Review Article

Phytosomes: A Novel Approach for Herbal Phytochemicals for Enhancing the Bioavailability

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ABSTRACT

The term "phyto" means plant "some" means cell-like. Most of the phytopharmaceutical, which contains bioactive phytoconstituents, but due to less lipophilicity the active constituents are poorly absorbed resulting in less bioavailability. The effectiveness of any herbal medication is dependent on the delivery of the sufficient level of the therapeutically active compound. Phytosomes are one the novel drug delivery system containing hydrophilic bioactive phytoconstituents of herbs surrounded by the outer lipophilic layer, which shows better absorption, hence produces bioavailability. The current review focus on necessary information, preparation, characterization, patented technologies, commercial products in the market and applications of phytosomes for novel delivery of herbal drugs.

Keywords: Phytosomes, phytoconstituents, bioavailability, novel drug delivery.

INTRODUCTION

Novel drug delivery system designed to deliver the drug at a rate directed by the needs of the body during the period of the treatment, and carries the active material to the site of action. Several vesicular drug delivery system has been developed such as liposomes, niosomes, transferosomes and pharmacosomes[1]. Advances have been made in the area of vesicular drug delivery, leading to the development of systems that allow drug targeting and the sustained or controlled release of conventional medicines[2]. Because of ancient times, the therapeutic uses of traditional medicines and phytomedicines have proved very popular for health maintenance by various routes. The improvement in the field of herbal drug delivery started recently to manage human diseases efficiently[3].

The whole nation is searching for health care beyond the traditional boundaries of modern medicine by turning to self-medication in the form of herbal remedies. Bioactive constituents of phytomedicines are water-soluble molecules like phenolics, flavonoids, glycosides etc.,[4]. Even though phytoconstituents are water-soluble, they are limited in their effectiveness because they are poorly absorbed when taken orally or when applied topically.

Many approaches have developed to improve oral bioavailability, such as the inclusion of solubility and bioavailability enhancer, structural modification and entrapment with the lipophilic carries and thus extensive research in the field of herbal drug delivery system as a means of developing the therapeutic indices of drugs is necessary.

Phytosome is not a liposome and structurally, both are different. The phytosome is a unit of a few molecules bonded together, while liposome is an aggregate of many phospholipid molecules and enclose other phytoactive molecules but without especially bonding to them[5]. Phytosome technology is a breakthrough model for marked enhancement of bioavailability, significantly higher clinical benefit, assured delivery to the tissues, without involving nutrient safety[6]. Thus, the phyto-phospholipid complexes are more readily absorbed and generate higher bioavailability when compared to free active constituents[7,8]. Reassuring, the technique of phospholipid complexes has overcome the hindrance of poor bioavailability for many active constituents[9,10].

New Vesicular Drug Delivery System

New vesicular drug delivery systems aim to deliver the drug at a rate directed by need of body during the period of treatment and carry the active entry to the site of action[11]. Many novel vesicular drug delivery systems have been arrived encompassing various routes of administration, to achieve targeted and controlled drug delivery. Targeted drug delivery is a mode of delivering the therapeutic agent to the tissues that improve the therapeutic efficacy and reduces the side effects. Drug targeting means the delivery of drugs to receptors, organs or any other specific part of the body. Few newly developed novel vesicular drug delivery systems are summarized in Table 1[12,13].

Table 1: Vesicular systems and their applications

S.No	Vesicular system	Description	Application
1	Aquasomes	Particle core is composed of noncrystalline calcium phosphate (ceramic diamond) is covered by a polyhydroxyl oligomeric film.	Specific targeting, molecular shielding.
2	Aracheosomes	Vesicles composed of glycerolipids of archeae with potent adjuvant activity.	Poor adjuvant activity.
3	Colloidosomes	Solid microcapsules formed by the self-assembly of colloidal particles at the interface of emulsion droplets, and they are also hollow, elastic shells whose permeability and elasticity can be precisely controlled.	Drug targeting.
4	Cryptosomes	Lipid vesicle with surface coat composed of PC and suitable polyoxyethylene derivative of phosphatidyl ethanolamine.	Ligand mediated drug delivery.
5	Cubosomes	Bi-continuous cubic phases, consisting of two separate, continuous, but non-intersecting hydrophyllic regions divided by a lipid layer that is contorted into a periodic minimal surface with zero average curvature.	Drug targeting.
6	Discosomes	Niosomes coupled with non-ionic surfactants.	Ligand mediated drug targeting.
7	Emulsosomes	Nano-sized lipid particles consisted of lipid assembly and a polar group.	Parentral delivery of poorly water soluble drugs.
8	Enzymosomes	The enzyme covalently immobilized to the surface of liposomes.	Targeted delivery to a tumour cell.
9	Erythrosomes	Liposomal system in which chemically cross-linked human erythrocytes cytoskeletons are used as to which a lipid bilayer is coated.	Targeting of macromolecular drugs.
10	Genosomes	Artificial macromolecular complex for functional gene transfer.	Cell-specific gene transfer.
11	Hemosomes	Hemoglobin containing liposomes prepare by immobilizing hemoglobin with polymerizable phospholipids.	High capacity oxygen carrying system.
12	Photosomes	Photolyase encapsulated in liposomes, which release the contents by photo-triggered charges in membrane permeability characteristics.	Photodynamic therapy.
13	Protostomes	High molecular weight multi submit enzyme complexes with catalytic activity.	Better catalytic activity turnover than non-associated enzymes.
14	Ufasomes	Vesicles enclosed by fatty acids obtained by long-chain fatty acids by mechanical agitation of the evaporated film in the presence of buffer solution.	Ligand mediated drug targeting.
15	Vesosomes	Nested bilayer composed of bilayers enclosing an aqueous core that contains unilamellar vesicle.	Multiple compartment o vesosomes give better protection to the interior content of serum.
16	Virosomes	Lipososmes spiked with virus glycoprotein's, incorporated in the liposomal bilayer based on retrovirus based lipids.	Immunological adjuvant.

Structure of Phytosome

The term 'phyto' means plant, while 'some' means cell-like. Phyto-phospholipid complexes are formed by interactions between active constituents and the polar head of phospholipids[14]. Interactions between active constituents and phospholipids permit phospholipid complexes to be an essential part in which the phospholipids head group is attached, but the two long fatty acid chains do not participate in complex formation. The two long fatty acid chains can move and encapsulate the polar part of complexes to form a lipophilic surface. Phyto-phospholipid complexes form agglomerates when diluted in water, which resembles a small cell that shows some similarity to liposomes; the differences between liposomes and phytosomes are shown in Figure .1[15].

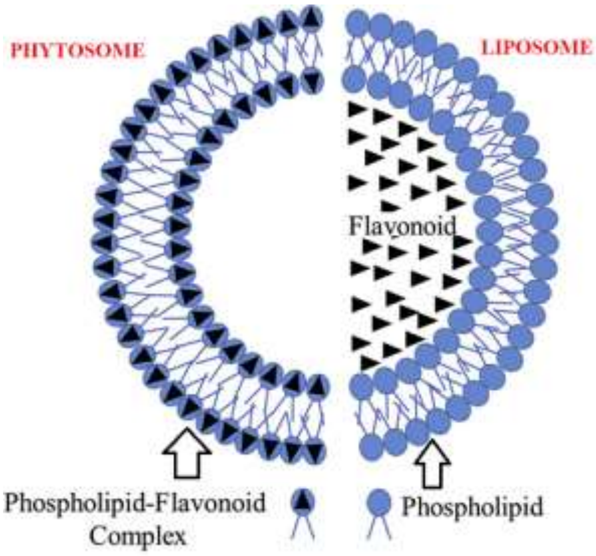

Figure 1: Difference between phytosome vs. liposome

Properties of Phytosomes

There are mainly two properties:

1. **Physico-chemical properties:**

a) Phytosomes are prepared by reaction of stoichiometric amount of phospholipid with the phyto-constituents in an aprotic solvent[16,17].

b) The size of phytosome varies from 50nm to a few hundred µm[18].

c) Phytosome, when treated with water, assumes a micellar shape resembling liposome and photon correlation spectroscopy (PCS) reveals this liposomal structures acquired by phytosome[19].

d) The H^1NMR and C^{13}NMR data deduced that the fatty chain gives unchanged signals both in free phospholipid and in the complex, which indicates that long aliphatic chains are protected around the active principle producing lipophilic envelope[20].

e) The complexes are often freely soluble in aprotic solvents, moderately soluble in fats, insoluble in water and relatively unstable in alcohol. However, phytosomes of certain lipophilic phyto-contituents like curcumin has shown an increase in water solubility upon complexation with phospholipid[21].

2. **Biological properties:**

Phytosomes are novel complexes that are better absorbed and utilized. Hence, they produce more bioavailability and better results than conventional herbal extract or non-complex extracts.

Advantages of phytosomes

1. There is a sudden improvement in the bioavailability of herbal extracts due to their complexation with phospholipid and better absorption in the intestinal tract.
2. They have been using to deliver liver-protecting flavonoids and can make bioavailable [22].
3. This technology offers cost-effective delivery of phytoconstituents and synergistic benefits[23].
4. They can also use for enhanced permeation of drugs through the skin for transdermal and dermal delivery[24].
5. The vesicular system is passive, non-invasive and available for immediate commercialization.
6. There is no problem with drug entrapment during formulation preparation.
7. The dose requirement is reduced due to improved absorption of the main constituent. They can also give in smaller quantities to achieve the desired results[25].
8. Low-risk profile because this technology has no large scale drug development risk since the toxicological profiles of the phytosomal components are well documented in the scientific literatures[26].

Patented Technologies:

Table 2: Patented technologies

S.No	Title of Patent	Innovation	Patent Number	Reference
1	Phospholipids complexes of olive fruits or leaves extract having improved bioavailability	Phospholipids complexes of olive fruits or leaves extracts or their compositions containing it which imparts improved bioavailability	EP/1844785	27

2	Compositions comprising *Ginkgo biloba* derivatives	Compositions containing fractions derived from *Ginkgo biloba* useful for treating asthma	EP/1813280	28
3	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	EP1690862	29
4	Treatment of skin and wound repair with thymosin β4	Complexation of thymosin β4 along with phospholipids for treatment of skin disorder	US/2007 0015698	30
5	Soluble Isoflavone compositions	Isoflavone compositions exhibiting improved solubility, taste, color and texture characteristics	WO/2004/045541	31
6	An antioxidant preparation based on plant extracts for the treatment of circulation and adiposity problems varicose veins, arteriosclerosis, high blood pressure and hemorrhoids	Preparations based on plant extracts which have an antioxidant effect and is particularly useful in the treatment of circulation problems such as phlebitis	EP/12114084	32

Commercial Products and Their Applications:

Table 3: Commercial products and their applications

S.No	Trade Name	Phyto-constituent Complex	Applications
1	Silybin phytosome	Silybin from *Silibium marianum*	Hepatoprotective, Antioxidant
2	Ginseng phytosome	Ginsenosides from *Panax ginseng*	Immunomodulator
3	Sericoside phytosome	Sericoside from *Terminalia sericea*	Skin Improver, Anti-Wrinkles
4	Hawthorn phytosome	Flavonoids from *Crataegus species*	Antihypertensive, Cardio Protective
5	Ginko select phytosome	Flavonoids from *Ginko biloba*	Anti-Aging, Protects Brain And Vascular Lining
6	Olea select phytosome	Polyphenols from *Olea europea*	Anti–Hyperlipidemia, Anti-Inflammatory
7	Green select phytosome	Epigallocatechin from *Thea sinensis*	Anti-Cancer, Antioxidant
8	Echinacea phytosome	Echinacosides from *Echinacea angustifolia*	Immunomodulatory, Nutraceuticals
9	Centella phytosome	Centella phytosome	Brain Tonic, Vein And Skin Disorder
10	Glycyrrhiza phytosome	18-β glycyrrhetinic acid from *Glycyrrhiza glabra*	Anti-Inflammatory ,Soothing
11	Mertoselect phytosome	Polyphenols, Antcinoside from *Vaccinium myrtilus*	Antioxidant
12	PA2 phytosome	Proanthocyanidin A2 from horse *Chestnut bark*	Anti-Wrinkles, UV Protectant
13	Ruscogenin phytosome	Steroid saponins from *Ruscus aculeatus*	Anti-Inflammatory, Improve Skin Circulation
14	Curbilene phytosome	Curbilene from *Curcurbita pepo* seeds	Skin Care, Matting Agent
15	Zanthalene phytosome	Zanthalene from *Zanthoxylum bungeanum*	Soothing, Anti-Irritant, Anti-Itching

Preparation of Phytosome

Phytosomes are novel complexes of herb extracts and lipids. Phytosomes were formulated in the process by which the standardized extract of active ingredients of the herb is bound to phospholipid like phosphatidylcholine. Phosphotidyl ethanolamine or phosphatidyl serine through a polar end[33]. Phytosome is prepared by reacting 3-2 moles of a natural or synthetic phospholipid with one mole of herbal extract. The reaction is carried out in an aprotic solvent such as dioxane or acetone from which the complex can be isolated by precipitation with non-solvent such as aliphatic hydrocarbons or lyophilization or by spray drying. In the complex formation of phytosome, the ratio between these two moieties ranges from 0.5-2.0 moles. The preferable ratio of phospholipid to flavonoids is 1:1. The stepwise procedure of phytosome preparation is shown in Figure 2.

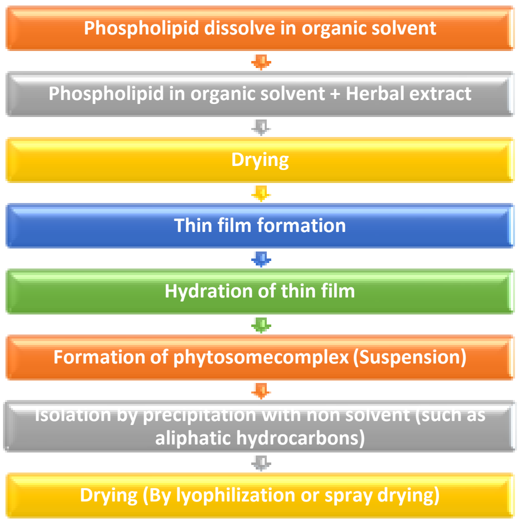

Figure 2: Preparation of phytosome flow chart

Characterization of phytosomes

There are various factors such as the physical size, membrane permeability, and percentage of entrapped solutes and chemical composition of the raw materials, which play a vital role in determining the behavior of phytosomes in the physical and biological system. The characterization techniques used for phytosomes are shown in Figure 3.

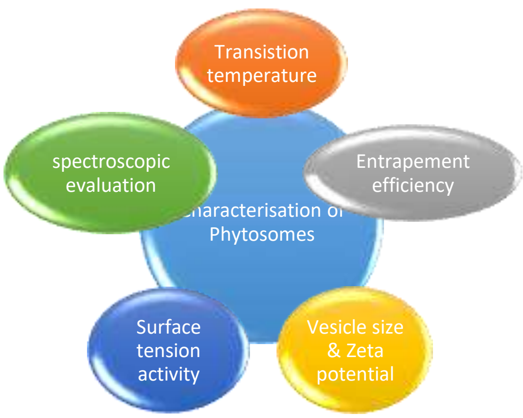

Figure 3: Characterization of phytosomes

1. **Transition temperature:** Differential Scanning Calorimetry (DSC)[34,35] can determine the transition temperature of vesicular lipid system.
2. **Entrapment efficiency:** The entrapment efficiency of a phytosomal formulation can be determined by subjecting the formulation to ultra-centrifugation technique[36].
3. **Vesicle size and Zeta potential:** The particle size and zeta potential of phytosomes can be determined by dynamic light scattering, which uses a computerized inspection system and photon correlation spectroscopy[37,38].
4. **Surface tension activity measurement:** The surface tension activity of the drug in aqueous solution will be measured by Du Nouy ring tensinometer[39].
5. **Spectroscopic evaluation:** The spectroscopic evaluations are widely employed in order to confirm the formation of the complex between phytoconstituents and the phospholipid moiety as well as to study the corresponding interaction between the two components [40]. High Performance Liquid Chromatography (HPLC)[41,42]or UV-Visible Spectroscopy method is used to determine the percentage drug entrapment by extracting the phytosomes with suitable solvent system by centrifugation and estimating its supernatant. The widely employed methods are:

   i) H^1NMR

   ii) C^{13}NMR

   iii) FTIR

CONCLUSION

The poor absorption and poor bioavailability associated with the polar phytoconstituents limits the use of herbal drugs. These hindrances can be overcome by formulating a novel drug delivery system i.e., phytosomes. The phyto-phospholipid complexation technique has offered a great opportunity and hope in improving the *in vivo* bioavailability of herbal drugs. The formulation methodology for phytosomes is simple that can be easily upgraded to a commercial scale. The characterization methodologies are well established for this type of novel formulation. Flavonoids are the most important group of phytochemicals. Different flavonoids which have shown antioxidant activity fifty to two hundred times more potent than vitamin C or E[43]. Many marketed formulations have already approved for innovative formulations, processes and applications of phytosomes. Up to the potential of phytosomes technique was concerned, it has an excellent future for use in the formulation technique and applications of hydrophilic herbal compounds.

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