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PHYTOSOMES: A NOVEL DRUG DELIVERY FOR HERBAL EXTRACTS

Rajesh Akki[1*], K. Navya Sri[1], K. L. Govardhani[1], M. Gayatri Ramya[2]

1. Department of Pharmaceutics, Hindu College of Pharmacy, Guntur 522 002, A.P, India.
2. University College of Pharmaceutical Sciences, Acharya Nagarjuna University, Nagarjuna Nagar, Guntur 522 510, A P, India.

ABSTRACT: Novel drug delivery system is a novel approach to drug delivery that addresses the limitations of the traditional drug delivery systems. Our country has a vast knowledge base of Ayurveda whose potential is only being realized in the recent years. The effectiveness of any herbal medication is dependent on the delivery of effective level of the therapeutically active compound. Severe limitation exists in their bioavailability when administered orally or topically. Phytosomes are recently introduced herbal formulations that are better absorbed and as a result produce better bioavailability and actions than the conventional phyto-molecules or botanical extracts. In the recent days, most of the prevailing diseases and nutritional disorders are treated with natural medicines. Several plant extracts and phytoconstituents, despite having excellent bioactivity in vitro demonstrate less or no in vivo actions due to their poor lipid solubility or improper molecular size or both, resulting in poor absorption and bioavailability. So, much work has been directed towards the development of new concept in herbal delivery system i.e.,"phytosomes" which are better absorbed, utilized and as a result produce better results than conventional herbal extracts owing to the presence of phosphatidylcholine which likely pushes the phytoconstituent through the intestinal epithelial cell outer membrane, subsequently accessing the bloodstream phytosomes have improved pharmacokinetic and pharmacological parameter which in result can advantageously be used in the treatment of the acute and chronic liver disease of toxic metabolic or infective origin or of degenerative nature.

KEYWORDS: Phytosomes, Herbosomes, Silybin, Herbal.

Corresponding Author: Dr. Rajesh Akki* Ph.D.
Department of Pharmaceutics, Hindu College of Pharmacy, Guntur, A.P, India.

1.INTRODUCTION

Novel drug delivery system is a novel approach to drug delivery that addresses the limitations of the traditional drug delivery systems. Our country has a vast knowledge base of Ayurveda whose potential is only being realized in the recent years. However, the drug delivery system used for administering the herbal medicine to the patient is traditional and out-of-date, resulting in reduced efficacy of the drug. If the novel drug delivery technology is applied in herbal medicine, it may help in increasing the efficacy and reducing the side effects of various herbal compounds and herbs. This is the basic idea behind incorporating novel method of drug delivery in herbal medicines. Thus, it is important to integrate novel drug delivery system and Indian Ayurvedic medicines to combat more serious diseases. For a long time herbal medicines were not considered for development as novel formulations owing to lack of scientific justification and processing difficulties, such as standardization, extraction and identification of individual drug components in complex poly herbal systems. However, modern phytopharmaceutical research can solve the scientific needs [such as determination of pharmacokinetics, mechanism of action, site of action, accurate dose required etc.] of herbal medicines to be incorporated in novel drug delivery system, such as nanoparticles, microemulsions, phytosomes, matrix systems, solid dispersions, liposomes, solid lipid nanoparticles and so on. In the past, almost all the medicines were from the plants; the plant being man's only chemist for ages. Herbs are staging a comeback, herbal ‘renaissance’ is happening all over the globe and more and more people are taking note of herbal therapies to treat various kinds of ailments in place of mainstream medicine. There are three main reasons for the popularity of herbal medicines:

1. There is a growing concern over the reliance and safety of drugs and surgery.
2. Modern medicine is failing to effectively treat many of the most common health conditions.
3. Many natural measures are being shown to produce better results than drugs or surgery without the side effects.

Also there is increasing evidence that many current drug therapies simply suppress symptoms and ignore the underlying disease processes. In contrast, many natural products appear to address the cause of many diseases and yield superior clinical results. Unfortunately, most physicians and patients are not aware that these natural alternatives exist. Some drugs have an optimum concentration range within which maximum benefit is derived, and concentrations above or below this range can be toxic or produce no therapeutic benefit at all. On the other hand, the very slow progress in the efficacy of the treatment of severe diseases has suggested a growing need for a multidisciplinary approach to the delivery of therapeutics to targets in tissues. From this, new ideas on controlling the pharmacokinetics, pharmacodynamics, non-specific toxicity, immunogenicity, bio-recognition and efficacy of drugs were generated. These new strategies, often called drug delivery systems [DDS], are based on interdisciplinary approaches that combine polymer science, pharmaceutics, bioconjugate chemistry.

Advantages of Herbal Medicines

1) Herbal medicines are very cheap in comparison to the conventional form of medication. It's something which every pocket can afford, unlike other forms of medication which can create a big hole in your wallet.
2) Herbal medicines are known to be more productive in comparison to other forms of medication in curing certain conditions. Unless mixed with other chemical components, they are known to be all natural.
3) One of the greatest benefit associated with herbal medicine is the less existence of side effects. Also, they tend to offer long lasting benefits in terms of overall wellness.
4) Obesity is a growing problem which is known to have hazardous issues on an individual's health. Herbal medicine can help one deal with the problem of obesity very effectively without consuming much time and efforts.

Disadvantages of Herbal Medicines

1) In some instances, individuals switch to herbal medication without realizing that the symptoms can be linked to a different ailment. Unlike, conventional medication which involves constant monitoring of your health, herbal medicines are taken without prescription which means that in some cases, individual might be undergoing a trial and error process with their medication.
2) Although herbal medicines has the potential to cure many ailments, the curing period is usually longer in comparison to conventional medication. One needs to have immense patience while undergoing herbal treatment.
3) Herbal medicines can cause allergic reactions in some cases. Before resorting to herbal medication you need to ensure that you are not allergic to the particular herb that you will be consuming. Conventional medication can also cause allergic reactions, but they are usually taken upon prescriptions which is why the chances of allergic reactions are less.
4) The government does not approve of any kind of herbal medication. It's usually consumed upon the person's own risk, and when it comes to branded herbal supplements one can't expect any kind of quality assurance.

Phytosomes

The effectiveness of any herbal medication is dependent on the delivery of effective level of the therapeutically active compound. Severe limitation exists in their bioavailability when administered orally or topically. Phytosomes are recently introduced herbal formulations that are better absorbed than extracts. The term "phyto" means plant, while "some" means cell-like. Over the past century; phytochemical and phyto-pharmacological sciences established the compositions, biological activities and health promoting benefits of numerous botanical products. Most of the biologically active constituents of plants are polar or watersoluble molecules. However, water soluble phytoconstituents [like flavonoids, tannins, glycosidic aglycones etc] are poorly absorbed either due

to their large molecular size which cannot absorb by passive diffusion, or due to their poor lipid solubility; severely limiting their ability to pass across the lipid-rich biological membranes, resulting poor bioavailability. [1,2]

The Phytosome Technology

Phytosome technology had improved the absorption and bioavailability of selected phytoconstituents, by incorporating phospholipids into standardized plant extracts.[3] When a stoichiometric amount of phospholipid [phosphatidylcholine] reacted with standardized extract in nonpolar solvent.[4] Phytosomes form a bridge between conventional delivery system and novel delivery system and is also called as phytolipid delivery system. The word "phyto" means plant and "some" means cell-like.[5] Phosphatidylcholine is bi-functional compound, where the nature of choline moiety is hydrophilic and phosphatidyl moiety is lipophillic. In phyto-phospholipid complex, the choline head of phosphatidylcholine molecule bind to the phytoactive constituent while the lipid-soluble portion wraps the choline bound material. Hence, it produces phytophospholipid complex. Through spectroscopic techniques, it was analyzed that molecules are hooked through chemical bonds to the choline head of phosphatidylcholine.[6,7] For enhancement of bioavailability, greater clinical benefit assured delivery to the tissue phytosome technology has been useful.[4]

Advantages: [8,9,10,11]

1. Phytosomes produces a little cell where the important components of herbal extracts are protected from destruction by gut bacteria and digestive secretions.
2. It assures proper delivery of drug to the respective tissues.
3. The safety of the nutrients of the herbal extractneed not be compromised by conveying the herbal drug as means of phytosomes.
4. As the absorption of active component is improved, its small dose can produce desired results.
5. The bioavailability of drug is enhanced remarkably.
6. Efficiency of entrapment is high and more over predetermined because drug itself is inconjugation with lipids in forming vesicles.
7. Formulation is easy as there is no problem in drug entrapment.
8. Phytosomes shows better stability due to the formation of chemical bonds between phytoconstituents and the Phosphatidylcholine molecules .
9. Besides acting as a carrier Phosphatidylcholine used in formulating phytosome process also nourishes the skin as it is an important part of a cell membrane.
10. Phytosomes are more useful than liposomes in skin care products.
11. Phytosomes have significantly greater clinical benefit.
12. Besides acting as a carrier Phosphatidylcholine used in preparation of phytosomes also acts as a hepatoprotective resulting in synergistic effect when hepatoprotective substances are employed.
13. They are less soluble in aqueous media which allows the formation of stable emulsions or creams.

14. Liver targeting is improved by increasing the solubility in bile salt.

Mechanism of Phytosome Technology: [12]

The lower absorption and bioavailability of polyphenolic constituents mainly due to two factors. These chief constituents are number of ringed molecule and are not too much small that it will absorbed by diffusion process. Second factor is that flavonoid molecule or chief constituents of polyphenols have poor solubility with lipids. These are the limitations that inhibit their absorption through biological membrane. Phytosome technology is mainly result with complexation of polyphenols with phospholipid in 1:1 ratio or 1:2 results in the formation.

Difference between liposome and phytosomes

A liposome is formed by mixing awatersoluble substance with phosphatidylcholine in definite ratio under specific conditions. Here, no chemical bond is formed; the phosphatidylcholine molecules surround the watersoluble substance. There may be hundreds or even thousands of phosphatidylcholine molecules surrounding the water-soluble compound. In contrast, with the herbosome process the phosphatidylcholine and the plant components actually form a 1:1 or a 2:1 molecular complex depending on the substance[s] complexed, involving chemical bonds [hydrogen bonds]. This difference results in phytosome being much better absorbed than liposomes showing better bioavailability. phytosomes have also been found superior to liposomes in topical and skin care [cosmetic] products.[13] Phytosomes are not liposomes-structurally, the two are distinctly different as shown in Fig.1. The phytosome is a unit of a few molecules bonded together, while the liposome is an aggregate of many phospholipid molecules that can enclose other phytoactive molecules but without specifically bonding to them [14,15]. This difference results in phytosome being much better absorbed than liposomes showing better bioavailability. Phytosomes have also been found superior to liposomes in topical and skin care [cosmetic] products. In liposomes, the active principles are water soluble and are hosted in the inner cavity, with little, if any, interaction taking place between the hydrophilic principle and the surrounding lipid core. Conversely, phytosome’s host their polyphenolic guest, generally little soluble both in water and in lipids, at their surface where the polar functionalities of the lipophilic guest interact via hydrogen bonds and polar interactions with the charged phosphate head of phospholipids, forming a unique arrangement that can be evidenced by spectroscopy. The phytosome formulation also increases the absorption of active ingredients when topically applied on the skin, and improves systemic bioavailability when administered orally. In water medium, a phytosome will assume a micellar shape, forming a spherical structure, overall similar to a liposome, but with a different guest localization. [16]

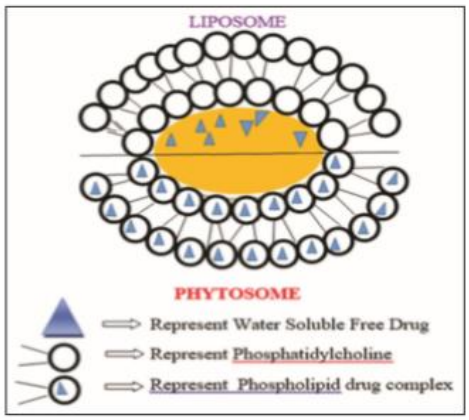

Fig.1: Difference between Phytosomes and Liposomes

Preparation Techniques For Phytosomes

a.Phytosome vesicles were made by thin layer rotary evaporator vacuum method. The phytosomal complex was mixed in anhydrous ethanol in 250 ml round bottom flask. The flask was attached to a rotary evaporator. The solvent will evaporate at a temperature about 60°C forming thin layer film around the flask. The film is hydrated by phosphate buffer having pH 7.4, and the lipid layer will peel off in phosphate buffer forming vesicle suspension. The phytosomal suspension was subjected to probe sonication with 60% amplitude. Phytosomal suspension will be stored in the srefrigerator for 24 hrs, before characterization [17].

b. Phospholipid, i.e., soya lecithin was reacted with polyphenolic extract in an equal ratio with 5 mL of dichloromethane [DCM] with stirring until evaporate. Once the DCM was evaporated 5 mL of n-hexane, was added to the thin film with stirring and left in a fume hood for complete removal of the solvent. After complete removal of n-hexane, the thin film was hydrated and sonicated for desired phytosomal complex [18].

c. Weigh accurate amount of phospholipid and polyphenolic extract. Put it in 100 ml round bottom flask and reflux it with 30 mL of DCM on 60°C for 3 hrs, reduced it to 5-10 mL and add 30 ml of n-hexane with continuous stirring to get precipitate. Collect the precipitate and stored in a vacuum desiccator overnight. The dried precipitate is then passed through #100 mesh size and stored in well closed ambered colored container [19].

d.Phytosomes can be prepared by reflux method. Polyphenolic extract and phospholipid were placed in 100 mL round bottom flask and refluxed in DCM for 1 hr not exceeding 40°C. The clear solution was evaporated and add 15 mL of n-hexane until a precipitate was obtained. The precipitate was taken and placed in a desiccator [20].

e. Accurately, weight the quantity of phospholipid and cholesterol in round bottom flask and dissolve it in 10 mL of chloroform followed by sonication for 10 minutes using bath sonicator. Organic solvent removal can be done by subjecting it under reduced pressure in a rotary evaporator (40°C). After complete removal of the solvent thin layer is formed which is hydrated with polyphenolic

extract of the drug in a rotary evaporator. Phospholipids mixture was sonicated in an ice bath for heat dissipation. Prepared phytosome were stored in an amber colored bottle [21].The diagrammatic representation of procedure is shown in fig.2.

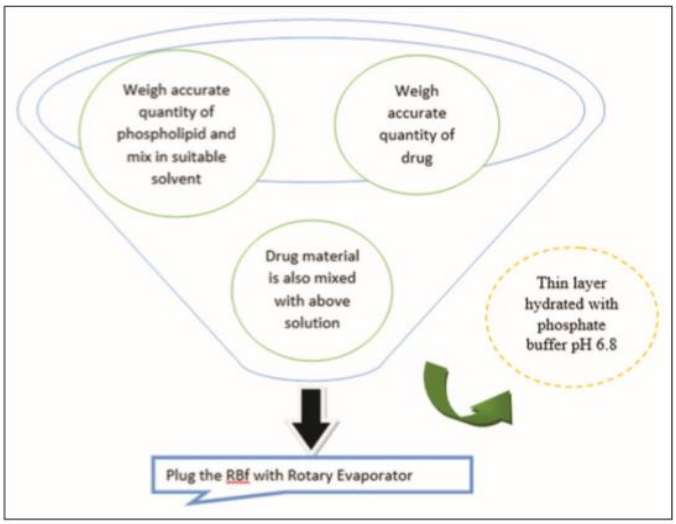

Fig.2: Preparation method for Phytosomes

Properties of Phytosomes

The term phytosome is used to define a complex between a natural product and natural phospholipids, like soy phospholipids that are obtained by the reaction of stoichiometric amounts of phospholipids and phytoconstituents in an appropriate solvent. Spectroscopic data reveal that the main phospholipid-substrate interaction is due to the formation of hydrogen bonds between the polar head of the phospholipids [i.e., phosphate and ammonium groups] and the polar functionalities of the substrate.

1. Phytosomes can accommodate the active principle that is anchored to the polar head of the phospholipids, becoming an integral part of the membrane. For example, in case of the catechindistearoylPCcomplex, there is formation of H-bonds between the phenolic hydroxyls of the flavones moiety and the phosphate ion on the PC side. [22]

2. Phosphotidylcholine: Study of comparisons of nuclear magnetic resonance of the complex with those of the pure precursors indicates that the signals of the fatty chain are almost unchanged. Such evidences inferred that the two long aliphatic chains are wrapped around the active principle, producing a lipophilic envelope that shields the polar head of the phospholipid and the catechin. [23,24]

3. Phytosomes are advanced forms of herbal products that are better absorbed, utilized and, as a result, produce better results than conventional botanical herbal extracts. The increased bioavailability of the phytosome over the non-complexed botanical derivatives has been demonstrated by pharmacokinetic studies or by pharmacodynamic tests in experimental animals and in human subjects. [25,26]

4. Phytosomes are lipophilic substances with a definite melting point, freely soluble in non-polar solvents, and moderately soluble in fats.[27,28]

5. When treated with water, they assume a micellar shape, forming structures that resemble liposomesexhibiting fundamental differences.[29,30]

Characterization Of Phytosome: [31,32]

The main aspect which regulate the performance of phytosomes in both biological and physical system are chemical composition and purity of the starting materials, membrane permeability, physical size and percentage entrapped solutes and hence the phytosomes are differentiated for specialties like size, shape, entrapped volume, percentage drug captured and released and chemical composition. 1H-NMR, 13C-NMR and IR spectroscopy is undertaken tostudy the complexation and molecular interactions between phosphatidylcholine and components. For the quantification of thermal effects such as fusion, loss of solvent and decomposition of the phytosome is performed by Thermal gravimetric analysis [TGA] and differential scanning colorimetry [DSC] [33,34].

In addition to those stated above the other methods used are Thin Layer Chromatography [TLC], Infra-Red Spectroscopy, NMR spectroscopy, X-Ray Diffraction Analysis, Scanning Electron Microscopy [SEM], Transmission Electron Microscopy [TEM], Percentage drug entrapment and Photon correlation Spectroscopy [PCS].[35]

- 1H-NMR The NMR spectrum is engaged for reckoning the formation of complex between the active constituents and phosphatidylcholine portion. In nonpolar solvents there is an evident change in 1H-NMR signal commencing from atoms included in the complex formation. The signals from protons are broadened. In phospholipids there is broadening of signals whereas the singlet correlative to the N-(CH3)3 of choline yields an upfield shift [36,37].
- 13C-NMR The 13C-NMR of phytosomes, when recorded in C6D6 at room temperature all the carbons of phytoconstituents are unobservable. The signals equivalent to the choline and glycerol portion is broadened whereas some are shifted and most of the resonance of the fatty acids chains maintains their initial sharp lines. [38]
- FTIR The spectroscopic interpretation of the resultant complex can be firmly established by FTIR. It also confirms the stability by comparing the spectrum of the complex with that of the micro-dispersion in water after freeze-drying at varying time interval [39].
- In HPTLC different retention factor values from the phytoconstituents are eluted with the preferred solvent system confirms the formation of a new moiety. [40]
- DSC and XRD The pure drug, which is crystalline in nature, indicates a sharp peak as high melting point in DSC thermogram whereas resultant phytosome shows a broader peak, which indicates the loss of crystallinity and low melting point than that of pure drug. Similarly the diffraction angle [2θ] of phytoconstituent, phospholipid and the phytosomes are compared which

indicates loss of crystalline peaks of drugs confirming the interaction and entrapment of drug within a sheath. [41,42]

- SEM The SEM shows photomicrograph of the phytosomes after coating it with a very thin layer of gold. It indicates no impurity on surface and confirms the spherical shape of the phytosomes. [43]
- TEM The TEM study investigates the enclosed elements where the drug is entangled and its distribution within the phospholipid mesh. [44]
- PCS and Percentage Drug Entrapment Photon Correlation Spectroscopy [PCS] technique is employed for inspecting the size of the phytosome and confirming its vesicular structure after hydration. The percentage drug entrapment is resolved by extracting the phytosomes with convenient solvent systems by centrifugation and analysing the supernatant for detection of drug by either High Performance Liquid Chromatography [HPLC] method or UV-Visible spectroscopy. [45]

Applications Of Phytosomes: [46.47,48]

The primordial study of phytosomes was focused on Silybummarianum[Family Steraceae], whose fruit contains flavonoids known for hepatoprotective effects and has shown convincing outcomes in treating liver diseases like hepatitis, cirrhosis, fatty infiltration of the liver and inflammation of the bile duct. Silymarin chiefly contains three flavonoids out of which Silybin overrule, superseded by silychristin and silydianin. It is fact that silybin is the one which is most potent as it shields the liver by conserving glutathione in the parenchymal cells. In its native form within the milk thistle fruit, silybin predominatly occurs in complexation with sugars [such as flavonolignan or flavonyl glycoside]. [49] Francesco et al., studied an oral formulation of coated tablets [Monoselect Camellia®][MonCam] containing greatly bioavailable green tea extract [GreenSelect® Phytosome] for analyzing overweight subjects [n=100] of both genders on a hypocaloric diet which results into the total absence of adverse effects and thus appears to be a an effective and safe tool for weight loss. [50,51] Mukerjee et al. developed a novel hesperetinphytosome by making complex of hesperetin with hydrogenated phosphatidyl choline. The complex was then evaluated for antioxidant activity, which communicate that the phytosome had higher relative bioavailability than that of active drug entity. [51,52,53] Ravarotto et al., asserted that silymarin phytosome shows better anti-hepatotoxic activity than crude silymarin. [54]

Table I: Commercial Phytosomes Products [55,56,57,58]

Phytosomes Phosphatidyicholine	Phytoconstituent complexed	Indication	Dose
Silybin Phytosome	Silybin from silymarin marium	Nutraceutical, antioxidant for Liver and skin	120mg
Ginkgo Phytosome	24%ginkgo flavonoids from *Ginkgo biloba*	Protect brain and vascular lining	120mg
Olive oil Phytosome	Polyphenols from Europaea oil	Antioxidant, antiinflammatory, Anti-hyperlipidemic	-
Grape seed phytosome	Procynid ins from *Vitis vinifera*	Nutraceutical, systemic antioxidant	50-100mg
Haw thorn Phytosome	Flavonoids from carteagus sp.	Nutraceutical, cardio protective, Anti hypertensive	100mg
Centella Phytosome	Terpenes	Vein and skin disorders	-
Ecdhinacea Phytosome	Echinacoside from *Echinacea augustifolia*	Nutraceutical, immunomodulator	-

2. CONCLUSION

This review is an attempt to present a concise profile of phytosomes as a delivery system. Herbosomes are novel formulations which offer improved bioavailability of hydrophilic favonoids and other similar compounds through the skin or gastrointestinal tract. They have many distinctive advantages over other conventional formulations. The formulation methodology for phytosome is simple and can be easily upgraded to a commercial scale. The characterization methodologies and analytical techniques are well established for this type of novel formulation. Many patents are already approved for innovative formulations, processes and applications of phytosomes. As far as the potential of phytosome technology is concerned, it has a great future for use in formulation technology and applications of hydrophilic plant compounds.

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CONFLICT OF INTEREST

Authors have no conflict of interest**.**

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