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DEVELOPMENT AND CHARACTERIZATION OF HERBOSOMES COMPLEX

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ABSTRACT

Herbal drugs have been most important selectiom of medicine in all cultures from ancient times. Various plant extract have been observed to show a multiplicity of biological activity such as immunomodulator activity, hepatoprotective activity, antilipidemic activity etc. Plant extract great bioactivity in-vitro, but poor bioactivity in-vivo or in animal models. Basic reasons for the poor bioactivity of herbal extracts are that the bioactive components of these herbs have multiring molecular structures which cannot be permeate into the blood by simple passive diffusion and the bioactive phytoconstituents are most part water dissolvable, consequently, their destitute lipid dissolvbility. To overcome this drawback pharmaceutical researcher developed novel lipid based drug delivery system is advantageous in delivering the herbal drug at the site of action which minimize the toxic effect and increase the absorption and bioavailability. One delivery system designed to improve the in vivo solubility and hence bioavailability of ineffectively dissolvable herbal drugs involves the incorporation of standardized herbal extracts into phospholipids to form a lipidfriendly complex called a herbosome. The aim of present study is compile all herbosomes related data these are helpful for researchers.

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INTRODUCTION

The vesicular system is beneficial in deliver the plant extract at the site of action, which minimize toxic effect and increase bioavailability. The objective of somal drug delivery system to deliver the drug at targeted site during the period of treatment to achieve targeted and controlled drug delivery system.(1) TDDS is a method of delivering drug to the tissue in a manner of that increase the amount of drug in targeted parts of the body, which improves therapeutic effect and reduce the unwanted effects. Drug targeting means deliver of drug to receptor, organ or any other specific part of the body. Few newly developed somal system are summarized in table no. 1

The herbosomal innovation was created by Indena S.P.A. of Italy, notably upgrading the bioavailability of chose phytomedicines, by consolidating phospholipids into institutionalized plant remove, which enhance their ingestion and usage.(2) The polyphenols are almost no solvent both in water and in lipids. The polar functionalities of the lipophilic gathering communicate by means of hydrogen securities and polar gathering connect with the charged phosphate head of phospholipids, framing a special course of action that can be seen by spectroscopy

Herbosomes, term "HERBO" means plant while "SOME" means cell-like. Herbosomes technology improve the bioactivity of plant extracts and act as bridge between NDDS system and traditional system.(3) It is a complex of phytoconstituents and lipid substances which enhance permeation of plant extract. Since two major drawbacks for molecules to across the cell membrane for their absorption in the systemic circulation mainly includes lipophilicity and multiring molecular structures. There are many plant extracts having excellent bioactivity in vitro but low or 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 constituents from plant extract and are destroyed in the gastric fluids when taken orally. Herbosomes are recent advanced noval drug delivery system of herbal formulations that have enhanced released rate and bioavailability than conventional dosage forms. Since they have improved pharmacological and pharmacokinetic parameters, they can be used in the treatment of the acute and chronic liver disease. Planterosomes assimilation in GIT is more prominent bringing about expanded plasma level than individual part. They go about as an extension between novel conveyance framework and regular conveyance framework. Phospholipids particle going about as indispensable transporter made up of water solvent head and two fat dissolvable tails, because of this nature they have double dissolvability and along these lines going about as a successful emulsifier. These medication phospholipids complex can be figured as arrangements, suspensions, emulsions, syrup, moisturizer, gel, cream, watery microdispersions, pill, case, powder, granules and chewable tablets. Planterosomes simply like Phytosomes innovation viably upgraded the bioavailability of numerous well known home grown concentrates including milk thorn, Ginkgo biloba, grape seed and ginseng and so forth.

Milk Thistle: The First Phytosomes:(18)

The first commercial phytosome preparation was depend on the flavonoHgnan silybin, the major constituent of silymarin. A flavonol complex separated from the drain thorn natural product (Siiyhum marianum, family Asteraceae/Compositae).

Mechanism of herbosomes formation[9, 10]

The polyphenolic constituents of plant extracts are well established for direct binding to phosphatidylcholine. Herbosomes are formed from the reaction of phospholipids like soy phosphatidylcholine with the standard extract or polyphenolic constituents as 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 phyto-phopholipid complex. Phytomolecules are joined by chemical bonds to the polar choline head of phospholipids and can be demonstrated by specific spectroscopic techniques. However, the specified chemical analysis indicates that the herbosome unit is usually a flavonoid molecule linked to at least one phosphatidylcholine molecule.

Merits of herbosomes over Conventional Drug Delivery System (11,12,13)

- It improves the ingestion of lipid insoluble polar phytoconstituents through oral and also topical course demonstrating better bioavailability, in this way fundamentally more prominent remedial advantage.
- Enhanced bioavailability because of phospholipid complex.
- High lipophilicity causes high penetrability,so it is utilized in beauty care products over liposome.
- Planterosomes have been utilized to convey liver-securing flavonoid since they can be made effortlessly bioavailable by this innovation.
- The planterosomal system is passive, non-invasive and can be suitable for immediate commercialization. The dose requirement is reduced due to improved absorption of the main constituent.
- Chemical bonds are framed between phosphatidylcholine atom and phytoconstituent of the herb, so the plantersomes indicate better stability profile.
- Dose requirement is reduced.
- Higher entrapment efficiency.
- Planterosomes assured drug delivery to the tissue.
- Planterosomes are superior in comparison to liposomes in skin care products.
- The low solubility of Planterosomes in aqueous media allows the formation of stable emulsions and creams.

Role of Phosphatidylcholine in Planterosome formulation

Phospholipids have a place with the class of lipids and are a major moiety in the piece of the cell films. They go about as normal digestives and furthermore go about as transporters to hydrophilic and lipophilic supplements in Homosapiens and Creatures. They can be separated from egg yolk or soya beans through mechanical or chemical strategies with the guide of hexane. Phosphatidylcholine contains two gatherings fundamentally phosphatidyl amass being the lipophilic gathering and the choline assemble which is the hydrophilic moiety. Choline moiety enhances memory capacity and helps muscle control. The choline portion binds to the herbal extract while the phosphatidyl group covers the phytoconstituents like a cell form which further protects the active constituent from destruction from the digestive juices.

Properties of Herbosomes:
Chemical Properties
Biological Properties

Chmical Properties:[14,15,16]

- A herbosomes is a complex between polar head of phospholipid and water soluble functional group of substrate.
- They formed hydrogen bond between polar head of phospholipid and polar portion of substrate.
- The shape of herbosomes development of micelle like liposome when treated with water.
- Freely soluble in non polar solvent moderately soluble in fats.

Biological Properties: [14,15,16]

Herbosomes display better absorption then conventional dosage form.
The bioavailability of herbosomes is much better than non complex conventional herbal extract which has been evaluated by pharmacokinetic studies and pharmacodynamic test in experimental and human beings.

Comparison between Planterosomes and Liposomes[14,17]
Layer of Membrane:

The main difference between liposomes and herbosomes is that in liposomes the active principle is dissolved in the medium contained in the cavity or in the layers of the membrane, whereas in the planterosomes it is an integral part of the membrane, being the molecules joined through chemical bonds to the polar head of the phospholipids shown in figure

Layer of phospholipid

Liposomes are utilized essentially in beauty care products to convey water-dissolvable substance to the skin. A liposome is shaped by blending a water-solvent substance. There might be hundreds or even a large number of phosphatidylcholine and the individual plant parts really from a 1:1 or a 2:1 complex relying upon the substance. Then again, in a herbosomes, the dynamic guideline can be contrasted with an essential piece of the lipid membrane.

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Substance of phospholipids:

In liposomes the substance of phospholipids is significantly higher, around five times one in herbosomes, making this conveyance not reasonable for oral clinical sensible measurements for normal mixes.

Content of phospholipid:

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Absorbance profile:

Planterosomes is much better absorption profile than liposomes.

Table no.1: Few newly developed vesicular drug delivery systems are summarized below (17,18)

Vasicular system	Description	Application
Aquasomes	Aquasomes water like properties, diameter 30 to 500 nm, these are nanoparticulate carrier system with three layered self assembled structure.the core composed of nsnocrystalline calcium phosphate coated with polyhydroxy polymeric film.	Carrier for delivering vaccine, Hemoglobin, drugs, dyes, enzymes.
Archaesomes	Archaesome were extracted from methanogenic archi bacteria.	Use in delivering cancer antigens when used in combination with checkpoint inhibitor immunotherepies.
Colloidosomes	Colloidosomes is a noval class of microcapsules whose shell consists of coagulated or fused colloid particles at interface of emulsion droplets.	Use in drug targeting.
Cryptosomes	Surface layer made of Phosphotidylcholine and of desirable polyoxyethylene derivative from phosphatidyl ethanolamine	Use in drug targeting.
Carbohydrosome	In this noval formulation multidimensional structures made of zwitterionic, cationic, or anionic carbohydrate based lipids.	Drug Targeting
Discosomes	Niosomes connected with non-ionic surfactants.	Drug targeting
Emulsomes	Nano-sized lipid fundamental particles made of lipid construction and a polar group	Parenteral delivery of poorly water soluble drugs.
Enzymosomes	The enzyme covalently trapped to the surface of Liposomes	Targeted delivery to tumor cells
Erythrosomes	The liposomal system in which chemically interconnected to human erythrocytes cytoskeletons is utilized to which a lipid bilayer is glazed	Targeting of macromolecular drugs
Ethosomes	Ethosomes are lipid “Soft, malleable vesicles” representing a permeation modifier and made of phospholipid, ethanol, and water	Targeted delivery to deep skin layer
Escheriosome	These are lipoidal vesicles, composed of polar lipids extracted from Escherichia coli	Drug Targeting
Genosomes	Synthetic macromolecular complex utilized in the transfer of functional gene.	Cell-specific gene Transfer
Hemosomes	Liposomes which consist of hemoglobin made by, immobilizing hemoglobin with polymerizable phospholipid.	High capacity oxygen carrying system
Layersome	The layersomes are a multilayered structure, coated with biocompatible polyelectrolytes in order to strengthen their structure.	Oral administration and incorporation in Biomaterials
Photosomes	Liposomes containing photolyase, which lose the ingredient through the membrane by photo triggered charges.	Photodynamic therapy
Pharmacosomes	Pharmacosomes are the amphiphilic structure of drugs with lipids. The drugs conjugated by hydrogen bonds to lipids. Represented as ultrafine vesicular, micellar, or hexagonal aggregates	Hydrophilic and lipophilic drugs delivery to improve their solubility, bioavailability and minimize the gastrointestinal toxicity of various drugs.
Proteosomes	A multisubunit enzyme which is high in molecular weight, which includes catalytic activity.	Better catalytic activity, turnover than nonassociated enzymes
Subtilosome	Subtilosomes are made from phospholipids separated from Bacillus subtilis.	A novel potential carrier system used in drug delivery.
Transfersome	Transfersomes are ultra deformable, selfoptimized aggregates for transdermal application, which contain a mixture of lipids and biocompatible membrane softeners.	

Ufasomes	Vesicles surrounded by fatty acids squeezed out from long chain fatty acids by mechanical agitation in the presence of buffer solution.	Ligand-mediated drug Targeting
Vesosomes	Nested bilayer made of bilayers surrounding an aqueous center, which contains unilamellar vesicle.	Multiple compartments of Vesosomes give better protection to the interior content of serum Virosomes
Virosomes	Liposomes pointed with virus glycoprotein's, added in the liposomal bilayer based on retrovirus-based lipids.	Immunological Adjuvant

DIFFERENT ADDITIVES EMPLOYED IN FORMULATION OF PHYTOSOMES:

Lipids: Phospholipid like Soya phosphatidylcholine, Egg phosphatidylcholine, Dipalmitoyl phosphatidylcholine, Distearyl phosphatidylcholine. Used as vesicle creating component.

Solvent:

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

Non-solvent: n-hexane and non- solvent i.e. aliphatic hydrocarbon. Used as a complex precipitating solvent.

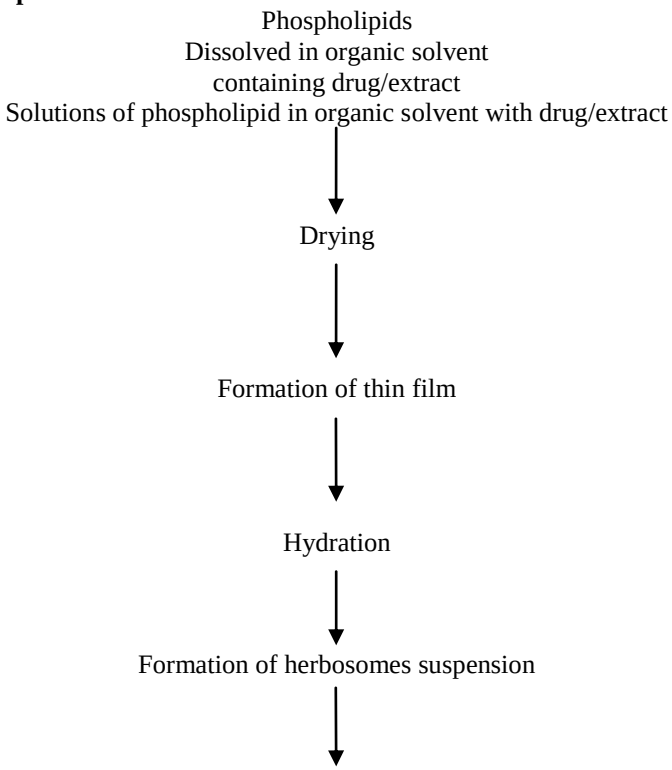
Alcohol: Ethanol, Methanol. Use as a solvent

Buffering agent: Saline phosphate buffer (pH 6.5) 7 % v/vEthanol Tris buffer ((pH 6.5). used as a hydrating agent.

FORMULATION METHODS OF HERBOSOMES:

The herbosome is a cell like structure, which is a combination of soyphosphatidylcholine with standardized extracts containing polyphenolic compounds, which improves their absorption and utilization.

General method of herbosomes preparation:



Common stages of preparation of Herbosomes

There are the following methods which are used for the preparation of Herbosomes:

A. Solvent evaporation method
B. Super critical fluid(SCF) technique
C. Gas anti-solvent method
D. Solution enhanced dispersion by supercritical fluids(SEDS)
E. Anti-solvent precipitation method

Solvent evaporation method:

The complex of plant extracts or specific active principles of plant with dietary phospholipids is generally prepared by solvent evaporation method using alcoholic or organic solvents as reaction medium. In this method, the drug and the phospholipids are placed in the same flask containing a suitable solvent system such as tetrahydrofuran or ethanol. After that the reaction is allowed to be carried out at suitable fixed temperature for a given period of time to get maximum possible yield and drug entrapment. The resultant formulation was then refrigerated and analyzed.

Supercritical fluid (SCF) technique:

The super critical fluids (SCF) techniques have emerged as an effective tool for preparing particles of size ranging from 5 to 2000 nm. Different methods of supercritical fluid have been utilized for improving solubility profiles of poorly soluble drug candidates some of which are compressed antisolvent process (PCA), supercritical antisolvent method (SAS), rapid expansion of supercritical solutions (RESS), gas anti-solvent technique (GAS) and solution Enhanced dispersion by supercritical fluids (SEDS).
Two SCF techniques viz. GAS and SEDS were widely used for the preparation of complexes.

Gas anti-solvent method:

In the GAS technique, a supercritical antisolvent is added to the drug and phospholipids solutions separately until the final pressure is reached. The reaction vessel isthen kept for 3 hour without any agitation at a fixed temperature of 38 °C with 10 mPa of pressure.

Solution enhanced dispersion by supercritical fluids(SEDS):

In this method the liquid solution and the supercritical antisolvent are continuously added into the precipitation unit. Carbon dioxide gas is allowed to pass through a nozzle of 0.1 mm diameter into the mixture of phospholipids and puerarin in the solvent. The experimental conditions are optimized at a temperature of 35 °C, pressure of 10 mPa, 1% mass ratio of drug to phospholipids and a 100 mg/ml concentration of puerarin.

Anti-solvent precipitation method:

The anti-solvent precipitation method has also been utilized by many researchers by incorporating n-hexane as the anti-solvent to precipitate out the drug phospholipids complex from the organic solvent.

CHARACTERIZATION OF HERBOSOMES [14,16]:

Entrapment efficiency:

The entrapment efficiency of a drug in planterosomes can be measured by the ultracentrifugation method.

Vesicle size and zeta potential:

The vesicle size and zeta potential of herbosomes can be determined by dynamic light scattering (DLS) with the help of computerized inspection system and photon correlation spectroscopy (PCS).

Visualization:

Visualization of herbosomes can be determined by transmission electron microscopy (TEM) and by scanning electron microscopy (SEM).

Drug Content:

The amount of drug in herbosomes can be determined by a modified high performance liquid chromatographic method or by U.V. spectroscopic method [20].

Transition temperature:

The transition temperature of the herbosomes can be determined by using differential scanning calorimetry.

Surface tension activity measurement:

The surface tension activity of the drug in aqueous solution can be determined by ring method using Du Nouy ring tensiometer.

Vesicle stability:

The stability of vesicle can be determined by measuring the size and structure of the vesicle for longer time. The mean size is measured by DLS and structural changes are monitored by TEM.

Spectroscopic evaluation:

There are the following spectroscopic methods which are used for the determination of the reciprocal interaction between the phytoconstituents and the phospholipids-

Fourier transforms infrared (FTIR) spectroscopic studies:

The formation of the complex can be also be confirmed by IR spectroscopy by comparing the spectrum of the phytoconstituents-phospholipids complex with the spectrum of the individual components and their mechanical mixtures. FTIR spectroscopy is also a useful tool for the control of the stability of herbosomes when micro-dispersed in water or when incorporated in very simple cosmetic gels. From a practical point of view, the stability can be confirmed by comparing the spectrum of the complex in solid form (herbosomes with the spectrum of its micro-dispersion in water after lyophilization, at different times. However in simple formulations, it is necessary to subtract the spectrum of the excipients (blank) from the spectrum of the cosmetic form at different times, comparing the remaining spectrum of the complex itself.

In-vitro and in-vivo evaluation:

Models of in-vitro and in-vivo evaluations are selected on the basis of the expected therapeutic activity of the biologically active phytoconstituents present in the herbosomes. For example; in-vitro antihepatotoxic activity can be determined by the antioxidant and free radical scavenging activity of the herbosomes. For measuring antihepatotoxic activity in-vivo, the effect of prepared herbosomes on animals against thioacetamide, paracetamol or alcohol- induced hepatoxicity can be examined.

Pharmaceutical Scope of Herbosomes

a. Herbosomes enhances the absorption of lipid insoluble polar phytoconstituents through oral as well as topical route and showing better bioavailability, hence significantly greater therapeutic efficacy.
b. By the herbosomal technology drug entrapment efficiency is increased.
c. Dose requirement is reduced, because the absorption of active constituents is improved.
d. Soy phosphatidylcholine which is used in the preparation of herbosomes also acts as a hepatoprotective and therefore giving the synergestic effects when hepatoprotective substances are used.
e. herbosomes improves the percutaneous absorption of phytoconstituents.

Selection of dosage form for delivering of herbosomes :

Soft gelatin capsules:

Soft gelatin capsules represent an ideal solution to formulate herbosome .The herbosome can be dispersed in oily vehicles like vegetable or semi-synthetic oil to obtain suspension to be filled in soft gelatin capsules.(23)

Hard gelatin capsules:

The herbosomes complex can be formulated in hard gelatin capsules as well. A direct volumetric filling process (without precompression) can be applied, even if the apparently low density of the herbosomes complex seems to limit the maximum amount of powder that can be filled into a capsule (usually not more than 300 mg for a size 0 capsule). With a piston tamp capsule filling process, however, it is possible to increase the amount of powder which can be filled in a capsule, but precompression might affect the disintegration time.(24)

Tablets:

The herbosomes complex can be formulated in tablet form**.** Due to several limitations like flow ability, stickiness and low apparent density of herbosome complex, a direct compression process can be applied only for lower unitary doses. The herboosome complex should be diluted with 60-70% of excipients to obtain tablets with appropriate characteristics. Wet granulation should be avoided due to the negative effect of water and heat on stability of the phyto-phospholipid .(23)

Topical dosage form:

Firstly prepare emulsion at low temperature (not higher than 40°C) after that incorporates The herbosomes complex into it. The phyto-phospholipid complexes are dispersible in the main lipid solvents employed in topical formulation.(25)

Table no-2: Commercial preparations of herbosomes and their use (19, 20,21,22).

Trade name	Phytochemical	Indication
18β-glycyrrhetinic acid phytosomes	18β-glycyrrhetinic acid from liquorice rhizome	Soothing
Centella phytosomes	Triterpenes from *Centella asiatica* leaf	Trophodermic
Crataegus phytosomes	Vitexin-2-O-rhamnosides from hawthorn flower	Antioxidant
Ginkgoselect phytosomes	Ginkgoflavonglucosides, ginkgolides, bilobalides from ginkgo biloba leaf	Vasokinetic
Ginselect phytosomes	Ginsenosides from *Panax ginseng* rhizome	Skin elasticity improver, Adaptogenic
Ginkgo biloba terpenes phytosomes	Ginkgolides and bilobalide from *Ginkgo biloba* leaf	Soothing
Greenselect phytosomes	Polyphenols from green tea leaf	Prevention of free radical mediated tissue damages and weight manager
Leucoselect phytosomes	Polyphenols from grape seed	Antioxidant, capillarotropic
PA_2 phytosomes	Proanthocyanidin A_2 from horse chestnut bark	Anti-wrinkles, UV protectant
Sericosides phytosomes	Sericoside from *Terminalia serica* bark root	Anti-wrinkles
Silymarin phytosomes	Silymarin from milk thistle seed	Antihepatotoxic
Mirtoselect phytosomes	Anthocyanosides of bilberry	Potent antioxidant
Sabalselect phytosomes	Saw palmetto berries	Benefit non-cancerous prostate enlargement
Lymphaselect TM phytosomes	*Melilotus officinalis*	For venous disorders, including chonic venous insufficiency of the lower limbs
Oleaselect phytosomes	Olive oil polyphenol	Anti-inflammatory, Antihyperlipidemic
Polinacea TM	*Echinacea angustifolia*	Neutraceutical, immunomodulator
Hawthorn PhytosomeTM	Flavonoids from *Crataegus sp.*	Nutraceutical, cardio-protective and antihypertensive
Olive oil Phytosome	Polyphenols from *Olea europaea* oil	Antioxidant, anti- inflammatory, anti-hyperlipidemic
Panax Ginseng PhytosomeTM	37.5 % ginsenosides from roots of *Panax Ginseng*	Food Product
Super Milk thistle Extract	Silybin from *Silymarin*	Food Product; antioxidant for liver and skin
Marviselect Phytosomes	Curcumin	Cancer Chemopreventive Agent
Lymphaselect Phytosomes	Curcumin	Hypotensive, Indicated in Insomnia
Echinacea Phytosome	Extract of Echinacea	Immunomodulatory,Nutraceuticals

Future Prospects:
Now there is need to isolate active drug and formulate it so that it might help to control adverse effect associated with modern drugs.

Conflict of Interest:
We declare that we have no conflict of interest.

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