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Phytosomes As A Novel Drug Delivery System For Enhancing Bioavailability Of Phytochemicals: A Comprehensive Review

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ABSTRACT

Phytochemicals derived from medicinal plants exhibit diverse therapeutic activities; however, their clinical application is often limited by poor bioavailability due to high polarity and low lipid solubility. The gastrointestinal membrane, being lipophilic, restricts the absorption of hydrophilic plant constituents such as flavonoids, terpenoids, and phenolic compounds. Novel drug delivery systems have emerged to overcome these limitations by enhancing solubility, stability, and targeted delivery of phytoconstituents. Phytosomes, developed using phosphatidylcholine and related phospholipids, exhibit improved pharmacokinetic and pharmacodynamic profiles compared to conventional herbal extracts. These complexes enhance drug stability, reduce degradation, and facilitate efficient transport across biological membranes. Various preparation methods such as antisolvent precipitation, solvent evaporation, rotary evaporation, and lyophilization are employed to formulate phytosomes. Characterization techniques including particle size analysis, zeta potential measurement, spectroscopic evaluation, and encapsulation efficiency assessment are essential to determine their physicochemical and biological properties Phytosomal formulations demonstrate significant improvements in therapeutic efficacy, including enhanced bioavailability, hepatoprotective, anticancer, antioxidant, transdermal, and antidiabetic activities. These systems also reduce dose requirements and minimize adverse effects. Overall, phytosomes offer a promising strategy for improving the delivery and effectiveness of herbal medicines, making them a valuable approach in modern pharmaceutical research.

Keywords: Phytosomes , Phytochemicals, Bioavailability, Phospholipid complexes, Drug delivery systems, Pharmacokinetics, Targeted delivery

INTRODUCTION

Since ancient times, phytochemical and phytopharmacological investigations have completely established various developments in natural behavior and their numerous health promising benefits of botanical plants (1). The majority of bioactive plant constituents, including as terpenoids, flavonoids, phenolic glycosides, and anthocyanins, are strongly polar (water soluble), i.e., hydrophilic. This has a significant impact on drug absorption because the GI membrane (highly lipophilic) does not allow the passage of highly water-soluble substances across it, hence the poor bioavailability. Bioavailability is the rate and extent at which an active ingredient, such as a drug or metabolite, reaches the blood and shows clinical efficacy as well as minimizing

the dose. For a drug to be bioavailable, it should have proper hydrophilicity as well as lipophilicity. In addition, other issues such as poor lipid solubility, insufficient molecular size, degradation in the gut, being widely disseminated throughout the body, having a shorter plasma half-life, low stability, and inability to reach the target area limit their bioactivity.(2) Drug delivery systems (DDS) can design drugs with increased bioavailability and controlled delivery by minimizing drug degradation or presystemic metabolism of plant actives, as well as preventing serious side effects induced by drug accumulation in non-targeted areas. In this novel drug delivery technology, drug distribution is achieved by incorporating the drug (plant actives) into the carrier system or by modifying the structure of the drug at the molecular level (3). A novel drug delivery system is a novel approach to drug delivery that overcomes the limitations of traditional drug delivery systems. When novel drug delivery technology is used in herbal medications, it should help to increase the efficacy and decrease the adverse effects of various herbal compounds and herbs (4) It includes novel herbal formulations such as nanoparticles, nanocapsules, phytosomes, niosomes, transferosomes, ethosomes, and proniosomes that have significant advantages over traditional plant extracts such as solubility enhancement, bioavailability improvement, targeted delivery, and sustained effect etc. (5)

PHYTOSOMES

The Phytosome, also known as the Phytolipids delivery system, forms a link between the convectional and novel delivery systems(6).Indena, a leading supplier of nutraceutical ingredients, created Phytosome in 1989 to incorporate phospholipids into standardized extracts, thereby enhancing absorption and efficiency.(7) These drug delivery system uses a double layer phospholipid membrane to form a vesicle system that is known to be capable of binding with polar and nonpolar compounds; it can also reduce the surface tension between poorly soluble compounds and the solvent, which can provide capability to improve the solubility, permeability, and stability of the compounds(8).Most of the bioactive constituents of phytomedicines are flavonoids (e.g., anthocyanidins from bilberry, catechins from green tea, silymarin from milk thistle). However, many flavonoids are poorly absorbed; this is most likely due to two factors. First, they are having multiple-ring molecules that are too large to be absorbed by simple diffusion. Second, flavonoid molecules typically poorly miscible with oils and other lipids, limiting their capacity to traverse the lipid-rich outer membranes of the enterocytes of the small intestine. Flavonoid molecules that are water soluble can be converted into lipid compatible molecular complexes known as phytosomes (9). Pharmacokinetic (tissue distribution) and activity studies in animals and humans indicate that phytosomes have higher bioavailability than simpler, lesser-complex plant extracts. Phytosomes has an added dimension the proven health-giving activity of the phospholipids themselves. Phytosome is also often known as Herbosomes. Phytosomes exhibit a better pharmacokinetic and pharmacodynamic profile than traditional herbal extracts. Molecular layer consisting of Phosphatidylcholine, phosphatidylserine, phosphatidylethanolamine, phosphatidylinositol are the phospholipids used, but phosphatidylcholine is commonly utilized because of their definite remedial quality and other phospholipids provides a continuous matrix into which the proteins insert (10). Phosphatidylcholine, phosphatidylserine, phosphatidylethanolamine, phosphatidylinositol are the phospholipids used, but phosphatidylcholine is commonly utilized because of their definite remedial quality (11). Phosphatidylcholine (or phosphatidylserine) is a bifunctional compound. The phosphatidyl moiety is lipophilic and the choline (serine) moiety is hydrophilic in nature. This dual solubility of the phospholipid makes it an effective emulsifier. Thus, the phosphatidylcholine molecule's choline head binds to these compounds, while the lipid-soluble phosphatidyl part, consisting of the body and tail, surrounds the choline-bound material. As a result, the phytoconstituents form a lipid compatible molecular complex with phospholipids, known as the Phyto phospholipid complex (12).

PROPERTIES OF PHYTOSOMES

Physicochemical properties

1.The term phytosome is used to define a complex between a natural product & phospholipids, like soy lipid that are obtained by the reaction of stoichiometric amounts of phospholipids and phytoconstituent in an appropriate solvent. Spectroscopic data indicate that the interaction of phospholipids with substrate takes place by the formation of hydrogen bonds between the polar head of the phospholipids and the polar functions of the substrate.

2. Nuclear magnetic resonance study of the phospholipids complex with some of pure precursor indicates that the signals of fatty chain are almost unchanged. Such evidences inferred that two long aliphatic chains are wrapped around the active principle, producing a lipophilic envelop that shields the polar head of the phospholipids.

3. Phytosomes are lipophilic substances with defined melting point that are freely soluble in nonpolar solvents and moderately soluble in fats (13).

4. When treated with water, phytosomes assumes a micellar shape, and form liposomal-like structures.

Biological properties

1. Phytosomes are advanced botanical technologies that enhance absorption, delivery, and bioavailability of herbal extracts.
2. They exhibit better efficacy and pharmacokinetic as per compare to conventional herbal extract. (14)

ADVANTAGES

- As the absorption of active constituent(s) is improved, its dose requirement is also reduced.
- 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.
- Chemical bonds are formed between phosphatidylcholine molecule and phytoconstituent, so the phytosomes show better stability profile (15)
- Phytosomes have the ability to permeate through skin with quite ease thus enhances their effectiveness. As a result, the therapeutic effects are improved
- Phosphatidylcholine nourishes skin besides acting as a carrier because it is part of cell membrane.
- The process of manufacturing phytosomes is relatively simple.
- It helps in proper drug delivery to targeted tissue.
- They can be used for systematic targeting because phytosomes are capable of transiting from a hydrophilic environment into the lipophilic environment of an enterocyte cell and then into the cell (16).
- As the absorption of active constituent(s) is improved, its dose requirement is also reduced.
- A cell-like structure produced due to complex formulation that protects the essential component of herbal extract from digestive fluid and gut bacteria. (17)

METHOD OF PREPARATION

Antisolvent Precipitation Technique

A specific amount of herbal extract and phospholipids is refluxed with 20 ml of organic solvents like acetone under specific experimental conditions below 50°C for 2-3 hours. The reaction mixture is concentrated to a minimum volume of 10 ml, and precipitates are formed by adding a solvent with low polarity, such as n-hexane, while stirring. Desiccators are used to hold filtered precipitates. The dried precipitates are pulverised, and the powdered involute is stored in a dark amber glass bottle at room temperature (18)

Rotary Evaporation Technique

Phytosome vesicles were made by thin layer rotary evaporator vacuum method. The phytosomal complex was mixed in anhydrous ethanol in 250 ml round bottom flask. The flask was attached to a rotary

evaporator. The solvent will evaporate at a temperature about 60°C forming thin layer film around the flask. The film is hydrated by phosphate buffer having pH 7.4, and the lipid layer will peel off in phosphate buffer forming vesicle suspension. The phytosomal suspension was subjected to probe sonication with 60% amplitude. Phytosomal suspension will be stored in the refrigerator for 24 hrs, before characterization (19)

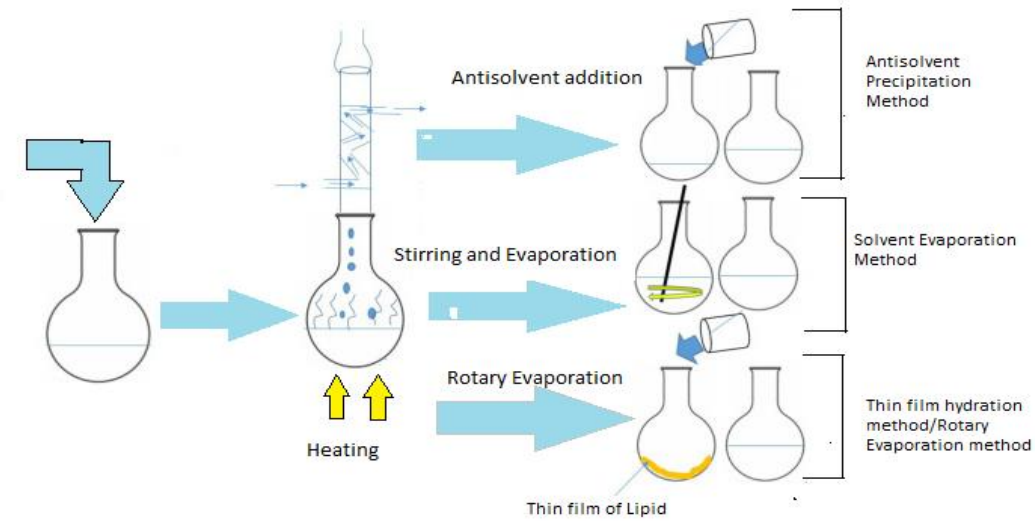
Solvent evaporation Technique

Phytosomes can be prepared by reflux method. Polyphenolic extract and phospholipid were placed in 100 mL round bottom flask and refluxed in dichloromethane for 1 hr not exceeding 40°C. The clear solution was evaporated and add 15 mL of n-hexane until a precipitate was obtained. The precipitate was taken and placed in a desiccator (20).

Lyophilization process

Both characteristic or manufactured phospholipid and phytoconstituent are broken down in a solitary arrangement and a phytoconstituent containing arrangement is added to a phospholipid arrangement followed by mixing until a perplexing plan. The structured structure is separated by lyophilization. The phospholipid used in the preparation of the phytosome contains a group of acyls that may be similar or different from phosphatidylcholine, phosphatidylserine, phosphatidyl ethanolamine and are more commonly found in palmitic, stearic, oleic, and linoleic acid. In the active phytosome it turns into a significant piece of the layer as the dynamic rule is joined to the polar top of the phospholipid (21).

Novel methods for the phospholipid complex preparation includes super critical fluids (SCF), which include gas anti-solvent technique (GAS) compressed anti-solvent process (PCA), super anti-solvent method (SAS) (22)



Different Methods for Preparation of Phytosomes

CHARACTERIZATION OF PHYTOSOMES

There are several parameters such as the physical size, membrane permeability, percentage of entrapped solutes, and chemical composition of the raw materials. They have a vital role in determining the behaviour of phytosomes in the physical and biological system.

1.Transition temperature:

The transition temperature of a vesicular lipid system can be determined using Differential Scanning Calorimetry (DSC) (23).

2.Solubility and partition coefficient

Determinations of solubility characteristics of drug (methanolic extract), physical mixture of drug & phospholipid and phytosomes were obtained by adding excess of the samples to 10 ml of water and n-octanol in sealed glass container at room temperature. The liquids were shaken for 24 h and centrifuged at

5000 rpm for 10 min. The supernatant was filtered, and the concentration of drug in water and n-octanol was determined spectrophotometrically using UV double beam after appropriate dilutions

The apparent partition coefficients were measured by the shake-flask method. In this method the two phases were mutually saturated before use. Equal volumes of water and n-octanol containing pure drug and phospholipid complex were mixed in the different volumetric flask and equilibrated under constant shaking at 37°C for 24 h. Both phases were then separated by using separating funnel and the concentration of drug was determined spectrophotometrically using UV double beam after appropriate dilutions. The partition coefficients were determined by using following equation:

Partition coefficient (P) = concentration of drug in n − octanol/ concentration of drug in water (24).

3.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 (25).

4.Visualization

Visualization of phytosomes can be achieved using transmission electron microscopy (TEM) and by scanning electron microscopy (SEM)

5.Surface tension activity measurement

The surface tension activity of the drug in aqueous solution can be measured by the ring method in a DuNouy ring tensiometer (26)

6.Vesicle stability

The stability of vesicles can be determined by assessing the size and structure of the vesicles over time. The mean size is measured by dynamic light scattering and structural changes are monitored by transmission electron microscopy

7. Drug content

The amount of drug can be quantified by a modified high performance liquid chromatographic method or by a suitable spectroscopic method (27)

8.Encapsulation Efficiency

Encapsulation efficiency (EE percent) describes the amount of phytochemical that is embedded in the phytosome. The process of encapsulation efficiency determination begins with the removal of free unencapsulated phytochemicals from the phytosome. Encapsulation efficiency by enzymatic assays, gel electrophoresis, fluorescence spectroscopy, and field flow fractionation chromatographic methods, such as HPLC, UPLC, or LC-MS (28).

9.Spectroscopic evaluations

1H-NMR

The NMR spectra are employed for estimating the complex formation between the active phytoconstituents and the Phosphatidylcholine molecule.

13C-NMR

In the 13C NMR of the phytoconstituents and the stoichiometric complex with the Phosphatidylcholine when recorded in room temperature all the phytoconstituents carbons are invisible. The signals corresponding to the glycerol and choline portion are broadened and some are shifted, while most of the resonance of the fatty acids chains retains their original sharp line shape.

FTIR

The spectroscopic evaluation of the formed complex can be confirmed by FTIR simply by comparing the spectrum of the complex and the individual components and that of the mechanical mixtures. FTIR can also be considered as a valuable tool in confirming the stability of the Phytosomal complex (29).

PHARMACOLOGICAL ACTIVITY OF NATURAL PRODUCT PHYTOSOMES

Enhance the bioavailability

Evodiamine, a quinoline alkaloid, is derived from the fruit of a Chinese herbs. It has been demonstrated wide range of pharmacological activities such as anticancer, anti-inflammatory, antinociceptive, anti-obesity, and thermoregulatory effects. Evodiamine phosphor-lipid complex are prepared by solvent evaporation method. The *in vivo* pharmacokinetic study of phytosomes evodiamine proved to have higher rate of *in vitro* dissolution, better absorption and bioavailability. The prolonged action time and increased bioavailability was observed due to the extended release of drug from phytosome and moreover, they reduce the first pass metabolism of Evodiamine. The bioavailability and T1/2 of evodiamine were 1,772.35 g h1 L1 and 1.33 hrs while the phytosomal form was 3,878.24 g h1 L1 and 2.07 hrs (30). The phytosome of terbinafine hydrochloride (TFH) was formulated with the molar ratio (1:2) of drug and phospholipid by using solvent evaporation technique. Terbinafine hydrochloride is a synthetic allylamine effective antifungal substance that is little soluble in water. According the mathematical models of kinetic release the determination coefficients, Korseymer peppas model was found (R2=0.951) to fit the release data best. Hence, that the drug was released from terbinafine phytosome by a controlled mechanism. The formulated terbinafine loaded phytosome having increasing the oral bioavailability (31).

Hepatoprotective activity

Compared to carriers employed in other drug delivery systems, phosphatidylcholine is a crude ingredient that also has significant therapeutic benefits. Phosphatidylcholine not only acts as an ingredient added to the formulation of phytophospholipid complexes, but also serves as a hepatoprotectant. Thus, the synergistic effect will be shown to protect the liver when the patient takes phosphatidylcholine. In certain situation, Phospholipids can also provide nutritional benefits (32). The effect of ginkgo selective phytosome of Rifampcin induced hepatoprotective action which is due to its antioxidant and free radical scavenging activity (33). Silymarin, a Phyto-constituent derived from the plant Silybum marianum, has been widely acknowledged for its hepatoprotective activities. The phytosomes were prepared using the solvent evaporation technique and were optimized using a full factorial design. The *in vivo* assessment studies revealed that the optimized silymarin phytosomal formulation efficiently exerted a hepatoprotective effect in a CCl4 -induced hepatotoxicity rat model via restoring the normal levels of antioxidant enzymes and ameliorating cellular abnormalities caused by CCl4 -intoxication. Most notably, as compared to pure silymarin, the optimized silymarin phytosomal formulation significantly improved silymarin oral bioavailability, as indicated by a 6-fold increase in the systemic bioavailability (34). The plants of Bombax ceiba are traditionally used as home remedy in the treatment of jaundice, spleen enlargement and hepatoprotective activity. The ethanolic extract of phytosome was prepared in soya lecithin by solvent evaporation method. The synergistic effect determined by free radical scavenging activity of Bombax ceiba phytosome using DPPH model. Bombax ceiba plant shows hepatoprotective activity as well as they are traditionally used in the treatment of diabetes (35).

Anticancer activity

The plant activities like flavonoids, anthocyanins, coumarins, lignans, catechins of herbal plants mainly exhibits the antioxidant activity which responsible for the anticancer potential. The plant active compounds show the toxicity at higher the concentrations and cause certain side effect. The conventional therapies for cancer like chemotherapy and radiotherapy possess the number of side effects which include myelosuppression and neurological, cardiac, pulmonary and renal toxicities. This study carried out preparing methanolic extract of Terminalia arjuna bark and Terminalia arjuna bark Extract phytosome in antiproliferative activity on human breast cancer MCF-7 cell line by MTT assay. The IC50 value obtained with the extract and its phytosomes were 25µg/ml and 15µg/ml respectively and show more antiproliferative activity as compared to pure extract (36). *Moringa oleifera* leaf polyphenols (Mopp) were encapsulated with phytosomes to enhance their efficacy on 4T1 cancer cell lines. Moringa oleifera

polyphenol-loaded phytosomes (MoP) were prepared with the nanoprecipitation method. The *in vitro* cytotoxic and antiproliferative activity were investigated with the (3-[4,5-dimethylthiazol2-yl]-2,5-diphenyltetrazole) MTT assay, MoP exhibited the highest antiproliferative effect on 4T1 cancer cells with an inhibitory concentration of 7.73 ± 2.87µg/mL and selectivity index > 3. The results indicated a significant difference ($p \leq 0.001$) in MoP when compared to Mopp and doxorubicin. The *in vivo* investigation showed the safety of MoP at a dose below 2000 mg/kg (37). Research work carried out chrysin loaded phytosomes and its cytotoxic effect against colorectal cancer cells by MTT assay. In HT-29 cells, the chrysin loaded phytosomes showed IC50 value of 17.92 µg/ml whereas pure chrysin showed IC50 value of 53.21 µg/ml. chrysin loaded phytosomes in the ratio of 2:1 showed better cytotoxic effect against HT29 cells and this provided indication for the use of Chrysin loaded phytosomes in experimental animals to further gain in depth analysis for anticancer activity of chrysin loaded phytosomes against colorectal cancer (38).

Antioxidant activity

Daemonorops (Indonesian: jernang) resin possess natural an antioxidants and sun protection activity. Ethanolic extract of Daemonorops acehensis resin and phytosome formulation proved that high antioxidant capacities and sun protection factor (SPF) values. Three antioxidant parameters—DPPH, CUPRAC, and ABTS—also have high correlations. Based on the yield value, antioxidant capacity, and SPF value, the extraction treatment with 100% ethanol was chosen as the best extract with the highest yield, the best antioxidant activity, and the highest SPF value (39). The metal pytosome prepared with the extract of *calendula officinalis* exhibited antioxidant activity. They carried out *in vitro* cell base antioxidant assay on vero cell line model. The result depicts that the cell viability is about 81% for the complex of metal phytosome loaded with plant extract and about 35% for the umcomplexed plant extract (40). The *Ellettaria cardamomum* phytosome was prepared by thin layer hydration technique. In *Ellettaria cardamomum* the presence of vitamin C, riboflavin, thiamin and some phytochemicals are the contributory antioxidant potential. The *Ellettaria cardamomum* phytosomes demonstrated significantly high antioxidant potential as compared to *Ellettaria cardamomum* extract in different antioxidant assays. 2, 2-Diphenyl-1-picrylhydrazyl assay of *Ellettaria cardamomum* phytosomes showed higher (72%) radical quenching activity at the 100µg/ml conc. as compared to *Ellettaria cardamomum* extract (65%). The lipid peroxidation inhibition of *Ellettaria cardamomum* phytosomes (50%) and of extract (42%) at 72 hours was lower than the ascorbic acid (72%). *Ellettaria cardamomum* phytosomes showed enhanced nitric oxide and super oxide inhibition as compared to the crude extract (41).

Transdermal activity

Ginger contains anti-inflammatory compounds (6-gingerol) that function in same as Cox2 inhibitors; 6-gingerol is used as excellent anti-inflammatory agent. Ginger phytosome prepared by solvent evaporation method. Ginger phytosome suspension exhibit better skin permeation through rat skin membrane. The phytosomal suspension shows transdermal flux in the ranged between 17.613 ± 0.01 µg/cm2/hr to79.94 ± 0.02 µg/cm2/hr (42). Rutin is the one of the most common flavonoids used to treat capillary fragility, hypertension, hepatic and blood cholesterol, cataract, cardiovascular activity, antioxidant, anti-inflammatory, antineoplastic and antiplatelet activity. The rutin phytosome prepared by solvent evaporation method. The rutin phytosomes exhibit better penetrability through the stratum corneum with that of its free form. The skin uptake of rutin phytosome was observed to be 33±1.33% and rutin was 13±0.87% (43). The phytosomal complex of saponins and plant extracts (Panax ginseng M.) proved to be more active in vasal protection, capillary permeability, protection against UV radiation. They were used in the development of cosmetics pharmaceutical formulations and they exhibit moisturizing effect on the cutis. These compositions can in particular be used for oral administration in the form of tablets, capsules, syrups,

granules, solutions (containing 1-500 mg dose of the complex) for treating conditions of inflammation, altered capillary fragility and permeability (44).

Antidiabetic activity

Rutin-phospholipid complex (RPC), a Phyto formulation were prepared and evaluated for its antidiabetic activity in streptozotocin induced diabetic model. Rutin-phospholipid complex were prepared by antisolvent precipitation method. The monoglycemic rat were subjected to the administration of higher and lower dose of rutin and rutin-phospholipid complex. The results shows that there is significant reduction in AUC glucose level that is achieved with the rutin-phospholipid complex form. The effect of rutin and rutin phospholipid complex (50 and 100 mg/kg) in streptozotocin induced diabetic rat for 1 day and 15 days was studied, in both studies, the phytosomal complex of rutin exhibits the dose dependent percentage reduction of serum glucose level in comparison with diabetic control group (45). *Murraya koenigii* (curry leaves) possess antidiabetic, stimulant, antidysentery, antioxidant,3,4 lipid-lowering, anti-nociceptive, antiaging, anticancer, hepatoprotective, cardio protective, antifungal, antibacterial properties. It used to treat various gastrointestinal disorders, to improve craving and metabolism. *Murraya koenigi*i Extract Loaded Phytosomes prepared using Antisolvent Precipitation Technique. Streptozotocin-nicotinamide induced diabetes model was used to evaluate *in vivo* antidiabetic activity in rats for extract as well as prepared phytosomes. The results showed that *Murraya koenigii* extract, optimized phytosomal formulation showed 39% and 42% reduction in serum glucose concentration at lower dose and enhancing its therapeutic efficacy (46).

CONCLUSION

Phytochemicals derived from medicinal plants possess immense therapeutic potential; however, their clinical application is often limited by poor bioavailability, low lipid solubility, and instability in biological environments. The development of novel drug delivery systems has significantly contributed to overcoming these limitations by enhancing solubility, permeability, and targeted delivery of plant-derived compounds. Among these, phytosomes have emerged as a promising and effective approach due to their unique ability to form lipid-compatible complexes with phytoconstituents. Phytosomal technology improves the pharmacokinetic and pharmacodynamic profiles of herbal drugs by facilitating better absorption across biological membranes, protecting active constituents from degradation, and enabling sustained and targeted delivery. Additionally, the use of phospholipids such as phosphatidylcholine not only acts as a carrier but also provides added therapeutic benefits, thereby enhancing overall efficacy.Extensive research on phytosomes has demonstrated improved bioavailability and enhanced therapeutic activities, including hepatoprotective, anticancer, antioxidant, transdermal, and antidiabetic effects, when compared to conventional herbal extracts. Furthermore, advancements in preparation techniques and characterization methods have enabled the development of stable and reproducible phytosomal formulations.In conclusion, phytosomes represent a significant advancement in herbal drug delivery, bridging the gap between traditional phytotherapy and modern pharmaceutical science. Their ability to enhance bioavailability, improve therapeutic efficacy, and reduce adverse effects makes them a valuable strategy for the future development of plant-based therapeutics. Continued research and clinical validation are essential to fully explore their potential and facilitate their wider application in healthcare systems.

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