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A JOURNEY OF PHYTOSOMES IN THE PHARMACEUTICAL WORLD

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ABSTRACT

Traditional sciences of medicines around the globe like Indian, Chinese, African have a huge potential and more natural ways for the treatment of diseases with the healing touch of mother nature and this fact is being proven by new researches in the field of herbal medicines. But the drug delivery system followed by these alternative sciences is outdated and can be improvised greatly using modern and scientific methods. Advancements have been made successfully for the improvising of drug delivery systems which generally focus on overcoming the shortcomings of conventional dosage forms like deficit lipid solubility, large molecular size, and degradation in the gastric environment of the gut, poor stability, low lipid solubility, which directly or indirectly affects the efficiency of the drug. Novel drug delivery system aids by making a drug therapeutically more efficacious and safe in comparison to already existing drug delivery systems. Phytosomes are one such novel drug delivery vehicle. The phytosomes technology has been successfully applied on many herbal drugs like curcumin, green tea, milk thistle, grape seeds etc. In this review, an attempt has been made to gather all the updated information and underscore the advantages, disadvantages, structure, characterization, methods of preparation, recent advancements pertaining to phytosomes.

Keywords: Novel drug delivery system, Dosage form, Phytosomes, Phospholipid

INTRODUCTION

Herbal medicines have been utilized as cure to various ailments since time immemorial as in Traditional systems like Ayurveda, Traditional chinese medicines, Japanese traditional medicines, Unani medicines, Siddha system that makes use of natural herbs but the drug delivery used for their administration to the patients remained antiquated leading to sub-therapeutic efficacy of the drug in treatment of disorder **[1]**. Due to limitations of conventional drug delivery systems with regards to bioavailability, the need for novel drug delivery systems arose. Advancements have been made successfully for improvising the novel drug delivery system which generally focus on overcoming the shortcomings of conventional dosage forms like deficit lipid solubility, large molecular size, and degradation in the gastric environment, poor stability, low lipid solubility, which directly or indirectly affects the efficiency of the drug. The effectiveness of any herbal medication is also dependent on the delivery of active compounds at therapeutically effective levels **[2-4]**. So, novel drug delivery systems are invented to improvise delivery and bioavailability of herbal or plant based medicines.

Herbal medicines are regaining the momentum and popularity for treatment of diseases and disorders. But the issue with this is that herbal extracts perform excellently in vitro but not in in-vivo studies for which the probable reason may be that most of the biologically active constituents of plants (flavonoids, tannins, glycosidic aglycones etc.) are polar or water soluble so are poorly absorbed by the biological membrane due to poor lipid solubility **[5]**. Another reason can be inability to passively diffuse across the membrane due to large molecular size resulting in poor bioavailability. To tackle this bioavailability issue, a novel drug delivery system came into existence. Apart from Liposomes, Micelles, Nanoparticles, Nanoemulsions, Microspheres etc. Phyto-somes have emerged to achieve targeted and controlled drug delivery. Phytosomes are more bioavailable and effective than the conventional dosage forms or extracts as shown by various in-vitro and in-vivo studies.

Phytosomes as the name suggests ‘Phyto’ means plants and some means ‘cell-like’. Phytosomes also known as herbosomes or plantersomes are biomimetic phospholipid complexes which are part of novel drug delivery systems but particularly belong to the domain of vesicular drug delivery systems (VDDS). VDDS is a micelle

consisting of a hydrophilic core and lipid bilayer outer shell **[6]**. Phytosomes was developed by an Italian drug and nutraceutical manufacturer, Indena S.p.A. These phospholipid complexes can be formulated in any form of viz. Capsules, chewable tablets, solutions, suspensions, emulsions, syrups, lotions, gels, creams, aqueous microdispersions, pills, granules, etc. Some examples of botanical extracts formulated with phytosomes technology are siliphos (silymarin and silybin), greenselect (green tea polyphenols), meriva (curcumin), casperome (Boswellia serrata), quercifit (quercetin) and vanguard (polyphenols of bergamot). Some marketed products formulated in the form of phytosomes are shown in **Table 1**.

Table 1: Marketed Products of Phytosome

S. No.	Product	Dosage form	Manufactured by
1.	Ginkgo Biloba phytosome	Capsules	Herbal Factors
2.	Greenselect Phytosome	Capsules	Hellenia
3.	Hawthorn phytosome	Capsules	Swanson ultra
4.	Meriva	Capsules	Jarrow formulas
5.	Siliphos phytosome	Capsules	Natural Factors
6.	Gotu kola phytosome	Capsules	Swanson Ultra
7.	Quercetin phytosome	Capsules	Thorne
8.	Grape Seed phytosome	Capsules	Herbal Factors
9.	Lymphaselect	Dry extract	Indena
10.	Ultra Thistle	Capsules	Natural Wellness

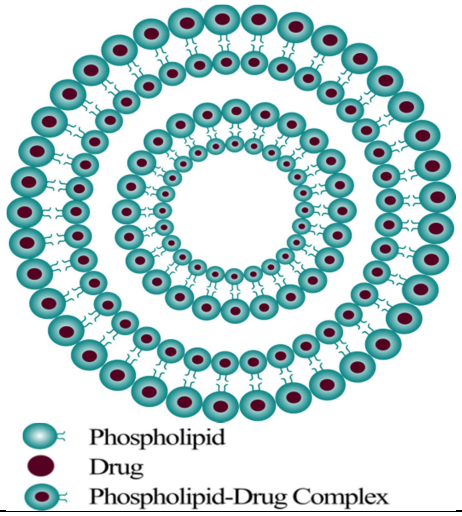
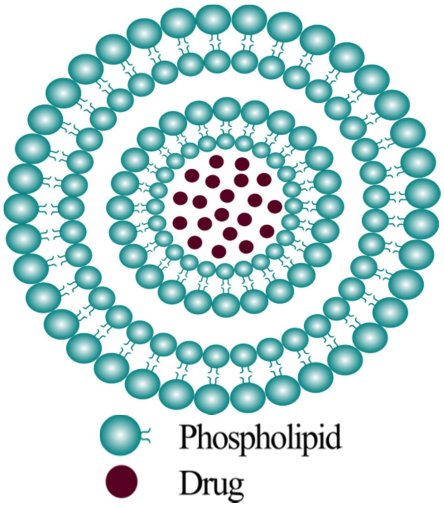
COMPONENTS OF PHYTOSOMES

Phytosomes structurally resemble a little cell. Phytosomes are lipid complexes between natural moieties (active phytoconstituents) and the phospholipids complex formed is called phyto phospholipid complex. Phospholipids can be obtained naturally or can be industrially prepared and can be classified depending upon the backbone into glycerophospholipids (phosphatidylcholine, phosphatidylethanolamine, phosphatidyl-serine, phosphatidic acid) with glycerol back-bone and sphingomyelin with sphingosine backbone **[7]**.

The phospholipid-phytoconstituent interacts due to the hydrogen bond between the OH group on hydrophilic moiety with the phospholipid group as the results of molecular docking performed by Yiqiong Pu *et al*. showed **[8]**. Phosphatidylcholine (PC) which is the principal molecular building block for cell membranes is an amphiphilic compound. The tail part i.e, phosphatidyl moiety is lipophilic that encapsulates the hydrophilic part of the complex thus providing hydrophobic surface whereas choline moiety is hydrophilic in nature that bind to the active phytoconstituent **[9]**.

It is similar to liposomes but not exactly the same as differentiated in **Table 2**.

Table 2: Comparison of Phytosomes With Liposomes

S. No.	Parameter	Phytosomes	Liposomes
1.	Diagram		
1.	1. Drug entrapped	2. Phytoconstituent is entrapped in 3. the lipid membrane of somes	4. Phytoconstituent is entrapped in the core 5. of somes
2.	6. Chemical Bond	7. Hydrogen bond is formed between 8. Pc and phytoconstituent	9. No chemical bond is formed between pc and active phytoconstituent
3.	Bioavailability	Better absorption and bioavailability	Lesser absorption and Lesser bioavailability
4.	Size	Smaller than liposomes	Much bigger than phytosomes
5.	Bond	The active ingredient is linked to the PC by hydrogen bond	No chemical bond is formed
6.	Stability	More stable due to hydrogen bond	Less stable
7.	Skin penetration	Better skin penetration	Less skin penetration
8.	Drug encapsulation	Higher drug encapsulation efficacy	Lesser drug encapsulation efficacy

Advantages of phytosomes over conventional drug delivery system: [10-12]

1. Enhanced bioavailability and cellular uptake. The probable reason can be due to increased permeability of phytoconstituents across the biological membranes.
2. Increased therapeutic effect due to enhanced bioavailability.
3. Phosphatidylcholine which is the building block of phytosome is hepatoprotective thus providing synergistic effect for liver protection.
4. Due to better transdermal absorption they can also be used on transdermal dermal delivery of drugs.
5. Phosphatidylcholine besides acting as a carrier also functions as a nourishment factor for skin as it's a significant constituent of cell membrane.
6. They are more stable than conventional dosage forms like free extracts.
7. The phyto-phospholipid complex formed is biodegradable so the drug

entrapment is not an obstacle in drug release.

8. Due to better transdermal absorption and skin penetration they can be successfully used in cosmetic products.
9. Dose requirement is minimized due to improved absorption of the principal constituent implying that they can also be administered in small quantities to achieve the desired results.
10. The drug is gastro protected i.e shielded from degradation by digestive secretions and bacteria in the gut, thus delivery of the drug to the tissues is assured.
11. Better dissolution than conventional dosage forms.
12. Drug release can be regulated.
13. Simple preparatory technique and novel methods are inexpensive too.
14. They can be formulated into any form like tablets, capsules, suspension, emulsions, creams depending on the use of drugs to be formulated into phytosomes.

Disadvantages of phytosomes: [13]

1. In phytosomes, the phytoconstituents sometimes get eliminated rapidly due to RES.
2. Drug seepage is another problem with phytosomes but this can be curbed with covalent linkage.
3. Short half life is one of the major drawbacks.
4. High chances of hydrolysis, fusion, and oxidation of phospholipid.
5. Allergic reactions may be caused due to the constituents of phytosomes.
6. In case of larger size of phytosome problems in targeting various tissues may arise.

METHODS OF PHYTOSOMES PREPARATION

There are many ways to prepare phytosomes and several new techniques have emerged for the same. Many researchers have employed these methods of preparation as shown in **Table 3** and following are the flow charts for the general methods of phytosome preparation:

1. Solvent evaporation technique
2. Anti-solvent precipitation process
3. Rotary evaporation process
4. Solvent ether injection
5. Co-grinding
6. Mechanical dispersion method
7. Novel methods

Solvent evaporation technique: [14]

Take Standardized phospholipid and drug in a round bottom flask(RBF) containing solvent

↓

Reflux with solvent (acetone 20ml) at temperature between 50-60°C for a specific interval of time to achieve highest drug entrapment.

↓

Solvent is evaporated using rotary evaporator

↓

Dried residues are obtained and stored in desiccator for24 hrs

↓

Store the phytosomes obtained in amber coloured glass bottle

Anti-solvent precipitation process: [15]

Specific amounts of phospholipid and phytoconstituent are taken in a (RBF) and reflux with dichloromethane (20ml) at temperature not more than 60°C.

↓

Mixture is allowed to concentrate to 5-10ml ie evaporation to 5-10ml is allowed

↓

Then with continuous stirring 20ml of anti-solvent like hexane is added to salt out the complex formed

↓

which is later filtered out and stored in an amber colored glass

Rotary evaporation process:

The phytoconstituent and phospholipid are taken and dissolved in tetrahydrofuran in a rotary RBF.

↓

Stirring is done continuously for 3 hrs at a temperature not more than 40°C.

↓

N-hexane is added to the Thin film of the sample obtained.

↓

Stirring is done using a magnetic stirrer which will give precipitates.

Solvent ether-injection process: [16]

React plant extract with lipids dissolved in organic solvent.

↓

Gradually inject Phospholipid solubilised in diethyl ether in aqueous solution of phytoconstituent

↓

Vesicles will be formed(shape depends upon the concentration)

Structure of phytosomes depends upon concentration, amphiphiles in mono state are produced when the concentration is less, but a variety of structures with different shapes viz. round, cylindrical, disc and cubic or hexagonal vesicles may be formed on increasing the concentration.

Co-grinding: [17]

Drug and phospholipid are kneaded together with mechanical forces in mortar and pestle for some time

↓

The resulting powder is dissolved in mixture of 90ml anhydrous ethanol and 40ml acetone

↓

Reflux at 40 degree for 24 hrs

↓

Remaining solvent evaporated

↓

The ppts are formed are collected and stored

Mechanical dispersion method: [18]

PC is dissolved in ether in a beaker and subjected to sonication

↓

Active drug constituent dissolved in distilled water is added drop wise into

The beaker while sonicating for some duration of time

↓

The resulting complex formed is stored in refrigerator

Novel methods:

Novel methods for the phytosome preparation include supercritical fluids which include Gas solvent technique, Compressed solvent process and Supercritical solvent method, Electroformation using copper electrodes **[19, 20]**.

Table 3: Phytosomes Prepared in Various Researches With Method of Preparation

S. No.	Phytosome	Complex formed	Method employed	Reference
1.	Milk thistle phytosome	Silybin and phosphatidylcholine complex	Solvent evaporation method	21
2.	Rutin phytosome	Rutin and phosphatidylcholine complex	Solvent evaporation method	22
3.	Evodia rutaecarpa phytosome	Evodiamine and phospholipid complex	Solvent evaporation method	23
4.	Umbelliferone phytosome	Umbelliferone and phospholipid complex	Anti-solvent precipitation method	24
5.	Aloevera phytosome	Aloe Vera extract and lecithin complex	Thin layer hydration method	25
6.	Gingerol phytosome	Gingerol and soya lecithin complex	Antisolvent precipitation method	26
7.	Lawsone phytosome	Lawsone and soya lecithin complex	Antisolvent precipitation method	27
8.	Mitomycin-C phytosome	Mitomycin-C and phosphatidylcholine complex	Solvent evaporation method	28
9.	Quercetin phytosome	Quercetin and phosphatidylcholine complex	Thin layer hydration method	29
10.	Berberine phytosome	Berberine and phosphatidylcholine complex	Solvent evaporation method	30
11.	Chrysin phytosome	Chrysin and egg phospholipid complex	Solvent evaporation method	31

CHARACTERIZATION OF PHYTOSOMES: [32-34]

Visualization: TEM (Transmission electron microscopy) and SEM (Scanning electron microscopy) can be performed for evaluating the surface morphology and to get details of internal composition from which many attributes of the phytosomes such as stress or magnetic domains, crystallization can be determined.

Complex size: For this optical image analysis, Coulter counter, Scanning electron microscopy, Dynamic light scattering technique, Laser diffraction, Photon correlation spectroscopy, Cascade impactor, Time of flight are some of the techniques by which size can be evaluated.

Shape and aggregation of Phytosome: This can be visualized using Transmission electron microscopy.

Melting point and freezing point: The freezing point of the phytosomes considerably vary from that of the individual phytoconstituents and also the lipids due to variation in the bonds and linkages.

Zeta potential: This is a crucial factor in case of phytosomes because nano-systems are susceptible to rapid clearance from blood

stream thus rendering the drug consumption of no use. Here surface charge modifications can be done in case of phytosomes for achieving desired therapeutic effect. This parameter can be checked using dynamic light scattering (DLC) and Photon correlation spectroscopy.

Percent yield: This can be calculated after drying the product formed using formula

$$\text{Percent yield} = \frac{\text{Weight of phytosome formed}}{\text{Weight of drug + Nonvolatile excipient}} \times 100$$

Entrapment efficiency: The entrapment efficiency i.e. capacity of the drug to get entrapped in phytosomes can be measured by Ultracentrifugation technique and then measurement of free drugs by UV-Vis spectroscopy can be done. It gauges the percentage of drug that is successfully entrapped into the phytosomes using the formula

$$\text{Entrapment efficiency} = \frac{\text{Amount of total drug - Free drug}}{\text{Total amount of drug}} \times 100$$

Transition temperature: This can be measured using differential scanning calorimetry.

Surface tension: Tensiometers can be used to measure the surface activity of the formulation.

Vesicle stability: This can be determined by monitoring structural changes over time using TEM.

Drug content: The actual quantity of drug can be measured by a modified high performance liquid chromatographic method or by a suitable spectroscopic method like UV Spectrophotometry.

Moisture content: This can be measured by placing the drug on the moisture balance analyzer.

Dissolution: Many factors contribute towards the dissolution of the solid like; wettability, surface energies and area, crystal habit, particle size. The wetting and dispersion action of the phospholipids contribute towards the higher solubilization of the drug which directly enhances the efficacy of the formulation. This attribute can be evaluated using Dissolution apparatus.

pH: In case the phytosomes is formulated in the form of gels or emulsions pH is another parameter that has to be analysed.

Uniformity and spreadability: This is done in case phytosome preparation is formulated for topical applications.

In-vitro drug release: For this Dialysis bag technique can be used. With Franz diffusion chamber the drug release can be gauged.

Polydispersity index: This can be quantified using photon correlation spectroscopy with zeta seizer at 25°C.

Retention factor: Thin layer chromatography is done to check if the retention factor.

SPECTROSCOPIC EVALUATIONS: [35]

Intermolecular interactions are studies using spectroscopic techniques

H NMR/C NMR: The complex formation between active phytoconstituents and phosphatidylcholine molecules can be estimated by this method. This measures the physical properties at the molecular level by observing the signal peaks obtained of each of the free constituents and the phospholipid complex and analysing changes in chemical shifts and shape in the spectra of phytosomes. Usually complex formation and interactions are associated with some characteristic signals like changes in chemical shift and line broadening in NMR spectra.

FTIR: Fourier transform infrared spectroscopy is done to investigate the intermolecular interactions between phosphatidylcholine and active ingredients. It can be used to verify the drug phospholipid complex formation by comparing the spectrum of the complex with that of each component and their physical mixtures.

PNMR: this can be performed on phytosomes to get information about lipid bilayer.

IR: complex formation and interactions is associated with some characteristic signals like the appearance of new bands in IR spectra. Oh upar wala bhi dekh

XRD: This can be used to check the microstructure of amorphous or crystalline material. It can also verify the drug-phospholipid Complex formation since PC Complexes don't give crystalline peaks

DSC: In Differential scanning spectroscopy, interactions can be studied by appearance of new peaks and disappearance of original peaks, change is relative peak area.

In-vivo evaluations:

1. Models of in-vivo evaluations are chosen and the phytosome preparation is administered to check its safety. The clinical signs of animals are examined for ataxia, hypothermia, tachypnoea, seizure, dyspnoea, dehydration, lack of movement, rapid movement around the cage etc. Further blood and urine tests are also done to check the effects of drugs.

RECENT ADVANCEMENTS:

ICA phytosome against ovarian cancer: Nabil *et al*. 2020 showed that ICA

phytosomes enhance the cytotoxic activity of ICAR against OVCAR-3 ovarian cancer cells. Thus proving that formulating a drug into phytosomes increases the bioavailability of that drug **[36]**.

Thymoquinone phytosome against lung cancer: Thymoquinone phytosome improved performance of thymoquinone against A549 Cells by causing 3 folds increase in cytotoxicity of thymoquinone in comparison with free thymoquinone treated cells thus proving that the phytosome delivery would be a promising nanocarrier for delivering cytotoxic drugs against lung cancer **[37]**.

Topical Anti-obesity formulation: phytosome of soybean prepared using solvent evaporation, co-solvency and salting out followed by its incorporation into thermogel showed local anti-obesity effect in male albino rats **[38]**.

Antioxidant phytosome preparation: Phytosome of *Diospyros kaki* L. (fruit) extract's phytosome prepared by encapsulating 97.4% of total phenolics exhibited higher antioxidant activity. Further, the decay rate of antioxidant activity shown by 1:1 and 1:2 loaded phytosome was respectively, 4 and 6 times lower of the antioxidant activity than that of free extract indicating that formulating the drug in phytosome technology helps to retain the function for longer duration as compared to conventional dosage forms **[39]**.

Anti-diabetic phytosomes: phytosomes prepared with extracts of *Citrullus colocynthis*, *Momordica balsamina* and *Momordica dioica* showed antidiabetic effect in low doses comparable to metformin **[40]**. Another study by Van Kudri *et al* 2016 studied the antidiabetic effect of Rutin Phytosomes in comparison to pure rutin showed that rutin phytosomes showed better therapeutic efficacy than pure rutin **[41]**.

Enhanced actions of umbelliferone phytosome: Umbelliferone phytosome showed better solubility in water and oil phase, better permeation, better anti-oxidant activity and better photoprotective activity when compared to free umbelliferone **[42]**.

Ocular delivery of phytosome preparation: L-carnosine phytosome was prepared for ocular delivery with hyaluronic acid and phospholipid using solvent evaporation method which showed that there was improvement in spreading capacity sustained infusion, rheological and tolerability features for successful delivery of drug **[43]**.

CONCLUSIONS

Phospholipids complex strategy is an excellent milestone in the field of novel drug delivery systems and has huge potential to

overcome the drawbacks of conventional dosage forms and make the herbal extracts therapeutically more effective. So more research in this domain, especially for development of medications using this technology for curing diseases and disorders like Cancer, Diabetes, cardiovascular disorder etc. is advocated.

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