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Original Research Paper

Pharmacy

PHYTOSOMES: AN UPDATED REVIEW

Prof. Kapil Kumar*	Samrat Prithviraj Chauhan, College Of Pharmacy, Kashipur, Uttarakhand, India *Corresponding Author
Meena Kausar	Samrat Prithviraj Chauhan, College Of Pharmacy, Kashipur, Uttarakhand, India
Amit Kumar Sen	Samrat Prithviraj Chauhan, College Of Pharmacy, Kashipur, Uttarakhand, India
Manish Kumar Saxena	Samrat Prithviraj Chauhan, College Of Pharmacy, Kashipur, Uttarakhand, India
Vaishali Rajput	Samrat Prithviraj Chauhan, College Of Pharmacy, Kashipur, Uttarakhand, India

ABSTRACT "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. 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. The phytosome technique reduces these tasks to reasonable extents. The phytosome or Herbosome technique increases the hydrophilicity of highly lipophilic drug there by making it suitable for drug delivery and increases the lipophilicity of hydrophilic phytoconstituents adequately to cross biological membrane. The topical application of phytosomes for cosmetic purpose has already been proven. 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.

KEYWORDS : Phytosomes, Novel drug delivery system, Phospholipid.

INTRODUCTION

Herbal products have gained immense attention and access to the medicine marketsthroughout the globe as safer and effective substitutes of modern synthetic medicines which are considered to be full of adverse and toxic interactions. In under developed and developing nations all over the world plant drugs in traditional forms have been supposed to satisfy the primary healthcare needs of about 80% of the population and even in developed nations these medicines are being utilized by about 65% of the population[1,2].

However, the bioavailability of the plant phytoconstituents has become an issue of concern for researchers because many of them have poor oral bioavailabilities, specifically those containing polyphenolic rings in their structures which are water soluble such as flavonoids, terpenoids and tannins[3]. The reasons for the poor bioavailability of these substances are low aqueous or lipid solubility, high molecular weight/size and poor plasma membrane permeability. Moreover,orally administered plant extracts are also subject to degradation or destruction in thepresence of gastric fluids (Bhattacharya, 2009). This has therefore restricted the use ofpharmacologically effective polyphenolic plant actives for treating various disorders[4]. In order to address these challenges and enhance the effectiveness of herbal therapy severalnovel delivery systems have been trailed in the recent time. These delivery systems include liposomes, niosomes and transferosomes with liposomalformulations being the most popular[5].

World Health Organization (WHO) estimates that 80% of the worldpopulations presently use herbal medicine for primary health care. Every nation is seeking healthcare beyond the traditional boundaries of modern medicine; turning to self medication in theform of herbal remedies. 1 Modern herbal medicine is based upon the combination of traditionalknowledge, clinical experience, understanding of medicinal science and scientific evidence ofherbal medicine[6]. People are slowly and gradually switching to alternative forms of medicine. One of these many alternative therapies include herbal system of medicine. It is made of from anextract taken from the plant parts (leaf, root, flower and bark). They are absolutely natural andsafe form of curing illness form occurring repeatedly. They help in curing the ailment and arealso known to prevent the illness from occurring repeatedly. Herbal medicines may have longcuring periods, but they eradicate the illness from it and prevent any future episodes of thesame[7,8].

Despite criticism of herbal medicine among mainstream medical professionals , it is wise to remember that many common drugs we use today were derived from plant based sources .Manyof the pharmaceuticals currently available to physicians have a long history of use as herbalremedies, including opium, aspirin , digitalis and quinine . According to World HealthOrganization (WHO) approximately 25% of modern drugs used have been derived from plants[9].At least 7000 medical compounds in modern pharmacopoeia are derived from plants. Amongthe active compounds currently isolated from the higher plants and which are widely used inmodern medicine today show a positive correlation between their modern therapeutic use and thetraditional use of the plants from which they are derived[10].

Advantages of herbal system of medicines[11]:

- Lower risk of side effects
- Widespread availability
- Effectives with chronic medicine
- Low cost effectiveness make them all the more alluring
- Efficacious for life style diseases for prolonged period of time
- Natural detoxification process of the body is effectively enhanced by herbal medicine.
- These type of formulation are best for the people who are allergic to various types of drugs.
- These types of medicines do not have any types of side effects as they are free from chemicals.

Disadvantages of herbal system of medicines[5]:

- Bulk dosing.

- Poor stability in higher acidic pH, liver metabolism etc.
- Large molecular size limiting the absorption via passive diffusion.
- Poor lipid solubility hence preventing their ability to cross the lipid-rich biological membranes.
- High mount of raw material is required for processing the medicine.
- Isolation and purification of individual components from whole herbal extract lead to partial or total loss of therapeutic activity

These limitation lead to reduced bioavailability and hence, low therapeutic index of plant activeconstituents. Often, the natural synergy is gone which is due to chemically related constituentspresent in herbal extract. Hence considerable attention has been given to development of noveldrug delivery system for herbal drugs[12].

Novel Herbal Drug Delivery System

Novel herbal drug delivery system opens new way for delivery of herbal drugs at right place, atright concentration, for right period of time and also gives scientific evidence to verify the standardization of herbal drug. With the progress in all fields of science and technology, the dosage forms have evolved from simple pills to highly sophisticated technology intensive drugdelivery systems, which are known as Novel Drug Delivery System (NDDS)[15]. In the past decadesconsiderable attention has been focused on the development of novel drug delivery systems forherbal drugs. Herbal drugs are becoming more popular in the modern world for their ability tocure various diseases with less toxic effects and better therapeutic effects[13].

Advantages of Novel herbal drug delivery system[14]

- Help to increase the efficacy and reduce the side effect of various herbal compounds.
- Quantity of component becomes less with improving quality of drug effect.
- Fewer raw material are required to achieve the desire effect and control drug delivery to provide exact specification regarding drug dose form.
- Ready to use devices are acceptable in today's fast life style where time is important.
- Carry maximum amount of drug to the site of action by passing all barriers such as acidic pH of stomach
- Increases prolong circulation of drug into blood due to their small particle size.
- Reduce repeat dose administration

Phytosomes

These are sometimes referred to as pharmacosomes, naturosomes or phospholipid-complexes. In recent years, the technique of complexing plant drugs with phospholipids has emerged as a challenging but one of the most successful methods for improving bioavailability and therapeutic efficacy of a number of poorly absorbed plant constituents. This technique uses phospholipid molecules containing phosphatidylcholine in their structure to form complexes (phytosomes) with standardized herbal extracts and/or the specific active pharmaceutical ingredient of the plant[15]. As a result, the phytosome complex improves the membrane permeability, oil-water partition coefficient and hence the systemic bioavailability of these drugs.Incorporation of water soluble drugs into phospholipid complexes considerably enhances bioavailability of the phytoconstituents by increasing penetration through the lipoidal plasma membrane while the phospholipid complexation of poorly water soluble drugs, increases bioavailability by improving solubility in gastric fluids. The phyto-phospholipid complexation technique in recent years has made it possibleto administer highly efficacious plant actives with an improved biological profile[16].

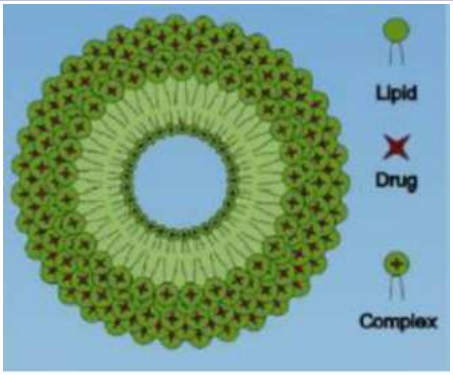

Figure 1: The phytosome complex

Background of phytosomes

Phytosomes were first developed by Indena® in 1988, an Italian nutraceutical company (Indena®, 2016; Simms, Quinn & Wendel, 2000). Within the framework of their studies, after observation that phospholipids had a marked affinity for flavonoids, they developed a new series of compounds designated "Phytosome®" which were essentially complexes from the complexation of polar botanical derivatives and phospholipids[25]. These complexes were considered to be novel entities on the basis of their physicochemical and spectroscopic characteristics. Their characterization revealed that they were solid lipophilic substances, with a defined melting point, freely soluble in aprotic solvents, moderately soluble in fats and insoluble in water. Interestingly, when treated with water the phytosomes assumed a micelle arrangement, similar to that of liposomal dispersions[17].

The fundamental difference is that in liposomes the active principle is the aqueous cavity enclosed by the phospholipids whereas in the phytosome the active principle is an integral part of the phospholipid through molecular interactions. The aforementioned structural differences are the basis of the advantages of the phytosomes over the liposomes[27]. For instance, due to the presence of molecular interactions in phytosomes, the complex is more stable than the liposome which is mainly prone to structural[18].

Also, on the basis of the chemical bonds present in the phytosome, the improved bioavailability is more pronounced than that with liposomes. The natures of the interactions present in the phytosome complex are dealt with in detail in the next section[19].

Phytoconstituent - phospholipid interactions

Phytoconstituents interact uniquely with phospholipid molecules through chemical bonds with them. This has been established by characterization techniques involving (Nuclear magnetic resonance (NMR), differential scanning calorimetry (DSC) and Fourier transform infrared (FT-IR) spectroscopy, where analysis of drug–phospholipid complexes were compared with respect to analyses of pure drug and their physical mixture with phospholipids[20].

Type of phospholipids

Phospholipids are indispensable components of all cellular and sub-cellular membranes, they can arrange as bilayer membranes. They are widely distributed in humans, animals and plants.These molecules possess a hydrophilic head group and hydrophobic acyl chains are linked toan alcohol[21]. The variation in head groups, aliphatic chains and alcohols leads to the existenceof a wide variety of phospholipids. Examples include phosphatidylcholine,phosphatidylinositol, phosphatidylethanolamine, phosphatidylserine, sphingolipids andcardiolipin, which are predominantly

found in eukaryotic cell membranes. In addition, the different sources of phospholipids also enhance the species of phospholipids. Various phospholipids, such as soybean phosphatidylcholine, egg phosphatidylcholine, o r synthetic phosphatidylcholine, as well as hydrogenated phosphatidylcholine, are commonly used in different types of formulations[22]. Phosphatidylcholine and phosphatidylethanolamine are most abundantly present in the lipidfraction of most biological membranes and they mainly constitute the matrix of thesemembranes.

Advantages Of Phytosome Vesicles[23]

1. They quickly pass across the cell membrane and enter the cell.
2. There is a noticeable increase in the drug's bioavailability.
3. Phytosomes ensure that herbal medicines have a long time of operation.
4. Phytosomes improve the bioavailability of hydrophilic polar phytoconstituents by increasing their absorption by nasal, topical, and other routes.
5. Phytosomes create a tiny cell that preserves the valuable components of herbal extracts from digestion secretions and intestinal bacteria.
6. Phytosomes persuade proper medication distribution to the necessary tissues.
7. Assigning the herbal medicine as phytosomes does not have to jeopardize the nutritional purity of the herbal extracts.
8. Due to the maximum absorption of the main constituents, the dose requirement has been reduced.
9. They enhance biologically active constituent absorption and reduce dosage specifications.
10. Chemical bonds formed between the phosphatidy lcholine molecule and phytoconstituents indicate that phytosomes have a strong stability profile.
11. Phytosomes enhance phytoconstituent transdermal absorption and are commonly used in cosmetics due to their increased skin penetration and high lipid profile.
12. Phytoconstituents in phytosomes can quickly pass through tissue walls in the intestine and are best absorbed.
13. The phytosome complex is biodegradable, and drug entrapment is not a concern.
14. Phytosomes enhance the effect of herbal substances by optimizing absorption, increasing biological activity, and supplying to the target tissue; as a result, they are appropriate for use as a drug delivery mechanism.
15. Since the compound is conjugated with lipids in the development of vesicles, entrapment efficiency is high.
16. Drug entrapment is not an issue when creating phytosomes.
17. Phosphatidylcholine, which is used to make phytosomes, not only acts as a messenger, but it also nourishes the skin since it is a component of the cell membrane.
18. In skincare items, phytosomes outperform liposomes.
19. Phytosomes have been shown to have a major therapeutic advantage.
20. Phosphatidylcholine, which is used in the preparation of phytosomes and serves as a transporter as well as a hepatoprotective, has a synergistic impact when combined with hepatoprotective compounds.
21. Their poor aqueous solubility allows for the formulation of a robust semisolid dosage type.
22. Facilitates liver targeting by rising bile salt solubility

Preparation methods

Various methods are used for production of phytosomes including anti-solvent precipitation, solvent evaporation, precipitation and anhydrousco-solvent lyophilization. The main methods, namely,anti-solvent and solvent evaporation, will be discussed[24].

Solvent evaporation

In the solvent evaporation method, the drug and the phospholipids are placed in the same flask containing a suitable solvent system such as tetrahydrofuran or ethanol or in separate flasks with different organic solvents. The reaction is allowed to be carried out by sonication, refluxing or stirring at suitable fixed temperature for a fixed duration of time to get maximum possible yield and drug entrapment. The solvent is then evaporated under vacuum or at room temperature to yield a residue which is then flushed with nitrogen gas. The resultant formulation was then refrigerated andon analyzing the complex showed 44% entrapment of marsupsin[25].

Anti-solvent precipitation

The traditional anti-solvent precipitation technique is the most utilised by many researchers. It incorporates n-hexane as the anti-solvent to precipitate out the drug–phospholipid complex from the organic solvent.

In this method, both the plant extract/active and phospholipids are dissolved in the same solvent, and refluxed for a fixed time at a fixed temperature resulting in a clear solution[26].

Properties of phytosomes

1. Chemical properties

Phytosomal complex is obtained by reaction of stoichiometric amounts of phospholipid and the substrate in an appropriate solvent. On the basis of spectroscopic data it has been shown that the main phospholipid-substrate interaction is due to the formation of hydrogen bonds between the polar head of phospholipids (i.e. phosphate and ammonium groups) and the polar functionalities of the substrate. in phytosomes the active principle is anchored to the polar head of phospholipids, becoming an integral part of the membrane This can be deduced from the comparison of the NMR of the complex with those of the pure precursors. The signals of the fatty chain are almost unchanged. Such evidences inferred that the two long aliphatics chains are wrapped around the active principle, producing a lipophilic envelope, which shields the polar head of the phospholipid and the phytoconstituent[27].

2. Biological Properties

Phytosome 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 thephytosome over the non-complexed botanical derivatives has been demonstrated by pharmacokinetics studies or by pharmacodynamic tests in experimental animals and in humansubjects[28].

3. Pharmacological properties

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Evaluation parameters of phytosomes

1) Particle size distribution

DLS (dynamic light scattering) is used to determine the size distribution, particle size as well as zeta potential of phytosomes formulation. The diluted formulation is injected to the zeta potential measuring cell to determine the electric potential such as zeta potential (stern layer)[30].

2) Entrapment efficiency

In order to determine the entrapment efficiency, centrifuged the formulation at 112000rpm for one hour. After that,

siphoned out the supernatant and take absorbance of supernatant at 420nm using UV spectrophotometer. Add 1ml of 0.1% triton-x100 into sediment, made the volume up to 100ml using phosphate buffer of pH 7.4,note down the absorbance at 420nm and find out the percentage entrapment[31].

% entrapment = amount of drug in sediment/total amount of drug added × 100

3) Optical microscopy

Pour one drop of diluted phytosomeformulation, wipe off the excess amount of liquid with the help of filter paper, allow it to dry and observed under optical microscope[25].

4) Stability studies

As per the ICH guidelines 30±2°C/60±5% and 40±2°C/75±5% RH for the period of 3 months, are the specific conditions to evaluate the stability of phytosomes formulation.

5) Compatibility studies (Drug-excipients)

FTIR (Fourier Transform Infrared Spectrophotometer) and potassium bromide (KBr) dispersion methods are used to examine the physicochemical compatibility in between herbal drug extracts and polymer used to formulate the phytosomes formulation.

6) In-vitro drug release

Dissolution apparatus is used to determine the in-vitro drug release, pour 900ml HCl (0.1N) into dissolution flask, maintain the temperature at 37±5°C and speed od paddle at 50 rpm[26].

S.N.	Trade Name	Active Compounds Formulated withPhytosome Technology
1	Boswellia Phytosome	Boswellic acids from Boswellia serrata's resin
2	Boswellic acids from Boswellia serrata's resin	Ginkgoflavon, glucosides, ginkgoterpenes and phosphatidyleseine from Ginkgo biloba's leaf
3	Centellaasiatica selected triterpenes phytosome	Selected triterpenes from Centellaasiatica's leaf
4	Ginkgo biloba dimeric flavonoids phytosome	Biflavones from Ginkgo biloba's leaf
5	Leucoselect phytosome	Proanthocyanidins from Vitis vinifera's seed
6	Ginkgo biloba terpenes phytosome	Ginkgoterpenes, bilobalide and ginkgolides from Ginkgo biloba's leaf
7	Rexatrol resveratrol rhytosome	Resveratrol from Polygonum cuspidatum's rhizome
8	Sericoside phytosome	Sericoside from Terminalia sericea's root bark
9	Siliphos silybin Phytosome	Silybin from Silybummarianum's fruit
10	Hawthorn phytosome	Vitexin-2"-O-rhamnoside from Crategus' flowering top
11	Greenselect phytosome	Polyphenols from Camelia sinensis' young leaf

Applications of phytosomes

1) Scientific studies have been proved that phytosomes made with Gingko biloba leaves exhibits prolonged and better therapeutic response due to sustained release of herbal drug as compared to Gingko biloba leaves extract. 24% ginkgo flavones glycoside and 6% terpenes lactones are present in Gingko biloba leaves extract. Studies were also conducted on gingko phytosomes which yielded better result as compared to the conventional form. For conducting the aforesaid studies ginkgo phytosomes was administered for 5 days in guinea pigs, in whom the bronchoconstriction was induced by three different agonists (histamine, PAF and Acetylcholine). The bronchospastic inhibition was measured at the maximum peak, expressed as variations versus the basal values. The result indicated that ginkgo phytosomes can not only counteract direct bronchoconstriction but also it possesses the tendency to reduce the TXA2 mediated bronchoconstriction of histamine and PAF. Studies have also proved the improved efficacy of ginkgo phytosomes over the conventional standardized extract in protecting rat isolated hearts against ischemia. The above-mentioned results clearly give an indication about the upper hand that phytosomes possess over the conventional preparations, thus proving its utility for herbal phytoconstituents.

2) Grape seed phytosomes is composed of oligomeric polyphenols (grape proanthocyanidins or Procyanidine from grape seed extract, Vitis vinifera) of varying molecular size complexed with phospholipids. The main properties of Procyanidine flavonoids of grape seed are an increase in total antioxidant capacity and stimulation of physiological defenses of plasma, protection against ischemia/reperfusion induced damages in the heart, protective effects against atherosclerosis thereby offering marked protection against the cardiovascular system.

3) Most of the Phytosomal studies are focused on Silybummarianum (milk thistles) which contains premier liver protectant flavonoids. Silymarin phytosomeare studied in rats for their pharmacokinetic properties. In the studies, the bioavailability of silybin in rat was increased remarkably after oral administration of silybinphospholipid complex due to an impressive improvement of the lipophilic properties of silybin-phospholipid complex and improvement of biological effect of silybin. It was also reported, Silymarin phytosome show better anti-hepatotoxic activity than silymarin alone and can provide protection against the toxic effects of aflatoxin B1 on performance of broiler chicks.

4) Phytosomes of curcumin (flavonoid from Curcuma longa, turmeric) and naringenin (flavonoid from grape fruit, Vitis vinifera) were developed. The antioxidant activity of the complex was significantly higher than pure curcumin in all dose level tested. In the other study the developed phytosome of naringenin produced better antioxidant activity than the free compound with a prolonged duration of action, which may due to decrease in the rapid elimination of the molecule from body.

5) Green tea leaves (Theasinensis) is characterized by presence of a polyphenolic compound epigallocatechin 3-O-gallate as the key component. These compounds are potent modulators of several biochemical process linked to the breakdown of homeostasis in major chronic-degenerative diseases such as cancer and atherosclerosis. Green tea also furnishes us with a number of beneficial activities such as antioxidant, anticarcinogenic, antimutagenic, hypocholesterolemia, and cardioprotective effects. In spite of such beneficial activities furnished by polyphenols from green tea extract the polyphenols suffer from the problem of poor bioavailability. The complexation of polyphenols derived from green tea with phospholipids strongly improves the oral bioavailability. A study on absorption of Phytosomal preparation was performed in healthy human volunteers along with non-complexed green tea extract following oral administration. Over the study period of 6 hours the plasma concentration of total flavonoids was more than doubled.

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 cosmoceuticals 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.

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