Review on Phytosomes: A Novel Approach for Herbal system

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ABSTRACT

Phytosomes are novel form of herbal formulations which contains the bioactive phytoconstituents of herb extract complexed with phospholipid to produce lipid compatible molecular complexes. Phytoconstituents are obtained from natural resources, fewer side effects and lower phytochemical costs are added advantages for their utilization in treatment of various diseases. Unfortunately, despite the wide therapeutic potentials of poly phenolic phytoconstituents such as flavonoids, glycosides, terpenoids etc. still they suffer with poor aqueous solubility, absorption and bioavailability problems when administered orally or by topical applications. Plant derived products or plant extracts are increasingly receiving attention as dietary supplements for the homeostatic management of inflammation, toxicities, cancers, weight loss and other chronic or acute degenerative disorders. But these products frequently face stability and bioavailability problems. Plant products after their isolation become prone to instability and are potentially unfit to cross the bio membrane as such. Some plant products show hydrophobicity and their delivery to systemic circulation is a quite difficult task. "Phyto" means plants and "some" resembles a covering around/or a structure. Phytosome is generally prepared by reacting one or two moles of polyphenolic phytoconstituents and phospholipid. The present review describes an updated overview of preparation of phytosomes, advancement in phytosomes technology, various herbal drugs for which phytosomes have been used as a carrier, its commercial availability and applications. The objective of this review is to focus on the application of phytosome technology along with its preparation, various properties and characterization. The recent development and conducted works of various researchers have been studied thoroughly to establish the novel route as a potential way to deliver phytoconstituents.

Keywords: *Phytosomes, phospholipids, bioavailability, topical route, novel drug delivery system.*

INTRODUCTION

Most of the biologically active constituents of plants are polar or water soluble but due to the problem in absorption, restricts the utilization of these type of compounds which ultimately decreases the bioavailability. For improvement of bioavailability, herbal products must have proper homeostasis between hydrophilic (for absorption into gastrointestinal tract fluid) and lipophilic (to cross lipid bio membrane balance) [1]. Plant preparations are widely used in traditional as well as modern medicine system. During the traditional time, various pharmacological studies have been carried out with many plants extracts and their constituents to check their therapeutic application. Over the past year, great advancement has been made for the development of novel drug delivery system (NDDS) for various plant extracts and their active constituents. Novel drug delivery such as targeted drug delivery which directly channels the active entity on the site of action and such delivery system could offer targeted and sustained release of drug so that pharmacological effect could be achieved at lower dose. The development in the area of herbal medicine started earlier to cure human diseases with lesser side effects [2].

A number of chief constituents of herbal medicine are easily soluble in water (glycoside, flavonoid); however, these constituents are bounded in their potency because they may be partially soluble or hydrophobic in nature, so when applied topically shows less therapeutic efficacy. Numerous efforts have been put forward to enhance the bioavailability of such drug by formulating them to target drug delivery system such as phytosomes and liposomes are good options. The use of these techniques in formulation development process may lead to good bioavailability of herbal drugs as compare to conventional herbal extracts [3].

Phytosomes means herbal drug loaded in vesicles, which is available in the Nano form. The phytosome provide an envelope, like coating around the active constituent of drug and due to this the chief constituent of herbal extract remains safe from degradation by digestive secretion and bacteria. Phytosome is effectively able to absorb from a water loving environment into lipid loving environment of the cell membrane and finally reaching to blood circulation. The current review highlights the future scope and emerging technologies in the field of NDDS for the benefit of herbal and traditional medicines prepared from plant origins [4].

The term “Phyto” means plant and “some” means cell like. It is also mentioned as ribosomes. This is a new patented technology, where standardized plant extracts or water soluble phytoconstituents are complexed with phospholipids to produce lipid compatible molecular complexes, there by greatly increasing absorption and bioavailability. Phosphatidylcholine, phosphatidylserine, phosphatidylethanolamine, phosphatidylinositol are the phospholipids used, but phosphatidylcholine are widely used because of their certain therapeutic value in case of liver diseases, alcoholic steatosis, drug induced liver damage and hepatitis. Phospholipids are also employed as natural digestive aids and as carriers for both fat miscible and water miscible nutrients. Phytosomes can easily traverse the lipophilic path of the enterohepatic cell membranes and also stratum corneum layer of the skin [5].

Standardized plant extracts mainly flavonoids are derived as phytosomes. Selection of flavonoids are done from the groups consisting of quercetin, kaemferol, quercretin-3, rhamnoglucoside, quercetin-3-rhamnoside, hyperoxide, vitexin, diosmine, 3-rhamnoside, (+)

catechin, (-) epicatechin, apigenin-7-glucoside, luteolin, luteolin glucoside, ginkgonetine, isoginkgonetine and bilobetine etc. [6].

A number of chief constituents of herbal medicine are easily soluble in water (glycoside, flavonoid); however, these constituents are bounded in their potency because they may be partially soluble or hydrophobic in nature, so when applied topically shows less therapeutic efficacy [7]. Numerous efforts have been put forward to enhance the bioavailability of such drug by formulating them to target drug delivery system such as phytosomes and liposomes are good options. The use of these techniques in formulation development process may lead to good bioavailability of herbal drugs as compare to conventional herbal extracts. Phytosomes means herbal drug loaded in vesicles, which is available in the nano form. The phytosome provide an envelope, like coating around the active constituent of drug and due to this the chief constituent of herbal extract remains safe from degradation by digestive secretion and bacteria. Phytosome is effectively able to absorb from a water loving environment into lipid loving environment of the cell membrane and finally reaching to blood circulation [8]. It can be used in the treatment of various fatal diseases without denaturing the active phytocompounds and enhanced bioavailability [9]. Phytosomes are obtained by reacting phospholipid (either of natural or synthetic origin) with selected botanical constituents with an appropriate solvent, and due to their physical and chemical efficiency, these phyto-complex can be considered as a novel entity [10]. The current review highlights the future scope and emerging technologies in the field of NDDS for the benefit of herbal and traditional medicines prepared from plant origins.

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. 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 No.1

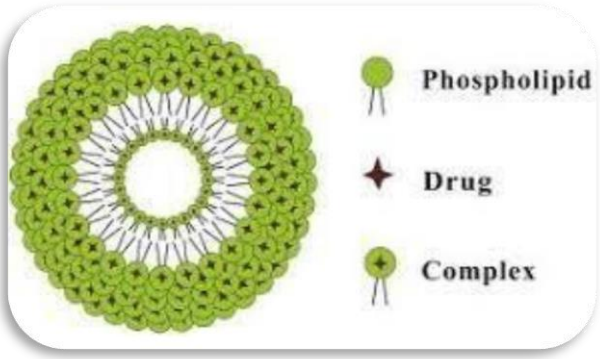

Figure No.1: Phytosome structure [10]

PREPARATION OF PHYTOSOME

Phytosomes are generally prepared by adding accurate amount of phospholipid, i.e., Soya lecithin with herbal extracts in an aprotic solvent. Soya lecithin contains main constituent, i.e., Phosphatidylcholine which is having a dual function. Phosphatidyl part is lipophilic in nature and choline part is hydrophilic in nature. The choline part attached with hydrophilic chief active constituents, whereas phosphatidyl part lipid soluble compound attached with choline bound complex. It results in the formation of lipid complex with better stability and bioavailability [10].

Advantages of phytosomes [11, 12]

Phytosomes have the following advantages:

1) It enhances the absorption of lipid insoluble polar phytoconstituents through oral as well as topical route showing better bioavailability, hence significantly greater therapeutic benefit.
2) Appreciable drug entrapment.
3) As the absorption of active constituent (s) is improved, its dose requirement is also reduced.
4) Phosphatidylcholine used in preparation of phytosomes, besides acting as a carrier also acts as a hepatoprotective, hence giving the synergistic effect when hepatoprotective substances are employed.
5) Chemical bonds are formed between phosphatidylcholine molecule and phytoconstituent, so the phytosomes show better stability profile.
6) Application of phytoconstituents in form of phytosome improves their percutaneous absorption and act as functional cosmetics.

Disadvantages [12]

1) There are several advantages of phytosomes but have some fatal disadvantages like proliferation on MCF-7 breast cancer cell line due to phospholipid (lecithin).
2) The main disadvantage of phytosome is lixiviate of the phytoconstituent off the „some“ which shows unstable nature due to decrease the desired drug concentration.

- **Physical Properties of Phytosomes**

  Phytosome has lipophilic substances with a clear melting point. Average size of phytosome range is 50 nm to a few hundred μm. They are easily soluble in non-polar solvents, insoluble in water and moderately soluble in fats and unstable in alcohol. Liposomal like structures of micellar shape are formed when phytosome are treated with water [13].

- **Chemical Properties of Phytosomes**

  On the basis of their physicochemical and spectroscopic data, it has been shown that, the phospholipids-substrate interaction is due to the formation of hydrogen bond between the polar heads of phospholipids (i.e. phosphate and ammonium groups) and the polar functional groups of substrate, In phytosomes the active principle is anchored to the polar head of phospholipids, becoming an integral part of the membrane [14].

- **Biological properties**

  Phytosomes are advanced forms of herbal products that are better absorbed, utilized and as a result produce better results than conventional herbal extracts. The increased bioavailability of the phytosome over the non-complexed botanical derivatives has been demonstrated by pharmacokinetic studies or by pharmacodynamics tests in experimental animals and in human subjects. [15]

Additives used in preparation of Phytosomes

- Phospholipids: Egg phosphatidyl choline, Disearyl phosphatidyl choline, Soya phosphatidyl choline etc.
- Solvents: Acetone, Dioxane, ethanol, methanol, n-hexane etc. [16]

Mechanism of Phytosome Formation

The photoactive components of herbal extracts are well suited to direct binding to phosphatidylcholine from soy. Phosphatidyl choline is a bifunctional compound, the phosphatidyl moiety being lipophilic and the choline moiety being hydrophilic in nature. Phospholipids are small lipid molecules in which the glycerol is bound to only two fatty acids, instead of three as in triglycerides, with the remaining site is occupied by a phosphate group. Specifically, the choline head of the phosphatidylcholine molecule binds to phytoconstituents while the fat soluble phosphatidyl portion, comprising the body and tail, then envelopes the choline-bound material. This results in small microspheres or the production of cells known as phytosomes [13]. Thus, phytosomes are also considered as a phytolipid delivery system. The phytosome process produces small cells which protect the valuable components of the herbal extract from the destruction by digestive secretions and gut bacteria. They improve transition of constituents from the water phase to the lipid friendly environment of the enterocyte cell membrane and from there into the cell, finally reaching the circulation [14].

Preparation of Phytosomes

Phytosomes are prepared by different methods by interacting 3-2 moles natural or synthetic phospholipid, mainly phosphatidylcholine with one mole of phytoconstituent. The most preferable ratio for complexes formation between these two moieties is in the range from 0.5 to 2.0 moles [15].

Common steps involved in the preparation of Phytosome: Phospholipid is dissolved in organic solvent containing drug/extract (1:1) solution of phospholipid in organic solvent with drug/extract.

Methods used for the Preparation of Phytosome

- **Anti-solvent precipitation technique**

  The specific amount of plant extract and phospholipid were taken into a 100 ml round bottom flask and refluxed with 20 ml of dichloromethane at a temperature not exceeding 60º for 2 h. The mixture is concentrated to 5-10 ml. Hexane (20ml) was added carefully with continuous stirring to get the precipitate which was filtered and collected and stored in desiccators overnight. The dried precipitate is crushed in mortar and sieved through #100 meshes.

Powdered complex was placed in amber colored glass bottle and stored at room temperature [16].

- **Rotary evaporation technique**
  The specific amount of plant extract and phospholipid were dissolved in 30 ml of tetrahydrofuran in a rotary round bottom flask followed by stirring for 3 hours at a temperature not exceeding 40ºC. Thin film of the sample was obtained to which n-hexane was added and continuously stirred using a magnetic stirrer. The precipitate obtained was collected, placed in amber colored glass bottle and stored at room temperature [17].

- **Solvent evaporation technique**
  The specific amount of plant material and phospholipids were taken into a 100ml round bottom flask and refluxed with 20ml of acetone at a temperature 50-600C for 2h. The mixture is concentrated to 5-10 ml to obtain the precipitate which was filtered and collected. The dried precipitate phytosome complex was placed in amber colored glass bottle and stored at room temperature [18].

- **Ether injection technique**
  In this technique, the drug lipid complex is dissolved in an organic solvent. This mixture is then slowly injected into a heated aqueous agent, resulting in the formation of vesicles. The state of amphiphiles depends on the concentration. When the concentration is less, amphiphiles introduce a monomer state but as the concentration is increased, variety of structures may be formed, that is, round, cylindrical, disc, cubic, or hexagon type [19].

- **Dehydration-rehydration technique**
  The bio active compound along with the phospholipid is dissolved in organic solvent. The organic solvent is then eliminated completely along with the aqueous content under a reduced temperature and pressure using a rotary vacuum evaporator. A thin layer containing a conjugated complex of phospholipid and bioactive compound would be formed in the round bottom flask. The mono layer is countered with water to remove the solvents completely. Then the mono layer is re hydrated with water to form micelles. The phospholipid thin layer upon exposure with the water forms micelles that are then probe sonicated to achieve desired micelle size [20].

Characterization Techniques of Phytosome [21-23]

Differential scanning calorimetery

Drug polyphenolic extract, phosphatidylcholine, a physical mixture of drug extract and Phosphatidylcholine, and drug-phospholipid complex were placed in an aluminum cell and heated to a temperature of 50-250°C/minutes from 0 to 400°C in the atmosphere of nitrogen.

Scanning electron microscopy (SEM)

SEM was used to determine the size of the particle and its appearance. Dry sample was placed on electron microscope brass stub coated with gold in an ion sputter. Random scanning of the complex at 100.

Transition electron microscopy (TEM)

TEM was used to characterize the size of phytosomal vesicles with 1000 magnification.

Drug entrapment and loading capacity

Drug phytosomal complex was centrifuged at 10000 rpm for 90 minutes at 4°C to separate phytosome from the untrapped drug. The concentration of free drug can be measured by doing ultraviolet spectroscopy. The percentage drug entrapment can be calculated as given formula.

$$Entrapment\ efficiency\ (\%) = weight\ of\ total\ drug - weight\ of\ free\ drug \div weight\ of\ total\ drug \times 100$$

Fourier transform infrared spectroscopy (FTIR) analysis

FTIR analysis will be done for checking the structure as well as chemical stability of drug, phospholipid. The phytosomal drug will be crushed with potassium bromide to obtain pellets at 600 kg/cm2 pressure. Scanning will be done between the ranges of 4000-400 cm−1.

Size analysis and zeta potential

Malvern Zetasizer is used to check the particle size and zeta size of phytosomal complex. Argon laser is used for this particle size and zeta sizer characterization.

In vitro and in vivo evaluations

In vitro and in vivo evaluation will depend on the properties of the drug, their chief phytoconstituents bounded by phospholipid layer and on the bases of that particular animal model is selected for its evaluation.

Advances in Phytosome Technology

There are number of research articles reveals the importance of phytosomal delivery system over conventional herbal extract. Advances in phytosomal delivery system are as follows:

- Bacopaside well-known chief constituents present in Bacopa-monnieri plant having antiamnesic activity. This study is an attempt to prepare phytosome from bacopaside and its in vivo evaluation on rodents. There is remarkably great change in the therapeutic efficacy of the compound prepared by phospholipid as compare to simple B. monnnieri extract [24].
- Another study also reveals that there is the preparation of berberine phospholipid complex solid dispersion, which not only increase the solubility of the compound but also increase its flow ability and dissolution rate for industrial production [25].
- Another research state that there is the preparation of sinigrin phytosome. The study was carried out for in vitro wound healing capacity and the result is also appreciable as compare to sinigrin alone [26].
- One research reported silymarin phytosomes with better antihepatotoxic activity as compare to

silymarin alone and also having great role for the protection against B1 aflatoxin on broiler chicks [27].

- The phytosomes from standardized extract of seeds of S. marianum have administered orally which is having great effect on foetus from maternally ingested alcohol [28].
- One clinical research reveals that the study of 232 patient with chronic hepatitis when treated with silybin phytosome at a dose of 120 mg twice or thrice a day up to 120 days having great role for recovery of liver function [29].
- Grape seed phytosome also having great role in ischemia induced damage in the heart, also having protective against atherosclerosis. The main chief constituents responsible for this is proanthocyanidins/procyanidins [30].
- Camellia sinensis or the extract of green tea when incorporated in phytosomes having improved oral bioavaiability as compared to uncomplexed green tea extract. Epigallocatechin 3-o-gallate is the main active constituents present in green tea [29-30].
- Further clinical trial suggested that phytosomes of green tea free from caffeine also having a significant effect on anti-obesity and antioxidant activity. It also having effect on low-density lipoprotein [31].
- Quercetin phytosomal complex reveals the better therapeutic property in rat liver injury induced by carbon tetra chloride [32].

Table No. 1: Innovation in Phytosome with Patent title and Patent number

Sr. No.	Patent Titled	Innovation Description	Patent No.	References
1	Phospholipid complexes of olive fruits or leaves extracts having improved bioavailability	Having improved bioavailability	EP/1844785	[33]
2	Fatty acid monoesters of sorbityl furfural and composition for cosmetic and dermatological use	Fatty acid monoester of sorbityl furfural selected from two different series of compounds in which side chain is linear alkyl radical optionally containing at least one ethylenic unsaturation	EP1690862	[34]
3	Cosmetic and dermatological compositions for the treatment of aging and photo damaged skin	Cosmetic or dermatological composition for topical treatment	EP1640041	[35]

4	Complex of saponin with phospholipid and pharmaceutical and cosmetic compositions containing them	High lipophilic and improved bioavailability and suitable for use in pharmaceutical cosmetic compositions	EP0283713	[36]
5	Phospholipid curcumin complex and piperine as chemo sensitizing agent	Treatment of drug resistant	EP2228062 A1	[37]
6	An antioxidant preparation based on plant extract for the treatment of aging or photo damaged skin	Used in circulation problems, arteriosclerosis and high blood pressure	EP1214084	[38]

Some Patented Technology of Phytosome

There is numerous work has been done for commercialization of Phytosome, out of them few patents technology are representing in Table No. 1 along with their patent title, description of innovation and patent number.

CONCLUSION

Herbal products always have great concern of denaturation and bioavailability. There is so many novel approaches are available in the form NDDS. Despite these approaches liposomes and phytosomes are most suitable novel approaches for herbal drugs to overcome this kind of problems. These delivery systems have improved the pharmacotherapeutics and pharmacokinetics of herbal drugs. This kind of delivery systems is also utilized in the field of nutraceuticals and cosmeceuticals for improving therapeutic effect and permeability in the skin. The formation of phytosomes are simple and reproducible a part of that phospholipids used in the preparation of phytosomes have their own beneficial effects in the body. The phytoconstiuents such as flavonoids, glycosides, terpenoids etc. have been found to possess great beneficial pharmacological activities to treat various diseases. But due to certain lacunae, especially the phenolic compounds, their phenolic nature affects the oral absorption and bioavailability. These aspects constitute a hindrance against the widespread use of these phytoconstituents in the pharmaceutical field. This review is an attempt to present a concise authenticated profile of phytosomes as a novel drug delivery system. Thorough study of them proves that the phytosomes are novel formulations which offer improved bioavailability of hydrophilic flavonoids and other similar compounds through skin or gastrointestinal tract. As far as potential of phytosome technology is concerned, it has great future since its formulation technology is simple with the characterization methodologies and analytical techniques are well established and therefore easily upgraded to a commercial scale.

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