ISSN PRINT 2319 1775 Online 2320 7876

 UGC CARE Listed (Group -I) Journal Volume 11, Iss 11, 2022

PHYTOSOMES IN DRUG DELIVERY SYSTEM

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ABSTRACT

The science of medication delivery has recently paid a lot of attention to phytosomes, which are a specialized delivery method. Unique structures with improved bioavailability and therapeutic efficiency are produced when active chemicals obtained from plants are complexed with phospholipids. This presentation offers a synopsis of phytosomes' potential as drug delivery vehicles. Improved solubility, stability, and absorption of poorly soluble phytoconstituents are only a few of the many benefits of using phytosomes in medication administration. Phytosomes are absorbed more easily into the body and their active chemicals are more readily absorbed

ISSN PRINT 2319 1775 Online 2320 7876

 UGC CARE Listed (Group -I) Journal Volume 11, Iss 11, 2022

because their phospholipid bilayer structure resembles the cell membrane. Furthermore, stability and shelf life are improved because to the interaction between phytoconstituents and phospholipids, which offers protection against degradation. Phytosomes have showed considerable promise in both preclinical and clinical investigations as medication delivery vehicles. When compared to standard formulations, they show considerable improvements in pharmacokinetic profiles, tissue targeting, and therapeutic effectiveness. Additionally, phytosomes have an impressive safety record, with few reports of negative side effects. This abstract emphasizes phytosomes' potential as a fresh strategy in medication delivery. More study is needed to determine their potential clinical use, determine the best formulation characteristics, and evaluate their long-term safety. Researchers and pharmaceutical scientists may improve the distribution of phytoconstituents and broaden the scope of customized treatment by taking use of the distinctive characteristics of phytosomes.

Keywords: Administration, drug delivery**,** medication, phytosomes, phytoconstituents, pharmacokinetic.

INTRODUCTION:

The phytosome drug delivery system becomes a promising modification technique for natural compounds due to the ability to improve the physicochemical properties and increase the effectiveness. Phytosomal formulation could be the excellent approach for cosmeceutical product with good effectivity in the future [1]. For several decades, medicinal herbs and their active constituents have been utilized to treat different diseases [2].There are some major reasons for the increased use of herbal drugs: 1) modern medicine is unable to efficiently cure all the human pathologies, 2) there are increasing interests and attention over the assurance and safety of synthetic drugs, and 3) many natural products are being shown to produce better results than synthetic drugs without adverse effects. Phytosome drug delivery system is a technique that utilizes a double-layer phospholipid membrane to form a vesicle system that is known to be able for binding with polar and nonpolar compounds; it also can reduce the surface tension between poorly soluble compound with the solvent, which can provide capability for increasing the solubility, permeability, and stability of the compounds [3]. Phytosome is a nanoparticle delivery

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system composed of monolayer or double-layer phospholipids which form vesicle and is used for the delivery of polar or nonpolar natural compounds. The phospholipid content in this system is able to mediate the increase in solubility by hydrogen-bonding interaction between water molecules with phosphate groups in double-layer system of phytosome carrier and improve permeability of the active compounds by phospholipid deformation of cells membrane with phytosome carrier. Currently, the use of phytosome has been carried out for modification of natural ingredients compounds intended to improve its effectiveness [4]. Indena's Phytosomes are a new set of patented technologies for creating and incorporating standard plant extracts [5]. Some means cell-like and phyto means plant [6]. Herbosomes are another name. According to Choubey A. *et al.* 2011, water-soluble phytoconstituent molecules can be transformed into Phytosomes, lipid-compatible molecular complexes [7]. The pharmacokinetic and pharmacological parameters have been enhanced by phytosomes. Due to their enhanced capacity to cross the lipid-rich biomembranes and ultimately reach the blood, phytosomes are more bioavailable than simple herbal extracts. Phospholipids from soy, particularly phosphotidylcholine (PC), are the lipid-phase substances used to make phytoconstituents lipid-compatible [8]. Phytosomes have shown promise as a delivery method for nutraceuticals and herbal medicines. Numerous well-known herbal extracts, such as Ginkgo Biloba, Grape seed, Hawthorn, Milk thistle, Green tea, and Ginseng, have been subjected to the phytosomes process [9].

Method of Preparation

Phytosomes are made by combining one mole of phytoconstituents with 3-2 moles of a natural or synthetic phospholipid, primarily phosphotidylcholine. For the formation of complexes, the ratio between these two moieties between 0.5 and 2.0 moles is the most desirable [10]. The solvent evaporation method involves refluxing a specific quantity of drug, polymer, and phospholipids for two hours in a spherical bottom flask at a temperature of 50-60 ^{o}C with a specific solvent. To obtain the precipitate, which can be filtered and collected, the mixture can be concentrated to 5-10 ml [11]. The phytosome-loaded dried precipitate can be stored at room temperature in an amber glass bottle.

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Rotary evaporation technique- The drug and soy lecithin were dissolved in 30 milliliters of tetrahydrofuran in a rotary round bottom flask, then stirred for three hours at a temperature not exceeding 40 degrees Celsius [12]. Using a magnetic stirrer, a thin film of the sample was produced, to which n-hexane was continuously added. The obtained precipitate was collected, put in a bottle made of amber glass, and kept at room temperature.

Antisolvent precipitation method: A specific amount of drug and soy lecithin were put into a 100-milliliter round bottom flask, refluxed with 20 milliliters of dichloromethane for two hours at a temperature of not more than 60 degrees Celsius, and the mixture was concentrated to 5 to 10 milliliters. After carefully adding 20 milliliters of hexane and continuously stirring, the precipitate was filtered, collected, and stored overnight in vacuum desiccators. Mortar is used to crush the dried precipitate before it is sieved through #100 meshes. The powdered complex was stored at room temperature in a bottle made of amber glass [13].

Salting out method

An aprotic solvent, such as dioxane or acetone, is used to dissolve the phytoconstituent or standardized extract and phosphotidylcholine. After the solution has been stirred for an entire night, the formed complex is precipitated from a non-solvent, such as n-hexane. [14]

Lyophilization technique

A second solution containing phytoconstituents was then added to a solution containing phospholipid and stirred until complex formation occurred. The phospholipid, whether natural or synthetic, and the phytoconstituents were dissolved in different solvents. Lyophilization is used to separate the formed complex. [15]

The phytosome-preparing phospholipids come mostly from palmitic, stearic, oleic, and linoleic acids and have an acyl group that can be the same or different in phosphatidylcholine, phosphatidylserine, and phosphatidyl ethanolamine. As the active principle is anchored to the polar head of phospholipid in phytosomes, it becomes an integral part of the membrane [16].

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Mechanical Dispersion method

The organic solvent-dissolved lipids are brought into contact with the drug-containing aqueous phase in this method [17]. Pc is first dispersed in diethyl ether, which is then slowly injected into an aqueous solution of the phytoconstituents that need to be encapsulated. The phyto-phospholipid complex is made when the organic solvent is removed from the system at a lower pressure. Supercritical anti solvent method (SAS), gas anti-solvent technique (GAS), compressed anti solvent process (PCA), and other novel methods for the preparation of phospholipid complexes [18].

Different additives used in the formulations of Phytosomes:

Phospholipids: Distearyl phosphatidyl choline, phosphatidyl choline from eggs, phosphatidyl choline from soy, and phosphatidyl choline from soy.

Aprotic solvent: Dioxane, acetone, methylene chloride

Non solvent: n-hexane and non-solvent i.e. aliphatic hydrocarbon

Alcohol: Ethanol, Methanol

Characterization and evaluation of phytosomes:

Techniques for characterizing [19]:

Visualization

Phytosomes can be observed using transmission electron microscopy and scanning electron microscopy.

Transition temperature

Differential scanning calorimetry is used to determine transiton temperature of vesicular lipid system.

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Surface tension measurement

In an aqueous solution of the drug, surface tension activity can be measured using the ring method in a Du Nouy ring tensiometer.

Vesicle stability

Over time, evaluating the size and structure of vesicles provides insight into their stability. DLS and TEM are used to measure mean size and monitor structural changes.

Scanning electron microscopy (SEM)

The complexes' surface morphology and distribution of particle sizes have been examined with scanning electron microscopy. A scanning microscope from Japan, the JEOL JSM-6360, was used to examine the samples. In an ion sputter, dry samples were coated with gold and placed on a brass stub for an electron microscope. Random scanning of the stub at 1000, 5000, 10000, and 30000 X magnifications yielded digital images of the phytosome complex of lawsone.

Entrapment efficiency

Using the ultracentrifugation method, the entrapment efficiency of a phytosomal formulation can be evaluated.

Evaluation of Phytosomes [20]:

The following spectroscopic techniques are used to confirm the formation of a complex or investigate the reciprocal interaction between the phyto-constituent and phospholipids.

1H-NMR: ***Bombardelli et al.*** studied the NMR spectra of (+)-catechin and its stoichiometric complex with distearoylphosphatidylcholine. In nonpolar solvents, there is a marked change of the 1H-NMR signal originating from the atoms involved in the formation of the complex, without any summation of the signal peculiar to the individual molecules. The signals from the protons belonging to the flavonoids are to be broadened that the proton cannot be relieved. In phospholipids, there is broadening of all the signals while the singlet corresponding to the N-

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(CH3)3 of choline undergo an uplift shift. Heating the sample to 60˚ results in the appearance of some new broad bands, which correspond mainly to the resonance of the flavonoid moiety.

13C-NMR: In the spectrum of (+)-catechin and its stoichiometric complex with distearoyl phosphatidylcholine, particularly when recorded in C_6D_6 at room temperature, all the flavonoid carbons are clearly invisible. The signals corresponding to the glycerol and choline portion of the lipid (between 60–80 ppm) are broadened and some are shifted, while most of the resonances of the fatty acid chains retain their original sharp line shape. After heating to 60˚C, all the signals belonging to the flavonoid moieties reappear, although they are still very broad and partially overlapping.

FTIR: The formation of the complex can be also be confirmed by IR spectroscopy by comparing the spectrum of the complex with the spectrum of the individual components and their mechanical mixtures. FTIR spectroscopy is also a useful tool for the control of the stability of phytosomes when micro-dispersed in water or when incorporated in very simple cosmetic gels. From a practical point of view, the stability can be confirmed by comparing the spectrum of the complex in solid form (phytosomes) with the spectrum of its micro-dispersion in water after lyophilization, at different times. In the case of simple formulations, it is necessary to subtract the spectrum of the excipients (blank) from the spectrum of the cosmetic form at different times, comparing the remaining spectrum of the complex itself.

***In vitro – In vivo* evaluations**

Models of in-vitro and in-vivo evaluations are selected on the basis of the expected therapeutic activity of biologically active phytoconstituents present in the phytosome. For example, in-vitro anti-hepatotoxic activity can be assessed by the antioxidant and free radical scavenging activity of phytosome [21].

For assessing in vivo anti-hepatotoxic activity, the effect of prepared phytosomes on animals against thioacetamide, paracetamol or alcohol induced hepatotoxicity can be examined. Skin

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sensitization and tolerability studies of glycyrrhetinic acid phytosome ointment, a commercial product, describe the in-vivo safety evaluation methodology [22].

Applications of phytosome technology and commercially available products based on phytosome technology

Milk thistle (Silybum marianum)

Much of the studies have been conducted on the application of phytosome technology to Silybum marianum (milk thistle) which contains flavonoids, a liver-protectant phytoconstituent [23]. Milk thistle has shown positive effects in treating various kinds of diseases (hepatitis, cirrhosis, fatty infilteration of the liver, etc.) S. marianum has a strong antioxidant activity which boosts the resistance of liver against toxic constituents. The three flavonoids which are present in S. marianum include silybin, silydianin and silychristin with silybin predominating followed by silydianin and silychristin. Silybin is the most potent of the three and is actually a flavonolignan. Silybin conserves glutathione in parenchymal cells and thus protects liver cells while as PC helps repair and replace cell membranes. It is clear that silybin has a better hepatoprotective effect which is limited by its poor bioavailability which can be overcome by producing a Silybin phytosome.

Green tea

Green tea is a strong antioxidant. According to a research from University of Kansas, the antioxidant potential of green tea is 100 times greater than vitamin C, 25 times greater than vitamin E and twice as strong as resveratol (CNN- American Chemical Society). A phytosome product with the commercial name GreenSelect® phytosome is available in the market. It contains a totally standardized poyphenolic fraction (containing not less than 66.5% and is mainly characterized by the presence of epigallocatechin and its derivatives [24]. Francesco *et al.*, 2009, conducted a research in which fifty subjects were fed with green tea extract plus hypocaloric diet while other fifty subjects were fed only with hypocaloric diet. After 90 days of treatment, a significant weight loss and decreased body mass index (BMI) was observed in the

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human subjects fed with both green tea extracts and hypocaloric diet than the human subjects fed with only hypocaloric diet. From the study, it was also observed that waistline in male subjects only.

Hesperidin

A novel hesperidin was developed by combining and complexing hesperidin with hydrogenated phosphatidyl choline. Mukherjee et al. (2008) also studied its antioxidant activity and pharmacokinetic studies in CC14 intoxicated rats along. The results of the study showed the phytosome has shown high antioxidant activity. Pharmacokinetic studies have revealed the improved bioavailability of phytosomes than the parent molecule at the same dosage [25].

Quercetin

The commercially available quercetin phytosome is Meriva® (500mg) 60VC. The constituents present in Curcumin (curcumin, demethoxycurcumin, bisdemethoxycurcumin) are poorly absorbed when taken orally which could be overcome by phytosome technology. In Meriva®, each curcuminoid molecule is individually complexed with molecules of the vital cell membrane nutrient phosphatidylcholine (PC). This results in better and faster entry of curcumin molecules into the cells and improving beneficial effects such as: it protects against premature molecular break down, promotes healthy functioning of joints and other organs [26]. Curcumins help in protecting cell membrane due to its high antioxidant activity. Curcumin helps to prevent the free radical damage on the cell membrane, DNA and genes. Membranes are prone to oxidative damage but curcumin acts as a guard to protect them from lipid peroxidation.

Ginkgo (Ginkgo biloba)

It contains 24% of ginkgo flavonoids from Ginkgo biloba. It protects brain and vascular linings and has an anti-skin ageing. According to some results, ginkgo phytosome produced better results as compared to conventional standardized Ginkgo biloba extract (GBE) containing 24% ginkgo flavones glycoside and 6% terpene lactones. A study was conducted on 15 healthy human volunteers in which the bioavailability of ginkgo phytosome has been compared with GBE.

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Volunteers were divided into two groups and were administered respectively with Ginkgoselct® and Ginkgoselect® phytosome. The subjects switched formulations after a week of wash out. Blood samples were taken from each human subject at 30, 60, 120, 180, 240, 300 and 400 minute after ingestion [27]. Detection of terpenes lactones was performed by liquid chromatography/atmospheric pressure chemical ionization mass spectrometry (LC/APCI-ITMS). It was found from the results that Ginkgolides A, B and bilobalide were absorbed to a higher extent (about three times after administration of Ginkgoselect® phytosome)

Olive (*Olea europaea*) oil

A commercially available phytosome- OleaselectTM PHYTOSOME is available in the market based on olive oil polyphenols [27]. It is a strong antioxidant, anti-inflammatory and anti-hyperlipidemic. It inhibits the oxidation of LDL cholesterol and is cardio protective.

PROPERTIES OF PHYTOSOMES

Chemical properties

Phytosomes is a complex between a natural product and natural phospholipids, like soy phospholipids. Such a complex is obtained by reaction of stoichiometric amounts of phospholipid and the substrate in an appropriate solvent. On the basis of spectroscopic data it has been shown that the main phospholipid-substrate interaction is due to the formation of hydrogen bonds between the polar head of phospholipids (i.e. phosphate and ammonium groups) and the polar functionalities of the substrate. When treated with water, phytosomes assumes a micellar shape forming liposomal-like structures, In liposomes the active principle is dissolved in the internal pocket or it is floating in the layer membrane, while in phytosomes the active principle is anchored to the polar head of phospholipids, becoming an integral part of the membrane for example in the case of the catechindistearoyl phosphatidylcholine complex, in this there is the formation of H-bonds between the phenolic hydroxyls of the flavone moiety and the phosphate ion on the phosphatidylcholine side.

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Phosphatidylcholine

This can be deduced from the comparison of the NMR of the complex with those of the pure precursors. The signals of the fatty chain are almost unchanged. Such evidences inferred that the two long aliphatic chains are wrapped around the active principle, producing a lipophilic envelope, which shields the polar head of the phospholipid and the catechin [28].

Biological Properties

Phytosome are advanced forms of herbal products that are better absorbed, utilized and as a result produce better results than conventional herbal extracts the increased bioavailability of the phytosome over the non complexed botanical derivatives has been demonstrated by pharmacokinetics studies or by pharmacodynamic tests in experimental animals and in human subjects [29].

CHARACTERIZATION OF PHYTOSOMES

The behavior of phytosomes in both physical and biological system is governed by the factors such as physical size membrane permeability; percent entrapped solutes, chemical composition as well as the quantity and purity of the starting materials. Therefore, the phytosomes are characterized for physical attributes i.e. shape, size, its distribution, percentage drug capture entrapped volume, percentage drug released and chemical composition [30].

APPLICATIONS OF PHYTOSOMES

Most of the phytosomal studies are focused to Silybum marianum which contains premier liver-protectant flavonoids [31]. The fruit of the milk thistle plant (S. marianum, Family Steraceae) contains flavonoids known for hepatoprotective effects. Silymarin has been shown to have positive effects in treating liver diseases of various kinds, including hepatitis, cirrhosis, fatty infiltration of the liver (chemical and alcohol induced fatty liver) and inflammation of the bile duct. The antioxidant capacity of silymarin substantially boosts the liver's resistance to toxic insults. Silymarin primarily contains three flavonoids of the flavonol subclass (having a fully

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 UGC CARE Listed (Group -I) Journal Volume 11, Iss 11, 2022

saturated C-ring). Silybin predominates, followed by silydianin and silychristin. Silybin is actually a flavonolignan, probably produced within the plant by the combination of a flavonol with a coniferyl alcohol. It is now known that silybin is the most potent of the three. Silybin protects the liver by conserving glutathione in the parenchymal cells, while PC helps repair and replace cell membranes. These constituents likely offer the synergistic benefit of sparing liver cells from destruction. In its native form within the milk thistle fruit, silybin occurs primarily complexed with sugars, as a flavonyl glycoside or flavonolignan. Silybin has been extensively researched and found to have impressive bioactivity, albeit limited by poor bioavailability.

Francesco *et al.,* (2009) studied on a recently developed oral formulation in the form of coated tablets (Monoselect Camellia®) (MonCam) containing highly bioavailable green tea extract (GreenSelect® Phytosome) was tested in obese subjects (n=100) of both genders on a hypocaloric diet. Fifty subjects were assigned to the green tea extract plus hypocaloric diet, while the other 50 subjects followed the hypocaloric diet only [32]. After 90 days of treatment, significant weight loss and decreased body mass index (BMI) were observed in the group taking the herbal extract (14 kg loss in the green tea group compared to a 5 kg loss in the diet-only group); waistline was reduced only in male subjects. Besides the effect on weight and BMI, biochemical parameters (LDL, HDL, and total cholesterol, triglycerides, growth hormone, insulin-like growth factor-1, insulin, and cortisol) were improved in both groups. Leptin, not tested in the diet-only group, was reduced in patients taking MonCam. Taking into consideration the high safety profile of the product and the total absence of adverse effects observed during and after the trial, MonCam appears to be a safe and effective tool for weight loss.

Mukerjee *et al.,* (2008) developed a novel hesperetin phytosome by complexing hesperetin with hydrogenated phosphatidyl choline. This complex was then evaluated for antioxidant activity in CCl4 intoxicated rats along with pharmacokinetic studies [33]. It was found that the phytosome had asustained release property for over 24 h and enhanced antioxidant activity. Pharmacokinetic study revealed that the phytosome had higher relative bioavailability than that of parent molecule at the same dose level.

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Yanyu *et al.,* (2006) prepared the silymarin phytosome and studied its pharmacokinetics in rats. In the study the bioavailability of silybin in rats was increased remarkably after oral administration of prepared silybinphospholipid complex due to an impressive improvement of the lipophilic property of silybin-phospholipid complex and improvement of the biological effect of silybin [34].

Ravarotto *et al.,* (2004) reported silymarin phytosome show better antihepatotoxic activity than silymarin alone and can provide protection against the toxic effects of aflatoxin B1 on performance of broiler chicks [35].

Busby *et al.,* (2002) reported that the use of a silymarin phytosome showed a better fetoprotectant activity from ethanol-induced behavioral deficits than uncomplexed silymarin [36].

Bombardelli *et al.,* (1974) reported Silymarin phytosomes, in which Silymarin (A standardized mixture of flavanolignans extracted from the fruits of S. marianum) was complexed with phospholipids. Phytosomes showed much higher specific activity and a longer lasting action than the single components, with respect to per cent reduction of odema, inhibition of myeloperoxidase activity, antioxidant and free radical scavenging properties [37].

Barzaghi *et al.,* (1990) conducted a human study designed to assess the absorption of silybin when directly bound to phosphatadylcholine. Plasma silybin levels were determined after administration of single oral doses of silybin phytosome and a similar amount of silybin from milk thistle in healthy volunteers [38]. The results indicated that the absorption of silybin from silybin phytosome is approximately seven times greater compared to the absorption of silybin from regular milk thistle extract (70-80 % silymarin content).

Green tea extract generally contains a totally standardized polyphenolic fraction (not less than 66.5%, containing epigallocatechin and its derivatives) obtained from green tea leaves (Thea sinensis) and mainly characterized by the presence of epigallocatechin 3-O-gallate, the key compound. These compounds are potent modulators of several biochemical processes linked to

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the breakdown of homeostasis in major chronic-degenerative diseases such as cancer and atherosclerosis. Green tea has got several long term benificial activities such as antioxidant, anticarcinogenic, antimutagenic, antiatherosclerotic, hypocholesterolemic, cardio-protective, antibacterial and anticariogenic effects [39]. Despite such potential actions green tea polyphenols have very poor oral bioavailability from conventional extracts. The complexation of green tea polyphenols with phospholipids strongly improves their poor oral bioavailability. A study on absorption of phytosomal preparations was performed in healthy human volunteers along with non-complexed green tea extract following oral administration. Over the study period of 6 hours the plasma concentration of total flavonoids was more than doubled when coming from the phytosomal versus the nonphytosomal extract. Antioxidant capacity was measured as TRAP (Total Radical-trapping Antioxidant Parameter). The peak antioxidant effect was a 20% enhancement and it showed that the phytosome formulation had about double the total antioxidant effect.

Phytosomes are advanced form of herbal extract that are better absorbed which results better than conventional herbal extract. Phytosomes have improved pharmacokinetic and pharmacological parameter, which in result can advantageously be used in treatment of acute liver diseases, either metabolic or infective origin. Absorption of phytosome in gastro-intestinal tract is appreciably greater resulting in increased plasma level than the individual component. This means more amount of active constituent becomes present at the site of action (liver, brain, heart, kidney etc) at similar or less dose as compared to the conventional plant extract [40]. Hence, the therapeutic action becomes enhanced, more detectable and prolonged. Several excellent phytoconstituents have been successfully delivered in this way exhibiting remarkable therapeutic efficacy in animal as well as in human models. Thorough study of literature reveals that several plant extracts (crude, partially purified or fractionated) are reported to possess different significant pharmacological or health promoting properties. These extracts can be standardized accordingly and may be formulated as phytosomes for systematic investigation for any improved potential to be used rationally. In this way after screening and selection of potential extracts or constituents from plants, phytosomes can be developed for different therapeutic purposes like cardiovascular,

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anti-inflammatory, immunomodulatory, anticancer, antidiabetic *etc.* or for prophylactic and health purposes as nutraceuticals.

PHYTOSOME DRUG DELIVERY SYSTEM

Phytosome is a nanoparticle delivery system composed of monolayer or double-layer phospholipids which form vesicle and is used for the delivery of polar or nonpolar natural compounds [39]. The phospholipid content in this system is able to mediate the increase in solubility by hydrogen-bonding interaction between water molecules with phosphate groups in double-layer system of phytosome carrier and improve permeability of the active compounds by phospholipid deformation of cells membrane with phytosome carrier. Currently, the use of phytosome has been carried out for modification of natural ingredients compounds intended to improve its effectiveness. Phytosome formulation containing skin whitening agent which has regulated to inhibit tyrosinase enzyme had been conducted for various extracts or isolated compounds from several plants. Phytosome system was prepared by several methods including solvent evaporation, thin film hydration, solvent evaporation-lyophilization, and antisolvent precipitation method. Phosphatidylcholine becomes a primary carrier in the phytosome system which consists of double-layer phospholipid complex [40]. The objective of the formulation of phytosome as a potential tyrosinase inhibitor compounds were to observe its potency in improving the solubility, the penetration, the bioavailability, and the effectiveness as an inhibitor.

In 2019, Priani *et al.* carried out a formulation of facial serum phytosome containing Cacao husk to increase the effectiveness of the tyrosinase inhibitor activity. The thin-layer hydration method was used in the production of phytosome. Here, the carrier that was used in improving the bioactive flavonoids of the phytosome was Phosphatidylcholine [40]. The result was a phytosome with a particle size of 672nm with an entrapment efficiency value of 90.5%. Impressively, the Cacao husk phytosome has tyrosinase inhibitor activity of 199.98 ppm. Phan Ke Son *et. al.,* (2017); Moringa oleifera phytosome Moringa is a plant that is proven to have strong tyrosinase inhibitory activity. This plant contains a compound which is not only able to reduce a formation of melanin but also can interfere and inhibit the tyrosinase enzyme activity called flavonoids. Phytosome formulation of *Moringa oleifera* had been conducted by ***Lim in***

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2019. This study has an objective study to maximize topical wound delivery of M. oleifera [41]. The results shows that M. oleifera phytosome appeared as multilamellar vesicles with an average particle size of 198 ± 21 nm and zeta potential of −28.30 ± 1.31 mV. M. oleifera has encapsulation efficiency of 52.2%, 82.8%, 8.44%, and 15.6% for kaempferol, quercetin, rosmarinic acid, and chlorogenic acid, respectively. In addition, the filtered M. oleifera phytosome exhibited the highest normal human dermal fibroblast cell migration and proliferation rate compared to the control. Banweer J *et. al.,* (2008) On the dissolution test results, this phytosome has a value of 85.21% within 4 h. In addition, the results of the stability study showed that the phytosome formula could improve the stability of the C. sinensis leaf extract. [42] Abdel-Tawab *et. al.,* (2013); *Centella asiatica* phytosome *Centella asiatica* (CA) is a plant that has been investigated to have activity as a tyrosinase enzyme inhibitor with an inhibition value of 31.25% at a concentration of 1.67 mg/mL [43]. The potential of this compound as an inhibitor allows it to be used as an active skin whitening agent formulated into cosmetic dosage form. In 2018, Ho *et al.* carried out a CA formulation using phytosome delivery system. In 2018, Ho *et al.* carried out a formulation of CA by using phytosome delivery system with solvent evaporation method, and the primary carrier was phospholipids. Histological analysis results showed that CA inhibited hyperkeratosis and mast cells proliferated by CA phytosome were found at concentrations (5, 10, and 20 µL/ml) as indicated by the results of histological analysis caused by the phytosome, which inhibited the production of induction nitric oxide in lipopolysaccharide (1 µL/ml) RAW 264.7 macrophages. Infiltration of the inflammatory cells and a reduction in the production of inducible nitric oxide synthase (iNOS) and cyclooxygenase-2 (COX-2) proteins also occurred in the concentration [44].

Advantages of phytosomes

Phytosomes have the following advantages [45]

1) It enhances the absorption of lipid insoluble polar phytoconstituents through oral as well as topical route showing better bioavailability, hence significantly greater therapeutic benefit.
2) Appreciable drug entrapment.

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3) As the absorption of active constituent (s) is improved, its dose requirement is also reduced.
4) Phosphatidylcholine used in preparation of phytosomes, besides acting as a carrier also acts as a hepatoprotective, hence giving the synergistic effect when hepatoprotective substances are employed.
5) Chemical bonds are formed between phosphatidylcholine molecule and phytoconstituents, so the phytosomes show better stability profile.
6) Application of phytoconstituents in form of phytosome improves their percutaneous absorption and act as functional cosmetics. Recent research shows improved absorption and bioavailability with phytosomes as compared to the conventional means.

CONCLUSION

Phytosome is a novel formulation for herbal extract that is more easily absorbed than standard herbal extract. The water-soluble phytonutrient's poor bioavailability and absorption could be overcome by phytosome technology, which delivers active phytonutrients optimally. Improved lipid solubility increases phytosome absorption through the skin and gastrointestinal tract, allowing them to cross biological membranes and increase bioavailability. Due to its increased bioavailability, it requires fewer doses than conventional herbal extract. In the future, the potential for pharmaceutical application will reveal numerous phytosome areas. Phytosome technology is a new method of delivering phytochemicals or herbal extracts that outperforms traditional herbal drug delivery systems in terms of drug absorption and therapeutic efficacy. With improved pharmacokinetics and pharmacological effects, the Phytosome bridges the gap between conventional and novel drug delivery systems, making it useful for treating a variety of diseases.

ACKNOWLEDGEMENT

The authors express their gratitude towards Faculty of Phamaceutical Sciences, Rama University, Kanpur for providing research environment and all necessary facility for conducting research.

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INFORMED CONSENT

Not Applicable.

DATA AVAILABILITY MATERIALS

The authors confirm that the data supporting the findings of this study are available within the article.

FUNDING

No funding was received for conducting this study.

CONFLICT OF INTEREST

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper. The authors declare no conflict of interest among themselves. The authors alone are responsible for the content and writing of this article.

FINANCIAL INTERESTS

The authors declare they have no financial interests.

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