. No chemical bond is formed; Hundreds or even thousands of phosphatidylcholine molecules surround the water-soluble compound. In contrast, herbosome is formed by mixing a water-soluble substance with phosphatidylcholine and here chemical bond is formed between individual plant components and phosphatidylcholine.

Figure 1: Phytosom and drug complex,

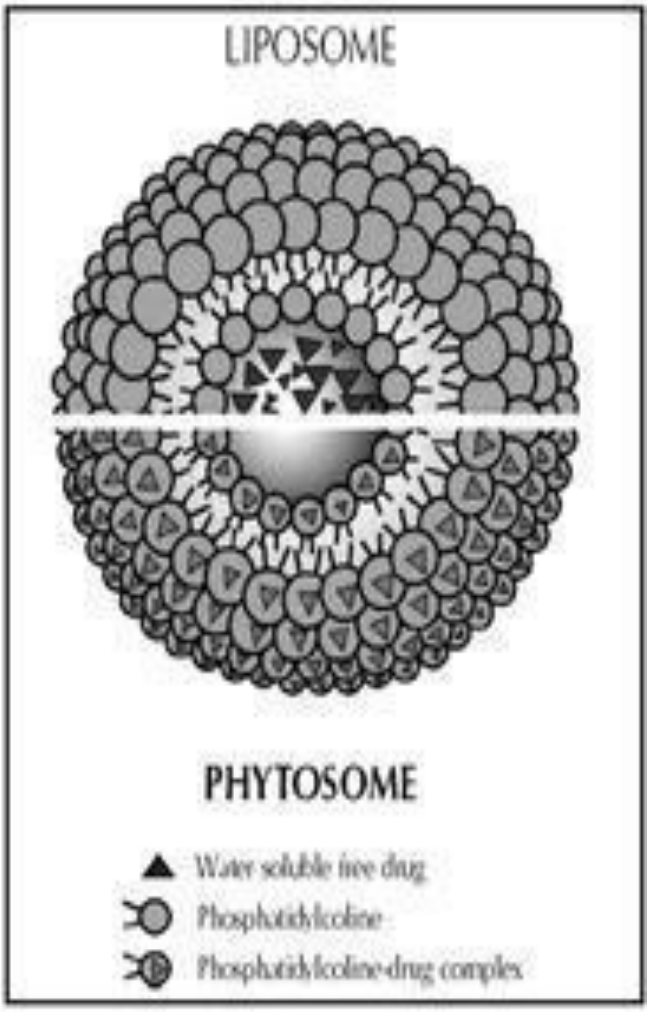


Figure 1.1: Process of phytosome comlex formation

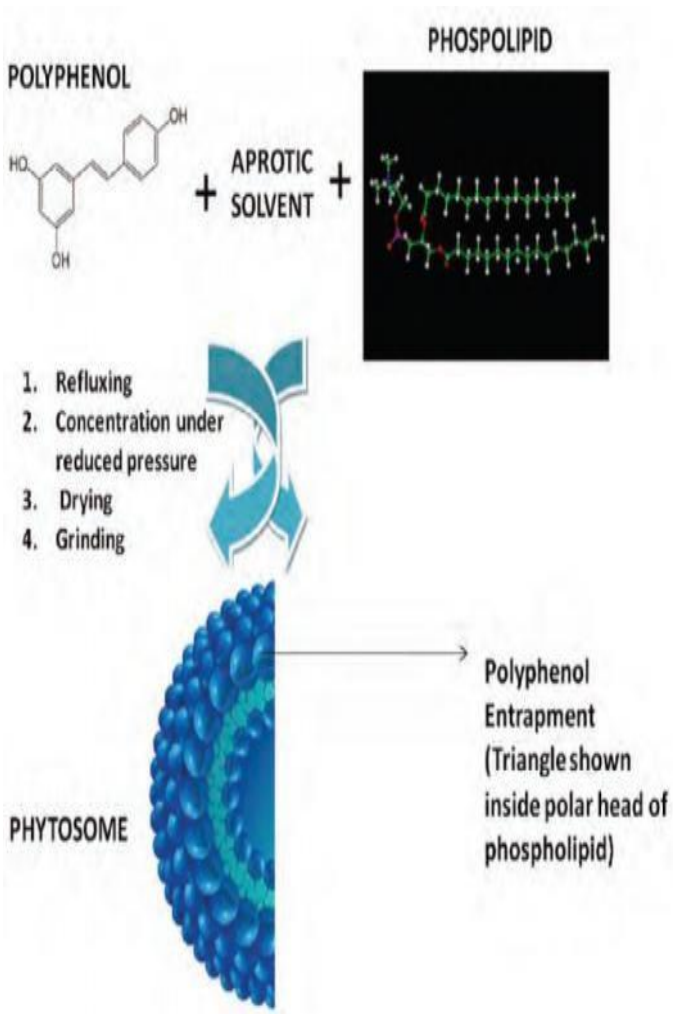


Table 1: difference between herbosome and liposomes

Herbosome	Liposomes
In phytosomes active chemical constituents molecules are anchored through chemical bonds to the polar head of the phospholipids	In liposomes, the active principle is dissolved in the medium of the cavity or in the layers of the membrane. No chemical bonds are formed.
In phytosomes, phosphatidylcholine and the individual plant compound form a 1:1 or 2:1 complex depending on the substance.	In liposoes,hundreds and thousands of phosphatidylcholine molecules surround the water soluble molecule.

Soichiometric 1:1 or 2:1 complexes form which depend on the extract or phytoconstituents and the phospholipid used. This difference results in increased absorption of active constituents from herbosome than from liposomes [4].

The principle of herbosome technology

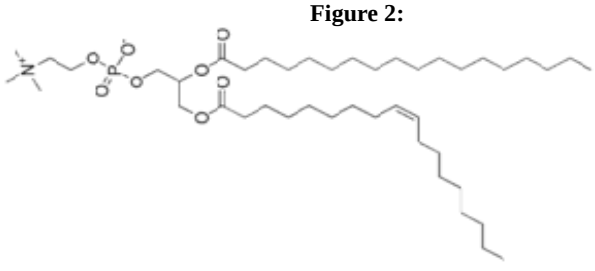
The flavonoid and terpenoid Phyto-chemical constituent's extracts provide them for the direct complex with phosphatidylcholine. Herbosome results from the reaction of a stoichometric amount of the phospholipid (phosphatidylcholine) to the standardized extract or polyphenolic constituents in a non-polar solvent [5].

The Phosphatidylcholine is a bi -functional compound and this (phosphatidyl) moiety being lipophilic and the choline moiety being hydrophilic in nature. In particular, the choline head of the phosphatidylcholine molecule binds to these compounds while the lipid soluble phosphatidyl portion comprising the body and tail which then envelopes the choline bound material. Hence, the Phytoconstituents build up a lipid compatible molecular complex with phospholipids, also called as phytophospholipid complex. By specific spectroscopic techniques [6].

Mode of phytophospholipid complex formation

The poor absorption of flavonoids or phytochemicals is likely due to two main factors. First, one 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 the standardized extract or polyphenolic constituents (like simple flavonoids) in anon polar 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 molecule binds to these compounds while the lipid soluble phosphatidyl portion comprising the body and tail which then envelopes the choline bound material. Hence, the phytoconstituents produce a lipid compatible molecular complex with phospholipids, also called as phytophospholipid complex. Molecules are anchored through chemical bonds to the polar choline head of the phospholipids, as can be demonstrated by specific spectroscopic techniques. Precise chemical analysis indicates the unit phytosomes is usually a flavonoids molecule linked with at least one phosphatidylcholine molecule. The result is a little microsphere or cell is produced.

Figure 2:



Benefits of herbal formulations

Potential enhancement of bioavailability.

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.

Pharmacologically Assured delivery to the different biological tissues.

No compromise of nutrient safety.

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.

No problem of drug entrapment.

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.

The structure of herbosome elicits peculiar properties and advantages in cosmetic application.

Significantly Enhanced ability of herbosome to cross cell membranes and enter cells.

Their low solubility in aqueous media allows the formation of stable emulsions or creams.

Preparation of herbosome

The herbosome are current herbal complex method which are prepared by reacting from 3-2 moles but preferably with one mole of a natural or synthetic phospholipid, such as phosphatidylcholine, phosphatidylethanolamine or phosphatidyiserine with one mole of component for example flavones, either alone or in the natural mixture in aproticsolvent such as- dioxane or acetone from which complex can be isolated by precipitation with non-solvent such as aliphatic hydrocarbons or lyophilization or by spray drying. In the complex formation of phytosomes the ratio between these two moieties is in the range from 0.5-2.0 moles. The most preferable ratio of phospholipid to flavonoids is 1:1. The molecular organization of the liposome (upper-segment) and The molecular organization structure of herbosome (lower segment) phospholipids are selected from the group consisting of soy lecithin, from bovine or swine brain or dermis, phosphatidylcholine, phosphatidylethanolamine, phosphatidyiserine in which acyl group may be same or different and mostly derived from palmitic, stearic, oleic and linoleic acid. Selection of flavonoids are done from Figure 3.

The group consisting of quercetin, kaempferol, quercretin-3, rhamnoglucoside, quercetin-3- rhamnoside,

hyperoside, vitexine, diosmine, 3 rhamnoside, (+) catechin, (-) epicatechin, apigenin- 7-glucoside, luteolin, luteolinglucoside, ginkgonetine, isoginkgonetine and bilobetine. Some liposomal drugs complex operate in the presence of the water or buffer solution where as herbosome operate with the solvent having a reduced dielectric constant. Starting materials like flavonoids are insoluble in chloroform, ethyl ether or benzene. They become extremely soluble in these solvents after forming herbosome. This chemical and physical property change is due to the formation of a true stable complex [7]. The herbosome preparations Flow diagram given in below.

Figure 3:

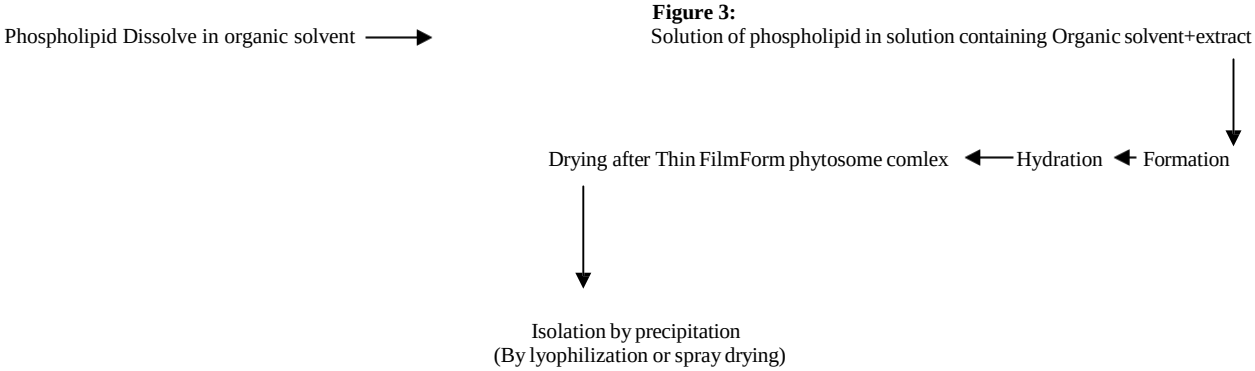


Table 2: Patented technologies of herbosome (phytosome)

Title of patent	Innovation	Patent no.	Reference
Phospholipids complexes of olive fruits or leaves extracts having improved bioavailability	Phospholipids complexes of olive fruits or leaves extracts or their compositions containing it which imparts improved bioavailability	EP/18447 85	13
Compositions comprising *Ginkgo biloba* derivatives	Compositions containing fractions derived from *Ginkgo biloba* useful for treating asthma	EP/18132 80	14
Fatty acids monoesters of sorbityl furfural and compositions for cosmetic and dermatological use	Fatty acid monoesters of sorbityl furfural selected from two different series of compounds in which side chain is a linear or branched C3 C19 alkyl radical optionally containing at least one ethylenic unsaturation	EP16908 62	15
Treatment of skin and	Complexation of thymosin β4 along	US/2007	16
US/2007 wound repair with 0015698 thymosin	phospholipids for treatment of skin disorder	US/2007/ 0015698	
Soluble isoflavone	Isoflavone compositions exhibiting improved	WO/2004	
			17
An antioxidant preparation EP/12114084 37 based on plant extracts for the treatment of, arteriosclerosis, high blood pressure and haemorrhoids	Preparations based on plant extracts which has an antioxidant effect and is particularly useful in treatment of circulation problems such as phlebitis	EP/12114 084 37	18
Complexes of saponins with natural EP0283713 with phospholipids and	bioavailability and are suitable for containing them use as active principle in pharmaceutical, dermatologic and cosmetic companies	EP02837 13	19
tic phospholipids possess pharmaceutical smetic compositions dermatological composition for the treatment of aging or photo damaged skin	comprises a substance that stimulates collagen synthesis that enhances the interaction between extracellular matrix and fibroblasts Cosmetic	41	

Physical and chemical properties 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:

Physical size.

Membrane permeability.

Percent entrapped solutes.

Chemical composition.

Quantity and purity of the starting materials.

Characterization of herbosome [8].

Characterization technique

Visualization: Visualization of herbosome can be measured by transmission electron microscopy (TEM) and by scanning electron microscopy (SEM) [9].

Entrapment efficiency: The entrapment efficiency of herbal formulations of drug by herbosome can be measured by the ultracentrifugation technique [10].

Transition temperature: The transition temperature of the vesicular lipid systems can be measured by differential scanning calorimetry [11].

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 [12].

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 [13].

Drug content: The amount of drug can be measured by a modified high performance liquid chromatographic method or by a suitable spectroscopic method [14].

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 behavior 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 phospholipid 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 amarked 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 [15].

CNMR

The ^{13}C NMR of phyto-constituents and stoichiometric complex with phosphatidylcholine, recorded in C6D6at room temperature all the phyto- constituents' 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 lyophilization at different times [16].

A current concept of herbal drug technology

A current stratgies of herbosome

The current drug delivery system used with herbal drugs should be able to channelize the active entity of herbal drug to its site of action at a rate directed by the needs of the body / chronopharmacology of the disease, throughout the period of treatment. 5 Various NDDS that have been used with herbal drugs and phytochemicals may be broadly classified into the following groups:

Vesicular delivery systems, which include liposomes, ethosomes, phytosomes, transferosomes

Particulate delivery systems, which include microspheres, nanoparticles, micropellets

Biphasic systems, such as micro/ nano emulsions

Vesicular delivery systems

Liposomes

Liposomes are artificial, colloidal and spherical vesicles of 0.05-5.0 μm diameter, composed of a lipid bilayer membrane entrapping an aqueous core. Used to convey vaccines, drugs, enzymes or other substances to target cells or organs [18].

Ethosomes

Ethosomes are vesicles composed of phospholipids with high concentration of ethanol. Due to high concentration of ethanol in the ethosomes enhance their permeability through the skin by fluidising the skin lipids. These carriers can penetrate through the skin deeply leading to improved drug delivery into deeper layers of skin and even into blood circulation. Ethosomes of Triptolide are used for topical delivery of the drug. The ethosomal formulation showed an increase in bioavailability in rats due to increase in the accumulation and reduction in erthema more rapidly as compared to the other formulations [16].

Ethosomal preparations of ammonium glycyrrhizinate – for the treatment of inflammatory diseases of skin – exhibited improved bioavailability as compared to ethanolic solution of drug. The ethosomes did not exhibit any toxicity [17].

Phytosome

It is a currently introduced patented concept in herbal drug technology. Hydrophilic phytoconstituents can be complexed with clinically useful nutrients such as phospholipids to convert them into lipid soluble complexes. Such complexes can be used to prepare liposome-like vesicles called as herbosomes (phytosomes) [19].

Transfersomes

Transferosomes is an artificially designed to be like cell vesicle particularly used as carriers for the transdermal delivery of the drug. They are reported to overcome the problem of penetration through the stratum corneum due to hydration or osmotic force in the skin. Transferosomes as a carrier engaged in exocytosist thus the transfersomes suitable for controlled and potentially targeted drug delivery. transfersome consist of phosphatidylcholine and cholate and are ultra-deformable vesicles with enhanced skin penetrating properties, The formulation of transferosomes includes phospholipids which act as vesicle forming material, surfactants to provide flexibility, alcohol as solvent and buffering agent as Hydrating medium[20].

Particuler delivery systems

Nanoparticles

Nanoparticles are the submicron size particles diameter of around 200 nm ade up of biodegradable and non-iodegradable polymers. Increased solubility of components and improved absorption of incorporated drug and reduction in the dose and dose related side effects. Nanoparticles can be used for controlled release as well as for targeting the drug to particular tissue or organ.

Microspheres

Microspheres are spherical particles of 1-1000 μm size, in which the drug is uniformly dispersed in polymer matrix and gets released following first order kinetics. Various natural and synthetic polymers used for microsphere preparation include albumin, gelatine, modified starches, polypropylene, dextran, polylactic acid and polylactide-co-glycolide etc. The microspheres and micropellets have large surface-to-volume ratio. The interfacial properties of microspheres often dictate their activity. It can be administered by either oral route or by injection. Emulsion – solvent evaporation, spray drying and chemical cross- linking are the major techniques used for preparation of microspheres. Gastroretentive floating microspheres of silymarin have been reported for sustained delivery of the drug.

Micro pellets

Micropellets are the solid particles with size range of 1-1000 μm. In micropellets, the drug could be either dissolved or dispersed in the polymeric solutions by spray-dried. Spray drying provides a single step, rapid drying process; this can be scaled up and be used for heat-sensitive drugs. Controlled release pellets are used for the delivery of drugs to specific sites and for the extended period of time. Micropellets prevent dose dumping, which is common with conventional dosage forms. Alginate- based micropellets of andrographolide from *Andrographis paniculata* have been reported to release the drug away from the upper GIT and hence prevent the GIT irritation and its associated problems such as loss of appetite, nausea and vomiting.41 Pectin-HPMC coated curcumin pellets are reported for delivery of curcumin to colon for the treatment of inflammatory disease. The extract of *Piper sarmentosumn* was entrapped into calcium alginate microbeads. It was found that the encapsulation efficiency of drug is independent of the encapsulation method. BIPHASIC SYSTEMS Tables-3 below

Micro/Nano emulsion

Micro and nanoemulsions are the o/w type emulsions with size range varying from several nanometers to few microns. It is thermodynamically stable dispersion of two immiscible liquids and stabilized by surfactants. They are prepared by the high pressure homogenization and microfluidization techniques. Many herbal drugs and phytoconstituents are incorporated into micro emulsions for different purposes,Types of vascular systems and with description and application summarygiven in Tables-3 below.

CONCLUSION

A wide number of phyto chemical constituents are Isolated from herbal drugs mostly the flavonoidal and the terpenoidal fraction furnishes with a number of application. The poor absorption and the poor bioavailability associated with the polar phyto- constituent's limits its use. The poor bioavailability can be removed by formulating an appropriate drug delivery system like Herbosome (Phospholipids) based drug delivery system have been found promising for better and effective delivery of drug and can increase bioavlaibility rate and extent of drug absorption across the lipoidal biomembrane. Herbosome are one of the phospholipids based herbal drug delivery system with a better absorption and stability profile as compared to other phospholipids based drug delivery system. The Herbosome can play a vital role in valuable delivery of phytoconstituents such as the flavones and the xanthones. Apart from the use of herbosome also has a wide scope in herbal formulations and cosmetics as well. Many areas of herbosome will be revealed in the future as part of their pharmaceutical use.

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