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PHYTOSOMES IN THE FIELD OF NOVEL DRUG DELIVERY SYSTEM

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ABSTRACT : the term "phyto" means plant while "some" means cell-like. Phytosomes are bioactive phytoconsituents of herb extract surrounds and bound by a lipid. Most of the bioactive constituents of phytomedicines are water-soluble compounds like flavonoids, glycosides; terpenoids in which flavonoids are a major class of bioactive compounds possesses broad therapeutic activities .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. 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. This review also contains a comparative account of liposomes and phytosomes along with recent advancements in the field of phytosome technology with a special concern to transdermal drug delivery.improved forms of herbal formulation which contain the bioactive phytoconstituents of herb essence enclosed and bound by a lipid.

KEY WORDS : Phytosomes; Bioavailability, Phospolipids, phytoconstituents , Herbosomes;
Plant extract, Drug delivery, Phosphatidylcholine

INTRODUCTION : Preparations of plants or parts of them were widely used in popular medicine since ancient times and till today the use of phytomedicines is widespread in most of the world's population. From time immemorial it has been the endeavour of the physician and the apothecary to provide patients with the best possible forms of medicines so that recovery from disease is faster and complete. The drugs are delivered in a suitable formulation keeping in view the safety, efficacy and acceptability among other factors, and the formulation is usually known as dosage form or drug delivery system. Phytosomes are developed by incorporating standardized plant extract or water soluble phytoconstituents into phospholipids to produce lipid compatible molecular complexes called phytosomes and so vastly improve their absorption and bioavailability. Phytosome process produces a little cell because valuable components of herbal extract are protected from destruction by digestive secretion and gut bacteria. Phytosomes are better able to transform from a hydrophillic enviroment into the lipid friendly environment of the enterocyte cell membrane and from there into the cell finally reaching the blood.

DIFFERENCE BETWEEN LYPOSOMES AND PHYTOSOMES

There is number of research has been carried out on phytosomes which state that phytosomes have good bioavailability, absorption, and excellent therapeutic efficacy over liposome. Comparison between phytosomes and liposomes is represented in Table 1 along with their structure : Likewise Phytosomes, a liposome is formed by mixing phosphatidylcholine with water soluble substance in definite ratio. The basic difference between liposomes and phytosomes is that in liposomes the active principle is dissolved in the medium contained in the cavity or in the layers of the membrane, whereas in the phytosomes it is an integral part of the membrane, being the molecules anchored through chemical bonds 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 complexed, involving chemical bonds [hydrogen bonds.. .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

HISTORY OF 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. The phytosomes process is a small cell in itself, as the valuable components of the herbal extract are protected from destruction by the digestive secretions and gut bacteria. Water-soluble phytoconstituents can be converted into lipid-compatible molecular complexes and therefore are aptly called phytosomes . 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. Phytosome is a newly introduced patented technology in which phytomolecule form complex with phospholipid by developing hydrogen bonds. Water-soluble phyto-constituent molecules (mainly polyphenols) can be converted into lipid-compatible molecular complexes, which are called phytosomes. Silybin predominates, followed by silydianin and silychristin. Silybin is a flavonolignan which is probably produced within the plant by the combination of a flavonol with a coniferyl alcohol.

PREPARATION TECHNIQUES FOR PHYTOSOMES:

A. THIN LAYER ROTARY EVAPORATOR METHOD:

Phytosomes vesicles were made by thin layer rotary evaporator vacuum method. The phytosomal complex was mixed in anhydrous ethanol in 250ml round bottom flask. The flask was attached to a rotary evaporator. The solvent will evaporate at a temperature about 60˚C forming a thin layer film around the flask. The film is hydrated by phosphate buffer having Ph 6.8, and the lipid layer will peel off in phosphate buffer forming vesicle suspension. The phytosomal suspension will be stored in the refrigerator for 24hrs, before characterization.

B. SOLVENT EVAPORATION METHOD: Phospholipid, i.e., soya lecithin was reacted with polyphenolic extract in an equal ratio with 5 ml of dichloromethane with stirring until evaporate. Once the dichloromethane 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.

C. REFLUX METHOD: Phytosomes can also be prepared by reflux method. Polyphenolic extract and phospholipid were placed in 100ml round bottom flask and refluxed in dichloromethane for 1hr not exceeding 40˚C. the clear solution was evaporated and add 15ml of n-hexane until a precipitatewas obtained. The precipitate was taken and placed in a desiccators.

APPLICATION OF PHYTOSOMES:

SILYMARIN PHYTOSOMES: Most of the Phytosomal studies are focused on Silybum marianum (milk thistles) which contains premier liver protectant flavonoids. Yanyu et a prepared silymarin phytosome and studied its pharmacokinetic in rats. 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 silybinphospholipid complex and improvement of biological effect of silybin. .Tedesco et al 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 . (1993) investigated that in one study of 232 patients with chronic hepatitis (viral, alcohol or drug induced) treated with silybin phytosome at a dose of 120 mg either twice daily or thrice daily for up to 120 days, liver function returned to normal faster in patients taking silybin phytosome .

CURCUMIN PHYTOSOMES: 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. 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 be due to decrease in the rapid elimination of the molecule from body. Maiti et al. developed the phytosomes of curcumin (flavonoid from turmeric, Curcuma longa linn) and naringenin (flavonoid from grape, Vitis vinifera) in two different studiesmpared to a group of controls treated with commercially available silymarin, 117 untreated or given placebo.

PHYTOSOMES OF GRAPE SEED: 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 procyanidin 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 and other organs through a network of mechanism that extend beyond their antioxidant.

PROPERTIES OF PHYTOSOMES: Phytosomes are prepared by reacting 3-2 moles or preferably 1 mole of phosphatidylcholine with 1 mole of active phytoconstituents mostly the flavonoids and the terpenoids in an aprotic solvent such as dioxane or acetone from which complex can be isolated by precipitation with non solvent such as aliphatic hydrocarbons or by lyophilization or by spray drying. Physico-Chemical properties: Phytosomes is a complex between a natural product and phospholipids. Such a complex is obtained by reaction of stoichiometric amounts of phospholipids and the substrate in an appropriate solvent. 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 catechin-distearoyl PC complex, there is formation of H-bonds between

the phenolic hydroxyls of the flavones moiety and the phosphate ion on the PC side. The complexes are often freely soluble in aprotic solvents, moderately soluble in fats, insoluble in water and relatively unstable in alcohol.

2. BIOLOGICAL PROPERTIES : Phytosomes are novel complexes that are better absorbed and utilized. Hence, they produce more bioavailability and better results than conventional herbal extract or noncomplex extracts. 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

LYPOSOMAL DRUG DELIVERY SYSTEM : Liposomes are ideal drug delivery system because its morphological structure resembles with cell membrane structure. Liposomes are spherical vesicles made up of phospholipid bilayer used as colloidal vesicular drug delivery systems Liposomes are condensed bilayered vesicles with a completely contained aqueous volume A lipid membrane bilayer consisting mainly of natural or synthetic phospholipids.The Face The liposome name comes from two Greek words: "Lipos" which means fat, "Soma" The flesh. A liposome can be produced in a range of sizes as single or multi-lamella the house, and its name concerns its building blocks, phospholipids, not Its dimension. Its scale.Phospholipid molecules are amphipathic in nature having a hydrophilic head and hydrophobic tail, which in contact with water forms a spherical vesicle with head aligned towards the aqueous region and tails entrapped in membrane, forming an aqueous core (aqueous domain) which can accommodate hydrophilic drugs and lipoidal domain entrapped in bilayer-membrane which accommodates hydrophobic drugs i.e. it can carry both hydrophilic and hydrophobic drugs. Liposomes can act as potential drug delivery system for cancer treatment due to its ability to reduce the side effects caused by non-selective nature of cancer treatment methods by increasing specificity for cancer cells.Liposomes are They are commonly composed of one or more amphiphilic phospholipid bilayer membranes (and thus also called as phospholipid vesicles) that can entrap both hydrophilic and hydrophobic drugs.

PHYTOSOMES IN CANCER THERAPY: One of the major causes of death on the globe is cancer. It has remained a significant obstacle for current therapies and has not yet been effectively treated. Conventional treatment strategies available for cancer such as surgery, chemotherapy, radiation therapy etc. have severe adverse effects. The use of herbal active constituents in cancer treatment has tremendous potential to increase the effectiveness of conventional cancer therapy. A mitomycin-C-Soybean phosphatidylcholine complex (mitomycin-c loaded phytosomes) has shown enhanced activity for cancer therapy and drug delivery Rutin-loaded transdermal systemic delivery was found to greatly improve upon loading into phytosomal systems, avoiding oral administration problems A mitomycin-C-Soybean phosphatidylcholine complex (mitomycin-c loaded phytosomes) has shown enhanced activity for cancer therapy and drug delivery Rutin-loaded transdermal systemic delivery was found to greatly improve upon loading into phytosomal systems, avoiding oral administration problems . The antiproliferative and anti-apoptotic activities were evaluated with the use of human breast cancer MCF-7 cell line. A four-factor Box–Behnken experimental design was used to prepare and optimize the different formulations of phytosomal systems, and the optimized formulations were chose

MECHANISM OF PHYTOSOMES FORMATION : The polyphenolic elements of herbal essence made themselves relatively healthy for straight conjugation with phosphatidylcholine. Phytosome ensues from the response of a stoichiometric quantity of the phospholipid-like phosphatidylcholine with the polyphenolic ingredients like simple flavonoids. (some e.g. shown in the table. The choline head of the phosphatidylcholine conjugate to these compounds while lipid-soluble phosphatidyl part containing the body and tail which then covers the choline bound material. Hence, the Phytomolecules yield a lipid soluble molecular compound with phospholipids named as phyto-phospholipid complex. . Phytomolecules are anchored through chemical bonds to the polar choline head of phospholipids, as can be confirmed by precise spectroscopic methods (Bombardelli et al. 1991). Frequently, detailed chemical examination designates that, the unit phytosome is typically a flavonoid molecule connected with not less than one phosphatidylcholine molecule. The outcome is a tiny microsphere or cell is formed (Murray et al. 2008). In the blue phytosome spectrum, the spectrum from the polyphenol (red) is obscured by the orange spectrum from phosphatidylcholine. The choline head of the phosphatidylcholine molecule attaches to these substances, while the lipid soluble phosphatidyl portion of the phosphatidyl molecule, which contains the body and tail, surrounds the choline bound material. As a result, the phytoconstituents form a lipid-compatible molecular complex with phospholipids (also known as phytophospholipid complex. The mechanism of phytosome production includes the following steps: Step 1: Presence of phospholipids and plant compounds in aprotic media (for example, dioxane and acetone), Step 2: Hydrogen bond formation Step 2: Wrapping the non-polar tail around the polar complex There are mainly three methods available for preparation of phytosome: 1) Solvent evaporation method, 2) Rotary evaporation method, 3) Anti-solvent precipitation method1. Solvent evaporation method: The phytosome can be synthesised utilising the solvent evaporation method. With magnetic stirring at 40°C, phosphatidylcholine is dissolved in 100 mL of non-polar solvent, such as chloroform.

NOVEL METHODS : Traditional methods have several drawbacks, including multistep processes, difficulty extraction, and time consumption. Supercritical fluid methods can be used to change the size, shape, and morphology of material of interest. Along with other benefits like as high product purity, crystal polymorphism control, the capacity to process thermolabile substances, a single-step process, and eco-friendly technology. Gas anti-solvents technique (GAS), Supercritical antisolvent technique (SAS), and Solution enhanced dispersion by supercritical fluids (SEDS) techniques use a supercritical fluid (typically CO2) as an anti-solvent to limit the solute's solubility in the solvent, whereas Rapid expansion of supercritical solutions (RESS) uses it as a solvent.

GAS ANTI-SOLVENTS TECHNIQUE (GAS): It is not required that the CO2 gas use as an antisolvent should be supercritical. It is injected into the solution in a closed chamber, ideally from the bottom, to achieve uniform mixing. As a result of CO2 gas dissolution, the organic solvent's solubilization power is reduced, resulting in the precipitation of solutes. The particles are washed with additional antisolvent to remove any leftover solvent. Otherwise, during the depressurization stage, the solutes may

resolubilize, jeopardising product stability. In comparison to the solvent antisolvent technique, the gas antisolvent technique produces better results when scaled up to industrial levels.

CONCLUSION: Phytosomes are an innovative drug delivery system designed for safe, effective, and proper delivery of hydrophilic, poorly absorbed phytoconstituents. These advanced forms of herbal extracts are better absorbed than conventional herbal extracts, making them suitable for treating acute liver diseases. Phytosomes have enhanced pharmacokinetic and pharmacological parameters, making them beneficial for various therapeutic purposes. They offer improved bioavailability of hydrophilic favonoids through the skin or gastrointestinal tract, offering advantages over conventional formulations. The preparation process for phytosomes is simple and can be easily scaled up to a commercial scale.

REFERENCE:

1) Cott J. Natural Product Formulations Available in Europe for Psychotropic Indications. Psychopharmacol Bull. 1995; 31:745.

2) Mandal SC, Mandal M. Current status and future prospects of new drug delivery system. Pharm Times. 2010;42(4):13-6.

3) Saharan VA, Kukkar V, Kataria M, Gera M, Choudhary K. Dissolution enhancement of drugs. part i: technologies and effect of carriers. Int J Health Res. 2009; 2:107- 124.

4) Sravanthi M, Krishna JS. Phytosomes: A novel drug delivery for herbal extracts. International Journal of Pharmaceutical Sciences and Research. 2013 Mar 1;4(3):949-59.

5) . Manach, A. Scalbert, C. Morand. Polyphenols: food sources and bioavailability, Am. J. Clin. Nutr. 79:727-47 (2004).

6) Roco MC, Bainbridge WS. (2005). Societal implications of nanoscience and nanotechnology: maximizing human benefit. Journal of Nanoparticle Research. 7 (1): 1-13.

7) Manach C, Scalbert A, Morand C (Polyphenols) (2004). Food sources and bioavailability, Am. J. Clin. Nutr., 79: 727-

8) Yie. W. Chien, Novel drug delivery systems, Marcel Dekkar. Inc, 1992, Revised 2nd edition, 1-133.

9) Dhiman A, Nanda A, Ahmad S. Novel Herbal Drug Delivery System (NHDDS) : the need of Hour [Internet]. [cited 2020 Jun 13]. Available from: /paper/Novel-Herbal-DrugDelivery-System-(-NHDDS-)-%3A-the-DhimanNanda/683c33dc1eb996aadf65820d39fd32fbcb4150fd

10) Soejarto DD. Biodiversity prospecting and benefit-sharing: perspectives from the field. J Ethnopharmacol. 1989;51:1–15
11) Phytosomes: A Technical Revolution in Phytomedicine [online]. 2010 [cited 2010 Mar 22].

12) Gupta A, Ashawat MS, Saraf S, Phytosome: A novel approach towards functional cosmetics, J Plant sci, 2(6), 2007, 644-649

13)SemaltySemaltyRawat MSM. The phyto-phospholipid complexes- phytosomes: a potential therapeutic approach for herbal hepatoprotective drug delivery.

14) Facino R, Carini M, Aldini G, Bombardelli E, Morazzoni P, Morelli R. Free radicals scavenging action and anti-enzyme activities of procyanidines from Vitis vinifera. A mechanism for their capillary protective action. Arzneimittelforschung. 1994;44(5):592-601

15) Jagruti Patela, Rakesh Patelb, Kapil Khambholjab, Nirav Patel. “An overview of phytosomes as an advanced herbal drug delivery system”. An overview of phytosomes/Asian Journal of Pharmaceutical Sciences 2009: 4(6); 363-371]

16) Abou El Wafa AA, Mursi NM, El-Shaboury KM. A pharmaceuticl study on certain ocular drug delivery systems. MS Thesis. Cairo Univercity, Cairo 2003.

17) Duric M, Sivanesan S, Bakovic M. Phosphatidylcholine functional foods and nutraceuticals: A potential approach to prevent non- alcoholic fatty liver disease

18) European journal of lipid science and technology. 2012 Apr;114(4):389-98. Bombardelli Ezio, Phytosome in functional cosmetics, Fitoterapia LXV (5): 1994, 387-401

19) ombardelli E, Spelta M, Sosa S, et al. Aging Skin: Protective effect of silymarin-Phytosome. Fitoterapia. 62(2):115-22, Revised 2005; 10(3):193-203

20) Yanyu Xiao, Yunmei Song, Zhipeng Chen, et al. The preparation of silybin-phospholipid complex and the study on its pharmacokinetics in rats. International Journal of Pharmaceutics. 2006; 307:77–82.

21) Ying L, Wei SP, Chen SL, et al, Comparison of pharmacokinetics between puerarin and its phospholipid complex in beagle dogs in vivo, Chinese herbal medicine, 37(5), 2006, 695-697

22) Giori A, Franceschi F, inventors;Indena S.p.A.,assignee, Phospholipid complexes of curcumin having improved bioavailability, EP 1837030A1.2007 Sep 26Amit P, Tanwar YS, Rakesh S. Phytosome : Phytolipid Drug Dilivery System for Improving Bioavailability of Herbal Drug. J Pharm Sci Biosci Res. 2013;3(2):51-57.

23) Kumar AB, Prasanna H, Lakshman T, Prabha H, Kumar RS. Phytosomes as Novel Drug Delivery System for Herbal Medicine –A Review. Syst Rev Pharm. 2017;8(1):5-7. doi:10.5530/srp.2017.1.2

24) El-Maghraby GM, Williams AC, Barry BW. Oestradiol skin delivery from ultra-deformable liposomes: Refinement of surfactant concentration. Inter J Pharm. 2000;196(1):63-74

25) . Gandhi A, Dutta A, Pal A. Recent trends of phytosomes for delivering herbal extract with improved bioavailability. J Pharmacog and Phytochem. 2012;1(4):6-14.

26) Gandhi A, Dutta A, Pal A. Recent trends of phytosomes for delivering herbal extract with improved bioavailability. J Pharmacog and Phytochem. 2012;1(4):6-14.

27) H Hiking; Y Kiso; H Wagner; M Fiebig; Antihepatotoxic actions of flavonolignans from Silybum marianum fruits. Planta Med. 50:248-250 (1984),

28) . Franco PG, Bombardelli E. Complex Compounds of Bioflavonoids with Phospholipids, their Preparation and Uses and Pharmaceutical and Cosmetic Compositions Containing Them, U.S. Patent/1998/275005; 1998.

29) Mascarella S. Therapeutic and anti-lipoperoxidant effects of silybin-phosphatidylcholine complex in chronic liver disease. Curr Ther Res 1993;53:98-102

30) Amit P, Tanwar YS, Rakesh S, Poojan P. Phytosome: Phytolipid drug delivery system for improving bioavailability of herbal drug. J Pharm Sci Biosci Res 2013;3:51

31) Maryana W, Rachmawati H, Mudhakir D. Formation of phytosome containing silymarin using thin layer hydration technique aimed for oral delivery. Mater Today Proc Asian J Pharm.sci and cli.Res2016;3:857-8.-7.

32) PM Kidd. Alt. Bioavailability and activity of phytosome complexes from botanical polyphenols: the silymarin, curcumin, green tea, and grape seed extracts.Med. Rev. 2009. 14(3). 226-246.

33) Freag M, Elnaggar Y, Abdallah O, “Lyophilized phytosomal nanocarriers as platforms for enhanced diosmin delivery: optimization and ex vivo permeation”, I J Medicine, 2013, 8;2385- 2397.

34) Abhishek Bhattacharjee. “An overview on Phytosome as a novel drug delivery system for herbal drugs”. International journal of innovative pharmaceutical sciences and research 2015:3(6); 730-739.

35) Roy Chowdhury Santanu, Bhandari Neeraj, Verma pooja. “Phytosomes an emerging technology in phytomedicine: A review”. International Research Journal of Pharmacy 2012:3(10); 61-64

36) Chaturvedi, Mayank, Manish Kumar, Amit Sinhal, and Alimuddin Saifi. "Recent development in novel drug delivery systems of herbal drugs." International Journal of Green Pharmacy (IJGP) 2011:5(2); 87-94.