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A REVIEW ON HERBAL PHYTOSOMES

Shelly Raghav*, Yogendr Bahuguna, Chandra Shekhar Tailor, Bhawana Bhatt

School of Pharmaceutical Sciences, SGRR University, Patelnagar, Dehradun, Uttarakhand, India.

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***Corresponding author: Shelly Raghav**

School of Pharmaceutical Sciences, SGRR University, Patelnagar, Dehradun, Uttarakhand, India.

ABSTRACT

During the last centuries, chemical and pharmacological studies have been performed on a lot of plant extracts to know their chemical composition and confirm the indications of traditional medicine. Phytosome plays an important role to facilitate absorption and improve bioavailability which include standardized plant extracts or water soluble phyto-constituents into phospholipids to provide lipid conformable molecular complexes. Phytosomes is a novel formulation technology which helps to overcome these problems. The term 'phyto' means plant while 'some' means cell-like. Phytosome is composed of phospholipids, mainly phosphatidylcholine, producing a lipid compatible molecular complex with other constituents. Phytosomes are more potent as compared to conventional herbal extracts owing to their enhanced capacity to cross the biological membrane and finally reaching the systemic circulation. They have anti-inflammatory, anti-oxidant, anticancer, anti-diabetic, hepato-protective properties. Phytosome has been an emerging trend in delivery of herbal drugs and nutraceuticals. This paper provides the detailed information about the preparation, advantages, characterization and evaluation of phytosomes. This review highlights information of commercial products of phytosomes as well as research on novel approaches for phytosomes drug delivery.

KEYWORDS: Phytosomes, Bioavailability, Herbal extract, Drug delivery, Phospholipid, Phosphatidylcholine.

INTRODUCTION

Phytosome is a patented technology developed by a leading manufacturer of drugs and nutraceuticals, to include standardized plant extracts or water soluble phyto-constituents into phospholipids to provide lipid conformable molecular complexes known as phytosomes so immensely improve their absorption and bioavailability. During the last centuries, chemical and pharmacological studies have been performed on a lot of plant extracts to know their chemical composition and confirm the indications of traditional medicine. Most of the biologically active constituents of plants are polar or water soluble molecules. However, water soluble phytoconstituents (like flavonoids, tannins, terpenoids etc) are poorly absorbed either due to their large moleculer 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. Extracts when taken orally some constituents may be destroyed in the gastric environment. Over the beyond century phytochemical and phyto-pharmacological sciences well-established the compositions, biological activities and health promoting benefits of herbal extracts and their derivatives.[1,2]

The phytosomes process produces a little cell because of that the valuable components of the herbal extract are shielded from destruction by digestive secretions and gut bacteria. Phytosomes have improved pharmacokinetic and pharmacological parameter. Phytosomes are more bioavailable as compared to herbal extract owing to their enhanced capacity to cross the lipid rich biomembranes and finally reaching the blood.[3]

Phospholipids are complex molecules liable for formation of cell membranes. They are main building block of life. Phospholipids are lipid molecules during which the glycerol is bonded to two fatty acids and therefore the remaining portion occupied by the phosphate group.

Phosphatidylcholine derived from soybean (Glycine max) is mostly employed phospholipid. Phytosomes are obtained by reacting 2-3 moles or 1 mole of phospholipid such as phosphatidylcholine, phosphatidylethanolamine or phosphatidyl-serine with 1 mole of bioactive

component (flavonoids or terpenoids) in an aprotic solvent (dioxane, acetone, methylene chloride, ethyl acetate). The flavonoid and therefore the terpenoid components of the herbal extract are ready to directly bind with phosphatidylcholine moiety hence they're widely prepared.[4,5,6]

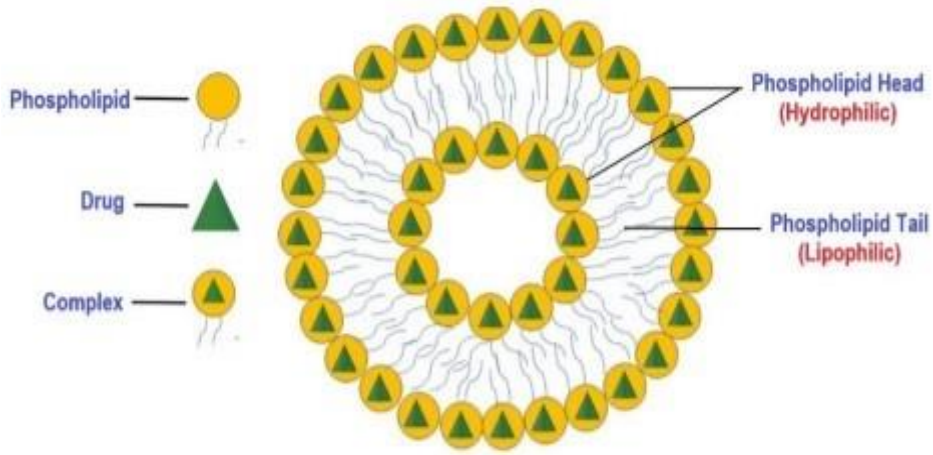

Fig. 1: Structure of Phytosome.[7]

Principle of Phytosome Technology

The flavonoid and terpenoid constituent of plant extracts lend themselves suitable for direct binding to phosphatidylcholine. Phytosomes are composed by the reaction of a stoichiometric amount of the phospholipid (phosphatidylcholine) with the standardized extract or polyphenolic constituents (like simple flavonoids) in a non-polar solvent.[1,8,9] Some commonly used synthetic phospholipids are dioleoyl-phosphatidyl-choline (DOPC), dioleoylphosphatidyl-ethanolamine (DOPE), distearoyl-phosphatidyl-choline (DSPC), distearoyl-phosphatidylethanolamine (DSPE).[2]

Phosphatidylcholine is a bifunctional compound, the phosphatidyl moiety is lipophilic in nature which is the head of the bifunctional compound and the choline moiety which is the tail of the bifunctional compound being hydrophilic in nature. The choline moiety of the phosphatidylcholine bounds to the hydrophilic phytoconstituents, whereas the lipid soluble phosphatidyl portion then envelopes the choline bound complex. As a result a phyto-phospholipid complex is formed with a better lipid solubility. The polar phytoconstituents binds to the choline head by means of a chemical bond.[4,10]

Advantages of Phytosomes

Phytosomes have the following advantages:

1. They form a little cell where herbal extracts are protected from deterioration by gut bacteria and digestive secretions.
2. It insures proper delivery of drug to the relevant tissues.
3. Small dose can produce desired results due to absorption of chief constituents.
4. It increases the absorption of lipid insoluble polar phytoconstituents through oral as well as topical route showing better bioavailability.
5. It shows better stability due to the formation of chemical bonds between phytoconstituents and the phosphatidylcholine molecules.
6. Phytosomes also have nutritional benefit of phospholipids.
7. They possess better drug entrapment efficiency.
8. Enhanced permeability of phytoconstituents across the biological membranes.
9. Enhancement in the bioavailabilty of drug occurs.
10. Phosphatidylcholine used in formulating phytosome process besides acting as a carrier also nourishes the skin as it is an essential part of a cell membrane.[1,4,8,12]

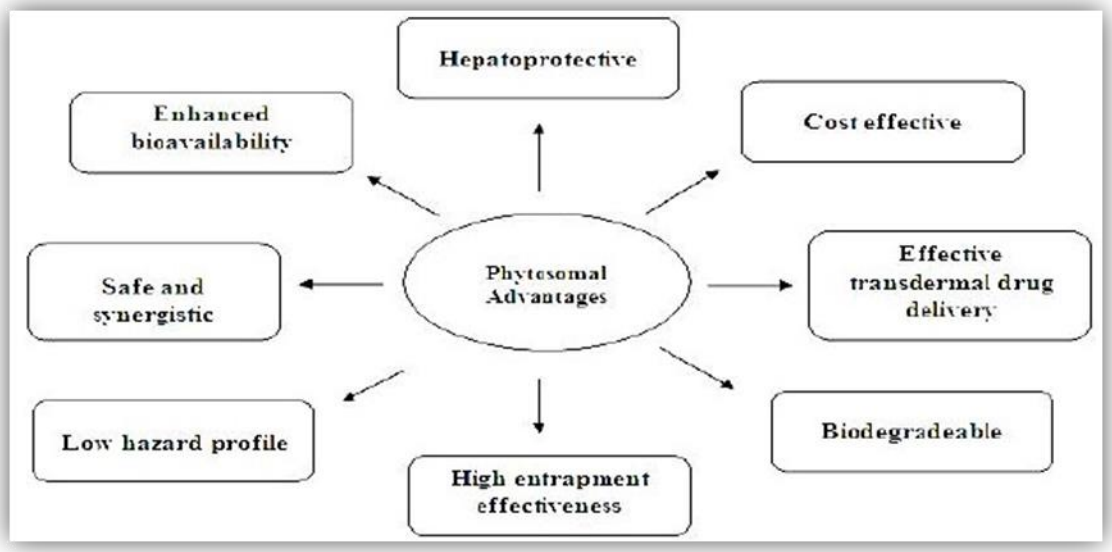

Fig. 2: Advantages of Phytosomes.[13]

Preparation of Phytosomes

Phytosomes are prepared by complexation of polyphenolic phytoconstituents in 1:2 or 1:1 ratio with natural or synthetic phospholipid like phosphatidylcholine, phosphatidylethanolamine or phosphatidyiserine, either alone or in an aprotic solvent, such as dioxane or acetone. The complex that is formed is isolated by precipitation with an aliphatic hydrocarbon or spray drying or lyophilization.[14-16]

General method of preparation of phytosome involves following steps.[4,17]

1. Phospholipids and substrate is mixed in an appropriate ratio (preferably 1:1) in the presence of aprotic solvent (example- dioxane and acetone).
2. Isolation of the complex is done by precipitation method. Precipitation can be done by any of the following:
   - Lyophilization
   - Aliphatic hydrocarbons
   - Spray drying method.
3. Drying of phytosomes
4. Hydration of prepared phytosomes to obtain phytosomal suspension.

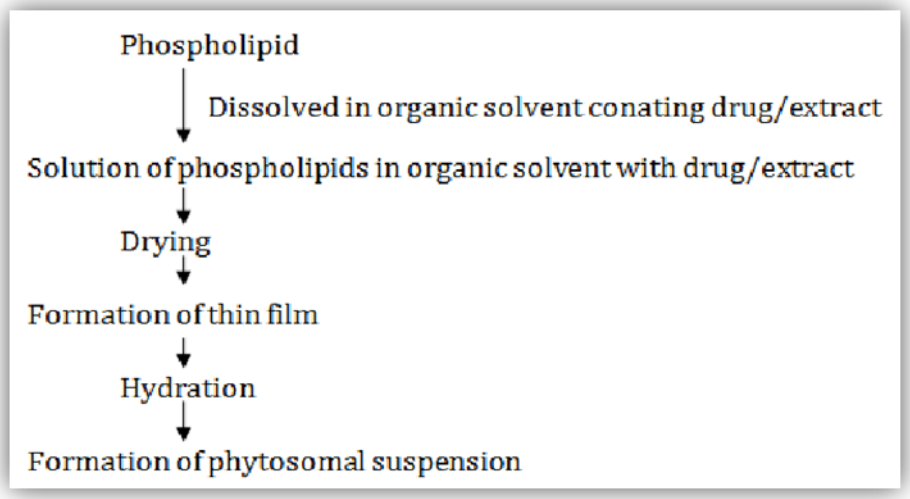

Fig. 3: Common stages for preparation of Phytosomes.[17]

Characterization 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 composition.

Different characterization techniques used for phytosomes

i) Visualization: Visualization of phytosomes can be achieved using transmission electron microscopy (TEM) and by scanning electron microscopy (SEM).[18]

ii) Vesicle size and Zeta potential: The particle size and zeta potential can be determined by dynamic light scattering (DLS) using a computerized inspection system and photon correlation spectroscopy (PCS).[19]

iii) Entrapment efficiency: The entrapment efficiency of a drug by phytosomes can be measured by the ultracentrifugation technique.[20]

iv) Transition temperature: The transition temperature of the vesicular lipid systems can be determined by differential scanning calorimetry.[21]

v) Surface tension activity measurement: The surface tension activity of the drug in aqueous solution can be measured by the ring method in a DuNouy ring tensiometer.[22]

vi) Vesicle stability: The stability of vesicles can be determined by assessing the size and structure of the vesicles overtime. The mean size is measured by DLS and structural changes are monitored by TEM.[23]

vii) Drug content: The amount of drug can be quantified by a modified high performance liquid chromatographic method or by a suitable spectroscopic method.[24]

viii) Spectroscopic evaluations: To confirm the formation of a complex or to study the reciprocal interaction between the phytoconstituent and the phospholipids, the following spectroscopic methods are used:

- 1H-NMR
- 13C-NMR
- FTIR

ix) In vitro and in vivo evaluations: Models of in-vitro and in-vivo evaluations are selected on the basis of the expected therapeutic activity of the biologically active phytoconstituents present in the phytosomes. For example, in-vitro antihepatotoxic activity can be assessed by the antioxidant and free radical scavenging activity of the phytosomes. For assessing antihepatotoxic activity in-vivo, the effect of prepared phytosomes on animals against thioacetamide-, paracetamolor alcohol- induced hepatoxicity can be examined.[25-27]

Research on Phytosomes

1. Maiti K et al (2009) prepared and evaluated a phospholipid complex of hesperetin for antioxidant activity and pharmacokinetic profile. The hesperetin content of the complex was determined by a spectrophotometer and the surface characteristics of the complex were studied by means of microscope. The antioxidant activity was evaluated in carbon-tetrachloride-intoxicated rats at a dose level of 100 mg/kg body weight, p.o. in vitro drug release characteristics and effect of complexation on serum concentration of hesperetin in rats was also studied. The results showed that the complex has a sustained release property and enhanced antioxidant activity ($P<0.05$ and <0.01) as compared to free hesperetin at the same dose level.[28]

2. Mishra et al (2012) developed and evaluated phytosomes of leaves of Vitex negundo Linn. The extract was prepared hot percolation method using soxhlet apparatus with 90% ethanol for 48 hours. Various physicochemical parameters of leaves were also determined such as ash value, extractive value, LOD etc. The phytosomes were prepared by hand rolling method and evaluated for its solubility and drug content study, scanning electron microscopy and formulated phytosomes have optimum size.[29]

3. El-Gazayerly O.N et al (2013) prepared and characterized silymarin phytosomes and to test the hepatoprotective effect of the phytosomes in CCl4 induced liver injury in rats compared to milk thistle extract. Phytosomes were prepared using lecithin from soybeans and egg yolk. Different formulations of phytosomes were prepared and determined using scanning electron microscopy, transmission electron microscopy, differential scanning calorimetry, Fourier transform infrared spectroscopy and proton nuclear magnetic resonance spectroscopy (H1NMR). The loading efficiency was >85% in all phytosomal formulations. . Formulations P2 (with the molar ratio of soybean lecithin to silybin 1:1) and P4 (with the molar ratio of egg-yolk lecithin to silybin 0.25:1) exhibited significantly ($p<0.05$) faster release than milk thistle extract. The in vivo study revealed that phytosomes significantly (p50.05) decreased glutamic pyruvic transaminase and super oxide dismutase activities compared to milk thistle extract.[30]

4. Das K. M et al (2014) developed and characterized Rutin phytosomes (RN-P) for transdermal application in inflammatory conditions. Phytosomes were prepared refluxing followed by solvent evaporation method in five molar ratios of Rutin (0.5 - 1.0) to Phosphatidylcholine (1.0 - 0.5). All phytosomal complexes showed aqueous solubility higher than pure Rutin. Phytosomes were evaluated using drug entrapment, particle size distribution, SEM, TEM, FT-IR etc. The results show higher permeability of RN-Ps (33 ± 1.33 %) as compared to Rutin (13 ± 0.87 %).[31]

5. **B. Keerthi et al (2014)** formulated and evaluated capsules of Ashwagandha phytosomes. Ashwagandha phytosome complexes were characterized by particle size, zeta potential, scanning electron microscopy (SEM), Fourier transform infrared spectroscopy and in vitro drug release. The results showed that the average particle size and zeta potential of optimized Ashwagandha phytosomes formulation were 98.4nm and −28.7 mV. In vitro drug release studies revealed that the cumulative % drug release of capsules of

Ashwagandha phytosomes was found to be 76.8%. The results showed that the Ashwagandha phytosome complex exhibited more antioxidant activity compared to the Ashwagandha extract.[32]

6. **Damle M. et al (2015)** developed a novel polyherbal phospholipid complex cream to improve cutaneous delivery of polyphenols for sustained anti-oxidant action using extracts of orange peel and liquorice powder. Phytochemical and in vitro anti-oxidant evaluation was also done on methanolic extracts of orange peel and liquorice powder. Total phenolic content, total flavonoid content, and anti-oxidant assays were done on different ratios of orange peel and liquorice extract. Phytosomes were prepared using Solvent evaporation method and evaluated using different methods such as scanning electron microscopy (SEM), Fourier transform infrared spectrophotometry (FT-IR), and differential scanning calorimetry (DSC). The complex was formulated as oil-in-water cream and evaluated for various parameters like Organoleptic Properties, pH, presence of foreign particles, spreadability, viscosity, etc. The optimized cream containing 1% complex was non-irritant and was found to be stable for 3-month period under conditions of stability study. Ex vivo diffusion studies showed that extract phospholipid complex cream had better retention of polyphenols in the skin when compared to conventional extract cream.[33]
7. **Dhase A. et al (2015)** prepared and evaluated phytosomes containing methanolic extract of leaves of Aegle marmelos (Bael) by solvent evaporation method. Different formulations were prepared & F3 formulation was selected as optimized formulation & was evaluated for its particle size, digital microscopy, SEM, TEM, FTIR, DSC, XRD analysis & invitro evaluation of antioxidant, antiproliferative and anticancer activity of extract and phytosomes were also carried out. They concluded that phytosomes has better actual attributes when contrasted with that of methanolic extract of leaves.[34]
8. **Singh R. et al (2015)** prepared & evaluated the phytosomes of Lawsone. Different formulations of phytosomes containing Lawsone having molar ratio 1:1, 1:2, 2:1 & 2:2 were prepared by antisolvent precipitate technique. The phytosomes was evaluated by SEM, DSC and FTIR. Ketoconazole used as a standard drug for the evaluation of antifungal activity of Candida albicans (NCIM 3471) fungi. Rat skin was used to study invitro permeation study & invivo anti-inflammatory activity was also evaluated on male wistar rats. Antifungal activity of phytosome complex (1:1) showed the largest zone of inhibition as compared to phytosome complex (1:2), plant drug and standard drug ketoconazole after 3 days. Ex-vivo permeation study of phytosome gel of lawsone through excised rat skin showed 92.91% of cumulative drug permeation up to 6 h. The anti-inflammatory activity of gel of phytosome of lawsone showed significant anti-inflammatory activity as compared to plant drug gel at 4 h.[14]
9. **Sharma S. et al (2016)** developed, characterized and evaluated the phytosomes containing the ethanolic extract of Abuliton indicum & Piper longum for hepatoprotctive effect. Indena's patented process was used for the preparation of phytoosmes by reaction of natural phospholipid (soy PC) with the extract refluxing it with the aprotic solvent. Chracterisation and evaluation was done by the different parameters like particle size determination, percentage yield, entrapment efficiency, differential scanning calorimetry, scanning electron microscope, fourier transform infrared spectroscopy, and high performance thin liquid chromatography. Liver damage was induced in adult Charles foster rats (150 ± 10 g) with CCl4 in olive oil (1:1 v/v, i.p) 1 ml/kg once daily for 7 days. LIV 52 (1ml/kg per oral [p.o]), ethanolic extract of A. indicum and P. longum combination (100, 200, and 400 mg/kg p.o) and phytosomes (100 mg/kg p.o.) was given 3 days prior to CCl4 administration. Histopathological study and liver markers enzymes were estimated. Consolidated extract has shown hepatoprotective activity however phytosomes has more intense hepatoprotective impact on CCl4 prompted liver poisonousness at exceptionally low portion near to a higher portion of consolidated extract.[35]
10. **Sundaraganapathy et al (2016)** formulated and evaluated phytosomes of *Clerodendron paniculatum* extract for the anti-cancer activity on DAL cells. Extract was prepared using the root part of the plant with ethanol by cold maceration process. Then extract was evaluated for the phytochemical investigation. The prepared phytosomes exhibited potent activity against cancer cells. The study revealed that *Clerodendron paniculatum* phytosomes possess better anti-cancer activity than the extract.[36]
11. **Vijaykumar S. et al (2017)** prepared phytosomes of methanolic extract of Allium sativum containing diallyl disulphide with other phenolic compounds to cure and prevent the growth of cancer cells. Bioactive constituents were determined by phytochemical screening. Antioxidant activity was done by DPPH assay which showed that the extract was rich in antioxidant. HPLC & GCMS analysis investigation was done to confirm the presence of diallyl disulphide having the anticancer activity. SEM & FTIR of phytosomal complex were studied for the surface morphology and functional group. Phytosomes showed 100% toxicity against cancer cell line (MCF 7) at 108.5 µg/ml.[37]
12. **Anwar E. et al (2018)** formulated & evaluated the phytosomes of *Camellia sinensis* extract using thin layer hydration method. Different formulations (F1, F2 & F3) were prepared & selected phytosomes were formulated into microsphere using maltodextrin and gum arabic as a carrier.

Dissolution study & stability study were evaluated. Formulation F3 showed best formula with spherical shape, Dmean volume of 42.58 nm, polydispersity index at 0.276, zeta potential at -48.2 ± 1.78 mV, and entrapment efficiency of 50.61±0.93%. Total cumulative amount of EGCG after 4 h dissolution test was 85.21%. It showed a good physicochemical stability through organoleptic, water content, and physicochemical properties study which was conducted for 6 weeks at various temperatures.[38]

13. **El-Bata A. at al (2018)** prepared nanocrystals by dissolving it in different solvent (acetone, acetonitrile, ethanol and methanol) and prepared phytosomes by combination between lecithin and silymarin. Determination of physicochemical characterization including dissolution, drug content in crystals or phytosome were done and the effect of gamma irradiation had been evaluated. Determination of crystal morphology was done using SEM and TEM. Solid state was characterized by XRD, DSC and FT-IR & particle size was determined using DLS. In-vitro drug release of nanocrystals and phytosomes was evaluated. They concluded that the nanocrystal (NCy6) and phytosome (Phy1) significantly increased the solubility of silymarin by 17.12% and 35.59%.[39]
14. **B.J. Jevana et al (2019)** prepared & evaluated the phytosomes of Naringin by rotary evaporation method and antisolvent precipitation method by using soya lecithin having seven different formulations. The prepared phytosomes were evaluated drug entrapment efficiency, invitro drug release & drug- excipient interaction studies were also done. They concluded that phytosomes prepared by rotary evaporation method have higher dissolution values than that prepard by antisolvent precipitation method. Formulation F7 revealed the highest percentage release of 84.5±0.39% in 60min and 99.7±0.24% in 120min.[40]
15. **Sachin et al (S. K. 2019)** developed & evaluated phytosomes of curcumin by using Rotary evaporator method. The phytosomes were subjected for SEM, measurement of particle size, zeta potential, drug content, drug entrapment efficiency, percentage yield, in-vitro drug release studies and also the release kinetics of curcumin phytosomes complex. They concluded that Curcumin phytosomes has better physical characteristics and improved permeability, solubility than that of curcumin drug to overcome the ability to cross lipid-rich biological membranes and which results in increase oral bioavailability.[41]
16. **Palachai N et al (2020)** prepared phytosome loading with the combined extract of ginger rhizome extract and ripen mulberry fruit (PMG). They studied the neuroprotective effect and possible underlying mechanism of PMG on brain damage in cerebral ischemic rat with MetS, male Wistar rats were induced MetS by high-carbohydrate high-fat diet (HCHF) for 16 weeks and subjected to the cerebral ischemia/reperfusion injury (CIRI) at the right middle cerebral artery (Rt. MCAO). All doses of PMG significantly improved brain infarction, brain edema, and neurological deficit score. The study revealed the neuroprotective effect against cerebral ischemia with MetS condition. They concluded that PMG is the potential neuroprotectant candidate against ischemic stroke in the MetS condition.[42]

Table 1: Commercial Products of Phytosomes.[6,43-49]

S.No.	Phytosomes	Phytoconstituents complex	Indications
1.	Silybin PhytosomeTM	Silybin from *Silybum marianum*	Hepatoprotective, antioxidant for liver and skin
2.	Ginkgo PhytosomeTM	Ginkgo flavonoids from *Ginkgo biloba*	Protects brain and vascular linings, anti-skin ageing
3.	Ginseng PhytosomeTM	Ginsenosides from *Panax ginseng*	Nutraceutical, immunomodulator
4.	Green Tea PhytosomeTM	Epigallocatechin from *Thea sinesis*	Nutraceutical, systemic antioxidant, anticancer
5.	Grape Seed PhytosomeTM	Procyanidins from *Vitis vinifera*	Nutraceutical, systemic antioxidant, cardio-protective
6.	Hawthorn PhytosomeTM	Flavonoids from *Crategus oxyacanthoides*	Nutraceutical, cardio-protective and antihypertensive
7.	Olive oil Phytosome	Polyphenols from *Olea europaea* oil	Antioxidant, anti-inflammatory, anti-hyperlipidemic
8.	Echinacea Phytosome	Echinacosides from *Echinacea augustifolia*	Nutraceutical, immunomodulator
9.	Centella phytosome	Terpens from *Centella asitica*	Brain tonic, Vein and Skin Disorder
10.	Visnadine (Visnadax) phytosome	Visnadine from *Ammi visnaga*	Circulation Improver, Vasokinetic
11.	Curcumin phytosomes	Polyphenol from *Curcuma longa*	Cancer Chemo preventive Agent
12.	Glycyrrhiza phytosome	Glycyrrhetinic acid from *Glycyrrhiza glabra*	Anti-inflammatory, Soothing
13.	Olea select phytosome	Polyphenols from *Olea europea*	Anti–hyperlipidemic, Antiinflammatory
14.	Bilberry (Mertoselect) phytosome	Anthocyanosides from *Vaccinium myritillus*	Antioxidant, Improvement of Capillary Tone.

15.	Melilotus (Lymphaselect) phytosome	Triterpens from *Melilotus officinalis*	Hypotensive, Indicated in insomnia
16.	Cucurbita PhytosomeTM	Tocopherols, steroids, carotenoids from *Cucurbita pepo*	Anti-inflammatory, Benign prostatic hyperplasia
17.	Soyselect PhytosomeTM	Genistein and daidzein from *Glycine max*	Antiangiogenic, anticancer, cardioprotective, immunostimulatory and hypocholesterolemic
18.	Ximilene and Ximenoil PhytosomeTM	Ximenynic acid, ethyl ximenynate from Santalum album	Improve microcirculation
19.	Swertia PhytosomeTM	Xanthones from Swertia alternifolia	Antidiabetic
20.	Madeglucyl PhytosomeTM	Tannins from Syzygium cumini	Antihyperglycemic, anti-inflammatory, antioxidant

CONCLUSION

Plant extracts or mainly polar phytoconstituents like flavonoids, terpenoids, tannins, when complexed with phospholipids like phosphatidylcholine give rise to a new drug delivery technology called phytosome. Phytosomes shows better abosortion profile followed by oral administration owing to improve lipid solubility which allows them to cross the biological membrane. Phytosomes or herbosomes are advanced and novel form of botanicals and phytoconstituents that are better absorbed both orally, topically and transdermally. They have improved pharmacokinetics and pharmacological parameters.

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. Manach C, Scalbert A, Morand C. Polyphenols: food sources and bioavailability, Am J Clin Nutr., 2004; 79: 727-47.
3. Goyal A, Kumar S, Nagpal M, Singh I, Arora S, "Potential of Novel Drug Delivery Systems for Herbal Drugs", Indian Journal of Pharmaceutical Education and Research, Jul-Sep 2011; 45(3); 225235.
4. Bhattacharya S: Phytosomes: Emerging strategy in delivery of herbal drugs and nutraceuticals, Pharma Times, 2009; 41(3): 8-12.
5. Parris K, Kathleen H: A review of bioavailability and clinical efficacy of milk thistle phytosome: a silybin-phosphatidylcholine complex, Altern Med Rev, 2005; 10(3): 193-203.
6. Vitamedics, Phytosome Products [online]. 2008 [cited 2008 Sep 19]. Available from: URL: http://www. vitamedics.com.
7. Singh A., Ray A., Mishra R., Biswal P.K., Yadav R., Ghatuary S., Phyto-Phospholipid Complexes: Innovative Approach to Enhance the Bioavailability and Therapeutic Efficacy of Herbal Extract, Pharmaceutical and Biosciences Journal, 2020; 8(4): 01-09.
8. Bombardelli E. Phytosome: new cosmetic delivery system. Boll Chim Farm, 1991; 130(11): 431-38.
9. Bombardelli E, Spelta M. Phospholipidpolyphenol complexes: A new concept in skin care ingredients. Cosm & Toil, 1991; 106(3): 69-76.
10. Franco PG, Bombardelli E: Complex coppouns of bioflavonoids with phospholipids, their preparation and use and pharmaceutical and cosmetic composition containing them, 1998. U.S.Patent No. EPO 275005.
11. Kidd P, Head K., A Review of the Bioavailability and Clinical Efficacy of Milk Thistle Phytosome: A Silybinphosphatidylcholine Complex. Altern Med Rev., 2005; 10: 193-203.
12. Bombardelli E, Spelta M, Loggia Della R, Sosa S, Tubaro A. Aging Skin: Protective Effect of Silymarin- Phytosome. Fitoterapia, 1991; 62: 115-22.
13. Kumar S., Baldi A., Phytosomes: A Modernistic Approach for Novel Herbal Drug Delivery Enhancing Bioavailability and Revealing Endless Frontier of Phytopharmaceuticals, Journal of Developing Drugs, 2020; 9(2).
14. Amin T, Bhat S. A review on phytosome technology as a novel approach to improve the bioavailability of nutraceuticals. Int J Adv Res Tech., 2012; 1: 1-15.
15. Rudra PS, Ramakant N., Preparation and evaluation of Phytosomes of Lawsone., Int J Pharma Sci Res., 2015; 5217-26.
16. Prachi U, Omprakash B., Phyto-phospholipid commplex vesicles for phytoconstituents and herbal extracts: a promising drug delivery system, Int J Herbal med, 2016; 4: 14-20.
17. N. K. Jain. Liposomes as drug carriers, controlled and novel drug delivery, 1st edition, CBS publisher, 2005; 308.
18. Maghraby El GMM, Williams AC, Barry BW. Oestradiol skin delivery from ultradeformable liposomes: refinement of surfactant concentration. Int. J. Pharm, 2000; 196; 63-74.
19. Fry DW, White JC, Goldman ID. Rapid secretion of low molecular weight solutes from liposomes without dilution. Anal Biochem, 1978; 90: 809-815.
20. Liposomes: A Practical Approach, Preparation of liposomes and size determination, New RRC [Ed], Oxford University Press, 1990; 36-39.
21. Cevc G, Schatzlein A, Blume G. Transdermal drug carriers: basic properties, optimization and transfer efficiency in case of epicutaneously applied peptides. J. Control. Release, 1995; 36: 3-16.

22. Berge BAI V, Swartzendruber VAB, Geest J. Development of an optimal protocol for the ultrastructural examination of skin by transmission electron microscopy. J. Microsc, 1997; 187: 125-133.
23. Dayan N, Touitou E. Carrier for Skin Delivery of Trihexyphenidyl HCl: Ethosomes vs Liposomes. Biomaterials, 2002; 21: 1879-1885.
24. Facino RM, Carini M, Aldini G., et al. Free radicals action and anti-enzyme activities of procyanidines vitis vinifera- a mechanism for their capillary protection. Arzneim. Forsch, 1994; 44: 592-601.
25. Semalty A, Semalty M, Singh R, Rawat MSM. Phytosomes in Herbal Drug Delivery. Indian drugs, 2006; 43: 937- 946.
26. S. Abrol, A. Trehan, O. P. Katare. Comparative study of different silymarin formulations: formulation, characterization and in vitro/in vivo evaluation. Current Drug Delivery, 2005; 2: 45-51.
27. A. Comoglio, A. Tomasi, S. Malandrino, et al. Scavenging effect of silipide-A new silybinphospholipid complex, on ethanol-derived free radicals. Biochem. Pharmacol, 1995; 50: 1313-1316.
28. Maiti K., Mukherjee K., Murugan V., Saha P. B.,and Mukherjee P., Exploring the Effect of Hesperetin–HSPC Complex—A Novel Drug Delivery System on the In Vitro Release, Therapeutic Efficacy and Pharmacokinetics, AAPS PharmSciTech, 2009; 10(3).
29. Mishra Ganesh P., Vyash L., Survanshi L. and Joshi H. M., Preparation and evaluation of phytosomes of Vitex negundo Linn., Novel Science International Journal of Pharmaceutical Science, 2012; 1(9-10): 671 -673.
30. El-Gazayerly O.N., Makhlouf A. I. A., Soelm A. M. A., Mohmoud M. A., Antioxidant and hepatoprotective effects of silymarin phytosomes compared to milk thistle extract in CCl4 induced hepatotoxicity in rats, Journal of Microencapsulation, 2013; 31(1): 23–30.
31. Das K. M, Kalita B., Design and Evaluation of Phyto-Phospholipid Complexes (Phytosomes) of Rutin for Transdermal Application, Journal of Applied Pharmaceutical Science, 2014; 4. ISSN 2231-3354.
32. B. Keerthi , Pingali S. P, Srinivas P., Formulation and Evaluation of Capsules of Ashwagandha Phytosomes, Int. J. Pharm. Sci. Rev. Res., 2014. ISSN 0976 – 044X.
33. Damle M., Mallya R., Development and Evaluation of a Novel Delivery System Containing Phytophospholipid Complex for Skin Aging, AAPS PharmSciTech, 2015; 17(3).
34. Dhase S. A, Saboo S. S, Preparation and Evaluation of Phytosomes Containing Methanolic Extract of Leaves of Aegle Marmelos (Bael), International Journal ofPharmTech Research, 2015; 8(6): ISSN: 0974-4304.
35. Sharma S., Sahu A., Development, Characterization, and Evaluation of Hepatoprotective Effect of Abutilon indicum and Piper longum Phytosomes, Pharmacognosy Research, 2016.
36. Sundaraganapathy & N. Leena, Development and Evaluation of Anti-Cancer Activity of Phytosome Formulated from the Root Extract of Clerodendron Paniculatum Linn, International Journal of Pharmacognosy and Phytochemical Research, 2016; 8(11): 1778-1781.
37. Nazeer A., Veeraiyan S. and Vijaykumar S., Anti-Cancer Potency And Sustained Release Of Phytosomal Diallyl Disulfide Containing Methanolic Allium Sativum Extract Against Breast Cancer, International Research Journal Of Pharmacy, ISSN 2230 – 8407.
38. Anwar E., Farhana N., Formulation and Evaluation of Phytosome-Loaded Maltodextrin-Gum Arabic Microsphere System for Delivery of Camellia sinensis Extract, J Young Pharm, 2018.
39. El-Batal A, Elmenshawi S., Abdelhaleem A., Eldbaiky E. G., Preparation and Characterization of Silymarin Nanocrystals and Phytosomes with Investigation of their Stability using Gamma Irradiation, Indian Journal of Pharmaceutical Education and Research, 2018; 52(4).
40. B. Jyothi, Ragalatha M., Development And In Vitro Evaluation Of Phytosomes Of Naringin, Asian J Pharmaceutical & Clinical Research, 2019; 12(9).
41. S. Sachin, J. Adlin, T. Tamizh, Preparation and Evaluation of Curcumin Phytosomes by Rotary Evaporation Method, International Journal of Pharmacy and Biomedical Engineering, 2019; 6(1). ISSN: 2394 – 2576.
42. Palachai N., Wattanathorn J., Muchimapur S., & Thukham-mee W., Phytosome Loading the Combined Extract of Mulberry Fruit and Ginger Protects against Cerebral Ischemia in Metabolic Syndrome Rats, Hindawi Oxidative Medicine and Cellular Longevity, 2020.
43. Murray D. Phytosomes- Increase the absorption of herbal extract, Available at: www.doctormurray.com /articles/silybin.htm Accessed- Sept. 28, 2008.
44. Phytosomes: A technical revolution in phytomedicine. Available at: http:// www.indena.com Accessed- Oct. 2, 2008.
45. Farinacci M, Gaspardo B, Colitti M, Stefanon B. Dietary administration of curcumin modifies transcriptional profile of genes involved in inflammatory cascade in horse leukocytes. Italian J Animal Sci., 2009; 8: 84-6.
46. Kohli K, Ali J, Ansari M, Raheman Z. Curcumin: a natural anti-inflammatory agent. Ind J Pharmacol, 2005; 37: 141-7.
47. Di Pierro F, Menghi A, Barreca A, Lucarelli M, Calandrelli A. Greenselect® phytosome as an adjunct to a low-calorie diet for treatment of obesity: a clinical trial. Alt Med Rev., 2009; 14: 154-60.
48. Singh A, Saharan VA, Singh M, Bhandari A. Phytosomes: Drug delivery system for

polyphenolics phytoconstituents. Iranian J of Pharma Sci., 2011; 7(4): 209-19.
49. Joshi A., Chaturvedi S., Kumar V., et al. Phytosomes-a revolution in herbal drugs. Pharma Review, Kongposh Publications, December, 2007–January, 2008.