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Novel Approach on Herbal Drug Delivery System: Phytosome A Brief Overview

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Abstract

Aim-The term phytosome is derived from two words, "Phyto" means plant and "Some" means cell. Phytosome is a patented technology developed by leading industrialist in phyto-pharmaceuticals to produce lipid drug molecular complexes. Complexing the polyphenolic phytoconstituents in the molar ratio with phosphatidyl choline results in a new herbal drug delivery system, known as "Phytosome". **Method-**Phytosomes were prepared by reacting the herbal extract in an aprotic solvent such as methylene chloride, dioxane and ethyl acetate with the phospholipid such as phosphotidylcholine, phosphatidylethanolamine or phosphatidylserine dissolved in the same solvent. After solubilization has been completed, the complex compounds are isolated by removing the solvent under vacuum evaporator, by freeze drying or by precipitation with non-solvents such as n-hexane. **Results-**Phytosome contains herbal or phyto-constituent entrapped in an aqueous core surrounded by a lipid bilayer, consists of phosphotidyl-choline. Phytosomes loaded leads to products that are highly absorbed and produces higher results as compare, to the conventional herbal extracts. **Conclusion-**Thus, the obtained complexes are lipophilic in character and soluble in a polar and aprotic solvent, in which the individual components of complexes are normally insoluble.

Keywords
Phytosomes, Phytoconstituents, Phospholipids, Herbal Extract, Herbal Drug Delivery System.

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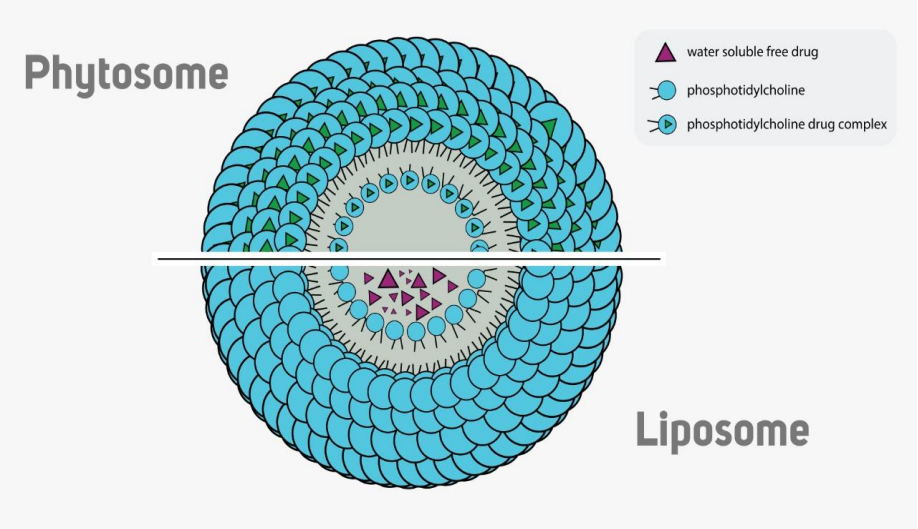
INTRODUCTION

The drug delivery system which aims to deliver drug at a rate directed by the needs of the body during the period of the treatment is known as Novel drug delivery system (NDDS) and forms network around the active entity to the site of action. A number of NDDS have been developed encircling several routes of administration, to attain targeted and controlled drug delivery which encapsulates the drug in systemic circulation that decreases the selective uptake of drug and tonicity. Subsequently numerous vesicular drug delivery systems like niosomes, pharmacosomes, transferosomes and liposomes were developed. Improvements have since been prepared in the zone of vesicular drug delivery, which leads to growth of systems that permit drug targeting, and the controlled or sustained release of conventional medicines [1].

Over the last few years, chemical and pharmacological studies have been accomplished on a lot of herbal extracts in order to confirm their indications of traditional medicine and find their chemical configuration [2].

Maximum of the plant drug biological constituents are water solvable molecules. Though, water soluble constituents of plants like many polyphenolics

compounds, flavonoids are absorbed poorly either because of their poor miscibility with oils and other lipids, or due to their multiple-ring huge size molecules which are not absorbed by simple diffusion, strictly restricting their capability to pass through the lipid-rich outer membranes of the enterocytes of the small intestine. Water-soluble phytoconstituent molecules can be converted into lipid-compatible molecular complexes, which are called "phytosomes" or "herbosomes"[3].The basic neccesicity of herbal products is to have suitable homeostasis among hydrophilic (for absorption into gastrointestinal tract fluid) and lipophilic (to cross lipid bio membrane balance) for the enhancement of bioavailability [4].Phytosome is a patented method developed by Indena, to integrate phospholipids into herbal extracts and so massively increase their use and absorption. Phytosomes are advanced herbal products manufactured by binding distinct constituent of herbal extract to phosphatidyl-choline resulting in a product that produces better results than the conventional herbal extracts and are better absorbed. Numerous phytoconstituents have multiple rings and, so, cannot be absorbed from the intestine into the blood by simple diffusion. Similarly, certain herbal phyto-molecules are poorly miscible with oils and other lipids and frequently fail to pass over the small intestine because of its lipoidal nature. The effectiveness of any herbal product is dependent upon delivering an operational level of the active compounds [5].The term "phyto" means plant whereas "some" means cell-like structure [6]. The phytosomes technology creates a little cell, whereby the herbal extract or its active constituent is secured from damage by gastric secretions and gut bacteria owing to the gastro-protective property of phosphatidyl-choline [7].The phytosome are recently acquainted structures, which contain the progressive constituent of herb enclosed and hold-in by phospholipids [8].The chief molecular building block of the cell membranes is phosphatidyl-choline, which is miscible both in oil and water surroundings, and when taken orally it is well absorbed. Chemical study specifies that phytosome is generally a phytoconstituent molecule associated with at least one phosphatidyl choline molecule. [9]Phytosomes are better able to transition from a hydrophilic environment into the lipid-friendly environment of the enterocyte cell membrane and from there into the cell finally reaching the blood. Phytosomes have improved pharmacological and pharmacokinetic parameter. [10] The phytosome method has been applied to numerous widespread plant extract including Grape seed, gingko biloba, milk thistle (Silybummarianum), hawthorn, ginseng (Panax ginseng) and green tea (Theasinensis). The terpenoid and flavonoid components of these plant extracts lend themselves quite well for the direct binding to phosphatidyl-choline. [11]



Principle

Phosphatidyl choline (or phosphatidylserine) is a bi-functional compound. The phosphatidyl moiety is lipophilic and the choline (serine) moiety is hydrophilic in nature. This twin solubility of the phospholipid makes it an operative emulsifier. Therefore, the choline head of the Phosphatidyl choline molecule binds to these compounds although the lipid soluble phosphatidyl portion comprises the tail and the body which then surrounds the choline bound material. Therefore, the phyto-constituents yield a lipid compatible molecular complex along with phospholipids (also called as phyto-phospholipid complex). [12]

Advantages of phytosomes-

Phytosomes have the following advantages:

- Phytosome as superior bioavailable herbal extracts, which enhance the bioavailability due to the formation of complex with phospholipids and provides better and faster absorption in intestinal tract, therefore considerably superior therapeutic effect.
- Phytosome infuses the non-lipophilic herbal extract to be well absorbed in intestinal lumen.
- As the absorption of active constituents progresses, the requirement of dose is concentrated and required results can be attained.[13]
- By enhancing the solubility of bile to herbal constituent, facilitates the liver targeting.
- The dose size is reduced, as the absorption of chief phyto-constituent is improved.
- Phosphotidylcholine used in preparation of phytosomes, besides acting as a carrier also acts as a hepato-protective, hence giving the synergistic effect.
- Unlike liposome, chemical bonds are formed between phosphatidylcholine molecule and phytoconstituent, so the phytosomes show better stability profile.
- Low risk profile- The toxicological profiles of the phospholipids are well documented in the scientific literature.
- It displays better bioavailability and pharmacokinetics parameters.[3]
- These are platform for the carriage of diverse and large group of drugs (protein molecules, peptides).
- The vesicular system is non-invasive, passive and is available for instant commercialization.
- Phosphatidylcholine, an vital part of the cell membrane used in phytosome technology, acts as a carrier and also nourishes the skin.
- Due to their high skin permeation and lipid profile phytosomes are broadly used in cosmetics.[13]
- There is no problem with drug entrapment during formulation preparation.
- Also, the entrapment efficacy is high and additionally predetermined; since the drug itself forms vesicles after conjugation with lipid.
- The dose requirement is reduced due to enhanced absorption of the chief constituent. They can also be given in reduced amounts to attain the desired results.
- Comparatively simple to manufacture with no complex methodological investment required for the manufacture of Phytosomes.[14]

Difference between phytosomes and liposomes

The basic difference between liposomes and phytosomes is that, in liposomes, the active biomaterial is dissolved in the medium encircled the cavity or in the coatings of the membrane, while in phytosomes, it is an necessary portion of the membrane, being the molecules stabled through chemical bonds to the polar head of the phospholipids. Liposomes are used in cosmetics to deliver water-soluble materials to the skin. A liposome is manufactured by mixing phosphotidyl-choline and a water-soluble substance, thus, no chemical bond is made, the phosphatidyl-choline molecules mount the water-soluble substance. There may be 100's or even 1000's of phosphatidyl-choline molecules surrounding the water-soluble compound. In difference with the phytosome technology, the phosphatidyl-choline and the plant active constituents from a 1:1 or a 2:1 complex (depending on the substance) are equated to liposomes. Phytosome is characterized by a high lipid/bioactive ratio with stoichiometry in the series of 1:1-1:3 among the active and the phospholipid formulation aid. This difference results that in comparison with liposomes; phytosomes are better absorbed; phytosomes are also superior to liposomes in skin care products.

In phytosomes, the polar groups of phospholipids interrelates with hydrogen bonds, and form a exclusive organization that is confirmed by spectroscopy, however, in liposomes, the active material is dissolved in the core of the complex, and there is no chemical bonding between the lipid and the guest substance. [14]

COMMERCIAL PRODUCTS OF PHYTOSOMES [4]

There is numerous commercially available product based on Phytosomes are available in the market which is having great therapeutic role as compared to conventional dosage form. Some of them are listed along with their trade name, chief constituents, source, dose, and use in Table1.

Flavonoids used in the preparation of phytosomes [4]

There are number of herbal chief constituents widely used in the preparation of phytosomes. Each active component having its own properties and therapeutic action. Some of important flavonoids are represented in Table 2.

Commercially Prepared Phytosomes (Table 1)

S.No.	Trade name	Chief constituents	Source	Use
1.	Centella phytosomes	Triterpine	*Centella asiatica*	Cicatrizing, trophodermic
2.	Ginselect phytosomes	Ginsenosides	*Gingko biloba*	Adaptogenic
3.	Greenselect phytosomes	Polyphenols	*Camellia sinensis*	Free radical scavenging activity
4.	Leucoselect	Polyphenols	*Vitis vinifera*	Antioxidant
5.	Meriva	Curcuminoids	*Curcuma longa*	Anti-inflammatory
6.	Silymarin	Silymarin	*Silybum marianum*	Anti-hepatotoxic
7.	Olea select TM phytosomes	Polyphenols of olive oil	*Olea europaea*	Anti-inflammatory, antioxidant
8.	Crataegus phytosomes	Vitexin-2'-O-rhamonoside	*Crataegus Mexicana*	Antioxidant
9.	Visnadine	Visnadine	*Ammi visnaga*	Circulation improver
10.	Bilberry	Triterpine	*Vaccinium myritillus*	Potent antioxidant
11.	Ruscogenin phytosomes	Steroid saponin	*Ruscus aculeatus*	Anti-inflammatory
12.	PA2 phytosomes	Proanthocynidin	*Horse chestnut bark*	Anti-wrinkles, UV protectant
13.	Zanthalene phytosomes	Zanthalene	*Zanthoxylum bungeanum*	Soothing, anti-itching
14.	Lymphaselect phytosomes	Triterpenes	*Melilotus officinalis*	Indicated in insomnia
15.	Sabaselect phytosomes	Fatty acid, sterols	*Serenoa repens*	Beningn prostate hyperplasia
16.	Sericoside phytosome	Sericosides	*Terminalia sericea*	Skin improver
17.	Echinacea phytosomes	Echinacosides	*Echinacea angustifolia*	Immunomodulators, nutraceuticals
18.	Rexatrol	Resveratrol	*Polygonum cuspidatum*	Antioxidant, antiaging

Common Flavonoid Used in Phytosome Preparation (Table 2)

Flavonoid/ Chief constituents	Plant Name
Genistein	Soy tea
Naringenin	Orange
Isoquercetin	Onion buckwheat hyptis
EGCG	Green tea

Future outlook of "somes" with their use [4]

"Somes" are devising an extensive region of thrust, not only phytosome is having its property but there are some other "Somes" such as ethosomes, sphingosomes, ufasomes, pharmacosomes, virosomes and quatosomes preparation also advise their clinical efficiency.

Pharmaceutical scope of phytosomes: [15]

- It improves the absorption of lipid insoluble polar phyto-constituents via topical as well as oral route displaying better bioavailability, hence considerably superior therapeutic benefit.
- Significant drug entrapment.
- As the absorption of active constituent(s) is enhanced, its dose requirement is also concentrated.
- Phosphatidyl-choline used in preparation of phytosomes, moreover acting as a carrier also acts as a hepato-protective, hence giving the synergistic effect when hepato-protective constituents are employed.
- Chemical bonds are formed amongst phosphatidylcholine molecule and phyto-

constituent, so the phytosomes display better stability profile.

- Application of phytoconstituents in form of phytosome improves their percutaneous absorption and act as efficient cosmetics.

PROPERTIES OF PHYTOSOMES-

Chemical Properties:

Physicochemical properties of phytosomes [16]

Phytosome is a complex formed, on reaction between a phyto-constituent and phospholipid in an appropriate solvent. From spectroscopic analysis data it confirms, that there is a hydrogen bond development because of chief phospholipid-substrate interaction between the polar head of phospholipids (i.e. phosphate and ammonium groups) and the polar functionalities of the substrate. When treated with water, phytosomes assumes a micellar shape forming liposomal-like structures.

Biological properties:

Phytosomes are innovative forms of herbal products that are better absorbed, used and as a outcome yield better results in comparison with conventional herbal extracts. [12]Phytosomes enhances bioavailability when administered orally. Phytosomes has improved pharmacokinetic as compare to simple herbal drugs. [6]

The increased bioavailability of the phytosome over the non complexed botanical derivatives has been represented by pharmacokinetics studies or by pharmacodynamics tests in experimental animals and in human subjects. [17]

Pharmacological properties: [18]

Pharmacodynamics and pharmacokinetics studies in experimental animals and in human subjects have been used to demonstrate the biological behavior of Phytosomes. The increased bioavailability of the phytosomes over the non-complexed botanical derivatives has been assessed from these studies.

MECHANISM OF PHYTOSOME FORMATION [19]

The phyto-active constituents of plant extracts are well matched to straight binding to phosphatidyl-choline. Phosphatidyl choline is a bi-functional 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 residual site is engaged by a phosphate group. Specifically, the choline head of the phosphatidyl-choline molecule binds to phyto-constituents while the fat soluble phosphatidyl portion, including the body and tail, then covers the choline-bound material. This results in small microspheres or the manufacture of cells known as phytosomes. Thus, phytosomes are also considered as a phyto-lipid delivery system. The phytosome method yields small cells which guard the valued components of the plant extract from the destruction by digestive secretions and gut bacteria. They advance transition of ingredients from the water phase to the lipid friendly environment of the enterocyte cell membrane and from there into the cell, finally reaching the circulation.

FORMULATION OF PHYTOSOMES:

Phytosomes are prepared by process in which the standardized extract or active ingredient of herbal is bind to the phospholipids. [20]

Phytosomes are prepared by reacting the herbal ext ract in an aprotic solvent such as methylenechloride , dioxane and ethylacetate with the phospholipid su ch as phosphatidylcholine, phosphatidylethanolami ne or Phosphatidylserine dissolved in the same solv ent. After solubilization has been completed, the complex compounds are isolated by removing the solvent under vacuum, by freeze drying or by precipitation with non-solvents such as n-hexane.Thus, the obtained complexes are lipophilic in character and soluble in a polar and aprotic solvent in which the individual components of complexes are normally insoluble.[21]

There are the following methods which are used for the preparation of phyto-phospholipid complex.

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 600 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 [22].

Rotary evaporation technique:

The specific amount of plant material 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 400^0C. 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. [22]

Solvent evaporation method:

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. [22]

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. [22]

EVALUATION OF PHYTOSOMES

a) Determination of percentage yield: Determination of % yield of phytosome complex was calculated by the following formula: [23]

$$\text{Percentage Yield} = \frac{\text{(Practical yield)}}{\text{(Theoretical yield)}} \times 100$$

b) Entrapment Efficiency: The entrapment efficiency of a phytosomal formulation can be determined by subjecting the formulation to ultracentrifugation technique.

$$\text{Entrapment Efficiency} = \frac{\text{Drug loading}}{\text{Theoretical drug loading}} \times 100$$

c) Vesicle size and Zeta potential: The particle size and zeta potential of phytosomes can be determined by using transmission electron microscopy (TEM) and by scanning electron microscopy (SEM). [23]

d) Visualization: Visualization of phytosomes can be achieved using transmission electron microscopy (TEM) and by scanning electron microscopy (SEM). TEM provides the details about internal composition and can show many characteristics of the phytosomes, such as morphology, crystallization, stress or even magnetic domains. SEM focuses on the phytosomes surface and its composition provides morphological details. [24]

e) Drug content:

The amount of drug can be quantified by a modified high-performance liquid chromatographic method or by a suitable spectroscopic method. The HPLC is mostly used analytical technique. HPLC can produce extremely pure compounds.

f) Transition temperature: The transition temperature of the vesicular lipid systems can be determined by differential scanning calorimetry. [23]

g) Surface tension activity measurement: The surface tension activity of the drug in aqueous solution can be measured by the ring method in a Du Nouy ring tensiometer.

h) Vesicle stability: The stability of vesicles can be determined 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. [4]

i) Compatibility Study-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 phytosomal 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. [23]

j) In vitro drug release study: In vitro drug release study of phytosomes can be studied by diffusion study using Franz diffusion cell. [23]

CONCLUSION

Many plant extracts and phytochemical constituents have excellent biological activity *in-vitro,* but shows low in-*vivo* activity due to inherent property of drug constituents like poor lipid or aqueous solubility, improper molecular size, destruction of components in gut etc. These problems result in decreased absorption of phyto-constituent. Low absorption problems can be improved by formulating complexes with phospholipids. Hence, phytosomal preparation enhances the bioavailability of active constituents because they become more permeable and easily cross the biological membranes. The most important principle component of the plant extract is confined from destruction which is caused due to digestive secretions and gut bacteria. So, by using phytosomes the quantity of herbal extracts and phyto-constituents which is administered into the body by various routes is required in very less amount for better therapeutic action. In modern years, the method of complexing herbal drugs with phospholipids has becoming as a demanding and one of the most successful way of enhancing bioavailability and therapeutic efficacy of large no. of poorly absorbed plant constituents. Phytosomal method involves the phospholipid molecules having phosphotidylcholine in their structure to form complexes with specific active pharmaceutical ingredient of herb which improves the membrane

permeability, water-oil partition coefficient and enhance the systemic bioavailability of these drugs. The inclusion of water-soluble drugs into their phospholipid complexes has considerably improved their bioavailability by increasing penetration through the lipoid plasma membrane while the phospholipids complexation poorly water-soluble drugs have improved bioavailability by enhancing their solubility in gastric fluids.

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