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A Novel Drug Delivery System with Better Bioavailability- A Phytosome

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Abstract: Considerable scientific research has recently focused on creating innovative drug delivery systems (NDDS) for herbal medications. When developing polymeric nanoparticles, nanocapsules, liposomes, phytosomes, and nanoemulsions from phytochemicals utilizing NDDS techniques, herbal medications have several advantages. They are enhancement in tissue macrophage dispersion, increased stability, protection against toxicity, enhanced pharmacological activity, more bioavailability, persistent delivery, and endurance against deterioration, both chemical and physical. The present review highlights the role of the preparation of phytosomes in influencing bioavailability and various research by using phytosome formulation.

Keywords: Phytosomes, Bioavailability, Herbal extract, Nanoemulsions, Drug delivery systems

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Introduction

Compared to traditional dosage forms, Novel Drug Delivery Systems (NDDS) provide several advantages. Traditional dose forms include the following issues: rapid release of pharmaceuticals, first-pass action, variability in plasma drug levels, and low bioavailability. NDDS will solve these issues through performance, protection, patient compliance, and product shelf life. Novel approaches that can improve the efficacy and safety of the treatment are continually being researched to overcome these limitations. Types of Novel Drug Delivery Systems include Phytosomes, Transferosomes, Niosomes and Liposomes.

The term "Phytosome", 'Phyto' denotes plants, while 'Some' denotes something that resembles a cell. Herbal components are typically Polar and are water-soluble. Because of their limited absorption and decreased bioavailability, they are rarely employed extensively. The effectiveness of

those Herbal Constituents depends upon their Absorption and to overcome that and for the improvement of Bio-availability, the Phytosome technology was used. Phytosome technology was used to deliver the Herbal Constituents and Drugs to improve their absorption and showed better results when compared to the conventional Dosage form. In most of the plant-based medicines, the major active substances are water-soluble compounds e.g. Glycosides, Terpenoids, and Flavanoids. Out of which Flavonoids are mostly used. Compared to plant-based medicines with pharmaceutical dosage form, phytosomes exhibit enhanced solubility due to phytosomes' lipophilic outer layer (Jain *et al.,* 2010). Due to large molecular size flavonoids, Tannins, and Terpenoids are not well absorbed. This prevents passive diffusion and because of poor lipid solubility, they cannot cross lipid-rich biological membranes. This leads to poor bioavailability. In the stomach environment, several elements of extracts may be degraded when consumed orally. Poor bioavailability frequently restricts the therapeutic value of established standardized extracts for the reasons mentioned above. On complexation with active substances, the bioavailability of phytosomes can be increased substantially. The nutrients so useful for boosting the absorption are the phospholipids. Phospho-lipids can be converted into phytosomes (lipid-compatible molecular complexes) with the use of standard plant extract. This patented technology was created by a top producer of pharmaceuticals and nutraceuticals. The water-soluble material in liposomes is surrounded by a large number of phosphatidylcholine molecules.

The ratio of phosphatidylcholine and plant components is usually 1:1 or 2:1 ratio based on complex substances. This process involves chemical bonding. Phospholipids are complex substances that are essential for all living beings in the construction of cell membranes. Phospholipids act as transport of both water and lipid solubility nutrients in humans and animals and they also aid in natural digestion problems. They have good oral absorption and are miscible in lipid and water environments. Compared to standard plant extracts, phytosomes have a high potential for reaching blood circulation. A new method for delivering herbal medications and nutraceuticals is the phytosome (Saraf, 2010). Phytosomes are also used in cosmetics and penetrate through skin easily (Tripathy *et al.,* 2013).

Advantages:

- The absorption of herbal constituents is low, but Phytosomes enhance the absorption and also the Bioavailability.
- Phosphatidylcholine has bifunctional activity, i.e. acts as a vehicle and also as a hepatoprotective agent.
- The existence of a chemical link between phosphatidylcholine and the phytoconstituent generally makes phytosomes more stable than liposomes.
- A Lipid layer surrounds the Phytoconstituent which helps the Phytosomes to permeate through the Skin.
- One can lower the drug's dosage required.
- Phytosomes have a major advantage in cosmetics and can penetrate into the skin easily.
- Phytosomes are used in transdermal drug administration systems due to more skin penetration.

Preparation of Phytosomes:

When phospholipid (phosphatidylcholine) combines with standardized extracts or polyphenolic components (terpenoids, tannins, flavonoids, and xanthones) in a non-polar solvent(aprotic and protic solvent solvent), phytosomes are formed (Singh *et al.,* 2013).

Components of Phyto-Phospholipid Complexes:

In accordance with Bombardelli, phospholipids can combine stoichiometrically with active ingredients that are isolated from plants to form phyto-phospholipid complexes (Bombardelli and Sabadie, 1990) and phytosome formation (Fig. 1).

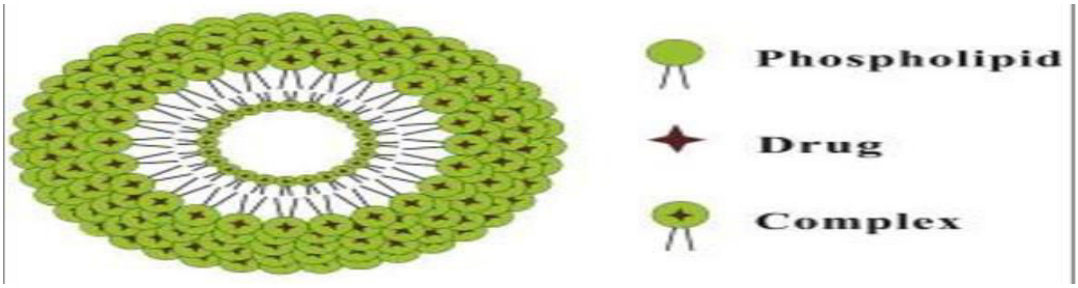


Fig.1: Phytosome formation by plant extract and phospholipids.

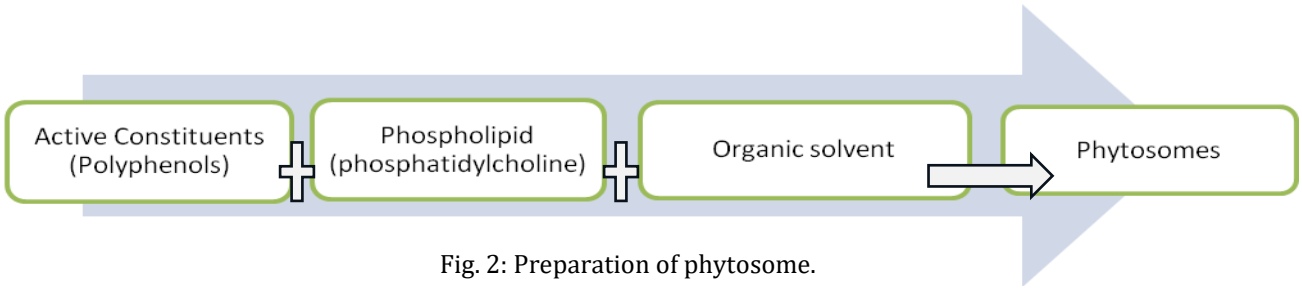


Fig. 2: Preparation of phytosome.

1. Phospholipids
2. Phyto active constituents (Polyphenols)
3. Solvents

Figure 2 explains the formation of Phytosome by interaction between phospholipid, phyto-constituents and solvents.

Phospholipids:

Plant seeds and egg yolks are excellent sources of phospholipids. Phospholipids produced in an industrial facility are now commercialized (Ghanbarzadeh *et al*., 2016). Common sources of industrially produced phospholipids include fish, eggs, chicken eggs, rapeseed, sunflower, soy, and so on. Every source has distinct qualities that are exclusive to each phospholipid species, and as a result, the food, pharmaceutical, and cosmetic industries have different uses for them (Perumal *et al*., 2014).

In this classification, Phosphatidylcholine (PC), Phosphatidylethanolamine (PE) and Phosphatidyl-serine (PS) are the 3 major phospholipids used (Perumal *et al*., 2014). PC is used mostly used for preparing complexes of phospholipid.

Phyto-active constituents (*polyphenols*):

Phyto-active constituents are the herbal extracts from the plants which has a major pharmacological effect on the body and those phytoconstituents are used to treat various diseases. Most of these compounds are polyphenolic compounds.

Hesperidin is one of the physiologically active polyphenolic components found in plants that don't prefer lipophilic membranes and passes through the aqueous phase. Certain substances, such as curcumin and rutin, are highly lipophilic and do not dissolve in aqueous gastrointestinal fluids. The aqueous phase solubility of lipophilic polyphenols can be enhanced by phyto-phospholipid complexes, while hydrophilic polyphenols from the same phase can also be more readily absorbed via membranes. Additionally, the synthesis of complexes can shield polyphenols from adverse environmental factors as oxidation, photolysis, and hydrolysis (Kidd, 2009).

Solvents:

Previously, aprotic solvents such as cyclic ethers,

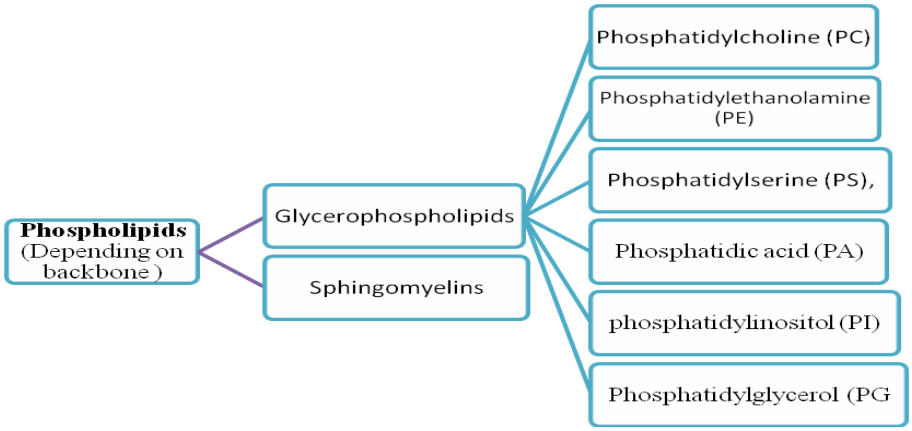


Fig. 3: Major phospholipids.

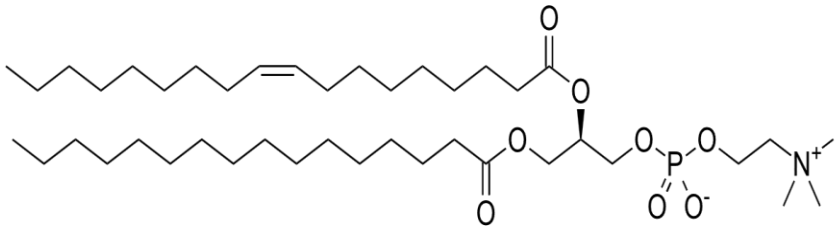


Fig. 4: Chemical structure of Palmitoyl-oleyl-*in*-phosphatidylcholine.

methylene chloride, ethyl acetate, aromatic hydrocarbons, and halogen derivatives have been used to create phytophospholipid complexes; however, ethanol and other protic solvents have largely replaced these techniques. Protonic solvents like methanol and ethanol have only lately been effectively applied in the phospholipid complex preparation process (Khan *et al.*, 2013; Shakeri and Sahebkar, 2016).

Methods of Preparation of Phytosomes:

Various methods are used for preparation of phytosomes. They are--

- Freeze drying co-solvency
- Reflux Method
- Salting out technique
- Anti-solvent precipitation
- Rotatory evaporator method

The evaporator approach and solvent evaporation are popular and widely utilised methods for creating phospholipid compound.

Phytosomes Based Products in Market:

Table 1 illustrates phytosomes which are derived from plants and uses of these phytosomes.

Phytosome Drug Delivery System in Cosmetics:

The Phytosome of Ginkgo Biloba Terpenes is useful in reducing individual contact responses to other ingredients in topical remedies (Loggia *et al.*, 1996).

In Silymarin Phytosome, the well-known calming effect of silymarin has been shown in animal models to rise by more than six times. The Phytosome form has enhanced activity in comparison to the free active principles, owing to the complex's increased affinity for skin phospholipids (Xiao *et al.*, 2006). Figures 3-5 explain the various phospholipid and its structure.

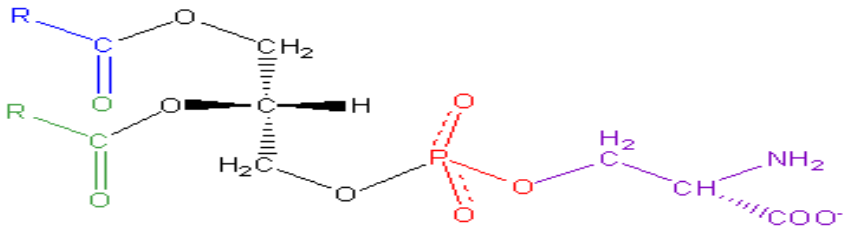
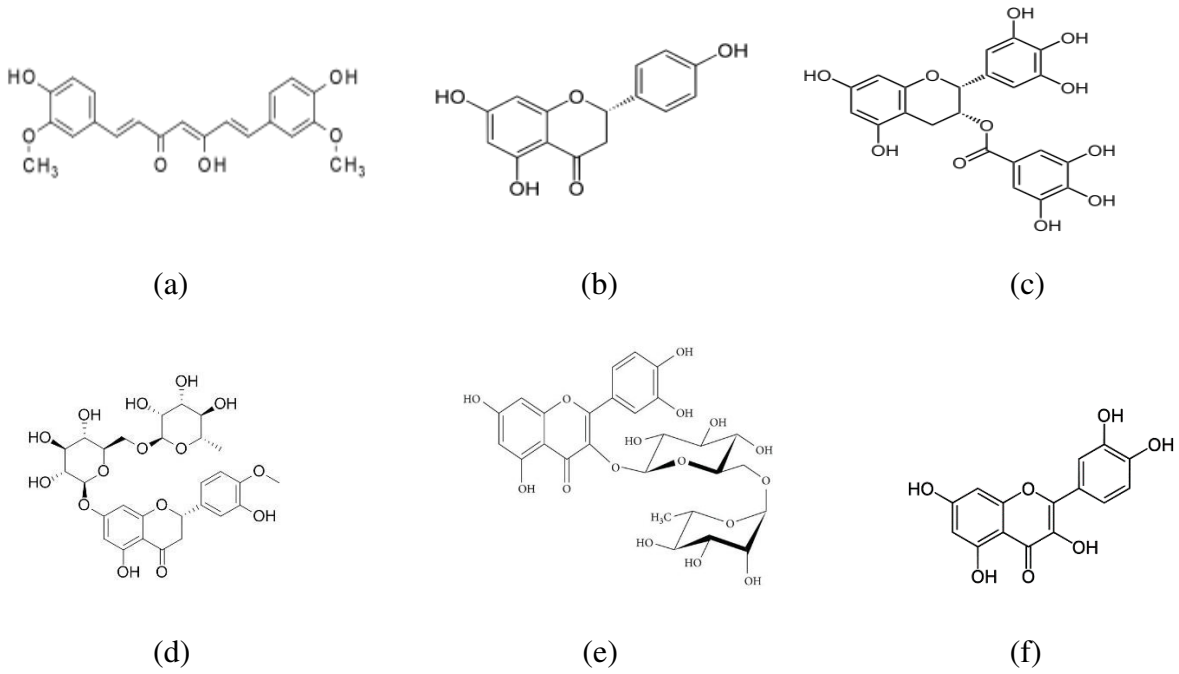


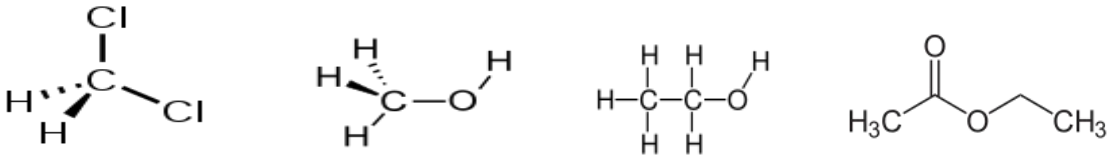
Fig. 5: Chemical structure of phosphatidyl serine.



(a) (b) (c)

(d) (e) (f)

Fig. 6: (a) Curcumin (Enol form); (b) Naringenin; (c) Epigallocatechin gallate; (d) Hesperidine; (e)Rutin; (f) Quercetin.



Methylene Chloride Methanol Ethanol Ethyl acetate

Fig. 7: Solvents used in preparation of Phytosome.

The retention of moisture in the corneal layer is due to the complex's phospholipids. As ginseng saponins can be found in the phospholipidic complex, Ginselect Phytosome has a transdermic effect (Kidd, 2007). Figure 6 explains the active constituents which can be used in the phytosomal formulations. Figure 7 explains the structure and solvents used in phytosome formulation. Phytosome drug delivery method is the main option for enhancing the physicochemical characteristics, which permits raising the effectiveness. Enhancing the solubility,

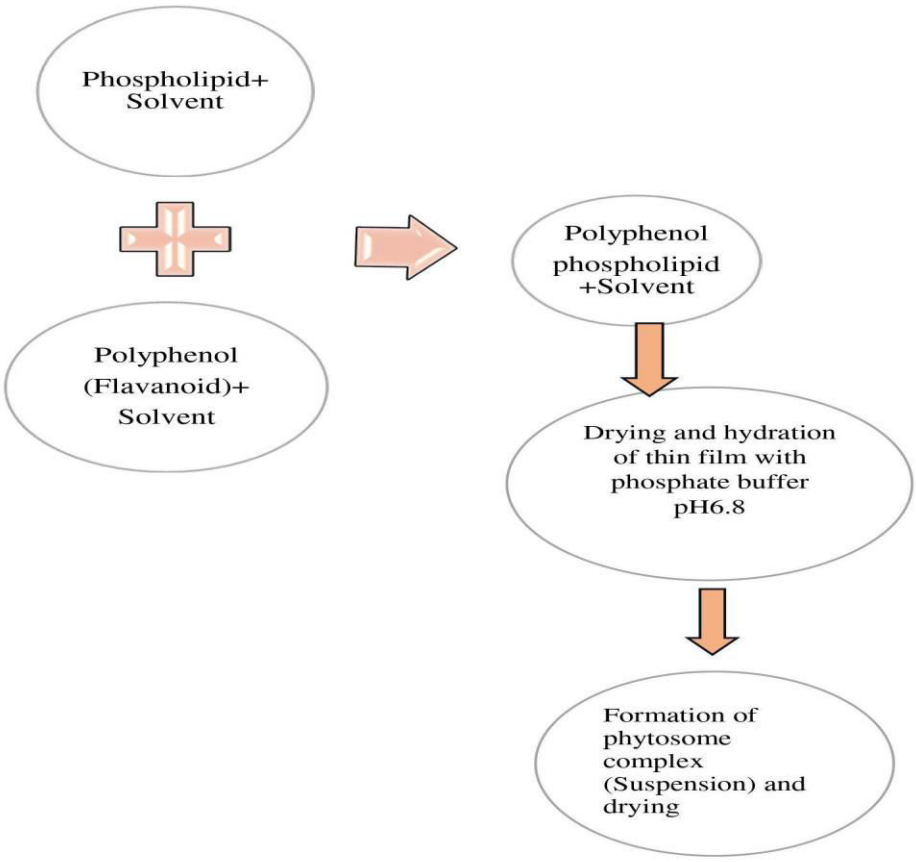


Fig. 8: Preparation of phytosome flow chart.

Table1: Phytosomes derived from Plants and its uses

S. No.	Plant Source	Family	Phytosome Product	Phytoconstituents	Uses	References
1	Milk thistle (*Silybum marianum*)	Asteraceae	Silybin phytosome TM	Flavonolignan (silybin)	Hepatoprotective, Anti-aging, Anti-inflammatory, Anti-oxidant	Sankar (2020)
2	*Vitis vinifera*	Vitaceae	Leucoselect® Phytosome	Grape seed polyphenol (GSP)	Improvement in Low density Lipoprotein cholesterol resistance to oxidation	Kumar *et al.* (2017)
3	*Camellia sinensis*	Theaceae	Greenselect® Phytosome	Green tea extract (Catachin and their gallate derivatives)	Anti-oxidant, Reduction in BMI, Anti cancer	Karimi *et al.* (2015); Lu *et al.* (2019)
4	*Ginkgo biloba*	Ginkgoacea	Ginkgobiloba terpenes Phytosomes	Ginkgolides (Terpenes)	Migraine	Karimi *et al.* (2015)
5	*Curcuma longa*	Zingiberaceae	curcumin phytosome (Merinoselect)	L-Rhizome	Cancer Chemo-preventive agent, Joint health, Anti-inflammatory, Soothing	Lu *et al.* (2019)
6	*Glycin max*	Fabaceae	Extract of	Saponins	Weight loss, Anti-	Kumar *et al.*

			Soybean seeds		cancer, Cardioprotective, Immunostimulatory, Anti-hyperlipidemic	(2017)
7	*Berberis vulgaris*	Berberidaceae	Berberine-phospholipid complex based phytosome	Berberine	Anti-diabetic	Kumar *et al*. (2017)
8	*Panax ginseng*	Araliaceae	Ginseng phytosome	Ginsenosides	Immunomodulator	Sankar (2020)
9	*Glycyrrhiza glabra*	Fabaceae	18 β-Glycyrrhetinic acid phytosome	Glycyrrhetinic acid	Anti-inflammatory, Soothing	Sankar (2020)
10	*Crataegus oxycantha*	Rosaceae	Haw thorn phytosome	Flavanoids	Antihypertensive activity, Cardioprotective	Lu *et al*. (2019)
11	*Crataegus Mexicana*	Rosaceae	Crataegus phytosomes	Vitexin-2'-O-rhamonoside	Anti-oxidant	Kumar *et al*. (2017)
12	*Centella asiatica*		Centella Phytosome	Asiatic acid, Madecassic acid, Triterpene	Skin disorder,Wound healing, Cicatrizing, trophodermic,	Sankar (2020)
13	*Curcuma longa*	Zingiberaceae	Meriva	Curcuminoids	Anti-inflammatory (200-300 mg)	Kumar *et al*. (2017)
14	*Citrus aurentium*	Rutaceae	Naringenin Phytosome TM	Naringenin	Anti-oxidant, Anti-inflammatory	Sankar (2020)
15	*Vaccinium myrtillus(Bilberry)*	Ericaceae	Mirtoselect phytosome TM	Anthocyanoside	Diabetic retinopathy Anti-oxidant, Anti-inflammatory	Sankar (2020)

penetration, and stability of the active ingredients was the primary goal of these phytosome formulations. Investigations showed that phytosome formulations can enhance the physicochemical properties and efficacy of drugs. The capacity to enhance the physicochemical characteristics and boost the efficacy of natural substances makes the phytosome drug delivery system a potential modification technology. In the future, phytosome formulation may prove to be a highly effective method for creating cosmeceutical products (Susilawati *et al*., 2021).

Priani *et al*. (2019) combined a phytosome containing cocoa pod extract with a face serum and assessed the extract's and the serum's tyrosinase-inhibiting and antioxidant properties. Using the thin-layer method and soy-phosphatidylcholine, it was converted into a phytosomal formulation. Figure 8 explains the flowchart to prepare phytosome. The phytosome then uses Viscolam MAC 10, a gelling ingredient, to grow into a face serum combination. The antioxidant activity and tyrosinase inhibitory activity was determined (Priani *et al*., 2019). Table 1 explains the details on phytosome formulation and its uses.

Surini *et al*. (2018) formulated a cosmetic serum that included phytosome extract from grape (*Vitis vinifera* L.) seeds. High-activity antioxidant phenolic chemicals are widely present in grape seed extract (GSE). Because GSE is hydrophilic, phenolic chemicals do not penetrate as well. This study showed that the presence of phytosomes could improve the drug's penetration in serum dose form (Surini *et al*., 2018).

Conclusion

Phytosomes are advanced novel drug delivery systems. Though Phytoconstituents have poor bioavailability, it can be improved by combining

them with Phytosomes. Overall Phytosomes increase the absorption and bioavailability of Phytoconstituents. They are extensively utilized in cosmeticology and have better pharmacokinetics, pharmacodynamics, and pharmacological characteristics. Phytosome formulation preparation is simple and easily repeatable. This technology serves as a link between the Novel medication delivery system and phyto-constituents.

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