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Review Article

PHYTOSOME: MOST SIGNIFICANT TOOL FOR HERBAL DRUG DELIVERY TO ENHANCE THE THERAPEUTIC BENEFITS OF PHYTOCONSTITUENTS

Bhuwanendra Singh^{1*}, Rajendra Awasthi², Arshad Ahmad³, Asif Saifi⁴¹Department of Pharmacognosy, NKBR College of Pharmacy & research Centre Meerut, Uttar Pradesh²Department of Pharmaceutics, NKBR College of Pharmacy & research Centre Meerut, Uttar Pradesh³Department of Pharmaceutical Chemistry, Shri Gopichand College of Pharmacy Baghpat, Uttar Pradesh⁴Department of Pharmaceutics, Shri Gopichand College of Pharmacy Baghpat, Uttar Pradesh

ABSTRACT

Traditional medicinal system relies on the knowledge and clinical expertization of physicians to regulate the indigenous medicinal system for the sake of well being to humans. Considering the bioavailability issues of phytoconstituents, in this review, we have focused on the various aspects of phytosomes in drug delivery. Phytosome technology is used to enhance the absorption of poorly absorbed lipid soluble active constituents from the herb extracts. So, the article covers a brief introduction of phytosomes, their method of development along with its formulation and evaluation parameters such FTIR, NMR *etc.* Different types of dosages forms are described in the review, merits and demerits are also discussed along with diagrammatic representation of phytosome development technique. So, the article is the direction for future research to increase the absorption of phytoconstituents.

Key words: Bioavailability, FTIR, lipid, NMR, niosomes, phytoconstituents

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*Address for Correspondence

Dr. Bhuwanendra Singh, Department of Pharmacognosy, NKBR College of Pharmacy & research Centre Meerut, Uttar Pradesh, India. Email ID: bhuwanendrasingh14@gmail.com, Contact: +91-9307634342

INTRODUCTION

Traditional medicines rely on the basis of knowledge and clinical experience of the practitioners for indigenous systems of medicine. Historically, many infectious diseases have been treated with the help of herbals. The traditional medicine is increasingly solicited through the traditional practitioners and herbalists in the treatment of infectious diseases. Among the remedies used, plant drugs constitute an important part. Current status of scientific investigations has highlighted the importance and the contribution of many plant families, *i.e.* Asteraceae, Liliaceae, Apocynaceae, Solanaceae, Caesalpinaceae, Rutaceae, Piperaceae, polypodiaceae¹. From the very beginning, the most important parameter is solubility and absorption to increase the bioavailability of phytoconstituents to

obtain more efficacies of the herbal drugs. It has been observed that most of the therapeutically active plant constituents such as the flavonoids and terpenoids, aglyconglycosides are of highly polar in the nature hence they are water soluble molecules. Thus, these are poorly absorbed due to their poor lipid solubility. Poor absorption might be due to their large molecular size which cannot absorb by passive diffusion. This limits their ability to pass across the lipid-rich biological membranes and thus resulting in poor bioavailability. There are several techniques available to overcome these problems, *viz* cosolvents, inclusion of solubility and bioavailability enhancers, structural modification and entrapment with lipophilic carriers²⁻⁸. Although even standardized plant materials having low solubility in the

lipids or possess highly polar nature to assimilate as lipid profile.

A new approach named as phytosome is developed which indicates like as “plant” and “cell” [phyto means plant and some means cell like] ⁹⁻¹¹. The phytosome technology, developed by Indena S.P.A. in Italy, markedly enhances the bioavailability of selected phytomedicines, by incorporating phospholipids into standardized extracts and so vastly improve their absorption and utilization ¹². These novel preparations make polar phytocells to obtain highly lipid compatible molecular complexes with enhanced absorption and bioavailability. Different chemical constituents obtained from medicinal plants are water soluble phytoactive such as flavonoids, glycosides, terpenoids are delivered using phytosome technique. Because of the water soluble nature, herbal extract lipophilic outer layer phytosomes have better absorption and can show better bioavailability profile than the conventional herbal extracts containing dosage form. These are produced by a process whereby the standardized plant extract or its constituents are bound to phospholipids, mainly phosphatidylcholine, producing a lipid compatible molecular complex formation of chemical bonds between phosphatidylcholine molecule and phytoconstituent produces better stability profile ⁶. It is laterally meant as a phytolipids delivery system ⁹ also known as herbosomes ¹⁰. It is a newly introduced patented technology ¹³, which forms a bridge between the conventional drug delivery system and novel drug delivery system for incorporating standardized phytoextracts or water soluble phytoconstituents into phospholipids to produce lipid compatible molecular complexes to obtain greater absorption and bioavailability to acquire the higher therapeutic effects of poorly absorbed water soluble phytoconstituents. Thus, most useful application of phytosomes is the absorption of drugs in the form of reversible complexes with phospholipids, which proved their higher and long lasting anti-inflammatory and vasokinetic activities due to complexation of active ingredients with phospholipids than those observed after administration of the same amount of substance in free form ⁹⁻¹³.

Formulation approach

Phytosomes are the reaction product of a stoichiometric amount of phospholipid (α -Lysophosphatidylcholine, α -phosphatidylcholine) and standardized plant extract in the presence of a solvent which is incapable of acting as a proton donor (aprotic solvent). α -lysophosphatidylcholine, α -phosphatidylcholine, α -phosphatidylethanolamine, α -phosphatidic acid are the most commonly used as phospholipid with herbal standardized plant extracts. α -lysophosphatidylcholine is a bifunctional chemical constituent in which

phosphatidyl fraction is lipophilic in nature which denotes the head of the bifunctional compound and the hydrophilic choline fraction is the tail of the bifunctional compound. Thus, choline part of α -lysophosphatidylcholine bounds to the hydrophilic phytoconstituents, while the lipid soluble phosphatidyl part join the choline bound complex. So, it leads to form a phyto-phospholipid complex to enhance lipid solubility. A chemical bond plays a vital role to bind the choline head with polar phytoconstituents. Thus, the phytosomes technique produces minute spheres or tiny cells, which helpful in the protection of the active phytochemical constituent from destruction by gastric microenvironment ¹⁴.

Development and formulation of phytosomes take place by taking one molecule of any bifunctional chemical compound such as α -lysophosphatidylcholine, phosphatidylcholine, phosphatidylethanolamine, α -phosphatidic acid, with one molecule of active plant constituent which has a water soluble chemical class for example flavonoids, terpenoids, or aglycon glycosides in a solvent which is incapable acts as proton donor *i.e.* aprotic solvent, *viz* dioxane, acetone, acetonitrile, DMF, DMSO. As a result isolation of complexes takes place by precipitation with spray drying. The most preferable ratio of phospholipid to phytoconstituents is 1:1. phospholipids generally used are given here such as α -phosphatidylcholine, α -phosphatidylethanolamine, α -phosphatidyl-L-serine, α -phosphatidylinositol, α -phosphatidic acid, α -phosphatidyl-DL-glycerol, α -lysophosphatidylcholine, sphingomyelin, cardiolipin but most commonly used is soy lecithin (Glycine max) and phosphatidylcholine ^{15, 16}. Illustration of the development of phytosome is shown in the Figure 1.

Characterization of phytosomes

To confirm the complex formation between phospholipids and herb constituents, spectroscopic evaluation, for example, FTIR and ¹HNMR, ¹³CNMR to reveal the that molecules of the phytoconstituents are bonded to phospholipid fraction by means of a chemical bond are carried out ^{17, 18} while evaluation of drug content can be done by HPLC ¹⁹ entrapment efficiency of the drug by phytosomes can be evaluated by ultracentrifugation technique ²⁰. Visualization of phytosomes can be done using transmission electron microscopy (TEM) and scanning electron microscopy (SEM) ²¹. Thermal analysis can be done using differential scanning calorimetry ²²⁻²⁴ Vesicle size and zeta potential are determined by dynamic light scattering which uses a computerized inspection system and photon correlation spectroscopy ^{25- 26}. Surface tension activity measurement of drug in aqueous solution can be measured by the ring method Du Nouy ring tensiometer ²⁷.

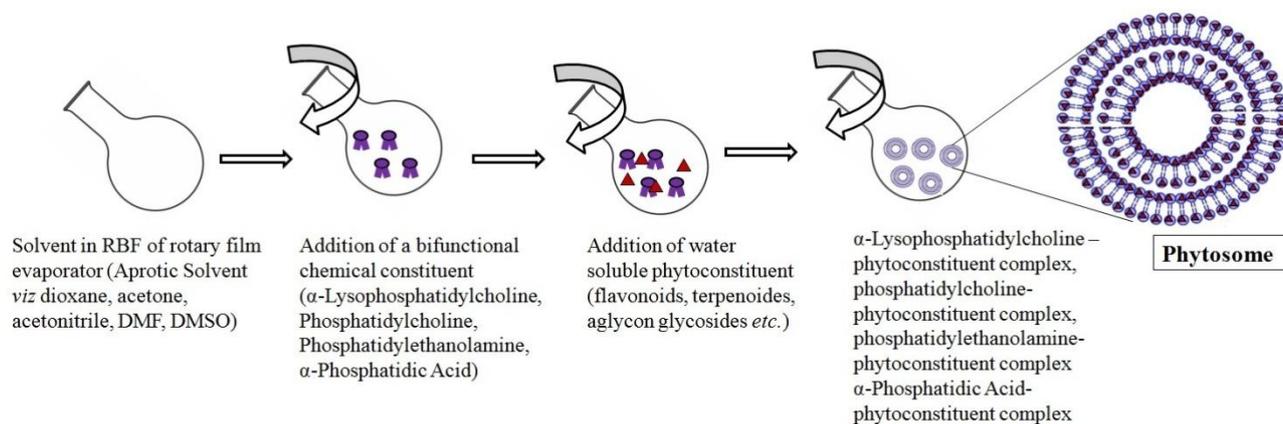


Figure1. Illustration of Phytosome development, evaluation and characterization

Table1. Details of the investigations based on phytosome technology.

Formulations / Phytosomal complex	Active principle/ secondary metabolites from plant drugs	Pharmacokinetics	Pharmacology	Method of preparation	Dose	Route of administration	Ref
Ginkgo biloba Phytosomes	Flavonoids	Flavonoids of GBP stabilize the Reactive oxygen species	Cardio-protective, antioxidant	Phospholipids complexation	100 mg	Subcutaneous	28
Ginkgoselect Phytosome	Flavonoids	Inhibits lipid peroxidation stabilize the Reactive oxygen species	Hepatoprotective, antioxidant	Phospholipids complexation	25 and 50 mg/kg	Oral	29
Silybin Phytosome	Flavonoids	Absorption of silybin phytosome from silybin is approximately seven times greater	Hepatoprotective, antioxidant for liver and skin	Silybinphospholipid complexation	120 mg	Oral	30
Ginseng Phytosome	Ginsenosides	Increase absorption	Nutraceutical, immunomodulator	Phospholipids complexation	150 mg	Oral	31
Green tea Phytosome	Epigallocatechin	Increase absorption	Nutraceutical, antioxidant, anticancer	Phospholipids complexation	50–100 mg	Oral	31
Grape seed Phytosome	Procyanidins	The blood TRAP (Total Radical-trapping Antioxidant Parameter) were significantly elevated over the control	antioxidant, cardio-protective	Phospholipids complexation	50–100 mg	Oral	31
Hawthorn Phytosome	Flavonoids	Increase therapeutic efficacy	Cardio-protective, antihypertensive	Phospholipids complexation	100 mg	Oral	31
Quercetin Phytosome	Quercetin	Exerted better therapeutic efficacy	Antioxidant, anticancer	Quercetin phospholipid complexation	–	Oral	32

Table 2: Marketed formulation based on phytosome technology

Brand name	Active principle	Drug Delivery system	Company	Ref.
Greenselect Phytosome	Polyphenols from green tea leaf	Phytosome	Indena	32
Leucoselect Phytosome	Polyphenols from grape seed	Phytosome	Indena	32
Virtiva Phytosome	bilobalide from Ginkgo biloba leaf	Phytosome	Indena	32
Silymarin Phytosome	Silymarin from milk thistle seed	Phytosome	Indena	32
Visnadex Phytosome	Visnadin from Ammi visnaga umbel	Phytosome	Indena	32

Advantages of phytosomes

Phytosomes are promising tiny spheres are gaining popularity for the delivery of phytoconstituents due to their following advantages:

- Phytosomes increase the absorption of active constituents from herbs and hence improve the bioavailability.
- Phytosomes enhances the solubility of bile to the chemical constituent, to facilitate the liver targeting.
- Dose requirement is also reduced by use of phytosomal drug delivery system because these carriers increase the drug absorption.
- Improved stability due to chemical bond formation between phytoconstituents bifunctional chemical compound such as phosphatidylcholine molecule.
- Phytosomes are safe to use for transdermal drug delivery.

Disadvantages of phytosomes

Despite of several advantages of phytosomes some fatal disadvantages such as phospholipids (lecithin) can induce proliferation on MCF-7 breast cancer cell line has been reported³³. A major disadvantage of phytosome is leaching of the phytoconstituents off the 'some' which reduces the desired drug concentration indicating their unstable nature³⁴.

Phytosomes containing dosage forms

Phytosome preparations can be administered by both routes as orally and topically, but to obtain the best result regarding bioavailability of formulation, it is

important to study the dissolution and disintegration time of dosage forms while some of the examples of dosage forms containing phytosomes are given below³⁵:

Soft gelatin capsules: Indena recommend a granulometry of 100 % < 200 µm in the suspension form vegetable or semi-synthetic oils can be used for this purpose.

Hard gelatin capsules: Usually not more than 300 mg in a size 0 capsule, without precompression method is used to fill the hard gelatins.

Tablets: Dry granulation represents the ideal manufacturing process to obtain tablets with higher unitary doses. Wet granulation is avoided due to adverse effect on phospholipid complex.

Topical dosage forms: The emulsion is used for this purpose to obtain the best result from phospholipid complex.

CONCLUSION

Phytosome technology connects both pharmacokinetics and pharmacology of the drug which help in better absorption of herbal drug extracts in comparison to other traditional dosage forms. Phytosomes offer the best bioavailability to the different classes of phytoconstituents such as flavonoids, aglycon glycosides and terpenoids through the skin and GIT. It also improves the intrinsic stability of nutraceuticals. So it can be concluded that phytosome is the best tool to enhance the absorption of phytoconstituents without any adverse drug effect.

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