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A COMPREHENSIVE REVIEW ABOUT THE DEVELOPMENT OF PHYTOSOMES WITH DIFFERENT TECHNIQUES AND THEIR USAGE IN THE TREATMENT OF VARIOUS DISEASES

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ABSTRACT

The herbal medicinal plants are very diverse and herbs contain a wide variety of different phytoconstituents that have different pharmacological activities. Medicinal plants contain various phenolic phytochemicals that are proven to cure and treat various diseases. The herbal use is rather a non-systematic way that includes direct usage of plant medicinal part and forming their dosage form (Like churn, bhasma, etc.). In this way of treatment, there are several drawbacks like allergic reactions, drug overdose, adulterations, un-specificity of site of drug action and more. Phytoconstituents of the herbal plants are a great way to re approach the treatment of diseases. This way of treatment can be combined with the pharmaceutical approach and the treatment can be done in a specialized and technical way i.e. Phytosomes.

In this article, we will discuss about the different methods by which phytosomes can be prepared and their usage in treating many diseases. Phytosomes are the novel drug delivery systems that have the unique ability to deliver drug molecules specially the plant phytoconstituents to the site where there is the need. Phytosomes are the specialized pharmaceutical formulation, which are capable of delivering the herbal phytochemicals inside the body.

KEYWORDS: *Phytosomes, Herbal medicines, Phosphatidyl choline, Liposomes.*

INTRODUCTION

The conventional treatment of diseases involves synthetic drug molecules that have many side/adverse effects and some even damage the tissues of organs, well our huge pharmaceutical industries are based on this and also, they are necessary in life saving situations. But when the matter of issue is with long term treatment/ chronic treatment, the best way is to go with the herbal usage of medicines. The herbal use of medicinal plants are rather non-systematic way that include direct usage of plant medicinal part and forming their dosage form (like churna, bhasma, etc.). In this way of treatment, there are several drawbacks like allergic reactions, drug overdose, adulterations, un-specificity of site of drug action and more. Phytoconstituents of the herbal plants are a great way to re approach treatment of diseases. This way of treatment can be combined with the pharmaceutical approach and the treatment can be done in a specialized and technical way i.e. Phytosomes.[1]

Novel Drug Delivery Systems are the drug formulations that are the specialized way of drug delivery in which the older side/adverse effects of the conventional dosage forms get reduced. Phytosomes are the novel drug delivery systems that have the unique ability to deliver the drug molecules specially the plant phytoconstituents to the site where there is the need. Phytosomes are the specialized pharmaceutical formulation, which are capable of delivering the herbal phytochemicals inside the body. Phytosomes constitute of hybrid structure involving the lipid molecules bound with the chemical ingredient. They are very small in size and serves in high penetration among the body tissues. This property helps in delivering drug molecules to the site of action. The phytosomes have a great absorption property and they get easily solubilized in many solvents.

Mechanism of phytosomes: When a standard amount of phosphatidyl choline is mixed with a standardized extract containing usually polyphenolic compounds, they react in a solvent to form Phytosomes. Phosphatidyl choline (PC) is an amphiphilic substance, with a hydrophilic choline structure attached with a lipophilic structure.

Phosphatidyl choline acts as a transporter and transports the drug molecule to the site of action. The PC structure envelops and binds to the polyphenolic compounds of the herbal extract and create a phospholipid structure having lipid soluble nature. Some of the spectroscopic techniques which were used to view the molecules in detail show that the molecules are linked to the polar choline head of the phospholipids by chemical bonds. It is

described by the chemical investigators that the phytosome is connected with one phophatidyl choline by a flavonoid molecule of the extract.[2]

The flavonoid and terpenoid components of the plant extract are bonded very easily to the choline moiety of the PC. PC is a bi-functional substance which has hydrophilic and lipophilic property. This function can be used in the pharmaceutics to purport the drug molecule inside the barriers of body.

The main purpose of making of the phytosome is that the herbal polyphenolic compounds and flavonoids are poorly absorbable in our tissues which are lipid in nature.

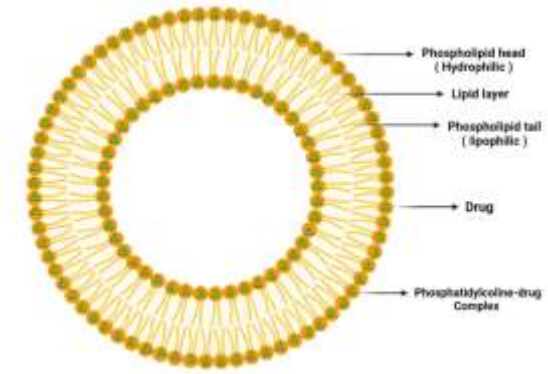

Fig. 1: Structure of phytosome.[18]

Advantages

1. Phytosomes are safe in use as they don't show any side/adverse effects.
2. They combine with the drug/API and show enhanced bioavailability.
3. They can be used to target the drug to the site of drug action.
4. They can be useful in increasing the solubility of water insoluble ingredients.
5. Lower dosage is required to incorporate into the phytosomes.
6. Phytosomes are comparatively more stable than the liposomes.
7. Phytosomes could be used to increase the nutritional potential of plant phytoconstituents.
8. The phospholipids in the phytosomes also protect the plant excipients from degradation by the gastric juice in stomach.
9. Phytosomes can be prepared easily in lower prices.
10. Phytosomes increase the penetrability of the molecules through the skin.

Structure of phytosomes

Phytosomes have the size of 50nm – few 100nm. The structure of the phytosomes is round, spherical in shape which has an empty void inside it that allows it to store or transport the chemicals/drug molecules inside the body. This spherical structure is composed of combination of choline moiety i.e. a polar head, and plant phytoconstituents. The polar head is covered by a chain of fatty acids which leads to lipophilic surface.

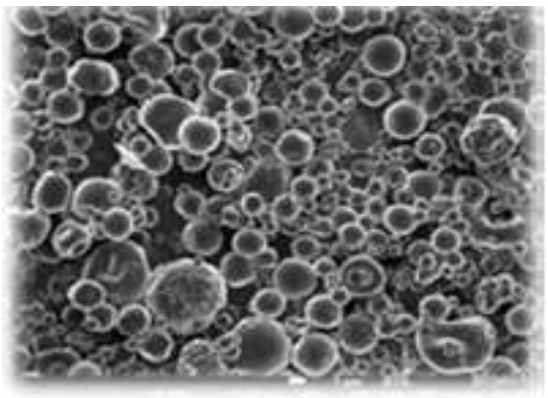

Fig. 2: SEM of Phytosome.[1]

Physico-chemical properties

Phytosomes are the semi-lipoid structures that have size less than a micro meter. This small size helps in the penetration of molecular membrane in our body. Phytosomes range between 50nm – few 100nm. When they are dissolved in water they show similar characteristics as of liposomes, like the micellar structure under microscope. This micellar structure is the result of bonding between the hydro and lipo part of the molecules which are arranged in the form of layered spheres.

According to the 1H-NMR and 13 C-NMR data it is observed that the structure of fatty acids are unchanged in phospholipid and in complex, which is due to the long chain aliphatic molecules arranged in such a form that it surrounds the active molecule. This property of phytosomes can be used for enveloping the drug/active pharmacological ingredient inside it.

The phytosomes are easily soluble in aprotic solvent, relatively less (Moderately) soluble in fats, not soluble in water, and unstable in alcohol.

But when these phytosomes are complexed with curcumin, which is lipophilic in nature, it shows increased effect in water solubility.[9]

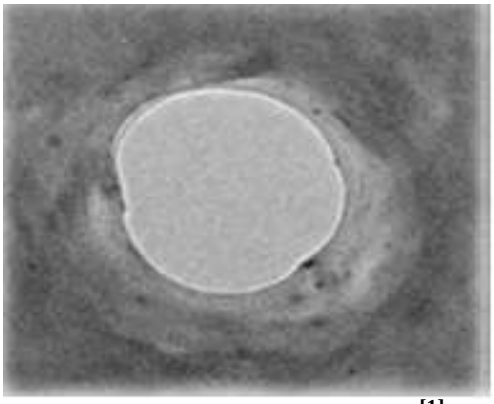

Fig. 3: TEM of Phytosome.[1]

Biological properties

Phytosomes are the novel delivery systems that can be absorbed quickly and shows improved bioavailability than mere drug, therefore it has can show improved result than the conventional dosage form as shown in many researches involving the animal and human pharmacokinetic studies.

Phytosomes consists of the entrapment of the polyphenolic content of herbal plant extract, whereas liposomes have the hydrophilic drug molecule that is enveloped between the lipid membrane of liposomes. In phytosomes there are 1-4 phospholipid molecules that interact with the plant phytoconstituents, but in liposomes there are several hundreds of lipid structures that interact and form the layer entrapping the drug molecules inside it.[9]

METHODOLOGY

Phytosomes constitute of 2 structures – phosphatidyl part, which is lipophilic in nature and choline moiety which is hydrophilic that's attached to the herbal plant phytoconstituents via a polar end, with the help of an ampiphilic solvent like ethanol/methanol. This makes the lipid complex which is highly stable and has increase bioavailability. The phospholipid used in the formation could be of natural or synthetic nature.[1,2]

Solvent evaporation: The solvent evaporation technique is simple and easy procedure, in which the cholesterol is dissolved in a solvent, and in another flask phospholipid and an appropriate solvent at a standard ratio (1:1) are mixed. Both the solutions are refluxed and made complexes by mixing them together. This is agitated until the solvent is evaporated and a film is formed at the bottom. This film is then hydrated with the polyphenolic extract and then sonicated in an ice bath. The phytosomes are collected and size reduction is performed after hydration.[3,7]

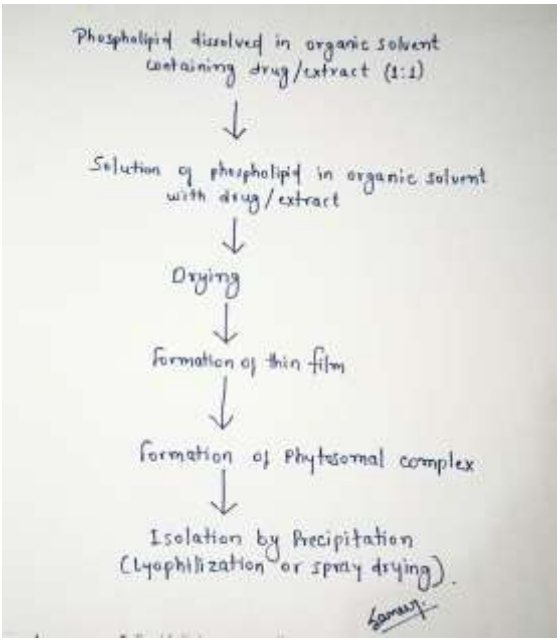

Fig. 4: Phytosome preparation.

Rotary evaporator technique can also be used for the preparation of phytosomes. In this technique herbal plant extract is taken in a 250 ml round bottom flask with anhydrous ethanol and phophatidylcholine. This is then connected with a rotary evaporator apparatus under reduced pressure with implying vacuum. The solution is heated at 60^0C until a thin lipid film is concentrated at the bottom.[3] This lipid layer can be dissolved in a phosphate buffer solution which makes it a suspension. Sonication was performed using a probe sonicator at 60% amplitude. This phytosomal suspension is then stored in a refrigerator for 24 hrs.

Reflux methods can be used for the formulation of phytosomes. Phospholipid and the plant extract were mixed in a solvent Dichloromethane and refluxed under reduced pressure with increased temperature at 40°C for 1 hour. The solution was evaporated and n-hexane (15mL) was added and precipitation was formed. This precipitate was removed, dessicated and stored (Sikarwar M. S. et.al, 2008).

Ether injection method:- In this method drug's lipid complex is dissolved by using an organic solvent. The vesicles are made by injecting this complex into an aqueous agent which is heated. Monomers are formed when the concentration is low and different structures (like sphere, cylinder, disc, cubes etc.) are formed at higher concentration.[1] (Kim SM et.al, 2019).

Table no. 1: Comparison of Lipid based drug delivery system.

Properties	Liposomes	Transferosomes	Phytosomes
Structure	They are made of the greater variety of lipids that have cationic, anionic, and neutral lipids in them.	They are also bilayered containing phospholipids, edge activator which can be a bile salt or surfactant, ethanol as solvent and water as carrier.	They have the lipid dual layered vesicles that are bound to the plant phyto- constituents via the phospholipid moiety
Preparation	The lipid moiety are mixed together ad complex is formed, after that the drug contents are added in the lipid thin film.	Same as liposomes, the drug ingredients are added after the thin film is formed by the lipid components.	They are formed by mixing a 1:1, or 2:1 ratio of phosphatidyl choline and plant phytoconstituents to make them complex
Encapsulation	The lipid dual layer membrane contains the drug contents.	The aqueous core contains the drug molecules	The phytochemicals are bonded to the phosphatidyl part of the PC by chemical bond.
Skin absorption stability	Reduced stability and absorption	Reduced absorption in skin but very stable.	They have high stability.

Phytsomes used for treating diseases

Phytosomes are used for the treatment of various diseases involving different herbal plant extracts, which encapsulate the phytoconstituents in them bound to the Phosphatidyl part of the phytosome. Phytosomes can be used for long term treatment as they have relative low doses and low to no side effects than the conventional treatment.

In Gastric/Bowel diseases:- Oral silibinin and silybinphytosome were used in this study by Pellegrini L et al. (2016) in mice at dose 100 mg/kg and they showed lowering the tumour effects in bowel cancer.

Gemcitabine and the curcumin phytosome were studied by Pastorelli D et al. (2018) on about 44 pancreatic cancer patients and the phytosomes showed advancement in the cancer condition.[1]

In treating diseases involving nervous system:- Wistar rats were treated with phenobarbitone to induce sleep and lower the neuronal activities, then Curcumin phytosomes were used in them and it showed decrease in the neuronal impairment.[1] (Sbrini G et al. 2020).

Ashwagandha phytosomal complex 85mg/kg was given to the rats with Brain Ischemia, which showed decrease in the cerebral infarction upto 82.7% which could result in neuronal protection.[1][13]

Asthma and Bronchitis:- The phytosomes of Boswellia serrate was given to the patients of asthma at dose 500mg/day for 4 weeks. In comparison to the patients with conventional treatment these patients showed decrease requirement of inhalation.

Naringenin phytosomes were tested in rats directly in lungs in the form of Dry powder inhalation a dose 10mg/rat and they showed protection against lung damage.[14]

Lung cancer treatment:- In a study done by Ibrahim A et al. (2020) mammary glamd tumr cells were injecte in mice to induce the cacer cell growth and then they were treated with curcumin phytosomes. These curcumin phytosomes were shown to reduce MMP-9, a protein which is responsible for cancer growth thus reducing cellular metastasis.[15]

In skin cancer treatment:- It was found out when sinigrin-phytosome complex was evaluated against A-375 melanoma cells, that the phytosomes showed cytotoxic nature against cancerous cells.[16]

In metabolic syndrome treatment: The curcumin phytosomes were evaluated in 11 individuals having macular oedema caused by diabetes mellitus, it was shown theat the phytosomes increased visual and retinal thickness.[17]

CONCLUSION

Phytosomes serve as a great carrier for the transport of phytochemicals inside the body and protecting the medicine from GIT degradation. Phytosomes are safe, have enhance

bioavailability, target drug action, and increase solubility of water-insoluble ingredients. They are stable, require lower dosage, and can increase plant phytoconstituent nutritional potential. Phospholipids protect excipients from stomach degradation. They can be prepared easily, cost-effectively, and increase molecules' penetration through the skin. The herbal medicines have proven to cure treatment of major diseases like Cancer, Diabetes mellitus, Cardiac Disorders, Neurological disorders and many more. Modern novel techniques must be used for the formulation of medicines with the help of plant phytoconstituents. There appears to be huge growth in the medicinal industry with the use of herbs as natural treatment. Many new companies are promoting the use of herbs as their main ingredient for preparing medicines. Although deep research is needed in this area but yet continuous work is being done in this way.

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