



Review Article

PHYTOSOME LOADED NOVEL HERBAL DRUG DELIVERY SYSTEM: A REVIEW

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ABSTRACT

Novel drug delivery system (NDDS) is an innovative approach to drug delivery that addresses the limitations of the traditional drug delivery systems. If the novel drug delivery system is applied in herbal drugs, it should facilitate in increasing the efficaciousness and reducing the side effects of various herbs. This is often the essential plan behind incorporating novel technique of drug delivery in herb compounds. So it's necessary to integrate novel drug delivery system and Indian Ayurvedic medicines to conflict additional serious diseases. For a long time herb medicines weren't considered for development as new formulations because of lack of scientific justification and process difficulties such as standardization, extraction and identification, purification of individual drug elements or phyto-constituents in advanced polyherbal systems. The on the market approaches for novel herb analysis will solve the scientific wants (such as determination of pharmacokinetics, mechanism and site of action, correct dose needed etc.) of herbal medicines to be incorporated in novel drug delivery system. Phytosomes are proprietary method developed by Indena, to include phospholipids into standardized extracts and then greatly improve their absorption and utilization. Phytosomes loaded are advanced herbal products made by binding individual part of herb or plant extract to phosphatidylcholine leading to a product that's higher absorbed and produces higher results than the traditional herbal extracts.

KEYWORDS: Novel drug delivery system (NDDS), Phytosome loaded, Phospholipids, Polymer.

INTRODUCTION

From the last century, there are valuable criteria has been keep it up and centered on the event of novel drug delivery system (NDDS) for herbal medicines. Researchers have reputable the potential edges of novel drug delivery in providing immense enhancements to deliver the drug and drug targeting. Improving delivery technique, minimize toxicity and improve efficaciousness offers an excellent potential edges to patients and exposes new markets for pharmaceutical and drug corporations. The novel carriers ought to deliver the drug at directed rate by the requirements of the body, over the period of cure and it ought to channel the active entity of herbal drug to the site of action.¹

Plant derived medication have gained huge quality and access to the drug market throughout the world as safer and effective substitutes of recent artificial medicines that are thought-about to be jam-packed with complicated and noxious interactions. With in the world plant are in ancient kind or as medicine are presupposed to satisfy the first health care wants regarding 80% of the population and even in developed nations. These seasoning medicines are being used by regarding 65% of the population.

Currently, as several as third to half of all the medicine more or less on the market are derived from plants or alternative natural sources. With the event within the field of phyto and analytical chemistry, specific ingredients or a group of comparable ingredients from plant is being extracted, isolated and tested for

their totally different meditative applications. However, the bioavailability of active principles of plant has become a problem of concern for researchers attributable to poor oral bioavailability of the many of plants, specifically those containing polyphenolic rings in their structures like flavonoids et al. like terpenoids and tannins. A number of the essential reasons for the poor bioavailability of active plant constituent are low liquid or macromolecule solubility, high molecular weight/size and poor cytomembrane porosity. More over the standardized extracts once administered orally, go down a number of their constituents within the presence of internal organ fluids.

To overcome these issues and to form botanical medicine more practical, the plant medicines are incorporated into many novel delivery systems within the current time. A number of the approaches for improvement of bioavailability are nano and small primarily based formulation like nanoparticles, binding with lipids as liposome's or herbosomes/phytosomes, release in the form of small emulsions, alteration in chemical structures, delivery as prodrug and complexation with cyclodextrins etc. have variety of benefits for herbal medicine as well as improvement of solubility and bioavailability, shield from toxicity, improvement of pharmacologic activity and stability, improve tissue macrophages distribution, sustained delivery, protection from physical and chemical degradation etc. Thus, the novel drug delivery systems of herbal medicines have a possible future for improvement the activity and overcoming issues related to plant medicines.^{2,3}

Phytosomes Loaded

The term “phyto” suggests that plant whereas “somes” suggests that cellular.^{4, 5} The phytosomes loaded structure may be a little cell in itself, because the necessary elements of the herbal extract are shielded from destruction by the organic process secretions and gut bacterium. Phytosomes are patented method developed by Indena, to include phospholipids into standardized extracts and then vastly improve their absorption and utilization. Phytosomes loaded are advanced herbal product created by binding entity part of herbal extract to phosphatidylcholine (Figure 1) and polymer leading to a product that's higher absorbed and produces higher results as compare to the conventional herbal extracts.

The polyphenolic active constituent of plant extracts offer themselves quite well for direct binding to phosphatidylcholine. Phytosomes loaded are created from the reaction of the phospholipids like phosphatidylcholine and polymer with the standardized plant extract or polyphenolic phytoconstituents or flavonoids of herbal extracts like ginkgo, grape seed, hawthorn, milk thistle, green tea and ginseng in aprotic solvent.^{6, 7} Phosphatidylcholine could be a bifunctional compound, in which the phosphatidyl moiety has lipophilic nature and the choline moiety has hydrophilic nature. Lipid soluble moiety phosphatidyl binds to body and tail and water soluble moiety choline binds to polyphenolic compounds and then forms a phyto – phospholipid complex or cell like structure shown in Figure 2. Hence, the Phyto-molecules produce a lipid soluble molecular complex with phospholipids known as phyto-phospholipid complex or little microsphere or cell or Phytosome Loaded (Figure 3). Phyto-molecules are anchored through chemical bonds to the polar choline head of phospholipids, as are often confirmed by specific qualitative analysis techniques.⁸

Many of the bioactive constituents of phytomedicines are flavonoids (e.g. silymarin from milk thistle, anthocyanidins from bilberry and catechins from green tea). However, most of the flavonoids are poorly absorbed. The low rate absorption of flavonoid nutrients is probable owing to 2 factors:-

- 1) They are multiplexing molecules giant to be absorbed by diffusion method, whereas they're not absorbed actively, as happens with some vitamins and minerals.
- 2) Flavonoids usually have less miscibility with oils and different lipids, severely limiting their ability to exceed across the lipid-rich outer membranes of the enterocytes of the small intestine.

METHODS FOR PREPARATION OF PHYTOSOME LOADED DRUG DELIVERY

There are numerous methods are offered for preparation of phytosome loaded drug delivery and common steps for preparation of phytosome loaded drug delivery is shown in Figure 4:

1. Solvent Evaporation Method: The particular quantity of drug, polymer and phospholipids can be taken into a spherical bottom flask and reflux with 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. The dried precipitate phytosome loaded can be placed in amber colored glass bottle and stored at room temperature.⁹

2. Rotary Evaporation Technique: The particular quantity of drug, polymer and phospholipids can be dissolved in specific solvent in a rotary spherical bottom flask followed by stirring

for 3 hours at a temperature not exceeding 40°C. Thin film of the sample can be obtained to which n-hexane is added and continuously stirred using a magnetic stirrer. The precipitate phytosome loaded obtained can be collected, placed in amber colored glass bottle and stored at room temperature.⁹

3. Antisolvent Precipitation Technique: The particular quantity of drug, phospholipids and polymer may be taken into a spherical bottom flask and reflux with specific solvent at a temperature not exceeding 60°C for 2 h. The mixture can be concentrated to 5-10 ml. N-hexane can be added carefully with continuous stirring to get the precipitate which has filtered and collected and stored in vacuum desiccators overnight. The dried precipitate is crushed in mortar and sieved through #100 meshes. The dried precipitate phytosome loaded can be placed in amber colored glass bottle and stored at room temperature.⁹⁻¹⁰

DIFFERENCE BETWEEN PHYTOSOMES AND LIPOSOMES¹¹

There are various differences between phytosome and liposomes are shown in Table 1 and Figure 5.

EVALUATION TECHNIQUES FOR PHYTOSOME LOADED DRUG DELIVERY

The activities of phytosomes loaded drug delivery system can be evaluated by % yield, particle size and shape, percentage drug entrapped, chemical composition, percentage drug release.¹²

Different evaluation techniques used for phytosomes loaded drug delivery:

% Yield

Determination of moral yield of phytosome loaded can be calculated by the subsequent formula:

$$(\%) \text{ Yield} = \frac{(\text{Practical yield})}{(\text{Theoretical yield})} \times 100$$

Differential Scanning Calorimetry (DSC)

The drug sample, phospholipids, polymer, physical mixture and phytosome loaded can be placed within the aluminum crimp cell and heated at 10°C/min from 0 to 400°C in the nitrogen atmosphere. Peak transition onset temperatures may be recorded by means of an instrument.¹³⁻¹⁵

FTIR Spectrographic Analysis

FTIR spectral data can be taken to determine the structure and chemical stability of phytosome loaded, phospholipids, polymer and drug sample. Samples can be crushed with KBr to get pellets at 600 kg/cm² pressure. Spectral scanning may be done in the range between 4000 - 400 cm⁻¹.¹³⁻¹⁵

Particle Size

The average diameter and zeta potential of the phytosome loaded may be each measured employing a Zetasizer ZEN 3600 at a fixed scattering angle of 90° at 25°C.¹³

Entrapment Efficiency

Phytosome loaded can be diluted 1-fold with 10 ml of solvent and so centrifuged at 18,000 rpm for 1/2 h at -4°C using cooling centrifuge machine. The supernatant was isolated and the quantity of free drug may be determined by UV/Vis spectrometry. To determine the entire quantity of drug, 0.1 ml of the phytosome loaded suspension can be diluted in fuel, adjusting the volume to 10 ml. The entrapment efficiency may be calculated according to the subsequent formula:¹³⁻¹⁴

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

Drug Content

Drug content of phytosome loaded can be determined by dissolving accurately weighed 100 mg of phytosome loaded in 10 ml solvent. After appropriate dilution absorbance may be determined by UV – Spectrophotometer. The drug content can be calculated by the subsequent formula:¹³

Drug Content (%) = (Total amount of drug) – (amount of free drug) × 100 / (Total amount of drug)

Scanning Electron Microscopy (SEM)

Scanning electron microscopy can be used to confirm particle size distribution and surface morphology of the phytosome loaded. Dry samples may be placed on an electron microscope brass stub and 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.¹³⁻¹⁵

In Vitro and In Vivo Evaluations

In vitro and *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.¹⁶

BENEFIT OF PHYTOSOME LOADED DRUG DELIVERY FOR HERBAL DRUGS

Numerous researches is being conducted by the researchers and therefore the recent works reveals that the phytosome loaded drug delivery may be a novel technique for rising the absorption and bioavailability of plant extracts considerably reducing the dose level. Some plant extracts are becoming more focus now-a-days because of their potential pharmacological effects, such as, silymarin, grape seed extract, quercetin, curcumin, hesperidins, ginkgo biloba extract, andrographolide etc. The suitability of this type of drug delivery system and raised demand for treatment of various diseases in current scenario has sealed the benefits for herb medicines. The summary of phytosome loaded drug delivery for herbal drugs are shown in Table 2.

Kidd et al.¹⁷ prepared four polyphenol preparations like Silybin and the alternative silymarin flavon olignans from milk thistle, Curcumin and its related diphenolic curcuminoids, green tea flavan-3-ol catechins and grape seed proanthocyanidin combine (including catechin and epicatechin monomers and oligomers) with poor bioavailability and their complexation into phytosomes to bypass this drawback and reported that for each of those preparations, conversion into phytosomes has improved effectivity without compromising safety. The phytosome technology creates intermolecular bonding between individual polyphenol molecules and one or more molecules of the phospholipid, phosphatidylcholine (PC). Molecular imaging suggests that PC molecule(s) cover each polyphenol; upon oral intake the amphipathic PC molecules probably “usher” the polyphenol through the intestinal epithelial cellouter membrane, later on accessing the blood. PC itself has proven clinical effectivity that contributes to phytosome *in vivo* actions. As a molecular delivery vehicle, phytosome technology considerably improves the clinical applicabilities of polyphenols and other poorly absorbed plant medicinal.

Malay et al.¹⁸ investigated that the oral bioavailability of Rutin is incredibly low necessitating its novel drug delivery approach. Phyto-phospholipid complex (phytosomes) is useful in

enhancing oral bioavailability and transdermic permeation of polyphenols and discovered phyto-phospholipid complex of Rutin enhanced its skin uptake to treat inflammatory conditions in inflammatory disease, rheumatism, athletic aches and delivered the drug for a long duration avoiding the issues related to oral administration.

Yang Li et al.¹⁹ compared FA-PEG-functionalized MMC loaded phytosomes (FFA-PEG-MMC-loaded phytosomes included enhanced cellular uptake in HeLa cells and better accumulation in H₂₂ tumor-bearing mice over that of the PEG-MMC-loaded phytosomes. furthermore, FA-PEG-MMC-loaded phytosomes related to increased cytotoxic activity *in vitro* and an improved antitumor effect *in vivo* compared to it resulting from free MMC injection. They recommended that FA-PEG-MMC-loaded phytosomes could also be helpful drug delivery systems for widening the therapeutic window of MMC in clinical trials.

Mehdi et al.²⁰ prepared nano phytosomes of luteolin to enhance the bioavailability of luteolin and improve passive targeting in carcinoma cells and discovered that co-treatment of cells with nano particles containing luteolin and antibiotic drug resulted within the highest percentage cell death in MDA-MB 231cells (p<0.05). They advised that luteolin-loaded nanoparticles reduced Nrf2 gene expression at the mRNA level in cells to a greater extent than luteolin alone (p<0.05) and equally, expression of downstream genes for Nrf2 including Ho1 and MDR1 reduced significantly (p<0.05). Inhibition of Nrf-2 expression caused a marked increase in cancer cell death (p<0.05). They also advised that phytosome technology can improve the effectivity of chemotherapy by overcoming resistance and enhancing porosity of cancer cells to chemical agents and may therefore be considered as a potential delivery system to boost therapeutic protocols for cancer patients.

Zhang J et al.¹³ developed a curcumin phytosome loaded chitosan microspheres (Cur-PS-CMs) by encapsulating curcumin phytosomes (Cur-PSs) in chitosan microspheres using ionotropic gelation and reported that the new Cur-PS-CMs system combined the benefits of chitosan microspheres and phytosomes, that had higher effects of promoting oral absorption and prolonging retention time of curcumin than single Cur-PSs or Cur-CMs. Therefore, the PS-CMs may be used as a sustained delivery system for lipophilic compounds with poor water solubility and low oral bioavailability.

Yiran Ma et al.²¹ prepared completely different formulations like daidzein-loaded PLGA nanoparticles, daidzein-loaded phospholipid complexes PLGA nanoparticles and daidzein-loaded cyclodextrin inclusion complexes PLGA nanoparticles and reported that the oral administration of daidzein-loaded phospholipid complexes PLGA nanoparticles and daidzein - loaded cyclodextrin inclusion complexes PLGA nanoparticles to rats, relative bioavailability increased, compared to daidzein suspension as control by pharmacokinetic studies. These results describe an efficient strategy for oral delivery of daidzein-loaded PLGA nanoparticles and may offer a recent approach to enhancing the bioavailability of drugs with poor lipophilic and poor hydrophilic properties.

Keyong Xu et al.²² prepared luteolin - phospholipid complex and reported that luteolin and phospholipid within the complex joined by non-covalent-bonds and didn't form a new compound. They advised that the complex has an efficient scavenger of DPPH radicals and powerful inhibitor activity within the Rancimat antioxidant test using animal oil as substrate.

Solmaz Rasaie et al.²³ prepared Quercetin-loaded nano phytosomes by using phosphatidylcholine (PC) and cholesterol (CH) and reported that Nano phytosomal formulation of Quercetin: PC: CH molar ratio of 1: 2: 0.2 has promising potential in fortification of food products with water insoluble antioxidants.

Zhenqing Hou et al.²⁴ developed phytosomes loaded with mitomycin C-Soybean phosphatidylcholine (MMC-SPC) complex (MMC-loaded phytosomes) by a solvent evaporation method combined with a nano precipitation technique for the aim of development of an MMC drug delivery system and discovered that *In vitro* drug release profiles indicated biphasic behavior with an initial burst release, followed by a subsequent prolonged sustained release. *In vitro* cytotoxicity assays with H₂₂ cells showed that the MMC-loaded phytosomes had exceptional cytotoxicity. *In vivo* antitumor effect of the MMC-loaded phytosomes additionally discovered a dose-dependent

and superior curative inhibitory effect on tumour growth without loss of body weight compared to free MMC. Histopathological analysis of specimens taken from tumour tissues indicated that MMC-loaded phytosomes had deadly effect to hepato cellular carcinoma cell. They also advised that the MMC-loaded phytosomes can serve as a promising and effective formulation for drug delivery and cancer therapy.

THERAPEUTIC USES OF PHYTOSOMES LOADED DRUG DELIVERY

There are various therapeutic uses of phytosomes loaded are explored in Figure 6 to examine the various benefits of phytosomes, particularly their ability to boost the bioavailability of phytoconstituents or plant extracts. Some application of phytosomes, their active constituents, daily dose and specific indications are given in Table 3.

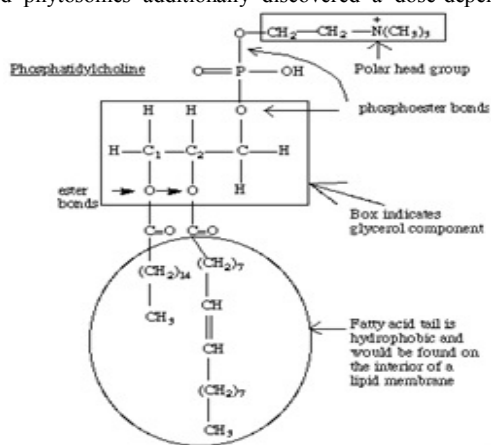


Figure 1: Structure of phosphatidylcholine

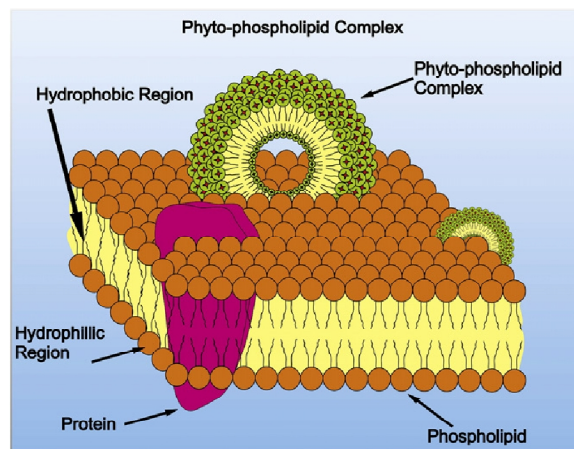


Figure 2: Mechanism of a Phytosome loaded

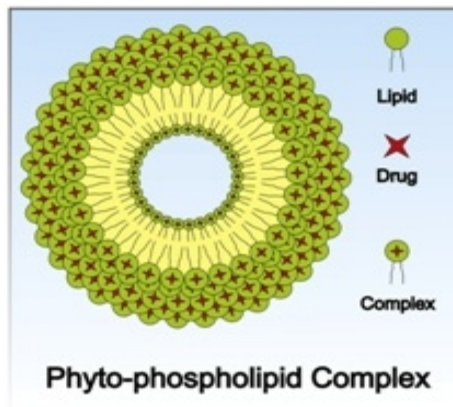


Figure 3: Structure of a Phytosome Loaded

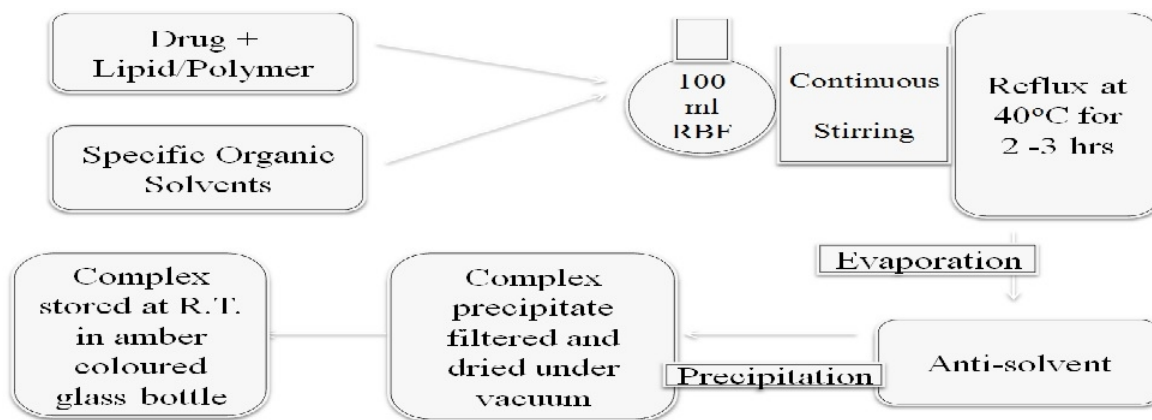


Figure 4: Common steps for Preparation of Phytosome loaded

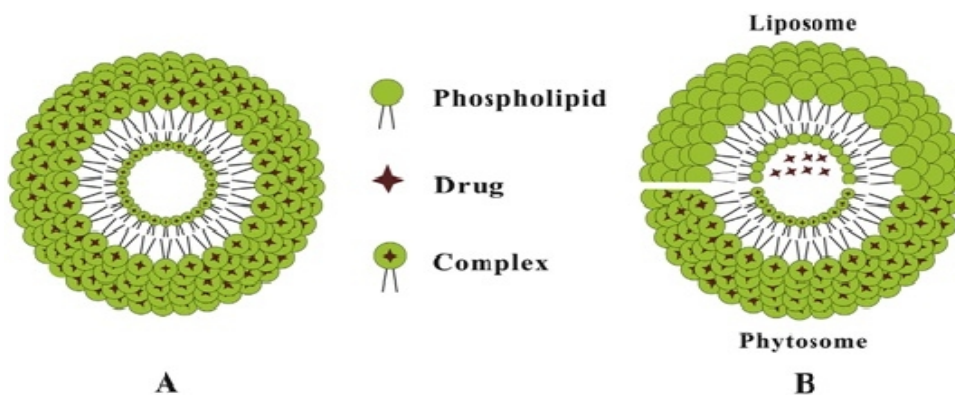


Figure 5: Difference between phytosome and liposome

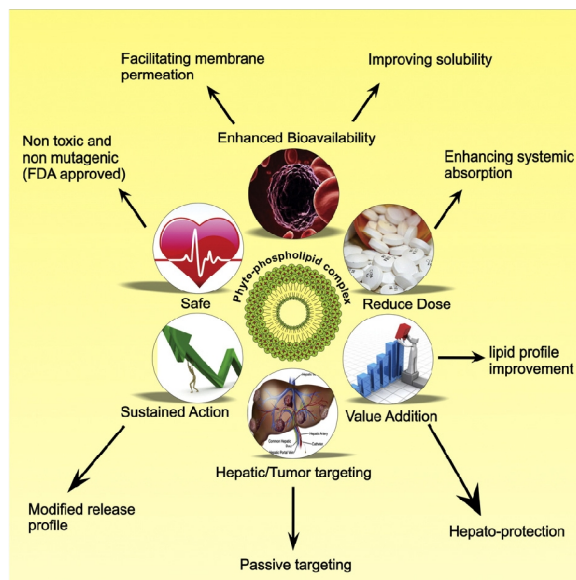


Figure 6: Therapeutic uses of Phytosome loaded

Table 1: Difference between phytosome and liposome

Sr. No	Features	Phytosome	Liposome
1.	Layer of phospholipids	In phytosomes, the active principle is often compared to an integral part of the lipid membrane.	In liposome, hundreds or perhaps thousands of phospholipids and therefore the individual plant parts really from a 1:1 or a 2:1 complex counting on the substance.
2.	Layer of membrane	In phytosomes, it's an integral part of the membrane, being the molecules anchored through chemical bonds to the polar head of the phospholipids	In liposomes, the active principle is dissolved within the medium contained within the cavity or within the layers of the membrane
3.	Content of phospholipids	Less higher	much higher
4.	Absorbance profile	Better absorbed	Good absorbed

Table 2: Summary of Benefits of Phytosome loaded drug delivery

Sr. No	Drug used for Phytosome load	Polymer used for Phytosome load	References
1	Silymarin, Curcumin, Green tea and grape seed	---	Kidd et al. ¹⁷
2	Rutin	---	Malay et al. ¹⁸
3	Mitomycin	PEG	Yang Li et al. ¹⁹
4	Lutolin	---	Mehdi et al. ²⁰
5	Curcumin	Chitosan	Zhang J et al. ¹³
6	Daidzein	PLGA, Cyclodextrin	Yiran Ma et al. ²¹
7	Lutolin	---	Keyong Xu et al. ²²
8	Quercetin	Cholesterol	Solmaz Rasaie et al. ²³
9	Mitomycin	---	Zhenqing Hou et al. ²⁴

Table 3: Therapeutic uses of phytosomes loaded with dose

Sr. No	Trade Name	Phytoconstituents complex	Daily Dose (mg)	Indications
1	Silybin phytosome	Silybin from <i>Silibium marianum</i>	120	Hepatoprotective, Antioxidant
2	Silyphos milk thistle	Silybin from <i>Silibium marianum</i>	150	Antioxidant, Hepatoprotective
3	Grape seed phytosome	Procyanidins from <i>vitis vinifera</i>	50-300	Antioxidant, Anticancer
4	Ginseng phytosome	Ginsenosides from <i>panax ginseng</i>	150	Immunomodulator
5	Hawthorn phytosome	Flavonoids from <i>crataegus species</i>	100	Antihypertensive, Cardioprotective
6	Ginko phytosome	Flavonoids from <i>Ginko biloba</i>	120	Anti aging, Protects Brain & Vascular lining
7	Olea phytosome	Polyphenols from <i>Oleauropea</i>	120	Anti-hyperlipidemic, Anti-inflammatory
8	Green phytosome	Epigallocatechin from <i>Thea sinensis</i>	50-300	Anti-Cancer, Antioxidant
9	Bilberry (Mertoselect) phytosome	Anthocyanosides from <i>Vaccinium myrtillus</i>	-	Antioxidant, Improvement of Capillary Tone
10	Centella phytosome	Terpens from <i>Centella Asiatic</i>	-	Brain tonic, Vein and Skin Disorder
11	Glycyrrhiza phytosome	18-β glycyrrhetic acid from <i>Glycyrrhiza glabra</i>	-	Anti-inflammatory, Soothing
12	Melilotus phytosome	Triterpens from <i>Melilotus officinalis</i>	-	Hypotensive, Indicated in Insomnia
13	Curcumin phytosomes	Polyphenol from <i>Curcuma longa</i>	200-300	Cancer Chemo preventive Agent
14	PA ₂ phytosome	Proanthocyanidin A2 from horse <i>Chestnut bark</i>	-	Anti-Wrinkles, UV protectant
15	Escin β sitosterol phytosome	Escin β-sitosterol from horse <i>Chestnut fruit</i>	-	Anti-Odema

CONCLUSION

The novel drug delivery system research area for herbal drugs is an innovative work that target for phyto-constituents and plant extracts regarding from the usefulness of plant product particularly that containing flavonoids and alternative poly phenolic resin compounds. The phytosome loaded preparation methods can be easily upgraded for commercial scale and has offered an excellent chance and hope in raising the in vivo bioavailability of herbal drugs that in spite of positive in vitro results have did not deliver the same response in vivo. Phytosome loading not only reduce the continual administration to beat noncompliance, but also facilitate to extend the therapeutic value by reducing toxicity and increasing the

bioavailability and so on. The polyphenolic constituents of plants like flavones et al. have immense therapeutic potential however because of their inability to cross lipid barrier their utilization in treatment of severe diseases like cancer, hepatic diseases and rheumatic conditions has remained an unresolved apprehension for quite a substantial period of time. The evaluation methodologies and analytical techniques are well established for this type of novel formulation. Several patents and marketed formulations are already approved for innovative formulations, processes and applications of phytosomes. As far as the benefits of phytosome technology are concerned, it's a great future for use in formulation technology and applications of hydrophilic plant compounds or extracts.

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