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A REVIEW ON PHYTOSOMES: A POTENTIAL NANOCARRIER FOR EMERGING DRUG DELIVERY OF PHYTOCONSTITUENTS

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ABSTRACT

The phytoconstituents extracted from plants show poor solubility and poor in-vivo absorption which greatly limits the widespread applications of the herbal active constituents. A phytosomes shows potential nanocarrier for emerging drug delivery of phytoconstituents by incorporation of phyto-phospholipid complexes to increase the in-vivo bioavailability of herbal active constituents, which contains phospholipids and phyto constituents. Hydrogen bond interactions between phyto constituents and phospholipids can be formulated as phytosomes. In this review, structure, properties, advantages, disadvantages, types, methods for preparation, characterization, therapeutic applications, marketed preparations of phytosomes are included.

KEYWORDS: Phytosomes, Phytoconstituents, Bioavailability.

INTRODUCTION

Phytosomes is a novel drug delivery system approach and is effective in distributing the herbal drug at a predetermined rate, distributing the drug at the site of action, reducing toxic effects, increasing drug bioavailability, regulating the distribution of the drug is accomplished by incorporating the drug into the carrier system or altering the drug structure at the molecular level. Phytosomes are newly introduced by Indian patent technologies for the production and incorporation of standardized plant extracts.[7]

The term 'phyto' means plant and 'some' means cell-like. Phytosomes are little cell like structures. This is advanced form of herbal formulations which contains the bioactive phytoconstituents of herb extracts surround and bound by lipids. Phytosomes are prepared by interactions between phyto constituents and the polar head of phospholipids. Most of bioactive phytoconstituents are water soluble compounds like flavonoids, glycosides. Due to their water soluble property, and lipophilic outer layer it shows better absorption and produce better bioavailability. The interaction between phytoconstituents and phospholipids permits phospholipid complexes is an essential part in which the phospholipids head group will be attached, but the two long fatty acid chains will not participate in the formation of complex. The two long fatty acid chains can move and encapsulate the polar part of complexes to form a lipophilic surface. Phytosomes forms the agglomerates when diluted in water, which resembles a cell-like structure that looks like similar to liposomes.[2] Liposomes are closed vesicles formed by lipid bilayers that can encapsulate compounds within an aqueous compartment or multiple lipid bilayers, but do not mix with compounds. Bombardelli et al. proposed that phytosomes can be prepared from the interaction of phospholipids with phytoconstituents that are extracted from plants.[1]

STRUCTURE OF PHYTOSOME

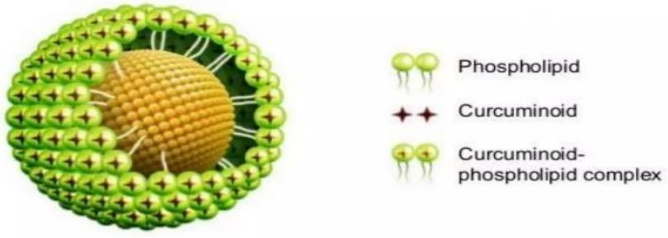

Fig. 1: Structure of phytosome (phyto-phospholipid complex)[1]

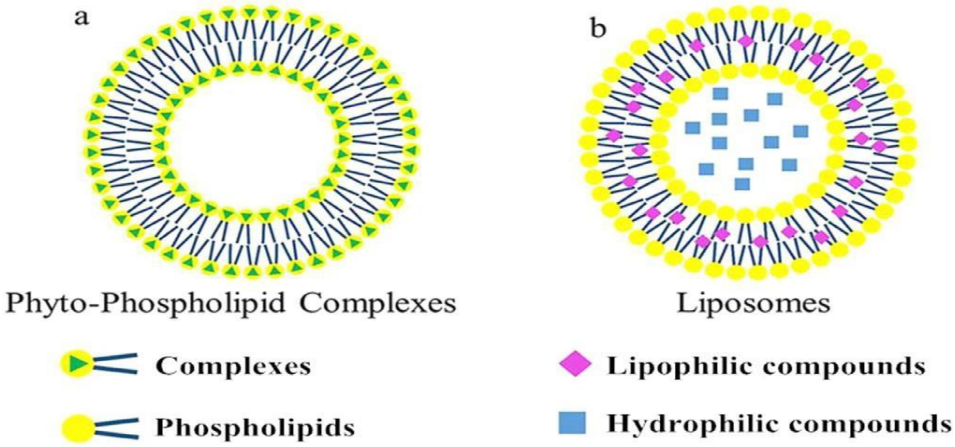

Fig. 2: Difference in structure of phytosome (phyto-phospholipid complex) and liposomes.[1]

COMPOSITION PHYTOSOMES

There are several components of phytosomes as follows.

1. Phospholipids
2. Phytoconstituents
3. Solvents

1. **Phospholipids:** Phospholipids are great source available in egg yolk and plant seeds. Phospholipids can be divided into glycerophospholipids and sphingomyelins depending on the backbone. The glycerophospholipids consists of phosphatidylcholine, phosphatidylethanolamine, phosphatidylserine, phosphatidic acid, phosphatidylinositol, and phosphatidyl glycerol. These are the major phospholipids used to formulate complexes that are composed of a hydrophilic head group and two hydrophobic hydrocarbon chains. Among these phospholipids, phosphatidylcholine is the most widely used to prepare phytosomes. It has amphipathic properties that give it moderate solubility in water and lipid medium. However, phosphatidylcholine is an important part of cell membranes, and it exhibits robust biocompatibility and low toxicity. Phosphatidylcholine molecules exhibits hepatoprotective activities, and have been reported that to show clinical effects in the treatment of liver diseases, such as hepatitis, fatty liver syndrome, and hepatocirrhosis. For Examples, egg phosphatidyl choline, disearyl phosphatidyl choline, soya phosphatidyl choline, etc.[1, 7]
2. **Phytoconstituents:** The phytoconstituents identified are generally defined based on robust in-vitro pharmacological effects, rather than on in-vivo activities. Most of these compounds are polyphenols. Certain polyphenolic phytoconstituents show affinity towards the aqueous phase and cannot be passed through lipidic biological cell membranes, such as hesperidin. By contrast, others have high lipophilic properties and cannot dissolve in aqueous gastrointestinal fluids, such as curcumin and rutin. Phytosomes cannot only improve the solubility of lipophilic polyphenols in aqueous phase but also the membrane permeability of hydrophilic compounds from aqueous phase. Also, formation of phytosomes can protect polyphenols from destruction by external forces, such as hydrolysis, photolysis, and oxidation. For Examples, acetone, dioxane, ethanol, methanol, n-hexane, etc. [1, 7]
3. **Solvents:** There are several solvents used as the reaction medium for preparation of phytosomes. Previously, aprotic solvents, such as aromatic hydrocarbons, halogen derivatives, methylene chloride, ethyl acetate, and cyclic ethers have been used to formulate phytosomes but they have been largely replaced by protic solvents like ethanol. Also, protonic solvents, such as ethanol and methanol, have been more recentlybeen successfully used to formulate phytosomes. For example, silybin phytosomes using ethanol as a protonic solvent, subsequently, the protonic solvent was removed under vacuum at 40°C.

The product yield of phytosomes will get sufficiently high, when ethanol has been used as solvent that leaves less residue and causes minimal damage. Some liposomal drug complexes operate in the presence of water or buffer solution, where the phytosomes interact with a solvent with a reduced dielectric constant.

Recently, many studies have used the supercritical fluid process to control the size, shape, and morphology of the materials. Supercritical anti-solvent process is one of the technology that are becoming a promising technique to produce micron and submicron particles with controlled size and size distribution. In this technique, a supercritical fluid such as carbon dioxide will be used as an antisolvent to reduce the solubility ofcompound in the solvent. Generally, phytosomes are prepared by reacting a synthetic or natural phospholipid with the active phytoconstituents in a molar ratio ranging from 0.5to 2.0. Whereas, a stoichiometric ratio of 1:1 is considered to be the most efficient ratio for formulating phytosomes. For example, quercetin-phytosomes were formulated by mixing lipoid S100 and quercetin at a molar ratio of 1:1.

Moreover, different stoichiometric ratios of active phytoconstituents and phospholipids have been utilized. Silymarin-phytosomes with different stoichiometric

ratios of 1:5, 1:10, and 1:15 has been formulated then it was found that the phytosomes with a stoichiometric ratio of 1:5 showed the best physical properties and the highest loading capacity of silymarin phytoconstituent. A comparative study was done by utilizing the stoichiometric ratios of 1:1, 1.4:1, 2:1, 2.6:1, and 3:1 to formulate oxymatrine- phytosomes then it was found that the optimum quantity obtained at a ratio of 3:1. So, a stoichiometric ratio of 1:1 is not always optimum for the formulation of phytosomes. By performing different experiments, stoichiometric ratio of active phytoconstituents and phospholipids can be adjusted for different types of drugs according to many uses, such as the highest drug loading.

Interactions between active phytoconstituents and phospholipids was done in 1989 by Bombardelli and it was observed that a chemical hydrogen bond formation between a flavonoid molecule and a phospholipid molecule.[1]

PROPERTIES OF PHYTOSOMES[2]

- Phytosomes are prepared by reaction of stoichiometric ratio of phospholipid with the active phytoconstituents in an aprotic solvent.
- The size of phytosomes differs from 50 nm to 100 µm.
- Phytosomes are when treated with water, assumes a micellar shape resembling like liposomes and photon correlation spectroscopy reveals the liposomal structures acquiredby phytosomes.
- The Proton (^{1}H) Nuclear Magnetic Resonance and Carbon (^{13}C) Nuclear Magnetic Resonance Spectroscopy reveals that the fatty acid chain provides unchanged signals are in free phospholipid and in the complex, which indicates that long aliphatic chains are protected around the active phytoconstituents producing lipophilic cover.
- The phytosomes are often freely soluble in aprotic solvents, moderately soluble in fats, insoluble in water and relatively unstable in alcohol.
- Moreover, phytosomes have the several lipophilic phytoconstituents such as curcumin has shown an increased water solubility by formation of complex with phospholipids.
- Phytosomes are emerging complexes that are better absorbed. Hence, they improves the bioavailability and better therapeutical effects at the site of action in the body than the conventional herbal extracts.

Table No. 1: Difference between Phytosomes and Liposomes.[2]

PHYTOSOMES	LIPOSOMES
In phytosomes, the active chemical constituent molecules are anchored throughchemical bonds to the polar head of phospholipids.	In liposomes, active principles are dissolved in the medium of cavity or in thelayer of membrane.
Chemical bonds are formed in between phytoconstituents and phospholipid molecules.	There are no chemical bonds formation between active principles and phospholipids.
In phytosome, phosphatidylcholine and plant compound form 1:1 or 2:1 complex depending on substance.	Liposomes consists of 100 to 1000 phosphatidylcholine molecules in surround the water soluble molecules.
Phytosomes are much better absorbed than liposomes showing better bioavailability.	The bioavailability of liposomes is less than the phytosomes.
In Phytosomes, phospholipid molecules are in less amount.	In liposomes, phospholipid molecules are in higher amount.

ADVANTAGES OF PHYTOSOMES[1,2,3]

- There is a sudden improvement in the bioavailability of herbal extracts due to their complexation with phospholipid and better absorption in the intestinal tract.
- They have been using to deliver liver-protecting flavonoids and can make bioavailable.
- This technology offers cost effective delivery of phytoconstituents and synergisticbenefits.
- They can also use for enhanced permeation of drugs through the skin for transdermal and dermal delivery.
- The vesicular system is passive, non-invasive, and available for immediate commercialization.
- There is no problem with drug entrapment during formulation preparation.
- The dose requirement is reduced due to improved percutaneous absorption of the main constituent. They can also give in smaller quantities to achieve the desired results.
- Phosphatidylcholine not only acts as an ingredient added to the formulation of phyto-phospholipid complexes, but also acts as a hepatoprotective. So, when phosphatidylcholine is taken by the patient, it will show the synergistic effect to protectthe liver. In some situations, phospholipids also have the nutritional benefits.

DISADVANTAGES OF PHYTOSOMES[3]

- When administered orally or topically they limit their bioavailability.
- Phytoconstituents are quickly eliminated from phytosome.
- Stability problem.
- Herbal medicines can cause allergic reactions in some cases. Before resorting to herbal medication,

there should need to ensure that the person will not allergic to the particular herb that person will be consuming. Conventional medication can also cause allergic reactions, but they are usually taken upon prescriptions which is why the chances of allergic reactions are less.

METHODS FOR PREPARATION OF PHYTOSOMES

1. **Spray Drying Method:** Phytosomes are novel complexes of herb extracts and lipids. Phytosomes were formulated in the process by which the standardized extract of active ingredients of the herb is bound to phospholipid like phosphatidylcholine. Phosphatidyl ethanolamine or phosphatidyl serine through a polar end. Phytosome is prepared by reacting 2 to 3 moles of a natural or synthetic phospholipid with one mole of herbal extract. The reaction is carried out in an aprotic solvent such as dioxane or acetone from which the complex can be isolated by precipitation with non-solvent such as aliphatic hydrocarbons or lyophilization or by spray drying. In the complex formation of phytosome, the ratio between these two moieties ranges from 0.5-2.0 moles. The preferable ratio of phospholipid to flavonoids is 1:1.[2]

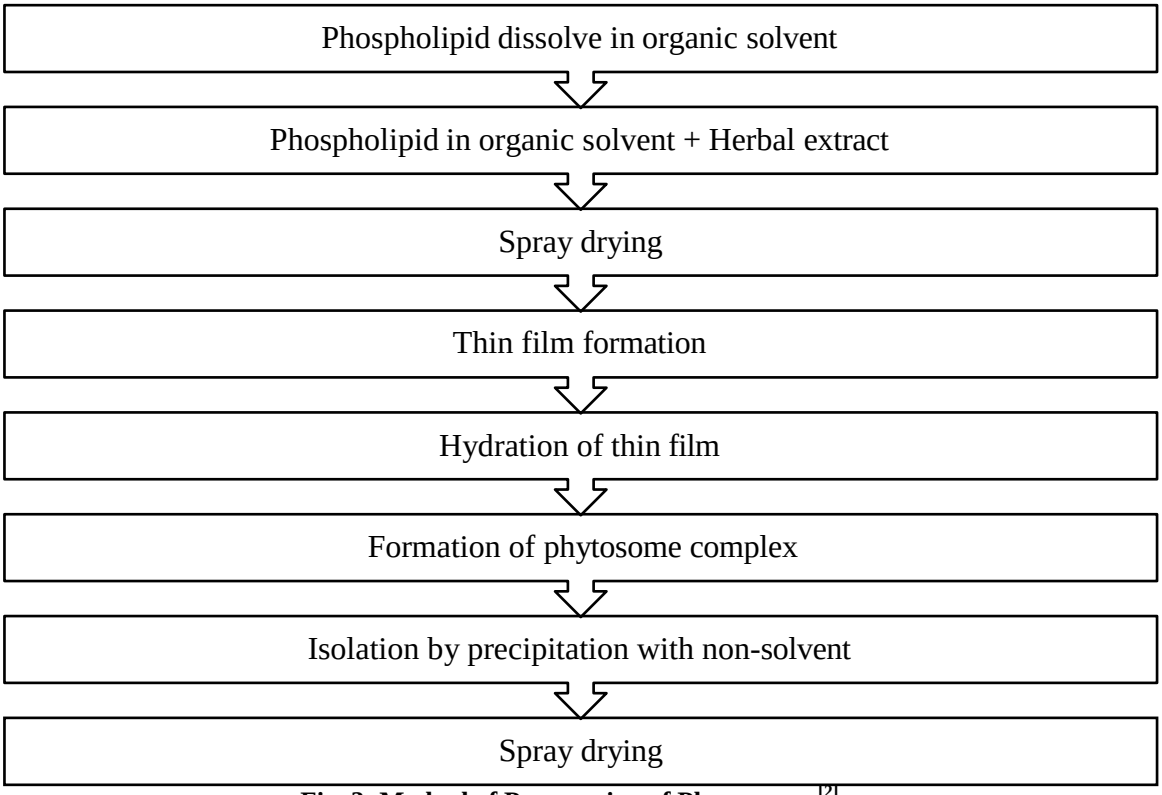

Fig. 3: Method of Preparation of Phytosomes.[2]

2. **Anti-solvent Precipitation Method:** Weighed quantities of the medication and soy lecithin were taken in a 100 ml round bottom flask and refluxed for 2 hours at a temperature not exceeding 60^{o}C with 20 ml of dichloromethane. The concentration of this mixture is 5-10 ml. 20 ml Hexane was carefully added with continuous stirring to get the precipitate filtered and collected and stored overnight in vacuum desiccators. In mortar, the dried precipitate is crushed and sifted through #100 mesh.[7]
3. **Rotary evaporation method:** Specific amounts of the medication and soy lecithin were dissolved in a rotary round bottom flask of 30 ml of tetrahydrofuran followed by stirring at a temperature not exceeding 40^{o}C for 3 hours. A thin film was obtained from the sample to which n-hexane was applied and continuously mixed by means of a magnetic stirrer. The acquired precipitate was gathered, placed, and stored at room temperature in an amber colored glass container.[7]
4. **Solvent Evaporation Method:** Weighed quantities of the drug and soy lecithin were taken in a 100 ml round bottom flask and refluxed for 2 h at a temperature of 50-60^{0}C with 20 ml of acetone. To get the precipitate that has been filtered and collected, the mixture is condensed to 5-10 ml. The dried precipitate phytosome complexes were placed in an amber colored glass bottle and kept at room temperature.[7]

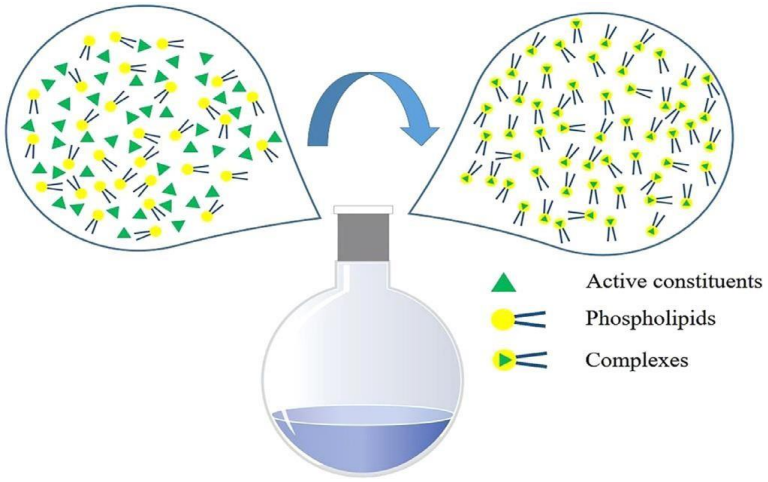

Fig. 4: Schematic representation of the preparation of phyto-phospholipid complexes by solvent evaporation method.[1]

CHARACTERIZATION OF PHYTOSOMES

1. **Solubility and partition coefficient:** Determining solubility in either water or organic solvents and the n-octanol/water partition coefficient is necessary to characterize active constituents, active constituent phytophospholipid complexes and physical mixtures. Generally, phytophospholipid complexes have better lipophilicity and hydrophilicity than active constituents, and typically exhibit improved lipophilicity.[1]
2. **Particle size and zeta potential:** Particle size and zeta potential are important properties of complexes that are related to stability and reproducibility. In general, the average phospholipid complexes particle size ranged from 50 nm to 100 µm.[1] The vesicle size of phytosomes can be determined by dynamic light scattering which uses a computerized inspection system and photon correlation spectroscopy. The zeta potential can be determined by zeta sizer.[5]
3. **Scanning electron microscopy and transmission electron microscopy:** Scanning electron microscopy has yielded important insights into the solid state properties and surface morphology of complexes. transmission electron microscopy is often used to study the crystallization and dispersion of nano-materials and to measure the particle size of nanoparticles. Scanning electron microscopy has shown that active compounds can be visualized in a highly crystalline state, but the shaped crystals disappeared after complexation. When diluted in distilled water under slight shaking, transmission electron microscopy showed that phyto-phospholipid complexes exhibit vesicle-like structures.[1]
4. **Determination of entrapment efficiency:** The entrapment efficiency for the formation of phytosomes can be determined by subjecting the formulation to ultracentrifugation technique. [5]
5. **Surface tension activity measurement:** It can be measured by ring method using Du Nouy ring tensiometer.[5]
6. **Determination of drug content:** The drug content of phytosome complex was determined by dissolving 100 mg of complex in 10 ml of methanol. After dilution, absorbance was determined by UV spectrophotometer at particular wavelength.[5]
7. **In-vitro and in-vivo evaluation:** It can be done according to the therapeutic activity andmeasurement of parameters for the biologically active phytoconstituents complexed in phytosomes.[5]
8. **Ultraviolet spectroscopy:** Samples that reflect different absorption in the ultraviolet wavelength range can be used to characterize own structural properties. Most studies have revealed no differences in the ultraviolet absorption characteristics of constituents before and after complexation.[1]
9. **Differential scanning calorimetry:** In this study, interactions can be observed by comparing the transition temperature, appearance of new peaks, disappearance of original peaks, melting points, and changes in the relative peaks area. Phytophospholipid complexes usually display radically different characteristic peaks compared to those of a physical mixture. It is assumed that, in addition to the two fatty chains of phospholipids, strong interactions occur in the active ingredients and the polar part of phospholipids also inhibits free rotation.[1]
10. **Fourier transform infrared spectroscopy:** The Fourier transform infrared spectroscopy is a powerful method for structural analysis, and yields different functional groups that show distinct characteristics in band number, position, shape, and intensity. The formation of phytophospholipid complexes can be verified by comparing the spectroscopy of phospholipid complexes to that of physical mixtures. Separate studies may show different results.[1]
11. **X-ray diffraction study:** Currently, X-ray diffraction is an effective method to examine the microstructure of both crystal materials and some amorphous materials. X-ray diffraction is usually performed on either active constituents or active constituent phytophospholipid complexes, and their

physical mixtures. X-ray diffraction of an active constituent and physical mixture shows intense crystalline peaks that indicate a high crystal form. By contrast, active constituent phytophospholipid complexes do not exhibit crystalline peak, which suggests that the constituents in complex with phospholipids exhibit a molecular or amorphous form. That may account for the observation that phytophospholipid complexes have better lipophilicity and hydrophilicity than active constituents.[1]

12. **Nuclear magnetic resonance spectroscopy:** The proton (^{1}H) and carbon (^{13}C) Nuclear magnetic resonance spectroscopic techniques play an important role in the identification of the structures of the complexes. The interactions between polyphenols and phospholipids are created by hydrogen bonds rather than chemical bonds.[1]

APPLICATIONS OF PHYTOSOMAL DRUG DELIVERY

1. **Silymarin Phytosomes:** The silymarin is an active phytoconstituent obtained from Silybum marianum plant. The fruit of the milk thistle plant of Silybum marianum belonging to steraceae family contains flavonoids for hepatoprotective effect. Silymarin has been shown to have positive effects in treating liver diseases of various kinds including hepatitis, cirrhosis, fatty infiltration of the liver and inflammation of the bile duct.[5]
2. **Phytosomes of grape seed:** Grape seed phytosome is composed of oligomeric polyphenols 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 defense of plasma.[5]
3. **Phytosome of green tea:** Green tea leaves is characterized by presence of polyphenoliccompound epigallocathechin-3-o-gallate as the key component. These are potent modulator of several biochemical process linked to the breakdown of homeostasis in major chronic degenerative diseases such as cancer and atherosclerosis.[5]
4. **Phytosomes of curcumin:** Curcumin is an active phytoconstituent of turmeric, curcuma longa linn plant rhizome part. The phytosomes of curcumin was enhanced the aqueous solubility and used in treatment of the certain life threatening diseases such as cancer, etc.[5]
5. **Phytosomes of naringenin:** Naringenin is an active phytoconstituent of grape, vitis vinifera plant fruit part. The phytosomes of naringenin was produced better antioxidant activity than the free compound with a prolonged deviation of action.[5]

Table No. 2: Marketed Phytosomal Preparations.[6,8]

Sr. No.	Phytosome	Herbal Drug	Indication
1	Ginkgoselect	Ginkgobiloba	Improve memory, Brain function, Anti-inflammatory agent
2	Silybin	Silybum marianum	Anti-oxidant activity, Anti-aging, Hepatoprotective
3	Hawthore	Crataegus oxyacantha	Help to strengthen heart and cardiovascular system
4	Ginselect	Panax ginseng	Promote adaptogenic functions and resistance to stress
5	Curcumin	Curcuma Longa	Chemoprotective agent
6	Grapseed	Grapeseed	Natural anti-oxidant, Protectant
7	Greenselect	Camellia sinensis	Anti-oxidant, Cardio-protectant, Nutraceutical

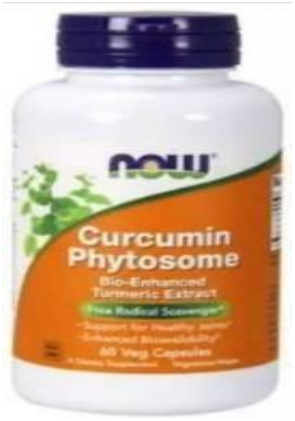

Fig. 5: Marketed Product of Curcumin Phytosome.[6]

CONCLUSION

The poor solubility associated with non-polar phytoconstituents and poor absorption associated with polar phytoconstituents that leads to poor bioavailability which limits the use of herbal active constituents. These issues can overcome by formulating a novel drug delivery system such as phytosomes, a phytophospholipid complex has offered a great opportunity and hope in improving the in-vivo bioavailability of herbal active constituents. The phytosomes is novel formulation approach that can be easily upgraded to a commercial scale. The characterization techniques are well developed for the evaluation of phytosomes. Flavonoids are the most important group of phytoconstituents. Many marketed formulations have approved for the emerging drug

delivery of phytoconstituents. Hence, the phytosomesis a potential nanocarrier formulations has an excellent for emerging drug delivery of phytoconstituents.

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