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PHYTOSOMES AS AN INNOVATIVE TECHNIQUE IN NOVEL DRUG DELIVERY SYSTEM: A COMPREHENSIVE REVIEW

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Abstract

Phytosomes are novel form of herbal formulations which contains the bioactive phytoconstituent(s) of herb extract complexed with phospholipid to produce lipid compatible molecular complexes. Since 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. The objective of this review is to focus on the application of phytosome technology along with its preparation, various propertiesand characterization. The recent development and conducted works of various researchers have been studied thoroughly toestablish the transdermal route as a potential way to deliver phytoconstituents. Plant derived products or plant extracts areincreasingly 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 bioavailabilityproblems. Plant products after their isolation become prone to instability and are potentially unfit to cross the biomembrane assuch. Some plant products show hydrophobicity and their delivery to systemic circulation is a quite difficult task.

Keywords: Phytosomes, phospholipids, bioavailability, topical route, transdermal drug delivery.

Introduction

Medicinal plants have been acknowledged and are extremely valued all over the world as a prosperous source of bioactives for the prevention and treatment of ailments. Herbal medicines are being used by about 80% of the world population primarily in the developing countries for primary health care1. They have stood the test of time for their safety, efficacy, cultural acceptability and minimal side effects, liver an imperative organ has a crucial in the metabolism of xenobiotics that causes it to succumb to numerous hepatic diseases. Phytosomes are the novel form of herbal formulations contains the bioactive phytoconstituent(s) of herb extract complexed with phospholipid to produce lipid compatible molecular complexes, when treated with water, these complexes form a micellar structures [5].Phytosome is a newly introduced patented technology in which phytomolecule form complex with phospholipid by developing hydrogen bonds. They are able to transfer from the water phase external to the enterocyte lipid layer and from there into the cell, finally reaching into the blood.6 Such a complex results from the reaction of stoichiometric amounts of phospholipid with the selected polyphenolic phytoconstituent (such as simple flavonoids) in a nonpolar solvent.The term "Phyto" means plant while "some" means cell-like structure [2]. It is a patented technology that was introduced and developed by a leading herbal drug manufacturer and nutraceuticals®. The bioavailability of active principles of plants has become an issue of concern for researchers and scholars because of poor oral bioavailability of many plants specifically those containing polyphenolic rings in their structures such as flavonoids and other water soluble constituents like terpenoids and tannins [3].

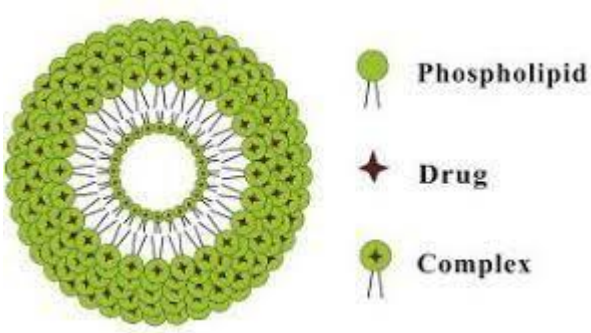

Figure 01: Phytosome structure.

Advantages of Phytosomes [4-7]

1. Phytosome have a simple formulation method in comparison with other nano drug delivery system like solid lipid nanoparticles and nanostructure lipid carriers. Phytosome help to drug protecting from unfortunate degradation. A Phytosome formulations leads to dose reduction when the absorption of active constituents is improved due to presence of phospholipids.
2. The entrapment efficacy increases because drug itself in conjugation and lipid is forming vesicle.
3. Phytosomal preparation helps to produce cosmetic and topical product with phytoconstituents.
4. The chemical bond between phosphatidylcholine molecule and phytoconstituents of plant extract shows better stability profile.
5. Phosphatidylcholine which is used as carrier in phytosomal formulations act as hepatoprotective and giving synergistic effect when used with hepatoprotective agent.
6. The phytosome can easily move from hydrophilic environment to lipophilic environment of the enterocyte cell membrane.
7. A cell like structure produced due to complex formulation which protect the important component of herbal extract from digestive fluid and gut bacteria.
8. The phytosomes are safe because the components used in phytosome preparation approved for pharmaceutical and cosmetic use.
9. The toxicological profile of phytosome component is well documented in scientific literature that is why it has no large scale drug development risk.

Disadvantages[8]

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 water9.

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 membrane10.

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 subjects11.

Additives used in preparation of Phytosomes

a. Phospholipids: Egg phosphatidyl choline, Disearylphosphatidyl choline, Soya phosphatidyl choline etc.

b. Solvents: Acetone, Dioxane, ethanol, methanol, n-hexane etc12.

Mechanism of Phytosome Formation

The phytoactive 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 phytosomes13. 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 circulation14.

Preparation of Phytosomes

Phytosomes are prepared by different methods by interacting 3-2 moles natural or synthetic phospholipid, mainly phosphotidylcholine 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 wasobtained 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 temperature18.

•**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 AND EVALUATION OF PHYTOSOMES

The behavior of phytosomes in both physical and biological systems is governed by factors such as the physical size, membrane permeability, percentage of entrapped solutes, and chemical composition as well as the quantity and purity of the starting materials. Therefore, phytosomes can be characterized in terms of their physical attributes i.e. shape, size, distribution, percentage, drug captured, entrapped volume, percentage drug released and chemical composition21.

Evaluation of Phytosomes

I. Characterization technique

1. Visualization: Visualization of phytosomes can be achieved using transmission electron microscopy (tem) and by scanning electron microscopy (SEM) [22].

2. Entrapment efficiency: The entrapment efficiency of a drug by phytosomes can be measured by the ultracentrifugation technique23.

3. Transition temperature: The transition temperature of the vesicular lipid systems can be determined by differential scanning calorimetric [22].

4. 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 densitometer24.

5. 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 tem25.

6. Drug content: The amount of drug can be quantified by a modified high performance liquid chromatographic method or by a suitable spectroscopic Method26.

Phytosome Formulations

Phytosome complexes can be formulated for oral as well as topical administration. Some possible phytosomal formulations are as follows,

Soft gelatin capsules

Soft gelatin capsules represent an ideal solution to formulate phytosome complexes. The phytosome complex can be dispersed in oily vehicles to obtain suspensions to be filled in soft gelatin capsules. Vegetable or semi-synthetic oils can be used to this purpose. Indena® recommend a granulometry of 100% <200 μm to best perform capsule production. According to Indena® experience, not all the phytosome complexes behave in the same way when dispersed in oily vehicles and when the oily suspension is filled in the soft gelatin capsules [27].

Hard gelatin capsules

The Phytosome complex can be formulated in hard gelatin capsules as well. A direct volumetric filling process (without precompression) can be applied, even if the apparently low density of the phytosome complex seems to limit the maximum amount of powder that can be filled into a capsule (usually not more than 300 mg for a size 0 capsule)12.

Tablets

Dry granulation represents the ideal manufacturing process to obtain tablets with higher unitary doses and with suitable technological and biopharmaceutical properties [11].

Topical dosage forms

The phytosome complex can be formulated topically as well. The ideal process to incorporate the phytosome complex in emulsion is by dispersing the phospholipidic complex in a small amount of the lipid

phase and add it to the already created emulsion at low temperatures (not higher than 40°C). The phytosome complexes are dispersible in the main lipidic solvents employed in topical formulations [10].

Applications of Phytosomes

1. Enhancing Bioavailability: Many researches have been done which shows improved absorption and bioavailability of phytosomes in comparison to the conventional methods. Most of the phytosomal studies are carried out on Silybummarianum (milk thistle) which contains liver-protectant flavonoids. The fruit of the milk thistle plant contains flavonoids which have hepatoprotective property [11].

2. Cancer treatment: The chemical components like flavones, isoflavones, flavonoids, anthocyanins, coumarins, lignins, catechins, and isocatechins of medicinal plants mainly possess antioxidant properties that contribute to their anticancer potential .However, a few plant based compounds are toxic at higher concentrations and induce certain side effects17.

3. Transdermal application: Rutin, one of the most common flavonoid (Rutagraveolens) used to treat capillary fragility, hypertension, ultraviolet radiation induced cutaneous oxidative stress, hepatic and blood cholesterol, cataract, cardiovascular disease and possesses antioxidant, anti-inflammatory, antithrombotic, antineoplastic, and antiplatelet activity [18].

Table 01: Commercial Products of Phytosomes Available [17,18,22].

Sl.no	Phytosomes trade name	Phytoconstituents complex	Indications
1.	Olea select phytosome	Polyphenols from *Olea europea*	Anti–hyperlipidemic, Anti inflammatory
2.	Green select phytosome	Epigallocatechin from *Thea sinensis*	Anti-cancer, Antioxidant
3.	Echinacea phytosome	Echinacosides from *Echinacea angustifolia*	Immunomodulatory, Nutraceuticals.
4.	Hawthorn phytosome	Flavonoids from *Crataegus species*	Antihypertensive, Cardioprotective
5.	Sericosidephytosome	Sericoside from *Terminalia sericea*	Skin improver, Anti-Wrinkles
6.	Ginko select phytosome	Flavonoids from *Ginko biloba*	Anti aging,Protects Brain and Vascular liling
7.	Melilotus (Lymphaselect) phytosome	Triterpens from *Melilotus officinalis*	Hypotensive, Indicated in Insomnia
8.	Curcumin (Merivaselect) phytosomes	Polyphenol from *Curcuma longa*	Cancer Chemo preventive Agent
9.	Mertoselectphytosome	Polyphenols, Antcinoside from *Vacciniummyrtilus*	Antioxidant
10.	Bilberry (Mertoselect) phytosome	Anthocyanosides from *Vaccinium myritillus*	Antioxidant, Improvement of Capillary Tone.

11.	Palmetto (Sabalselect) phytosome	Fattyacids, alcohols and sterols from *Serenoarepens*	Anti-oxidant, Benign Prostatic hyperplasia

Conclusion

Thephytoconstiuents 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 literature proves that the phytosomes are novel formulations which offer improved bioavailability of hydrophilic flavanoids 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.

References

1. Bombardelli E, Curri SB, Loggia Della R, Del NP, Tubaro A, Gariboldi P, Complexes between phospholipids and vegetal derivatives of biological interest, Fitoterapia, 1989,60,1-9.
2. Singh, A., Gowtham, S., Chakrapani, L.N., Ashokkumar, S., Kumar, S.K., Prema, V., Bhavani, R.D., Mohan, T. and Sathyamoorthy, Y.K., 2018. Aegeline vs Statin in the treatment of Hypercholesterolemia: A comprehensive study in rat model of liver steatosis. Functional Foods in Health and Disease, 8(1), pp.1-16.
3. Uppugalla S, Male U, Srinivasan P. Design and synthesis of heteroatoms doped carbon/polyaniline hybrid material for high performance electrode in supercapacitor application. ElectrochimicaActa. 2014 Nov 10;146:242-8.
4. Male U, Uppugalla S, Srinivasan P. Effect of reduced graphene oxide–silica composite in polyaniline: electrode material for high-performance supercapacitor. Journal of Solid State Electrochemistry. 2015 Nov;19(11):3381-8.
5. Elsaied EH, Dawaba HM, Ibrahim EA, Afouna MI. Investigation of proniosomes gel as a promising carrier for transdermal delivery of Glimepiride. Universal Journal of Pharmaceutical Research2016; 1(2): 1-10.
6. Uppugalla S, Srinivasan P. High-performance supercapacitor coin cell: polyaniline and nitrogen, sulfur-doped activated carbon electrodes in aqueous electrolyte. Journal of Solid State Electrochemistry. 2019 Jan;23(1):295-306.
7. Chioma ED. Formulation and evaluation of etodolacniosomes by modified ether injection technique. Universal Journal of Pharmaceutical Research2016; 1(1): 1-4.
8. Freag MS, Saleh WM, Abdallah OY. Self-assembled phospholipid-based phytosomalnanocarriers as promising platforms for improving oral bioavailability of the anticancer celastrol. Int J Pharm. 535(1-2), 2018, 18-26.
9. Elsaied EH, Dawaba HM, Ibrahim ESA, Afouna MI. Effect of pegylatededgeactivator on Span 60 based nanovesicles: comparison between Myrj 52 and Myrj 59. Universal Journal of Pharmaceutical Research 2019; 4(4):1-8.
10. Singh, A., Kumar, A. and Kalaiselvi, P., 2018. Aegeline, targets LOX1, the receptor for oxidized LDL to mitigate hypercholesterolemia: a new perspective in its anti-atherosclerotic action. Free Radical Biology and Medicine, 128, p.S41.
11. Ugochukwu AE, Nnedimkpa OJ, Rita NO. Preparation and characterization of Tolterodine tartrate proniosomes, Universal Journal of Pharmaceutical Research2017; 2(2): 1-3.
12. Uppugalla S, Srinivasan P. Polyaniline nanofibers and porous Ni [OH] 2 sheets coated carbon fabric for high performance super capacitor. Journal of Applied Polymer Science. 2019 Nov 5;136(41):48042.
13. Nwobodo NN, Adamude FA, Dingwoke EJ, Ubhenin A. Formulation and evaluation of elastic liposomes of decitabine prepared by rotary evaporation method. Universal Journal of Pharmaceutical Research2019;4(3):1-5.

14. Singh, A., 2022. Role of microbial metabolites in cardiovascular and human health. In Microbiome, Immunity, Digestive Health and Nutrition (pp. 137-148). Academic Press.
15. Uppugalla S, Boddula R, Srinivasan P. Methyl triphenylphosphonium permanganate as a novel oxidant for aniline to polyaniline-manganese (II, IV) oxide: material for high performance pseudocapacitor. Journal of Solid State Electrochemistry. 2018 Feb;22(2):407-15.
16. Singh, A., Srinivasan, A.K., Chakrapani, L.N. and Kalaiselvi, P., 2019. LOX-1, the common therapeutic target in hypercholesterolemia: a new perspective of antiatherosclerotic action of aegeline. Oxidative medicine and cellular longevity, 2019.
17. Abhilasha, S., Narasimhan, C.L., Kumar, S.A., Kumar, S.N.K., Bhavani, R.D., Thangarajeswari, M., Prema, V. and Kalaiselvi, P., 2017. Ethanolic extract of aeglemarmelos mediates its hypocholesterolemic effect by retarding circulatory oxidized ldl formation via 12/15 lipoxygenase pathway.
18. John DF, Yunus AA, Chigbo UJ, Paul US, Ikenna E. Tolnaftate loaded liposomes-design, and in-vitro evaluation. Universal Journal of Pharmaceutical Research2016; 1(2): 29-31.
19. Singh, A., 2022. Role of microbial metabolites in cardiovascular and human health. In Microbiome, Immunity, Digestive Health and Nutrition (pp. 137-148). Academic Press.
20. Varde N M Et Al, Phytosomes: A Potential Phospholipid Nanoparticulate Carrier For The Bioavailability Enhancement Of Herbal Extracts PharmacieGlobale (Ijcp). 2012: 10 (2), 1-7.
21. Chauhan N, Kumar K, Pant NC. An updated review on transfersomes: a novel vesicular system for transdermal drug delivery. Universal Journal of Pharmaceutical Research 2017; 2(4): 42-45.
22. Shiv Chandra Singh, A., Yu, A., Chang, B., Li, H., Rosenzweig, A. and Roh, J.D., 2021. Exercise Training Attenuates Activin Type II Receptor Signaling in the Aged Heart. Circulation, 144(Suppl_1), pp.A14259-A14259.
23. ALGIN YAPAR E, ESENTÜRK İ, ŞAHİNER A, HALAT E, KARA BA, BALA R, SINDHURK. Cosmetotextiles and evaluation of their performance. Universal Journal of Pharmaceutical Research 2021; 6(3):64-67.
24. Roh, J., Hill, J.A., Singh, A., Valero-Muñoz, M. and Sam, F., 2022. Heart failure with preserved ejection fraction: heterogeneous syndrome, diverse preclinical models. Circulation Research, 130(12), pp.1906-1925.
25. Boini, K.M., singh, A. and Koka, S.S., 2021. Gut Microbial Metabolite Trimethylamine N-oxide Enhances Endoplasmic Reticular Stress and Promotes Endothelial Dysfunction. Circulation, 144(Suppl_1), pp.A14071-A14071.
26. Obanewa OA, Oyeniran OT. Development and estimation ofanti-inflammatory activity of topical etoricoxibemulgel by carrageenan induced paw oedema method. Universal Journal of Pharmaceutical Research2019;4(3):22-26.
27. Roh, J.D., Kitchen, R.R., Guseh, J.S., McNeill, J.N., Aid, M., Martinot, A.J., Yu, A., Platt, C., Rhee, J., Weber, B. and Trager, L.E., 2022. Plasma proteomics of COVID-19–associated cardiovascular complications: implications for pathophysiology and therapeutics. Basic to Translational Science, 7(5), pp.425-441.