JOURNAL OF NATURAL REMEDIES
DOI: 10.18311/jnr/2022/30831

REVIEW ARTICLE

Phyto Vesicular Drug Delivery System: A Review

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Abstract

Natural phytoconstituents face challenges in exploring the *in vivo* effect despite having enormous *in vitro* therapeutic potential because of their low solubility and large complicated structures. To get over these obstacles, the phyto vesicular combination comprising phytoconstituents and phospholipid complex is effective. This review offers details on the phyto-vesicular complex, including information on the types of phytoconstituents and phospholipids, solvents, ratios of phytoconstituents to phospholipids, and evaluation factors. The review compiles information on a few medicinal plants and their active ingredients, from which phytosomes are formulated and evaluated.

Keywords: Herbal Extracts, Phospholipids, Phytoconstituents, Phyto Vesicular Complex

1. Introduction

The relationships between man and plants have been much closer during the evolution of human culture. Nature has given us a vast supply of cures for every disease that affects people. Herbal drugs have been in use for ages and are thus a valuable and precious gift from nature. India's traditional systems of medicine (Ayurveda and Siddha) are deeply rooted in the Indian psyche. Plants continue to be one of the primary sources of medications in both the traditional and modern systems of medicine around the world, despite the enormous advancements made in the field of allopathy during the 20th century[1]. Because of increased awareness about the toxicity and side effects of synthetic medications, interest in the research and usage of crude drugs has significantly expanded during the past 20 years. Active phytoconstituents like flavonoids, terpenoids, polyphenols, tannins, glycosides, alkaloids, steroids, etc. are responsible for therapeutic action. Generally, most of the phytoconstituents are polar in nature and hence face hurdles when crossing biological membranes. The inability of phytoconstituents to dissolve in lipids and their larger molecular structure restrict their absorption via the cell membrane. Conventional therapy used in traditional systems includes various dosage forms like decoction, *churna*, *vati*, *bhasma* etc., and have the main drawback of patient non-compliance[2]. It is challenging to take the drug orally because of its bitter taste as well as its interaction with gastric juice. A number of constituents of the plant do not survive the gastric environment when taken orally. Many of the herbal extracts and active constituents show admirable activity during *in vitro* studies, but in *in vivo* set up, they have been found to display lesser or no therapeutic activity because of their polar nature, molecular size, or both, which results in poor absorption and ultimately lack of bioavailability of active constituents[3]. The potency of a drug depends mainly on the effective delivery of phytoconstituents. So, the urge to integrate modern pharmaceutical knowledge with conventional delivery of herbal drugs to overcome these barriers. Novel drug delivery systems enhance the bioavailability, stability and therapeutic effect of natural products. Numerous novel herbal vesicular delivery systems have been fruitfully developed in recent years, including liposomes, phytosomes, niosomes, tansferosomes, ethosomes and various other vesicular systems to meet the challenges. Drug targeting and the sustained release of the active molecule are made possible by vesicular drug delivery systems[4].

The novel delivery system known as phytosomes was invented in Italy by Indena. Phytosomes are also known as phyto-vesicles, herbosomes, or planterosomes, and they improve the absorption of natural extracts and active plant

Article Received on: 27.09.2022 Revised on: 20.10.2022 Accepted on: 26.10.2022

constituents. It is a phyto-phoshphatidyl complex that consists of phospholipids and phytoconstituents linked together by a chemical bond. This approach ameliorates the pharmacokinetic profile of natural active molecules without adding bioavailability enhancers or chemical structure modifications[5].

Due to its dual solubility, phospholipid functions as an effective emulsifier. The phospholipid molecule structure contained two tails that are soluble in fat and two heads that are soluble in water. By mixing standardised plant extracts with the phospholipid's emulsifying abilities, phytosome preparation accelerates bioavailability[6].

Any conventional pharmaceutical dosage forms are further formulated using phyto-vesicles. The drug-phospholipid complexes are well absorbed and produce superior benefits to the plain herbal extracts. The first and most considerable benefit of a phospholipids-based vesicular system is that phospholipids are compatible with human internal membranes and skin[7].

2. Component of Phytosomes

The reaction of herbal extract or phytoconstituents with phospholipids in the presence of an aprotic solvent produced the phyto-vesicles known as phytosomes or phyto-vesicles (Figure 1). The phyto-complex is isolated by the removal of solvent using different techniques like vacuum drying, freeze drying, or the use of non-solvent like hexane. Table 1 illustrates the significance of each component of phytosomes. Phytosomes are formulated according to weight basis for standardized extract, while molar ratios are calculated for pure phytoconstituents and phospholipids by using different solvents[6,7].

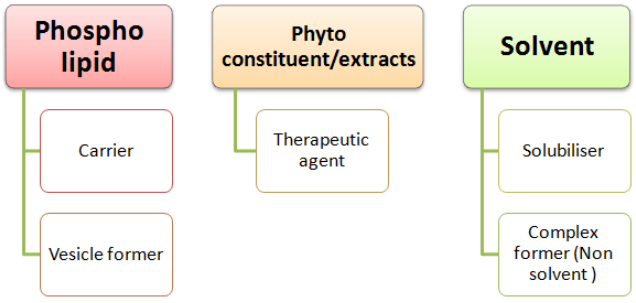

Figure 1. Component of Phytosomes.

Table 1. Components of Phytosomes with Significance[8]

Components	Examples of different ingredients	Significance
Phospholipids	α-lysophosphatidyl choline Phosphatidylcholine Phosphatidylserine Phosphatidyl ethanolmine, α-phosphatidic acid	Act as vesicle former and carrier
Aprotic Solvents	Dioxane, Acetone Acetonitrile Diethyl ether Chloroform Dichloromethane (DCM) Dimethyl suphoxide (DMSO) Ethyl acetate	As a solvent and reaction medium, Acting as a proton donor
Non solvent	Hexane	Phytosome complex precipitating agent
Protic solvent	Ethanol Methanol	As a solvent
Phytoconstituents / Extracts	Contains free hydrogen to form H- bond with phospholipids may lipophilic or hydrophilic	Therapeutically active constituents
Buffering agent	Saline phosphate buffer Tris buffer Distilled water	As a hydrating medium

2.1 Phytoconstituents

A plant extract or phytomolecule is generally selected on the basis of its solubility and pharmacokinetic profile. The active constituents with multiple ring- chemical structures are too large in size to be absorbed by the simple diffusion method. Also, they are less permeable to the cell membrane. In phytosomes, a chemical bond is generated between phytoconstituents and phospholipids. Hydrophilic or lipophilic drugs having active hydrogen

atoms or π electrons can form a bond with phospholipid molecules to form a highly bioavailable phospholipid complex[5].

2.2 Phospholipids

Phospholipids are lipids that have phosphorus in them and are structured with polar and non-polar regions. The phospholipids are the predominant lipids of the cell membrane, which act as vehicles or carriers. Different types of phospholipids, like phosphatidylethanolamine (PE), phosphatidylinositol (PI), phosphatidylcholine (PC) (Figure 2), phosphatidic acid (PA), and phosphatidylserine (PS), are part of biological membranes[9].

The unique molecular property that renders phospholipids miscible in both lipid and water is due to its two neutral tail groups and positive head group, which contain an oxygen atom in the phosphate group that has a strong tendency to receive electrons while nitrogen loses them. Phospholipids can be found in both natural and artificial sources. Phospholipids are abundant in both plants and animals, with vegetable oils, soy beans, sunflower seeds, rapeseed, cotton, egg yolk, and bovine brain serving as the primary sources. While only a small number of studies have employed egg lecithin, the majority of the literature recommends using soya bean phosphatidylcholine[10].

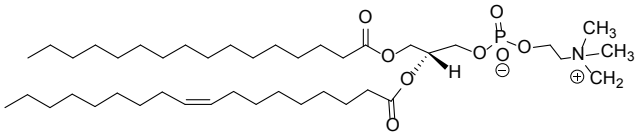

Figure 2. Structure of Phosphatidylcholine.

2.2.1 Advantages of Phosphatidylcholine

Phosphatidylcholine is a major component of the stomach's gastric mucosa lining that prevents ulcers, has excellent emulsifying activity, hepatoprotective function, is a nutritional supplement to maintain brain health, is nourishing to the skin, and is a precursor to acetylcholine.

2.3 Solvents

The choice of solvent in the phospholipid complexion approach depends on the active molecule and the phospholipids' ability to dissolve in the selected solvent. The literature recommends the use of both aprotic and protic solvents, and even many others have revealed the use of mixtures of solvents for improved solubility. Recently, ethanol, which is safer than the previous alternatives, has largely replaced aprotic solvents.

3. Method of Preparation of Phyto-vesicles[5]

3.1 Antisolvent Precipitation Method/ Salting Out Method

The mixture of a specific amount of drug and phospholipids is refluxed in a round bottom flask with an aprotic solvent at 40°C for 2-3 hours. The n-hexane (Non solvent) is mixed with continuous stirring to get the precipitates. After filtration and drying, the collected complex is crushed in a mortar and passed through a sieve of 100 mesh size.

3.2 Solvent Evaporation

Drugs and phospholipids are dissolved in a particular solvent at the temperature 40-60 °C for 2 hours. Further solvent is evaporated by simple evaporation or rotary evaporation techniques.

3.3 Mechanical Dispersion

Diethyl ether is used to dissolve phospholipid, which is then slowly added to an aqueous solution of the phytoconstituents to be encapsulated. The subsequent elimination of the organic solvent under low pressure causes the development of the phyto-phospholipid complex.

3.4 Thin Layer Hydration Method

Active molecules and phospholipids dissolved in a specific solvent. The solvent is evaporated using a rotary evaporator, and finally generated thin film is hydrated with water or buffer in the rotary evaporator at 40-45 °C for one hour.

3.5 Super critical fluid process[8]

The modern techniques used to prepare phytosomes include the use of carbon dioxide as a anti solvent to precipitate out the phospholipid complex. This super critical antisolvent method produces the phytosomes with controlled size and size distribution.

4 Characterization Parameters of Phyto-vesicles

The different characterization parameters are utilized to check the size, shape, entrapment efficiency, spectroscopy, crystalline nature and polymorphism and *in vitro* and *in vivo* evaluations[8]. All the parameters and their significance are listed in Table 2. All the evaluation parameters are done individually for phytoconstituents, phospholipids, physical mixtures, and phytosomes.

Table 2. Characterization parameters of Phytosomes[8]

Parameters	Method	Significance
Shape Visualization	SEM (Scanning electron microscopy)	Shape and surface properties of a solid state of material.
	TEM (Transmission electron microscopy)	To determine particle size and shape of dispersed phyto vesicles.
Size	Zeta Sizer	50 nm to a few 100μm
Zeta Potential	Zeta Sizer	Surface potential
Poly disparity index (PDI)	Zeta Sizer	More than 0.5 PDI value, indicating that the sample has a very broad size and is unstable.
Entrapment Efficiency	Ultra Centrifugation Technique	Amount of drug entrapped by phospholipid.
Spectroscopic evaluation	Nuclear magnetic resonance (NMR)	Confirm Hydrogen Bond establishment; Some distinguishing features in NMR spectra include line broadening and chemical shift shifts.
	Fourier transform infrared spectroscopy (FT-IR)	The development of different bands in the IR spectra is correlated to complex formation and interactions.
Crystallinity and Polymorphism	Differential scanning calorimetry (DSC)	DSC interactions are often seen as the disappearance of endothermic peaks, the emergence of new peaks, modifications to the peak's beginning and shape, peak temperature or melting points, relative peak area, or enthalpy in phospholipid complexes.
	X-ray diffraction (XRD)	Complete absence, disappearance, or a decrease in the strength of diffraction peaks are characteristics of complexity.
in vitro release rate	Franz diffusion cell Dialysis bag diffusion	Release rate
in vitro & *in vivo* estimation	On the basis of the anticipated therapeutic action of the current physiologically active phytoconstituents, models of i*n vivo* and *in vitro* evaluation are chosen.	Explore therapeutic effect.
Stability Studies	As per ICH guidelines	Stability of formulation

5. Merits of Phytosomes[11,12]

- Protect the phytoconstituents from gastric acid and gut microorganisms.
- Increase the bioavailability of phytoconstituents by increasing absorption both orally and topically.
- The quantitative requirement is reduced, resulting in a lower the toxicity profile.
- Better stability.
- Phytosomal herbal formulations enhance the absorption of phytoconstituents through the skin, so they have a marked application in cosmetic preparations.
- Phosphatidylcholine, one of the ingredients in phytosomes, shows a hepatoprotective effect.
- Further provides the nutritional benefit of phospholipids.
- It ensures adequate drug distribution to the targeted tissues.
- Higher entrapment efficiency
- The manufacturing process is easy.

6. Limitations

The main drawback of the phytosome is the loading issue and leakage of the phytoconstituents that decreases the predictable drug concentration[4].

7. Mechanism of Phytosome Complex Formation[3,13]

When phospholipids and phytoconstituents are mixed together in the presence of a suitable solvent in a stoichiometric amount, they form phyto-vesicles known as phytosomes. Phospholipid, like phosphatidylcholine, is a bifunctional molecule that consists of lipophilic (Non polar) and hydrophilic (polar) portions[2]. Phytoconstituents and the polar head of lipid react and form the complex that is further envelop by the non-polar part of lipid (Figure 3). Phytoconstituents generally consist of active hydrogen that binds with the polar part of phospholipid through hydrogen bonding and forms lipid-compatible vesicles[4] (Figure 4). An updated phospholipid complex of different active constituents and herbal extracts is shown in Table 3.

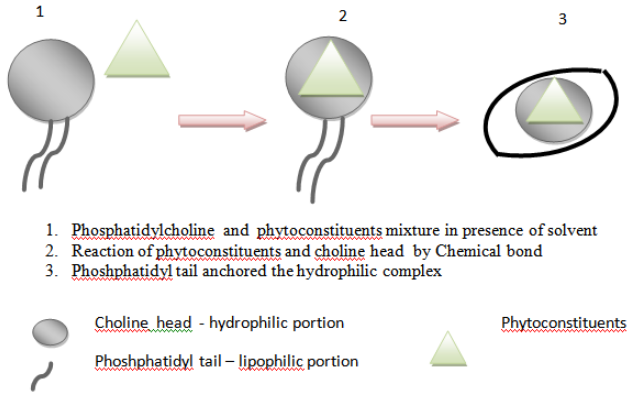

Figure 3. Mechanism of phytosome complex formation.

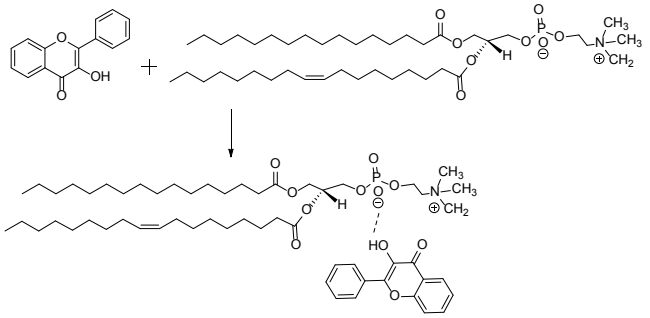

Figure 4. Hydrogen bond formation between phytoconstituent and phosphatidylcholine.

Table 3. Compilation of recent work on phospholipid complex of different active constituents and herbal extracts

Phytoconstituent/ Extract	Method of Preparation	Ratio (Drug : lipid)	Solvent	Types of Lipid	Therapeutic Evaluation	Ref.
Andrographolide	Rotary Evaporation, Antisolvent Method	1:1	DCM	Phosphatidylcholine	Hepatoprotective Activity	(14, 15)
Apigenin	Antisolvent Rotary Evaporation	1:1 1:2 1:3	1,4Dioxane :Methanol(14:6)	Phoshpholipone90H	*In vivo* Antioxidant Study Pharmacokinetic Study	(16)
Chrysin	Thin Layer Hydration (Rotary Evaporation)	1:1	Ethanol, DCM	Soya Lecithin		(17)
Curcumin	Anti-Solvent Rotary Evaporation	1:1	DCM	Hydrogenated Soy Phosphatidyl Choline	Pharmacokinetic Study Hepatoprotective Activity *Antioxidant Activity*	(18)
Diosmin	1. Solvent Evaporation 2. Salting Out 3. Lyophilization Techniques	1:2	Dioxane-Methanol Mixture (7:3), DMSO, Ethanol &Chloroform (2:2:3) DMSO, T-Butylalchol	Lipoid® S100	*Ex vivo* Intestinal Permeation Studies	(19)
Diosmin	Solvent Evaporation Method	0.5:1, 0.75:11:1, 2.5:1 3:1	DMSO, DCM	Phosphatidylcholine	–	(20)
Ferulic Acid	Rotary Solvent Evaporation Method	1:1	Anhydrous Ethanol	Soy Lecithin	Inhibition Of Melanogenesis • B16F10 Cell Viability Assay • Measurement Of Melanin Content	(21)
Gingerol	Antisolvent Precipitation Method	1:1 1:2 2:1 2:2	DCM	Soya Lecithin	*In vitro* Anti-Oxidant, Anti-Microbial And Anti-Inflammatory Activity Pharmacodynamics Study	(22)

Table 3. (Continued)

Phytoconstituent/ Extract	Method of Preparation	Ratio (Drug : lipid)	Solvent	Types of Lipid	Therapeutic Evaluation	Ref.
Hesperidin	Solvent Evaporation Method	1:0.5 1:1 1:2 1:3	DCM	Soya Lecithin	Antioxidant Activity Study Of The Complex By Reducing Power Method	(23)
Kaempferol	Anti Solvent Precipitation Method	1:1	Anhydrous Ethanol	Lipoid S 100	Pharmaco-Kinetic Study	(24)
Kaempferol	Lyophilization	1:1, 1:2, 1:3	1, 4-Dioxane	Phospholipon® 90H	*In vivo* Antioxidant Activity	(25)
Lawsone	Antisolvent Precipitation Technique	1:1 1:2 2:1 2:2	DCM, Hexane	Soya Lecithin	Gel Antifungal Activity Anti-Inflammatory Activity	(26)
Luteolin	Thin Layer Hydration	1:3	Methanol	Soybean Phosphatidylcholine	Pharmacokinetic Study	(27)
Luteolin	Thin Layer Hydration	–	–	Phosphatidyl choline, Phosphatidyl etanolamine And Phosphatidyl serine	MTT Assay (Human Breast Carcinoma MDA-MB231 Cells) Real-Time Quantitative PCR	(28)
Mangiferin	Rotary Evaporation Washing With Hexane	1:1	DCM	Soya Phosphatidylcholine (SPC) (Lipoid S 100)	Hepatoprotective Activity	(14)
Marsupsin	Mechanical Dispersion Method.	1:2	Diethyl Ether	Soy Lecithin	Pharmacokinetic Study	(29)
Morin	Solvent Evaporation Technique		DCM	Phospholipon 90G	Antioxidant Activity	(30)
Puerarin	Supercritical Fluid Technology	1:1.2	Ethanol CO2	Phoshpholipid	No verification Therapeutic potential	(31)
Quercetin	Thin Layer Hydration Method	–	Methanol And DCM	Soybean Phosphatidylcholine, Cholesterol	No verification Therapeutic potential	(32)

Table 3. (Continued)

Phytoconstituent/ Extract	Method of Preparation	Ratio (Drug : lipid)	Solvent	Types of Lipid	Therapeutic Evaluation	Ref.
Resveratrol	Solvent Evaporation	1:0.75	Methanol And DCM	Egg Lecithin	Transdermal Polymeric Patch *In vivo* Anti-Inflammatory Study In Carrageenan-Edema Model	(33)
Rosmarinic Acid	Solvent Evaporation Method	1:1.5	Methanol	Phoshpholipid	Radical Scavenging Activity Assay Cell Viability Assay	(34)
Rutin	Thin Layer Hydration Method	1:1 1:2 1:4	Methanol And Chloroform (1:4)	Soy Phosphatidylcholine And Cholesterol	–	(35)
Silymarin	Thin Layer Hydration	1:5	Ethanol	Soy Phosphatidylcholine; Lipoid® S100	–	(36)
Umbelliferone	Salting Out	1:2	DCM Hexane	Phospholipon90 H	Photo-Protective And Antioxidant Activity	(37)
Umbelliferone	Solvent Evaporation	1:0.55 1:1.05, 1:1.78 1:2.51 1:3	Ethanol Hexane	Phospholipon90 H	Anti-Inflammatory Activity	(38)
Ursolic Acid	Salting Out	0.6:1 To 1.8:1	DCM Hexane	Hydrogenated Soybean Phosphatidylcholine	Hepatoprotective Activity	(39)
Wedelolactone	Salting Out, Thin Layer Hydration	1:1	DCM	Phosphatidylcholine	Hepatoprotective Activity	(40)
Abutilon indicum and *Piper longum*	Antisolvent Precipitation	1:1	Methylene Chloride And N-Hexane	Soy Phosphatidylcholine	Hepatoprotective Activity	(41)
Citrullus colocynthis (L.) *Momordica balsamina* and *Momordica dioica* Fruits Methanol Extracts	Solvent Evaporation	1:1	Ethanol	Lipoid® S45	Antidiabetic Activity	(42)

Table 3. (Continued)

Phytoconstituent/ Extract	Method of Preparation	Ratio (Drug : lipid)	Solvent	Types of Lipid	Therapeutic Evaluation	Ref.
Bacopa	Antisolvent Precipitation	–	DCM	L A-Phosphatidylcholine	Antiamnesic Activity	(43)
Ethanol Extract of *Bombax ceiba* Leaves	Anti-Solvent Precipitation	0.5:1, 1:1, 1.5:1, 0.5:2, 1:2, 1.5:2,	Acetone	Soya Lecithin	*InVitro* Antioxidant Activity	(44)
Methanol Extract of Leaves of *Aegle marmelos*	Solvent Evaporation Method	1.5:5	Chloroform	Phosphatidylcholine And Cholesterol	Antioxidant, Antiproliferative And Anticancer Activity	(45)
Boswellia serrata	Casperome™ By Indena	1:1	Gift sample	Soya Lecithin	As Complementary Intervention In Asthmatic Patients, Clinical Trial	(46)
Boswellia serrata	Mechanical dispersion method	1:1	Ethanol	Phospholipon90 G	–	(47)
Camellia sinensis	Thin Layer Hydration Method	1:1	Dichloromethane, Ethanol	Phosphatidyl Choline (Lipoid P 30	*In vitro* Antioxidant Activity Maltodextrin-Gum Arabic Microsphere Prepared	(48)
Syzygium cumini Seeds Hydro Ethanol Extract	Thin Film Hydration Technique	1:2 1:1 2:1	Chloroform And Methanol	Cholesterol And Lecithin	Capsule Of Phytosomes Prepared.	(49)
Centella asiatica Ethanol Extract	Antisolvent Precipitation	1:1	Chloroform	Phosphatidyl Choline	Anti Inflammatory Activity In Atopic Dermatitis	(50)
Citrus limon Extract	Solvent Evaporation Method	0.5:1, 0.75:1, 1:1, 2.5:1, 3:1	Dichloromethane And Methanol	Phosphatidylcholine	Antioxidant Activity	(51)
Diospyros kaki L.	Rotary Solvent Evaporation Method	1:1 1:2	Ethanol Acetic Acid	Phosphatidylcholine	Antioxidant Activity	(52)
Ginkgo biloba Extract	Gift Sample From Indena	1:1	–	Soy Phospholipids	Effect On Isoproterenol-Induced Cardiac Necrosis In Rats	(53)

Table 3. (Continued)

Phytoconstituent/ Extract	Method of Preparation	Ratio (Drug : lipid)	Solvent	Types of Lipid	Therapeutic Evaluation	Ref.
Glycine max Methanol Extract	Solvent Evaporation Salting Out Cosolvency	1:1	Ethanol	Phosphatidylcholine	Preparation Of Phytosomal Thermogel. Anti-Weight-Gain Effect Of Soy Phytosomal Thermogel.	(54)
Citrus auranticum and *Glycyrrhiza glabra* Methanol Extract	Film Formation, Salting out, Solvent Evaporation Method.	1:1	Methanol, DCM, Hexane	–	Anti-Oxidant Activity, *In vitro* Anti-Elastase Activity Cream Of Phytosomes	(55)
Extract of *Phyllanthus amarus*	Salting Out Method	1:1	DCM, N- Hexane	Phospholipon 85G	Tablet	(56)
Methanol Extract of *Terminalia arjuna* Bark	Salting Out Method, Solvent Evaporation Method	1:1	Methylene Chloride, Hexane	Hydrogenated Phosphatidylcholine (Phospholipon 90H)	Antiproliferative Effect On Human Breast Cancer Cell Lines (MCF-7)	(57)
Hydro-alcohol Extract of *Terminalia chebula*	Salting Out Method	0.5:0.4:1, 1:0.8:11.5:1.2:1, 2:1.6:1	Methanol, Hexane	Phospholipids, Cholesterol	*In vitro* Antioxidant Activity	(58)
Milk Thistle Extract	Precipitated With Petroleum Ether	1:1	Methanol	Soybean Lecithin Egg Yolk Lecithin	Antioxidant And Hepatoprotective Effects	(59)
Bitter Melon Ethanol Extract	Thin Layer Hydration Method.	1: 1, 1: 2 1: 3.	DCM	Phosphatidylcholine	–	(60)
Methanol Extract of *Phyllanthus emblica*	Solvent Evaporation	1:1, 1:2, 1:3.	DCM	Soya Phosphatidylcholine	Photoprotectant Cream Prepared using Phytosome	(61)

8. Utilization of Phytosomes in Medical Science

Phytosomes are valuable in the field of medical science as they assure target-specific drug delivery to the respective tissue without compromising the nutrient value of herbal extracts or phytoconstituents. The technology can be used to treat a various disorders by decreasing the dose due to better bioavailability by oral and topical administration.

9. Conclusion

The phytosome is formed by the proper combination of components such as phospholipid, phytoconstituents, solvent, and stocheometric ratio. The better phytosome formulation is produced by variation and advancement in the types of components. The bioavailability of complex has been improved compared to pure extract or phytoconstituents due to the non-polar envelope that has been developed by the lipophilic part of phospholipid around the phytoconstituent to improve the solubility, as well as the hydrogen bond formation between phytoconstituents and phospholipid to improve the stability. This review provides information regarding the phytosome and research carried out on it using different phospholipids, phytoconstiuents and solvents.

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