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Phytosomal Drug Delivery System A Novel Approach To Enhance Bioavailability: A Review

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Abstract : Novel drug delivery system is a novel approach to drug delivery that addresses the limitations of the traditional drug delivery systems. Our country has a vast knowledge base of ayurveda whose potential is only being realized in the recent years. The effectiveness of any herbal medication is dependent on the delivery of effective level of the therapeutically active compound. Severe limitation exists in their bioavailability when administered orally or topically. Phytosomes are recently introduced herbal formulations that are better absorbed and as a result produce better bioavailability and actions than the conventional phyto-molecules or botanical extracts. In the recent days, most of the prevailing diseases and nutritional disorders are treated with natural medicines. Several plant extracts and phytoconstituents, despite having excellent bioactivity 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 bioavailability. So, much work has been directed towards the development of new concept in herbal delivery system i.e.,"phytosomes". The term 'phyto' means plant while 'some' means cell-like. Phytosomes are little cell-like structure. The present review highlights the method of Preparation, properties, advantages, characterization, applications of phytosomes and highlights key findings of recent research work conducted on phytosomes with our own viewpoints which can give the new directions and advancements to herbal dosage forms and the technical aspects of phyto-phospholipid formulations to face the future challenges.

Index Terms: *Phytosomes, Phospholipid, Phosphatydilcholine, Bioavailability*

I. INTRODUCTION

Most of the biologically active constituents of plants are polar or water soluble but due to the problem in iiabsorption,restricts the utilization of these type of compounds which ultimately decreases the bioavailability. For improvement of bioavailability, herbal products must have proper homeostasis between hydrophilic (for absorption into gastrointestinal tract fluid) and lipophilic (to cross lipid biomembrane balance) Plant preparations are widely used in traditional as well as modern medicine system. During the traditional time, various pharmacological studies have been carried out with many plants extracts and their constituents to check their therapeutic application. Over the past year, great advancement has been made for the development of novel drug delivery system (NDDS) for various plant extracts and their active constituents(Mahadev B. Khanzode et al., 2020).

Novel drug delivery system is a novel approach to drug delivery that addresses the limitations of the traditional drug delivery systems(Gaikwad et al., 2021).If the novel drug delivery technology is applied in herbal medicine, it may help in increasing the efficacy and reducing the side effects of various herbal compounds and des Novel herbal formulations like nanoparticherbs. This is the basic idea behind incorporating novel method of drug delivery in herbal medicines. It inclules, nanocapsule, phytosomes, niosomes, transferosomes, Ethosomes, proniosomes having remarkable advantage Over traditional plant extracts including solubility Enhancement, bioavailability improvement, targeted Delivery, sustained effect etc. Herbal drug delivery uses various formulation technology to improve drug absorption and provide better efficacy than conventional plant extract(Singh et al., 2011). To enhance the bioavailability of drug by formulating them to target drug delivery system such as phytosomes and liposomes are good options. Phytosomes means herbal drug loaded in vesicles, which is available in the Nano form(Mahadev B. Khanzode et al., 2020).

The Phytosome technology, developed by Indena S.P.A. of Italy. Phytosome is a patented technology Including, to incorporate standardized plant extracts or water soluble phytoconstituents into phospholipids to produce lipid compatible molecular complexes. The phytosomes process produces a little cell because of that the valuable components of the herbal extract are protected from destruction by nodigestive secretions and gut bacteria. Phytosomes are better able to transition from a hydrophilic environment into the lipid-friendly environment of the enterocyte cell membrane and from there into the cell finally reaching the blood(Dhase & Saboo, 2015). Phytosomes have improved pharmacokinetic and pharmacological parameter which in result can advantageously be used in the treatment of the acute and chronic liver disease of toxic metabolic or infective origin or of degenerative nature. It can also be used in antiinflammatory activity as well as in pharmaceutical and cosmetic compositions(Gandhi et al., 2012).

The phytosome technology characterisation:

Phytosome technology had improved the absorption and bioavailability of selected Phytoconstituents, by incorporating phospholipids into standardized plant extracts(Sravanthi & Pradesh, 2013). Phytosomes form a bridge between conventional delivery system and novel Delivery system and is also called as phytolipid delivery system. The word "phyto" means plant and "some" means cell-like.Phytosomes are created when the individual of an herbal extract are bound to Phosphatidylcholine (an emulsifying compound derived from soy)(Basis & Erectile, 2015).

1. Phytosomes are lipophilic substances with a definite melting point, freely soluble in non-polar solvents, and moderately soluble in fats(Arsul, 2014).
2. The flavonoid and terpenoid constituents of plant extracts lend themselves quite well for the direct binding to phosphatidylcholine. Phytosomes results from the reaction of stoichiometric amount of the phospholipid (phosphatidylcholine) with the standardized extract or polyphenolic constituents (like simple flavonoids) in a non polar solvent(A. B. Kumar et al., 2016).
3. Phospholipids are lipids that contain phosphorus, Phospholipids are amphiphilic, meaning they have both hydrophilic(polar) and hydrophobic(non polar) components. Different phospholipids are used to construct vesicular systems. These are Classified into two types: a) Glycerophospholipid and b) sphingolipids.
4. Phosphatidylcholine (PC), Phosphatidylethanolamine (PE), Phosphatidylglycerol (PG), and Phosphatidylinositol (PI) are examples of glycerophospholipid. According to certain studies, PC is widely utilized for phytosome formation(Joseph et al., 2013).
5. Phosphatidylcholine (PC) is a phospholipid attached to a choline particle.
6. Phosphatidylcholine is a bifunctional compound, the phosphatidyl moiety being lipophilic and the choline moiety being hydrophilic in nature.Specifically the choline head of the phosphatidylcholine molecule binds to these compounds while the lipid soluble phosphatidyl portion comprising the body and tail which then envelopes the choline bound material. Hence, the phytoconstituents produce compatible molecular complex with phospholipids, also called as phyto-phospholipid complex(A. B. Kumar et al., 2016).

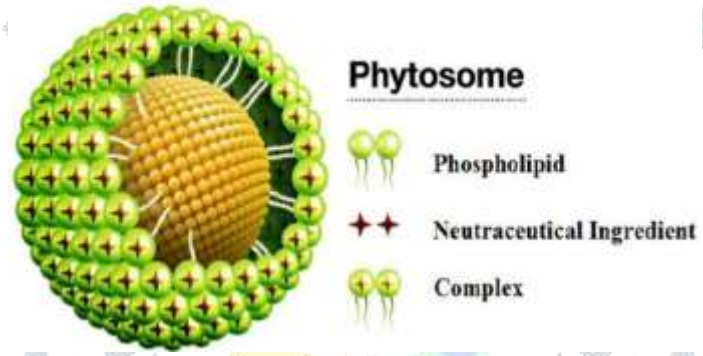


Figure 01: Diagramatic representation of phytosome

Advantages(Arsul, 2014; Gandhi et al., 2012; A. B. Kumar et al., 2016; Sravanthi & Pradesh, 2013)**:**

Phytosome have the following advantages -

1. It enhances the absorption of lipid insoluble polar phytoconstituents through oral as well as topical route showing better bioavailability, hence significantly greater therapeutic benefit.
2. Phosphatidylcholine used in preparation of phytosomes, besides acting as a carrier also acts as a Hepatoprotective, gives the synergistic effect.
3. Chemical bonds are formed between phosphatidylcholine molecule and phytoconstituent, So the phytosomes show better stability profile.
4. Phytosomes are widely used in cosmetics due to improved skin penetration and high lipid profile.
5. It assures proper delivery of drug the respective tissues.
6. Dose requirement has been reduced due to the maximum absorption of chief constituents.
7. Valuable components of herbal extracts are protected from destruction by digestive secretions and gut bacteria.
8. Marked enhancement in the bioavailability of drug occurs.
9. Phospholipids add to the nutritional value of the plant extract.
10. High market demand for products.
11. The process of manufacturing phytosomes is relatively simple.
12. Phytosomes have the ability to permeate through skin with quite ease and thus enhances their effectiveness.
13. Phytosomes are more useful than liposomes in skin care products.
14. Phytosomes have significantly greater clinical benefit.
15. The bioavailability of drug is enhanced remarkably.

Disadvantage(Basis & Erectile, 2015)**:**

1. Regardless of all advantages phytosome may rapidly exclude the phytoconstituent.
2. Phospholipids (lecithin) can encourage proliferation on MCF-7 breast cancer cell line.
3. Leaching of phytoconstituent.
4. Possibility of phospholipid oxygen and hydrolysis like reaction.

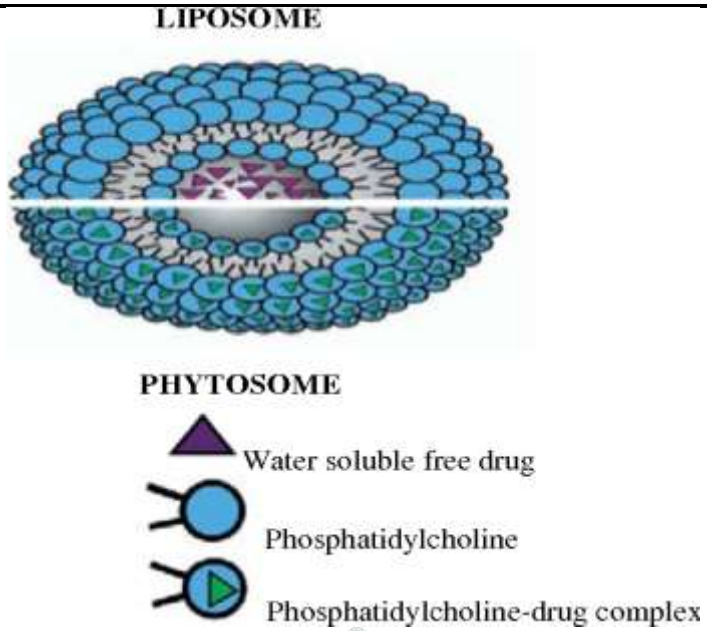


Figure 02: Structure of phytosome

Properties of Phytosomes: There are mainly 3 properties -

- **Physico-chemical properties** (Soman, 2020)-
  1. Phytosomes are prepared by reaction of stoichiometric amount of phospholipid with the phyto-constituents in an aprotic solvent.
  2. The size of phytosome varies from 50nm to a few 100 µm.
  3. Phytosome, when treated with water, assumes a micellar shape resembling liposome and photon correlation spectroscopy (PCS) reveals this liposomal structures acquired by phytosome.
  4. The H1NMR and C13NMR data deduced that the fatty chain gives unchanged signals both in free phospholipid and in the complex, which indicates that long aliphatic chains are protected around the active principle producing lipophilic envelope.
  5. The complexes are often freely soluble in aprotic solvents, moderately soluble in fats, insoluble in water and relatively unstable in alcohol. But the phytosomes of certain lipophilic phytoconstituents like Curcumin has shown increase in water solubility upon complexation with phospholipid.

1. **Biological properties-**(Soman, 2020; Sravanthi & Pradesh, 2013)
   1. Phytosomes are novel complexes that are better absorbed and utilized. Hence, they produce more bioavailability and better results than conventional herbal extract or noncomplex extracts, which has been demonstrated by Pharmacokinetic studies or by pharmacodynamic tests in experimental animals and in human subjects.
   2. has better pharmacokinetic as compare to simple herbal.

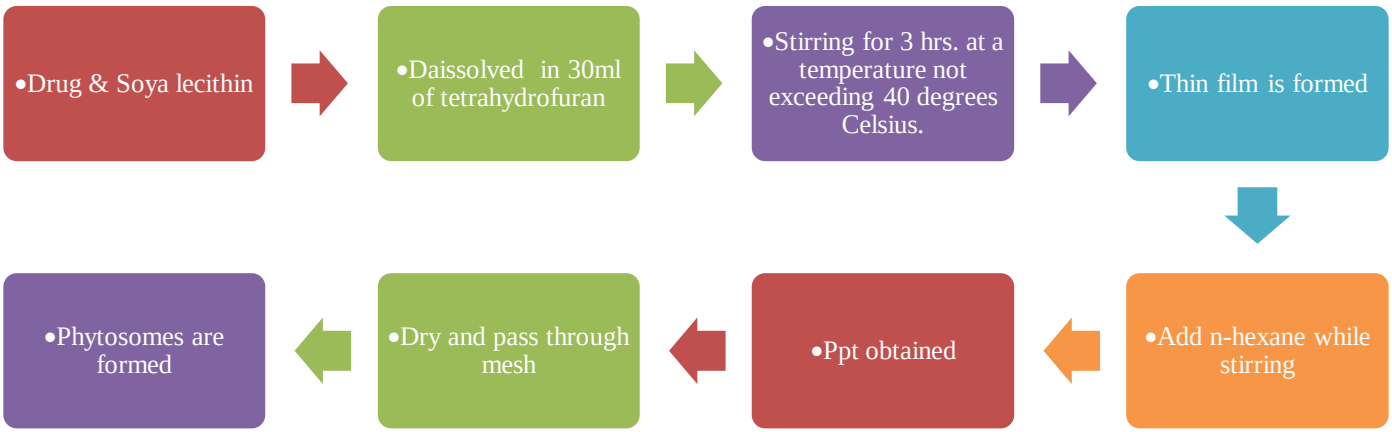
- **Pharmacological properties -**[6]
  1. Phytosomes are advanced and progressing novel drug delivery technology applicable for natural product which cause better absorption and exploit, as result exhibited preferable outcome over conventional herbal extracts.
  2. The extraordinary bioavailability of Phytosomes formulation over conventional herbal products have been demonstrated by pharmacokinetics and pharmacodynamics Experiments in human and animals.

Preparation Methods of phytosome -

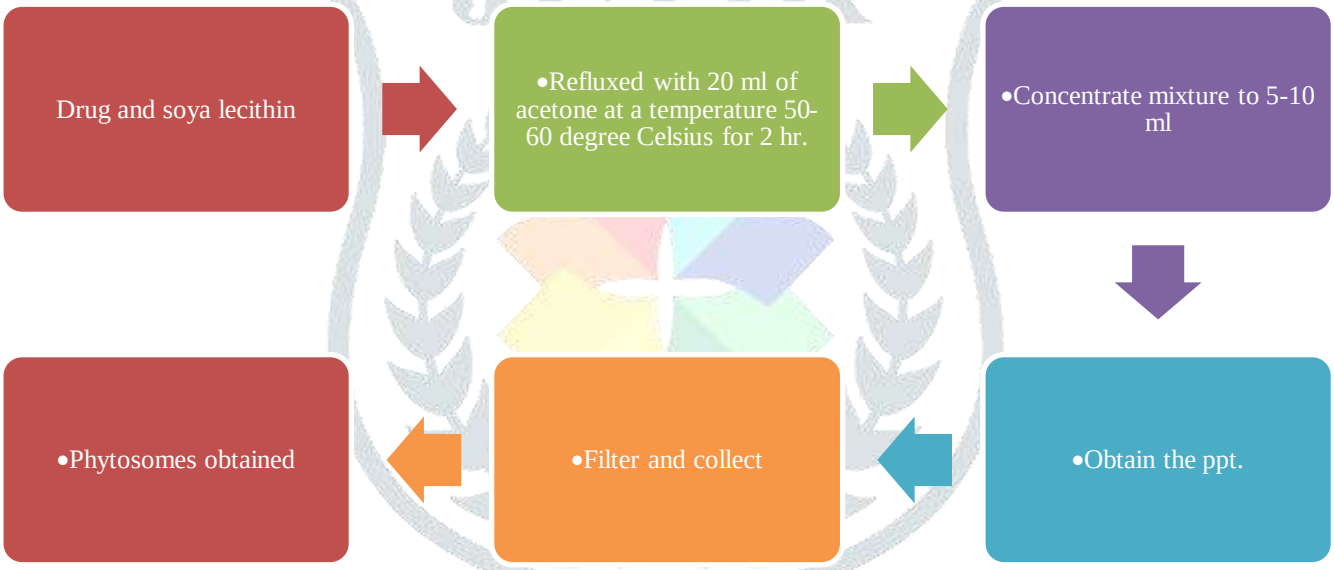
Generally in the preparation of Phytosomes, the phytoactive ingredients such as bioflavonoids, flavolignan and polyphenolic components are reacting drop by drop with a natural or synthetic solution of phospholipids like Phosphatidylcholine (PC) with continuous stirring. For this preparation, phospholipids choose from the different category, for example, Phosphatidyl, ethanolamine, phosphatidylcholine, soy lecithin, from cow-like or swine cerebrum or dermis, phosphatidylserine in which equal functional group might be same or differ and generally derived from palmitic, stearic, oleic and linoleic acid. The prepared Phytosomes will be isolated then by precipitation with non-solvents, for example, aliphatic hydrocarbons or by Lyophilization or by spray drying(Ingalhalli et al., 2019). Generally in the phytosome complexes the ratio between phytoconstituent and phospholipids are in the proportion 0.5-2.0 moles. The most Ideal proportion of phospholipid to flavonoids is [1:1](Sravanthi & Pradesh, 2013).

There are different methods involves in Phytosomes preparation as follows:

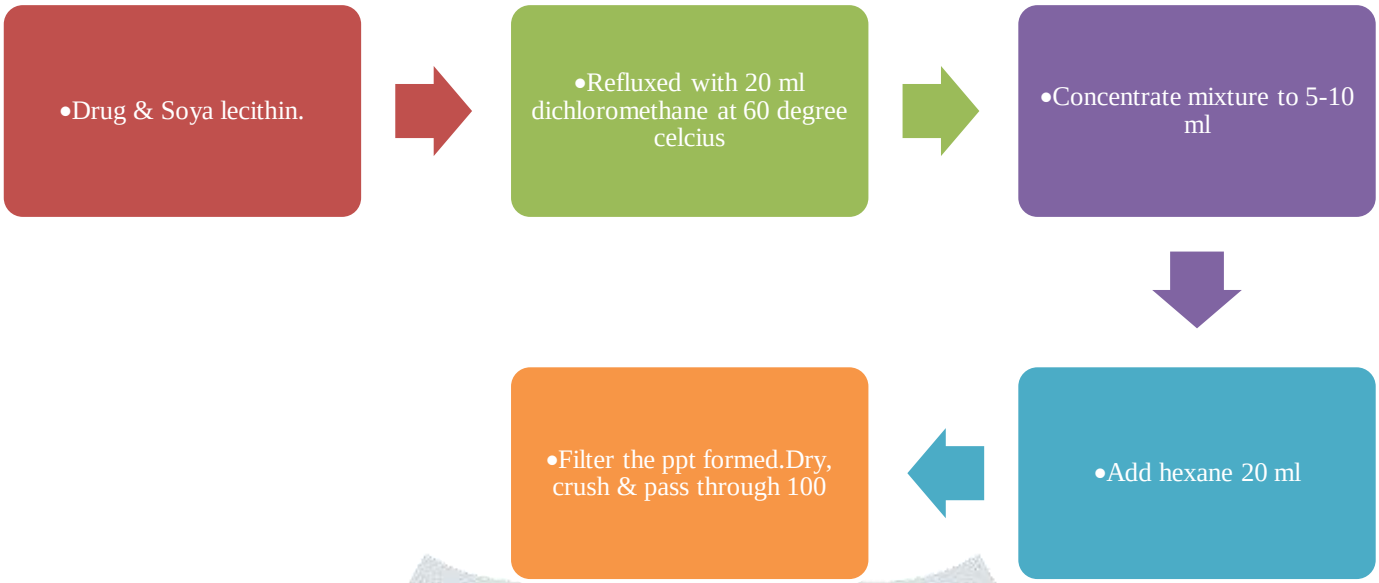
1.Rotary Evaporation Technique(Basis & Erectile, 2015; Journal & Pharmaceutical, 2023)**:**



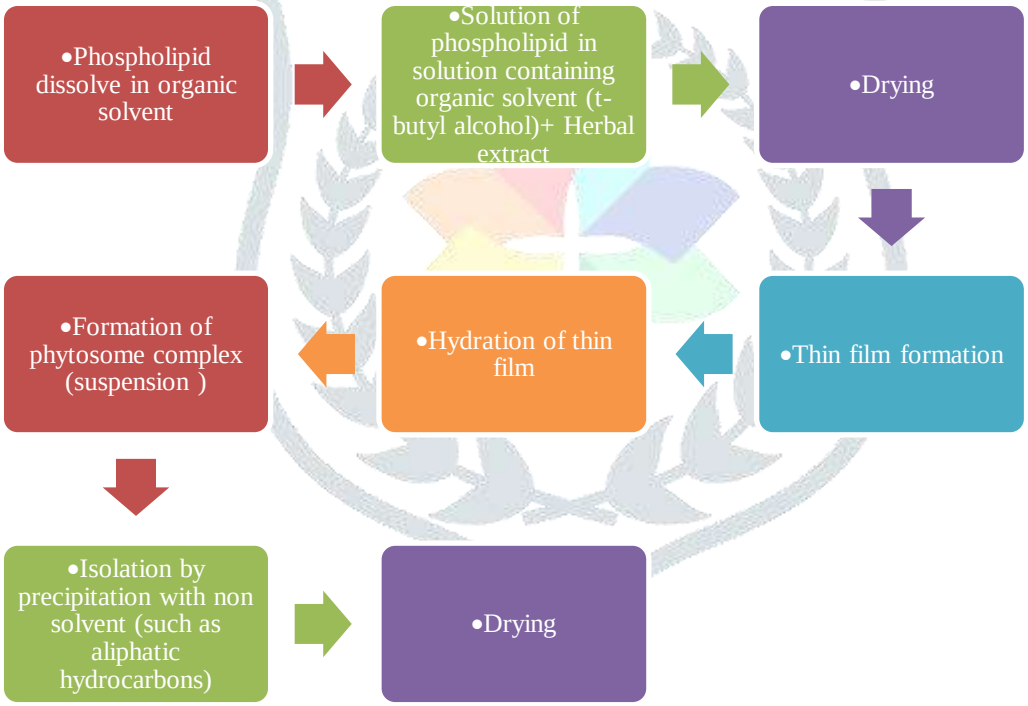
2.Solvent Evaporation Technique(Ahmed & Ahmed, 2020; Basis & Erectile, 2015; Journal & Pharmaceutical, 2023)**:**



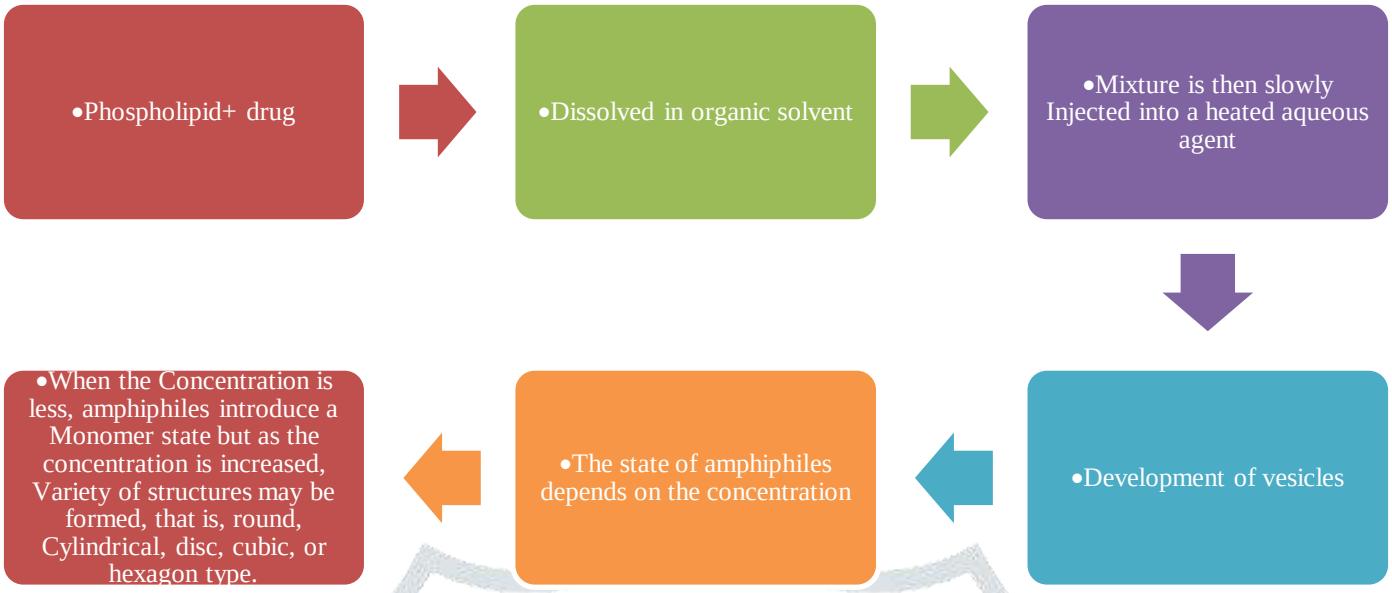
3.Lyophilization or spray drying technique(Sravanthi & Pradesh, 2013)**:**



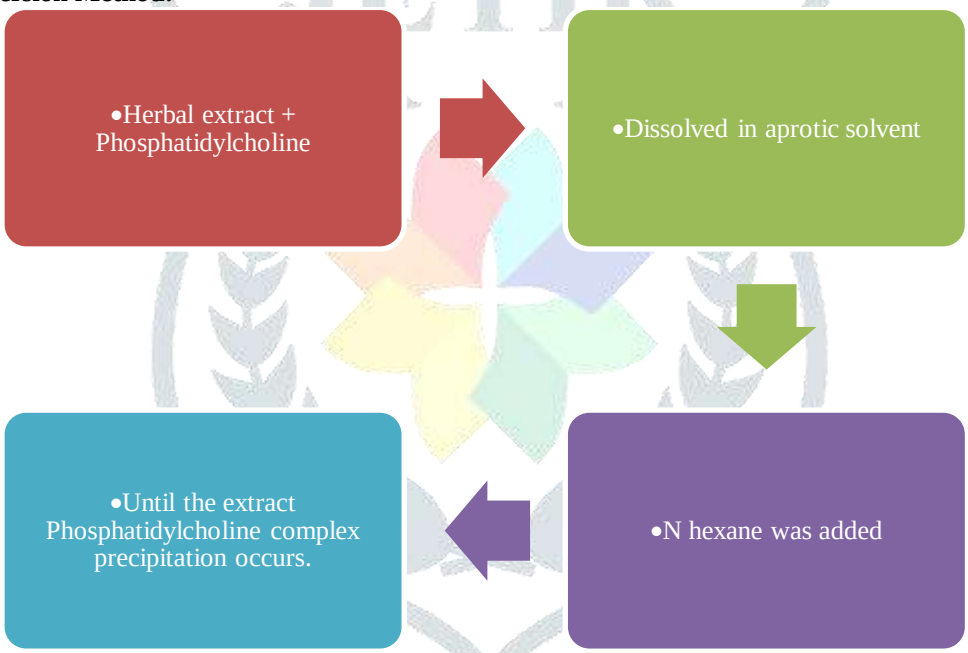
4.Ether Injection Technique(Sravanthi & Pradesh, 2013)**:**



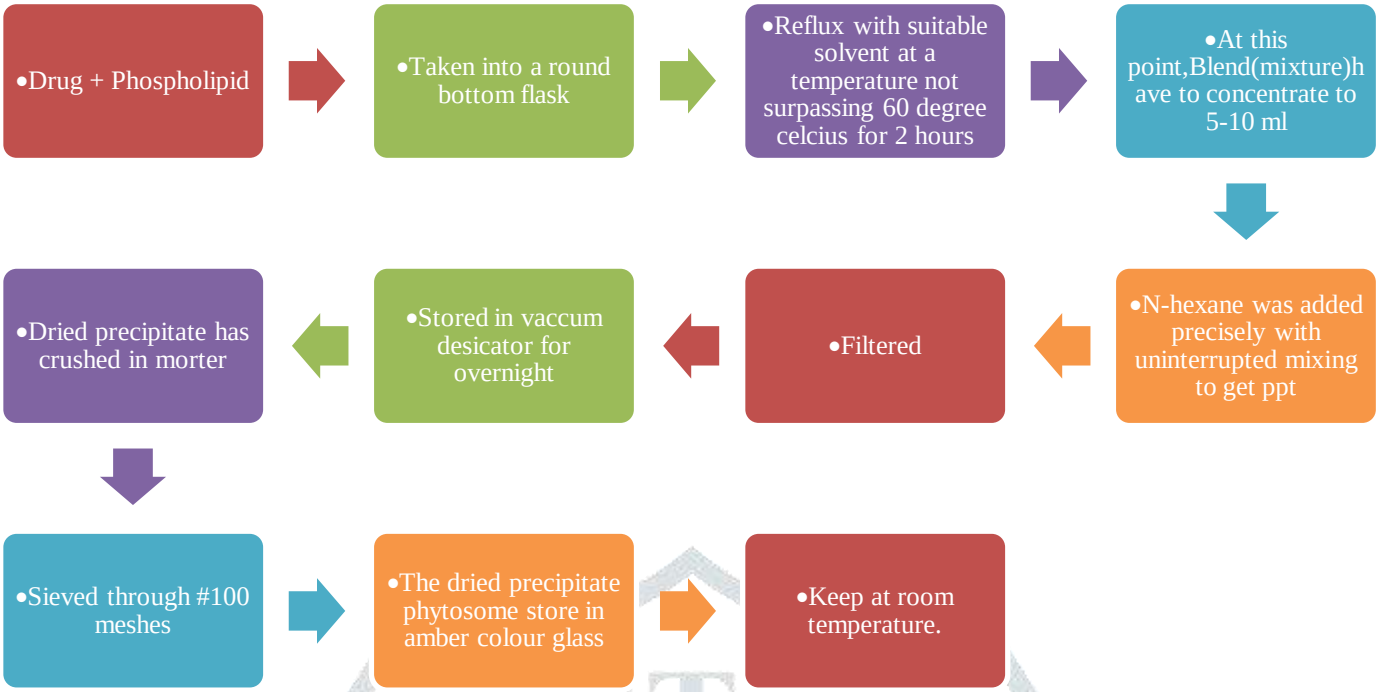
5.Salting out technique(Basis & Erectile, 2015)**:**



6.Mechanical Dispersion Method:



7.Antisolvent precipitation technique(Ahmed & Ahmed, 2020; Basis & Erectile, 2015)**:**



8.Super Critical Fluid(SCF)(Journal & Pharmaceutical, 2023)**:**
Three separate traditional procedures were used to create the complex. Comparing the complex created by the supercritical anti-solvent precipitation process favorably to solvent evaporation, lyophilization, and micronized puerarin. Two SCF techniques were used. GAS (Gas anti-solvent technique) and SEDS (Solution enhanced dispersion by Supercritical fluids) have been used for the preparation of complexes.

A)Gas Antisolvent Technique:

- Supercritical antisolvent will be added to active ingredient & Phospholipid solution separately
- Continuous till the point that the final pressure shows
- Reaction vessel will be then keep for 3 hours with no disturbance
- At settled temperature of 38 degree celcius with 10 mPa of pressure.

B) Solution enhanced scattering by supercritical liquids(SEDS) :

- The supercritical anti-solvent and Liquid solution were constantly added to the precipitation unit
- A 0.1 mm diameter Nozzle was used to introduce carbon dioxide gas into a solvent-containing combination of phospholipids and purarin
- With a temperature of 35 °C, a pressure of 10 MPa
- A drug-to-phospholipid mass ratio of 1%, and a purarin concentration of 100 mg/ml, the experimental conditions were optimized
- The final procedure generated a 93% yield Complex.

Mechanism of phytosome Technology(A. Kumar et al., 2017; Sravanthi & Pradesh, 2013)**:**

- The lower absorption and bioavailability of polyphenolic constituents mainly due to two factors
- First factor -These chief constituents are number of ringed molecule and are not too much small that it will absorbed by diffusion process.
- Second factor is - flavonoid molecule or chief constituents of polyphenols have poor solubility with lipids
- These are the limitations that inhibit their absorption through biological membrane
- Phytosome Technology is mainly result with complexation of polyphenols with phospholipid in 1:1 ratio or 1:2 results in the formation of phytosomal complex with lipid covering around the constituents.

Factors affecting Phytosomes(Lu et al., 2019)**:**

1. **Choice of Phospholipid type:**
   The choice of phospholipid can impact the stability and bioavailability of phytosomes. Common phospholipids used include phosphatidylcholine and phosphatidylserine.
2. **Plant Extract Quality:**
   The quality and potency of the herbal extract used play a crucial role. The source of the plant material, extraction method, and concentration of active compounds all affect phytosome efficacy.
3. **Ratio of Extract to Phospholipid:**
   The optimal ratio between the plant extract and phospholipid needs to be determined for each specific formulation to maximize phytosome formation and bioavailability.

4. **Particle size:**
   The size of the phytosome particles can affect their absorption and bioavailability. Smaller particles generally have higher surface area and may be absorbed more readily.
5. **Temperature & pH:**
   The temperature and pH conditions during phytosome preparation can impact the formation and stability of the complex. These conditions need to be carefully controlled.
6. **Storage conditions:**
   Proper storage conditions, including temperature and exposure to light and air, are crucial for maintaining the stability and effectiveness of phytosomes over time.
7. **Solvent selection:**
   The choice of solvent used during the phytosome preparation can influence the encapsulation efficiency and stability of the complex.
8. **Patient factors:**
   Individual factors such as a person's digestive health, metabolism, and genetics can also influence the absorption and effectiveness of phytosomes.
9. **Dosage form:**
   The choice of dosage form (e.g., capsules, tablets, liquid) can impact how well phytosomes are absorbed in the body.
10. **Other Ingredients :** If other excipients or additives are used in the formulation, they can interact with the phytosome and affect its properties and bioavailability.
    It's essential to consider these factors when formulating and using phytosomes to ensure their effectiveness in delivering the desired herbal compounds to the body.

Application(Chandran et al., 2023)**:**

- **Nervous system :**
  Studies have proved the improved efficacy of phytosome on nervous system over the conventional standardized extract. In one study,Ginkgo biloba phytosomes generated a significant increase in spontaneous locomotor motor activity indicating higher excitability/stimulation of the central nervous system after treatment with phytosomes. Prolongation of the transfer latency (time to enter the dark chamber) in a dose-dependent way after administration of Ginkgo biloba phytosomes in a scopolamine-induced amnesia test in mice clearly indicates its memory-enhancing characteristics and supports their therapeutic usage in alzheimer's illness, Since the scopolamine-amnesia test has been widely acknowledged as a primary screening test for anti-alzheimer drugs.
- **Cardiovascular system:**
  Many studies on grape seed phytosome reported an increase in total antioxidant capacity and stimulation of physiological defenses of plasma, protection against ischemia/reperfusion induced damages in the heart, protective effects against atherosclerosis thereby offering marked protection against the cardiovascular system. In another study, significantly less aortic plaque in the aortas and carotid arteries of rabbit following the grape seed phytosome treatment group than did the control group which received conventional standardized grape seed extract in similar regimen. Studies have proved the improved efficacy of ginkgo phytosome over the conventional standardized extract in protecting rat isolated hearts against ischemia.
- **Inflammation:** Many studies reported better anti-inflammatory activity of phytosome over the pure herbal extract. A study was conducted on the skin uptake of rutin phytosome and found that the rutin phytosomes are better able to penetrate the highly impermeable stratum corneum than free rutin. Retention of this higher quantity of rutin will be available for slow passage through the viable dermis and prolonged antiinflammatory effect. In a carrageenan induced inflammatory study in rats, inflammation was significantly inhibited by test group rutin phytosome compared to standard diclofenac gel. Because rutinphytosomes are lipophilic, they have been found to be deposited in the Epidermal-dermal region, where the medicine is slowly released to offer a long-lasting anti-inflammatory effect [38]. A pthalic anhydride (PA)-induced inflammatory study in mice, inflammatory symptoms like erythema, oedema, and erosion on ear and back of mice were drastically reversed after Centella asiatica phytosome therapy Compared to control and PA treatment group. In another study, the Lawsone phytosome gel therapy exhibited significant antiinflammatory action when compared to plant lawson gel at 4 hours in Carrageenan-induced rat paw oedema.
- **Oxidative stress :**
  Studies have shown that phytosomes are having improved antihepatotoxic activity compared to standardized herbal extract from plant. In one study on silymarin phytosomes showed higher specific activity and a longer lasting action than pure silymarin with respect to the reduction of oedema, inhibition of myeloperoxidase activity, antioxidant and free radical scavenging activity. In another study, CCL4 was used to induce hepatotoxicity via degradation of parenchymal cells and damage to adipose tissue when compared to the control group. The anti-oxidant capabilities of apigenin phospholipid complex therapy have a strong hepatoprotective effect by reversing these damages. They also discovered pharmacokinetic parameters like Cmax, Tmax, and AUC increased while clearance rate and volume of distribution dropped, indicating improved bioavailability of apigenin
  Nanoparticles (APLC). This is due to two main factors: 1) Higher Aqueous phase solubility leads to increased intestinal absorption (because of phospholipid based molecular aggregates) 2) Phospholipids protect apigenin from hepatic first-pass metabolism.
- **Diabetes :**
  In a streptozotocin-nicotinamide induced diabetis study in rats, phytosomes formulation of plant Momordica dioica at a lower dose showed more significant blood glucose lowering effect than the conventional total methanolic extract group, which is comparable to the standard metformin group, an anti-diabetic drug .

- **Cancer:**
  Many researchers reported enhanced anti-tumour effect of phytosome formulation compared to normal plant extract. A study of targeting phytosome tumour therapy reported that phytosomes with a molecular weight more than 40 kDa and a nanometric size range of 100–1200Nm actively targets tumour cells because of their improved penetration and retention impact. Active targeting specifically delivers the pharmaceuticals in the site of action, while passive targeting boosts the bioavailability of the drugs. The two are combined in phytosomes to deliver the bioactive ingredients. In another study, MCF-7 cells were treated to increasing concentrations of phytosomal-curcumin and 5-fluorouracil singly and in combination. They found that phytosomal-curcumin suppresses cell growth/invasion in a dosedependent manner and induces tumour shrinking considerably when compared to single-treated groups, which was linked to higher levels of E-cadherin and MMP9.
- **Obesity**:
  A study of soy phytosomal thermogel applied topically on rats was found to have a local anti-obesity effect on rats' abdomen with lowering effect on the serum lipid profile. It can be explained by the fact that nanosized particles of phytosome vesicles have a high skin permeation ability that may let it reach the blood circulation showing the cholesterol-lowering property of orally administered soy proteins.
- **Fungal infection:**
  Phytosomal complexes are reported to have increased anti-fungal activity compared to plain herbal extract from plant. One example of the phytosome complex of lawsone showing better antifungal activity when compared to the plant medicine lawsone, and the plain Ketoconazole, demonstrated by the maximum zone of inhibition.

Conclusion:

Phytosome are advanced form of herbal extract that are absorbed better than conventional herbal extract. The article thus reviews the benefits, physicochemical characteristics, biological and pharmacological properties, and method of preparation of phytosomes. The formulation methodology for phytosome is simple and can be easily upgraded to a commercial scale. These are novel complexes showing much better absorption profile following oral administration owing to improved lipid solubility which enable them to cross the biological membrane, resulting in enhanced bioavailability i.e. more amount of active principle in the systemic circulation. Also phytosomes are superior to liposomes due to much better absorption and stability profile. As mentioned in the literature, phytosomes have been therapeutically used for hepatoprotective and liver diseases. After screening and selection of herbal extracts, one can develop Phytosomal drug delivery systems for various drug categories like anticancer, cardiovascular, and anti-inflammatory activities, antidiabetic activities etc.

Phytosomes enable pharmaceutical companies to create new products based on water-soluble drugs, as well as include new innovations in the pharmaceutical industry . Phytosomes are a promising drug delivery mechanism for enhancing the effectiveness, quality, and targetability of active plant constituents and herbal extracts.

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