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# NANOPHYTOSOMES AN IMPERATIVE TECHNOLOGY FOR ENHANCING THE BIOAVAILABILITY OF BIOACTIVE CONSTITUENTS

D. Lavanya * and A. Sri Devi

Department of Pharmaceutical Chemistry, Seven Hills College of Pharmacy, Tirupati - 517561, Andhra Pradesh, India.
Department of Pharmaceutical Chemistry, Sri Padmavathi Mahila Viswavidyalayam, Tirupati - 517502, Andhra Pradesh, India.

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**Correspondence to Author:**
**D. Lavanya**

Assistant Professor,
Department of Pharmaceutical Chemistry Seven Hills College of Pharmacy Tirupati - 517561, Andhra Pradesh, India.

**E-mail:** lavanya.daddala@gmail.com

**ABSTRACT:** Herbal medicine has been widely accepted as a promising approach for the treatment of various diseases with lower cost and minimized toxicity. Bioactive constituents isolated from the herbal source are equipped with synthetic drugs. The potency of any herbal medication is contingent on the delivery of the effectual level of the therapeutically active constituent. The integration of a novel drug delivery system in a traditional system of medicine enriches the potentiality of herbal drugs. Several plant extracts and phytoconstituents, despite having excellent bio-activity *in-vitro* demonstrate less or no *in-vivo* actions due to their poor lipid solubility or improper molecular size or both, resulting in poor absorption and poor bioavailability. Nan technological systems have been developed for use as various types of carrier systems to improve the delivery of bioactive compounds and thus, obtain a greater bioavailability. Phytosome technology is one such novel approach that enabled in making phytoconstituents more bioavailable. In this review, a comprehensive discussion with respect to the methods and characterization of nanophytosomes of herbal preparations is presented.

**INTRODUCTION:** Plant-derived substances are increasingly gaining attention as dietary supplements and due to their role in health ailments as medicinal applications. The therapeutic efficacy of any drug obtained from plant, animal, sea or synthetic depends on the ability of dosage form to deliver the drug to the site of action at a rate and potency to elicit the pharmacological response. This attribute of the dosage form is referred to as physiologic availability, biological availability or simply bioavailability [1].

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The contributions of phytochemicals in public health cover various issues world widely and thus it is seen by researchers, industries, and general society and policymakers as a new tool to manage public health. Phytomedicines have been serving as a crucial source of drugs since ancient times. The usage of phytomedicine has been increased due to their improved therapeutic efficacy and minimal adverse drug reactions as compared to allopathic medicines.

Phytomedicines show impressive *in-vitro* activity but less *in-vivo* efficacy due to their poor water solubility, lipophilicity, and inappropriate molecular size resulting in poor absorption with poor bioavailability. A better understanding of the biopharmaceutics and pharmacokinetics of phytomedicine can also help in designing rational dosage regimens [2, 3].

Nanotechnology has become the threshold of providing new materials and approaches in revolutionizing the medical and pharmaceutical fields. Several areas of medical care are already profiting from the advantage of nanotechnology [4]. Over the past several years, great advances have been made on the development of novel drug delivery systems (NDDS) for plant actives and extracts. A variety of novel formulations like polymeric nanoparticles, nan capsules, liposomes, herbosomes, nan emulsions, microsphere, transferosomes, and ethosomes have been reported using bioactive constituents and plant extracts [5]. Phytosome approach has shown to overcome such problems and become more bioavailable as compared to conventional herbal extract owing to their enhanced capacity to cross the lipoidal bio-membrane and achieving bioavailability [6, 7].

**Phytosome Technology:** Active constituents extracted from natural plants have been shown to exhibit robust *in-vitro* pharmacological effects, but poor *in-vivo* absorption. Many active constituents extracted from plants have poor absorption when administered orally, limiting their widespread application [8, 9]. The poor absorption of these compounds results from the large multi-ring structures of polyphenols to be absorbed by passive diffusion or non-active absorption and the poor aqueous or lipid solubility of these compounds prevents them from passing across the outer membrane of gastrointestinal cells [10, 11].

Phospholipid complex technique can serve as a potent drug delivery system for increasing therapeutic index, which encapsulates, plant bioactive compounds. The complex actives have become safer than its original form and can even serve as a better targeting agent to deliver these encapsulated agents at specific sites thereby proving promising candidates in various medical fields for improving health aspects [12].

Phytosomes form a complex between natural water-soluble phytoconstituents and natural phospholipids which are prepared by reaction of stoichiometric ratios in a solvent to achieve lipid compatible molecular complexes and improve their absorption and bioavailability [13]. Phytosomes show more bioavailability as compared to conventional herbal extracts, because of them being much better absorbed than liposomes, showing better bioavailability. Therefore, pyrosomes have been found superior benefits compared to the liposomes in the delivery of herbal medicines and nutra-ceuticals [14, 15]. The phytosome technology is a breakthrough model for marked enhancement of bioavailability, significantly greater clinical benefit, assured delivery to the tissues and without compromising nutrient safety [16]. They have been improved for pharmacokinetic and pharmacological parameters that are advantageous in the treatment of acute diseases as well as in pharmaceutical and cosmetic compositions [17].

**Carrier Phospholipids in Phytosome Preparation:** In general, fats, phospholipids, and steroids are different types of lipids present in the body and execute various physiological functions. Among them, phospholipids are major components of cell membrane, which also serves as a vehicle, thus making the design of drug delivery systems more flexible and are suitable for the body needs [18]. Phospholipids are bio-friendly and offer various advantages such as formulation flexibility and the choice of different NDDS based on the intended usage [19]. Phospholipids are lipid-containing phosphorus, a polar portion and non-polar portion in their structures [20]. These are small lipid molecules in which the glycerol is bonded only to two fatty acids, instead of three as in triglycerides, with the remaining site occupied by a phosphate group.

A cell membrane is composed of different classes of phospholipids like Phosphatidyl ethanolamine PE, Phosphatidylinositol PI, Phosphatidyl-choline PC, Phosphatidic acid PA and Phosphatidyl-serine PS [21]. PC possesses two neutral tail groups and a positive head group which contains an oxygen atom in the phosphate group, which has a strong tendency to gain electrons, while nitrogen to lose electrons, a rare molecular characteristic that makes PC miscible in both water and lipid environments [22].

From a commercial perspective, lecithin refers to PC, PE, PS, PI, and other phospholipids. But from a historical point of view lecithin includes lipids that contain phosphorous obtained from brain and egg. However, scientifically lecithin refers to PC [23]. In the herbal formulation research, incorporating the nano-based formulation has a great number of advantages for phytomedicine, including improve-

ment of solubility and bioavailability, safeguard from toxicity, enhancement of pharmacological activity, improvement of stability, increase in tissue macrophages distribution, sustained delivery, protection from physical and chemical degradation *etc* [24]. Thus, nano-phytomedicines have a prospective future for improving the activity and overcoming problems associated with herbal drugs.

**Preparation of Nano-phytosomes:** Phytosomes can be prepared by reacting phosphatidylcholine and phytoconstituents in 1:1 ration in an aprotic solvent. In phyto-phospholipid complex, the ration between phospholipid and phytoconstituent is in the range 0.5-2 mole. The most preferable ration between phospholipid and phytoconstituents is 1:1.

The phospholipids are mostly selected from the group consisting soya lecithin PC, PS and PE. Spectroscopic study shows that the molecules of phospholipid are bonded with phytoconstituents by means of chemical bonds [25, 26].

**TABLE 1: ADDITIVES EMPLOYED IN PREPARATION OF PHYTOSOMES: [27, 28]**

| Alcohols | Phospholipids | Aprotic solvents | Non-solvents |
|---|---|---|---|
| Ethanol Methanol | Soya phosphatidyl choline Distearyl phosphatidylcholine Dipalmityl phosphatidyl choline Egg phosphatidyl choline | Dioxane Methylene chloride Acetone | n-hexane Aliphatic hydrocar bons |

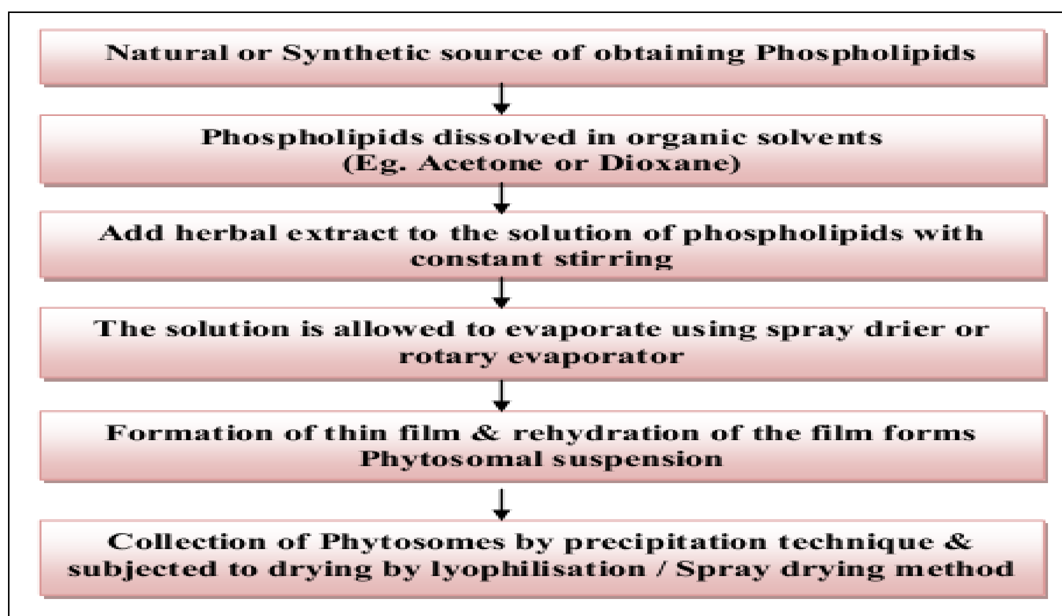


**FIG. 1: GENERAL MECHANISM OF PHYTOSOME PREPARATION**

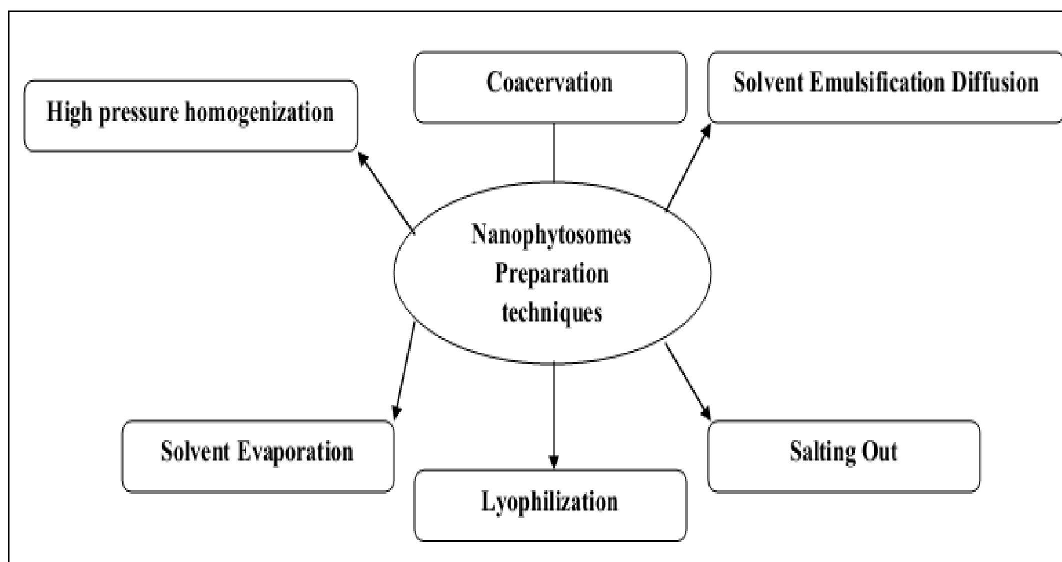


**FIG. 2: VARIOUS METHODS INCLUDED IN PREPARATION OF NANOPHYTOSOMES**

**High Pressure Homogenization:** In this method, the drug is dissolved in the lipid being melted at approximately 5-10 °C above its melting point. The drug-containing melt is dispersed under stirring in a hot aqueous surfactant solution of identical temperature, in order to obtain pre-emulsion [29]. Then it is pushed with high pressure (100-2000 bar) through very high shear stress, resulting in disruption of particles down to the nanometer range. High-pressure homogenization method is a very reliable and powerful technique for the large scale production of nanostructured lipid carriers, lipid drug conjugate, solid lipid nanoparticles (SLNS) and parenteral emulsions [24, 30]. However, besides all its advantages and its versatility, high-pressure homogenization involves critical process parameters like high temperatures, high pressures, which may cause significant thermodynamic and mechanical stress for the resulting product: in particular, this method is not suitable for thermo-liable drugs. Suitable alternative methods for lipid nanoparticle preparation have been widely investigated [31].

**Coacervation Method:** This method allows the incorporation of drugs, without using complex equipment or dangerous solvents and is therefore inexpensive for laboratory and industrial applications. It is based on the interaction between a micellar solution of a fatty acid alkaline salt (soap) and an acid solution (coacervating solution) in the presence of different amphiphilic polymeric stabilizing agents: fatty acid nanoparticles precipitate as proton exchange occurs between the coacervating solution and the soap solution [32]. The precursor for nanoparticle preparation is a soap micellar solution, obtained at a temperature above its Krafft point (that is the solubilization temperature of the soap in water): drug can be dissolved directly in the micellar solution, or pre-dissolved in a small amount of ethanol, in order to enhance micellisation. As for microemulsion templates, the good solubilizing properties of micellar solutions allow an advantageous drug loading within nanoparticles for many drugs, especially for poorly water-soluble drugs [33, 34].

**Solvent Emulsification Diffusion Method:** The method involves preparation of an o/w emulsion using oil phase containing polymer and oil in an organic solvent, which is emulsified with the aqueous phase, containing stabilizer, in high shear mixer, followed by addition of water to induce the diffusion of organic solvent, thus, resulting in formation of nanoparticles [24].

**Salting-out Method:** This method is based on the phenomenon that solubility of a non-electrolyte in water is decreased on the addition of an electrolyte [24]. The phytoconstituent or standardized extract and phosphotidylcholine is dissolved in an aprotic solvent, such as dioxane or acetone where the solution is being stirred overnight then the formed complex is isolated from by precipitation from non-solvent like n-hexane [35].

**Lyophilization Technique:** Both natural and synthetic phospholipid and phytoconstituent are dissolved in a different solvent and a further solution containing phytoconstituent is added to a solution containing phospholipid followed by stirring till complex formation takes place. The formed complex is isolated by lyophilization [17].

**Solvent Evaporation Method:** A natural or synthetic phospholipid phosphatidylcholine and phytoconstituent are suspended in an appropriate solvent, further, refluxed for a few h. The resultant clear mixture is being evaporated under vacuum [36]. The particular quantity of drug, polymer, and phospholipids can be taken into a spherical bottom flask and reflux with a specific solvent at a temperature 50-60 °C for 2 h. The mixture may be concentrated to 5-10 ml to get the precipitate which can be filtered and collected [13].

**Characterization of Nano-phytosomes:**

**Crystallinity and Polymorphism:**

**Differential Scanning Calorimetry (DSC):** Phyto-phospholipid complexes usually display radically different characteristic peaks compared to those of a physical mixture. In DSC, interactions can be observed by comparing the transition temperature, the appearance of new peaks, the disappearance of original peaks, melting points and changes in the area of the relative peak. The sample is placed in an aluminum crimp cell heated from 30 to 300 °C at a rate of 10 °C/min under nitrogen flow (60 ml/min) [62].

**X-Ray Powder Diffraction (XRD):** X-ray diffraction is an effective method to examine the microstructure of both crystal materials and some amorphous materials. The sample is scanned in the

angular range of 6°-40° using an X-ray powder diffractometer. Cu Kα1 radiation selected by a Ni monochromator and the diffraction patterns will be recorded in a step scan model with a current of 30 mA, a voltage of 30 kV and a step size of 0.02°. Phytophospholipid complexes if do not exhibit crystalline peak, which suggests that the constituents in complex with phospholipids exist in a molecular or amorphous form. That may account for the observation that phytophospho-lipid complexes have better lipophilicity and hydro-philicity than active constituents [63].

**TABLE 2: VARIOUS METHODS FOLLOWED IN PREPARATION OF NANOPHYTOSOMES**

| Phytoconstituent | Method | Solvent/ polymer | Anti-solvent | Ratio (drug Polymer/solvent) |
|---|---|---|---|---|
| Berberine [37, 38] | Antisolvent precipitation with a syringe pump APSP | Ethanol | Deionized water | 1:10, 1:15, 1:20 v/v |
| Berberine [37, 38] | Evaporative precipitation of Nanosuspension EPN | Ethanol | Hexane | 1:10, 1:15, 1:20 v/v |
| Celastrol [39, 40, 41] | Self-assembly technique | Anhydrous ethanol Soy phosphatidylcholine | - | 1:1, 1:2, 1:3 |
| Curcumin [42] | Solvent evaporation | Dichloromethane Phosphatidylcholine | N-hexane | 1:1, 1:2, 1:4 |
| Delphinium denudatum [43] | High-pressure homogenizer | Ethanol, phospholipon 90H (Hydrogenated soy phosphotidylcholine) | - | 1:2 |
| Centella extract [44, 7] | Solvent evaporation | Ethanol, phospholipon® 90H | N-hexane | 0.5:1, 1.01:1, 1.75:1, 2.49:1, 3:1 |
| Rutin [46] | Thin layer hydration | Methanol chloroform cholestrol | - | 1:1, 1:2, 1:4 |
| Rutin [47, 48, 49] | Thin layer hydration | Ethanol phosphatidylcholine | - | 1:1, 1:2, 1:3 |
| Quercetin [50] | Thin layer hydration | Methanol dichloromethane Phosphatidylcholine cholesterol | - | - |
| Umbelliferone [51] | Solvent evaporation | Dichloromethane Phospholipon 90H | N-hexane | 1:1, 1:2, 1:3 |
| Green tea polyphenol [52, 13, 53] | Antisolvent precipitation | dichloromethane Phosphatidylcholine | N-hexane | 0.5:1, 0.75:1, 1:1, 1:0.75 and 1:0.5 |
| Gingerol[54, 55, 56] | Anti-solvent precipitation | dichloromethane Soya lecithin | N-hexane | 1:1, 1:2, 2:1, 2:2 |
| Rutin [57, 58, 59] | Solvent evaporation | Methanol phosphatidylcholine dichloromethane | - | - |
| Curcumin [60] | Co-solvent technique | Tetrahydrofuran soybean phosphatidylcholine | - | 1:4 |
| Silibinin [61] | Antisolvent precipitation with a syringe pump APSP | Ethanol | Deionized water | 1:10, 1:15, 1:20 v/v |
| Silibinin [61] | Evaporative precipitation of nanosuspension EPN | Ethanol | N-hexane | 1:10, 1:15, 1:20, v/v |

**Spectroscopic and Chromatographic Techniques:**

**Fourier Transform Infrared Spectroscopy (FTIR):** Samples blended with dry crystalline KBR in a ratio of 1:100 then compressed to form pellets. A spectrum is recorded for each sample within the wavenumber region 500-4000 $cm^{-1}$.

FTIR 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 phyto-phospholipid complexes can be verified by comparing the spectroscopy of phospholipid complexes to that of physical mixtures [64].

**Nuclear Magnetic Resonance (NMR):**

**H-NMR:** The sample of phyto phospholipid complex dissolved in a suitable solvent and analyzed with an NMR spectrometer. The spectrum obtained is compared to the drug and complex.

**13C-NMR:** The 13C-NMR spectrum is taken for confirmation of the interaction between drug and phospholipid and the formation of the complex.

The sample of the phyto-phospholipid complex is dissolved in a suitable solvent and then analyzed with the NMR spectrometer. The spectrum obtained can be compared for the drug and complex [65, 66].

**High-Performance Thin Layer Chromatography (HPTLC):** A standard solution of Phyto-phospholipid complex is applied using Hamilton syringe in triplicate to an HPTLC plate. The plates developed in a suitable solvent system at 25 ± 2 °C temperature and 40% relative humidity until the required distance is achieved. After development, the plates are dried and scanned. The peak areas are found and $R_f$ values are recorded and compared for the plain drug and complex using winCATS software [67, 68].

**Vesicle size and Zeta-potential:** The mean particle size (PS) and Zeta potential (ZP) of Phytosomal formulation can be measured by dynamic light scattering (DLS) technique. This system adopts a non-destructive backscattering technique to measure the particle size at a detection angle of 173°. Particle size and zeta potential are important properties of complexes related to stability and reproducibility. In general, the average phospholipid complex particle size ranged from 50 nm to 100 µm.

**Complexation Efficiency:** The Complexing efficiency of drugs with phospholipids is determined by an indirect method. The sample of phyto phospholipid complex dispersed in deionized water under vigorous vortexing. Owing to the solubility difference, the free uncomplexed drug will precipitate its insolubility nature in water. The residual unreacted drug is separated by centrifugation at low speed, dissolved in ethanol then quantified spectrophotometrically against phospholipid as blank solution [69, 70].

$$\text{Complexation rate (\%)} = (m2/m1) \times 100 = [(m1 - m3)/m1] \times 100$$

Where m1 is the total content of drug added, m2 is the content of drug present as a complex and m3 is a free drug

**Determination of Partition Coefficient (log P) Value:** Each sample of phytosome is added to n-octanol and agitated for 24 h in sealed glass containers at 25 °C at 100 rpm in a shaking water bath. The aqueous phase constituted of potassium dihydrogen phosphate (pH 6.8) was added to the n-octanol solutions and shaken for an additional 24 h at 25 °C at 100 rpm. The n-octanol phase and water phase are separated and then centrifuged at 10000 rpm for 15 min. The n-octanol and water phases are filtrated through a (0.45 µm) membrane filter. The filtrates are suitability diluted with ethanol and phytosome amount was quantified by spectrophotometrically [71]. Log P values of free drug and phyto-phospholipid complex is calculated using the following equation:

$$\text{Partition Coefficient} = Co/Cw$$

Where Co-Concentration in the oil phase, Cw-Concentration in the water phase

**Solubility Studies:** The phyto-phospholipid complexes have better lipophilicity and hydrophilicity than active constituents and typically exhibit improved lipophilicity. The required amount of the phyto phosphor-lipid is added to distilled water and different vehicles, sealed in glass vials and placed in a shaking water bath for 24 h, at 25 °C, at 100 rpm. After equilibrium for an additional 24 h at 25 °C, samples were centrifuged at 10000 rpm for 10 min and the supernatant was filtered using millipore filters (0.45 µm). The filtrates are analyzed by UV spectrophotometry using the corresponding proper medium as a blank [63].

***In-vitro* Release Study:** *In-vitro* release profiles of Phytosomal formulation can be investigated using a dialysis bag method. Aliquots of phytosomes are placed into a sealed dialysis bag (molecular weight cutoff 12–14 KDA). The dialysis bags are immersed in the release medium constituted of buffer saline, pH 6.8 containing (0.25% (w/v) 80 to achieve sink conditions and incubated in shaking water bath at 37 °C and 75 rpm. Samples of release medium are withdrawn at different time points followed by compensation with the same volume of fresh release medium. The samples were filtered through a 0.45 millipore filter and measured spectrophotometrically against the fresh release medium as a blank.

**Release Kinetics:** The concentration data obtained from the *in-vitro* release study can be fitted to common kinetics release models (Zero-order, First order, Higuchi, and Korsmeyer Peppas models) using DD-solver excel sheet software for better understanding the mechanism of drug release from phytosomes.

**Drug Content:** The phytosome is dissolved in methanol to form a solution to obtain 2 μg/ml and evaluated spectrophotometrically. Prepare the blank using phospholipid and methanol with subsequent dilution to prepare 2 μg/ml solutions. This solution is used as a blank. The drug content is calculated for the optimized batch as follows [72, 73].

Drug-loading content (%) = Amount of drug in the NPS/ Amount of the NPS × 100

**Stability Study:** A short term chemical stability of the phyto phospholipid complex can be examined for three months at 30 ± 2 °C at 65 ± 5% RH. The complex samples should be analyzed at an interval of 30 days for 3 months and the *in-vitro* permeation is compared [74]. This data is statistically analyzed and validated by using ANOVA.

**Drug Entrapment:** Phytosomes are diluted 1-fold with 10 ml of solvent and centrifuged at 18,000 rpm for 30 min at -4 °C using a cooling centrifuge machine. The isolated supernatant liquid and the quantity of free active constituent may be determined by UV spectrometry. To determine the entire quantity of active constituent, 0.1 ml of the phytosome loaded suspension can be diluted in fuel, adjusting the volume to 10 ml [55, 73]. The entrapment efficiency may be calculated according to the subsequent formula.

Entrapment efficiency (%) = (Total amount of drug) - (amount of free drug) × 100 / Total amount of drug

**Visualization Techniques:**

**Transmission Electron Microscopy (TEM):** Morphological examination of selected phytosome is performed using TEM. Dilute the sample with distilled water (1:20) and sonicated for 5 min. A drop of the drug-loaded phytosome dispersion is put onto a carbon-coated copper grid and left to form a thin film. The resulted film will then be negatively stained by 2% (w/w) ammonium molybdate and remove the excess stain with a filter paper then left for air drying. The stained films were then viewed under TEM.

**Scanning Electron Microscopy (SEM):** Scanning electron microscopy can be used to confirm particle size distribution and surface morphology of the phytophospholipid. Place the dry sample on an electron microscope brass stub coated with gold in an ion sputter. Digital pictures of phytosome loaded may be taken by random scanning of the stub at 1000, 5000, 10000 and 30000 X magnifications [55, 73, 75].

***In-vivo* Evaluation:** *In-vivo* evaluations can be done according to therapeutic activity measurement parameters of the biologically active phytoconstituents present in the phytosomes loaded with the help of suitable animal models.

**CONCLUSION:** The treatment of any disease can be improved by the development of novel drugs or with more effective and safer use of existing drugs. The phyto-phospholipid complexation technique has emerged as an imperative tool in improving the bioavailability of herbal drugs effectively solving the issue of sufficient lipid membrane permeability at higher concentration and sustained therapeutic levels in plasma with a slower rate of elimination.

This multidisciplinary research including traditional herbal therapeutics in combination with modern novel drug delivery systems has given away to the development of better nanosized herbal drugs as future phytopharmaceuticals that would prove to be of value for enhancing the health of the public.

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