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PHYTOSOMES, AN UPHEAVALS IN BIOAVILABILITY OF HERBAL DRUG DELIVERY

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Abstract

From ancient time use of medicinal plant for its therapeutic and cosmetic activity was prevalent, nowadays due to hazards of synthetic drugs the attention towards herbal drug is increasing. Apart from all benefits of phytoconstituent of herbal extract over synthetic medicine their absorption and subsequently their bioavailability is considerably low, which may cause them to be less effective and require high dose and long term consuming to show desire response. These obstacles can be overcome by formulating them as lipid compatible complex known as Phytosomes. Phytosomes are cell like structure which are result of reaction of 2 to 3 mole of phytoconstituent with 1 mole of phospholipid which lead to encapsulation of phytoconstituent in individual phosphatidylcholine head .Each phosphatidylcholine moiety has hydrophilic head and two lipophilic tail which make it bifunctional in nature, this bifunctionality will help the complex to better absorption and eventually increase the bioavailability of herbal medicine by make them acid liable and help them to permeate through biological membrane. due to formation of chemical bonds between phytoconstituent and phosphatidylcholine they show better stability compare to liposomes. Phytosomes have great capability of passing through hydrophilic bioenvironmental into the lipid- friendly bioenvironmental of the enterocyte cell membrane and from there into the cell, and as a consequence can be used for systemic targeting.

Keywords: Herbal extract, Phytosomes, phosphatidylcholine, bioavailability.

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INTRODUCTION

Since ancient time the remedial engagements of habitual pharmaceuticals and phyto-meds have demonstrated extremely reasonable for wellbeing running by different means [1]. During the most recent century, chemical and pharmacological investigations have been performed on many plant extracts permitted the end goal to research their chemical configuration and assert their therapeutic effectiveness [2]. In the current scenario, the most majority of the predominant diseases and nutritious issue are treated with natural medicine [3]. yet their full therapeutic capability can't acquire due to their poor systemic bioavailability as a result of their poor absorption from the GIT [4]. The effectiveness of any herbal medicine is contingent upon delivery of the actual level of the therapeutically active compounds. However, extreme constraints exist in their bioavailability when administered orally or by topical application [5]. Several plant extracts and phytoconstituent, regardless of having greater bioactivity in vitro show less or no in vivo activities. Numerous reasons are there which are in charge of the same e.g. Some have multiple ring framework because of which they can't be inactively diffuse through the GIT membrane (as the molecular weight of the particles expands), some have poor lipid phase miscibility [4]. Because of their poor lipid solubility or inappropriate molecular size or both, bringing about poor absorption and bioavailability [3]. The bioavailability can be enhanced by the utilization of delivery systems, improving the rate and the degree of drug solubilizing into the aqueous intestinal fluid and the ability to cross the lipid-rich bio membranes [5]. Numerous methodologies have been created to enhance the oral bioavailability, for example, consideration of solubility and bioavailability enhancers, structural modification and entrapment with the lipophilic carriers. An advance and most encouraging methodology for delivery of such herbal extract is the development of Phytosomes [6].

PHYTOSOMES

Water-soluble phytoconstituent particles can be changed over into lipid-compatible molecular complexes, which are called Phytosomes. [7] Phytosomes or Phytolipid delivery system or planterosomes or herbosomes (in certain literature) [8], are inventive lipid carriers. [9] It is a protected innovation, created by Indena [10] Phytosomes presented superior pharmacokinetic and pharmacodynamics feedback than standard natural extracts. [11] The expression "Phyto" implies plant while "some" means cell-like. [12] Phytosomes are more bioavailable when differentiated with traditional herbal extract attributable to their upgraded ability to cross the lipoidal bio membrane and eventually reaching to the systemic circulation. [13] The Phytosomes innovation creates a little cell, better capable of travel from a hydrophilic domain

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into the lipophilic bio-environment of the enterocyte cell membrane and from that point into the cell, at last reaching the blood. In such way, it ensures the safely delivering the significant parts of the phytoconstituent from wiping out by digestive secretion and gut bacteria. [14] Phytosomes are created when the individual components of an herbal extract are bound to phosphatidylcholine (an emulsifying compound derived from soy). [15]

PHOSPHOLIPID

Phosphatidylcholine (PC) is a phospholipid, a bulky organic particle that is a common building block for cell membranes. [16] Phosphatidylcholine has different characteristics that upgrades its accessibility as a nutritive supplement. PC is additionally protected and entirely compatible with pharmaceuticals and with other nutrients. It is likewise completely bioavailable (around 90%of administered quantity is absorbed over more than 24 hours) and it is a great emulsifier that elevations the bioavailability of supplements with which it is Co administered. [17]

PRINCIPLE

The Phosphatidyl moiety is lipophilic and the choline (serine) moiety is hydrophilic in nature. This twofold solubility of the phospholipid marks it as an operational emulsifier. Accordingly, the choline head of the phosphatidylcholine molecule binds to phytoconstituent while the lipid soluble Phosphatidyl portion embracing the body and tail which then surrounds the choline bound material.Hence, the phytoconstituent produce a lipid compatible molecular complex with phospholipids (also called as phytophospholipid complex). [18]

PROPERTIES

The property of Phytosomes greatly depends on the method of formulation as well as a drug polymer complex formation. In this clause we will survey the chemical, physical, pharmacological and biological properties of Phytosomes.

CHEMICAL

- Phytosomes are result of reaction of defined ratio of phospholipid and chosen phytoconstituent (a complex between an herbal product and phospholipids), in a nonpolar solvent. Based on their physicochemical and spectroscopic information, it has been demonstrated that the primary phospholipid-phytoconstituent (substrate) interaction is because of the arrangement of hydrogen bonds among the polar head of phospholipids (i.e. Phosphate and ammonium groups) and the polar functional group of the substrate. [2]
- An encounter with hydrophilic media Phytosomes demonstrates a cell-like structure like liposomes, however, in a liposome, the main constituent interacts inside the inner

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pocket while in Phytosomes the principal active constituents are covered in the polar head of phospholipid and turning into an essential piece of the membrane. [19] Phosphatidylcholine can be found from the examination of H-NMR and 13C-NMR spectra of the complex with those of the pure compound. The signals of the fatty chain remain untouched. [20] Such confirmations affirm that too long aliphatic chains are folded over the active parts, shaping a lipophilic envelope, which guards the polar head of the phospholipid and phytoconstituent molecules and makes the complex dissolvable in low polarity solvent. [21]

PHYSICAL

- Their size variation is between fifty NM to a couple of hundred μm. [22]
- Phytosomes are lipid bodies with a clear melting point. [23]
- Solubility of Phytosomes examined as; the products are sometimes freely soluble in aprotic solvents, moderately soluble in fats, insoluble in aqueous and moderately insoluble in alcohol. On the other hand, the Phytosomes of certain lipophilic phytoconstituent like curcumin has representing upgraded aqueous solubility via complexation with phospholipids. [24]

PHARMACOLOGICAL

- 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. [25]
- The extraordinary bioavailability of Phytosomes formulation over conventional herbal products have been demonstrated by pharmacokinetics and pharmacodynamics experiments in human and animals. [26]

BIOLOGICAL

- The performance of the Phytosomes in both physical and biological systems is run by the features, like physical size, membrane permeability, %content entrapment, chemical configuration and also the ratio and purity of the starting materials. Hence, Phytosomes are described for physical properties i.e. Shape, size, its dispersion, % drug content, % drug release and chemical composition. [27]
- Several studies have demonstrated the Phytosomes to be a superior alternative for liposomes regarding membrane permeability and stability. [24]

ADVANTAGES

Phytosomes as novel formulation of herbal medication has several advantages over the conventional dosage form of the same, these advantages are as follows:

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1. It heightens the absorption of lipid insoluble polar phytoconstituent through oral along with topical route presenting better bioavailability, therefore significantly greater therapeutic advantage. [28]
2. Phytosomes increases the topical 9through the skin) absorption of botanical phytoconstituent. [29]
3. In Phytosomes, demonstrate excellent stability due to formation of chemical bond between phosphatidylcholine molecules. [30]
4. Phytosomes creates a small cell where the respected components of botanical extracts are sheltered from destruction by digestive secretions and gut bacteria. [31]
5. Phytosomes cause enhancement of bile solubility into phytoconstituents and hence facilitates liver Targeting. [32]
6. The phytosome complex is biodegradable. [31]
7. Phosphatidylcholine that is using in preparation of Phytosomes, alongside performing as a carrier also acts as a hepatoprotective, hence giving the synergistic effect when hepatoprotective substances are employed. [28]
8. Phytosomes certify to be of considerably greater clinical advantage. [31]
9. Phytosomes have excellent capability of passing from a hydrophilic medium into the hydrophobic environment of the enterocyte cell membrane and from that point into the cell, and accordingly can be used for systemic targeting. [33]
10. Owing to complexation of drug with lipid in formation of phytosome vesicles, its entrapment efficacy is high. [31]
11. Phytosomes have huge usage in cosmetics thanks to their good skin penetration capability and high lipid profile skeleton. [34]
12. Phytosomes guarantees improved duration of action of botanical drugs. [31]
13. Phosphatidylcholine have the advantage of nourishes the skin due to its similarity as an essential part of a cell membrane.
14. Phytosomes technique assures and protects The nutrient safety of the herbal extracts (this system is fully compatible with phytoconstituent).
15. Phytosomes ensures accurate delivery of drug to the targeted tissues.
16. As phytosome will excellently increase bioavailability Dose requirement can be minimized.
17. It has high market interest and demands for its products. [35]

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DISADVANTAGES

1. Regardless of all advantages phytosome may rapidly exclude the phytoconstituent. [36]
2. phospholipids (lecithin) can encourage proliferation on MCF-7 breast cancer cell line.
3. A foremost drawback of Phytosomes reported as leaching of the phytoconstituent off the 'some' which diminishes the anticipated drug concentration. [37]

PHYTOSOMES VERSUS LIPOSOMES

Liposomes may appear to be fundamentally the same as Phytosomes yet there are numerous specific qualifications. Like Phytosomes, liposomes are prepared utilizing comparative procedures of blending phosphatidylcholine and a water soluble phytoconstituent in a particular stoichiometry proportion. Moreover, dissimilar with Phytosomes, the choline moieties don't make chemical bonds with the water dissolvable particles, rather the phosphatidylcholine molecules totally wrap them making a lipid bilayer encircling a center containing the water soluble molecules. [36]

Whereas in Phytosomes, the choline sections are chemically bonded to the phytoconstituent by means of hydrogen bond, attach them firmly to the membrane, bringing about the arrangement of 2:1 or 1:1 ratio between phosphatidylcholine and the phytoconstituent. [35]

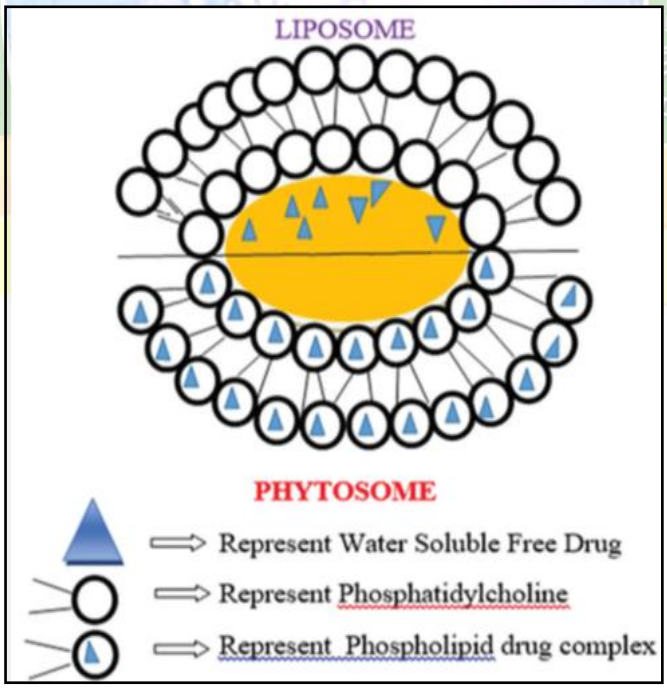

Fig.1: Difference between phytosome and liposome [19]

Hence phytosome can be study by comparing with liposome different property as mentioned in table number 1:

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Table 1: Difference between phytosome and liposomes [38,39]

Sl No.	PHYTOSOMES	LIPOSOME
1	Phytosomes are a unit of a complex particle attached together.	Liposome is an aggregate phospholipid particle that can encase other active molecules, but without making any particular bonds with them.
2	Phytosomes process the phosphatidylcholine and the plant components actually form a 1:1 or a 2:1 molecular complex depending on the substances (s) complexes. Involving chemical bonds. So they better absorbed and shown better bioavailability	In liposome no chemical bond is formed. The phosphatidylcholine molecules surround the water soluble substance. There may be hundreds or even thousands of phosphatidylcholine molecules surrounding the water soluble compound
3	Phytosomes complex can somewhat be compared to an integral part of the lipid membrane. Where the polar functionalities of the lipophilic guests interact via hydrogen bonds with the polar head of a phospholipids (i.e. Phosphate and ammonium groups). Forming a unique pattern which can be characterized by spectroscopy	In liposomes. The active principles are dissolved in the central part of the cavity. With no possibility of molecular interaction between the surrounding lipid and hydrophilic substance
4	Phytosomes act with the solvent having a reduced dielectric constant such as Acetone, Dioxane, Metyhlenechloride, Hexane and Ethyl Acetate etc.	Liposomal drug complex is formed in the presence of the water or buffer solution

BIOAVAILIBILITY OF PHYTOSOMES

Maintaining bioavailability of drugs is a huge obstacle in the pharmaceutical formulation, and diverse systems have been formed to fix the absorption. As well, different approaches have been found in botanical formulations to accomplish this objective (overcome their low absorption). The first approach could possibly be similar to the medicinal chemistry approach in some points: the goal of chemical derivatization of the herbal extract is to get products with improved bioavailability. Though by this technique will produce numerous chemical analogues which should be analyzes accurately. An alternative approach (second approach) that is additionally being studied is the blend of the active principle with different compounds as excipients and as a result boosting active principle absorption. A third approach includes broad formulation research of configurations equipped for both stabilizing natural particles and improving their intestinal absorption. Different formulate which are subjects for research, study, are comprising between different novel development of liposomes, micelles, nanoparticles, nano emulsions, microsphere or other complexes. The Phytosomes approach which will demonstrate the enhancement in pharmacokinetic profile is acquired without falling back on pharmacological adjuvant or structural modification it will acquire just by formulating them with edible ingredients such as phospholipids. [40]

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The Phytosomes technology has been tested by numerous famous natural concentrates including Ginkgo biloba, grape seed, hawthorn, drain thorn, green tea, and ginseng and it is proven by latest research which are demonstrated enhanced absorption and bioavailability with Phytosomes in comparison with the conventional forms. Many standardized concentrate extract containing flavonoids and polyphenolics have been reported for enhanced bioavailability when formulated as phytosomal preparation. [41]

Some of the recent research which are proven the high bioavailability of phytosomal formulation are as follow:

- ***Hamadneh et al (2018):*** Their investigation was on anti-hyperglycemias activities of phytosome loaded of bitter melon and olive oil extract in glucose-induced hyperglycemic rats**.** The phytosome were prepared by reacting phytoconstituents and phospholipid in ratio of 1:2. The prepared Phytosomes were evaluated for hypoglycemic effects by oral glucose tolerance test in induced hyperglycemic rats. their results demonstrated that the loaded Phytosomes were more potent in anti-hyperglycemic activities than pure extracts.[42]
- ***Freag et al (2018)*:** They have been investigated on formulation of phytosome loaded tripterin which were coated with protamine layer to overcome pharmaceutical issues related to buccal absorption of the drug. Convincingly, they have proven that Chitosan: HPMC mucoadhesive sponges which were loaded with mucus-penetrating protamine coated tripterin phytosomes, could significantly upgrade the absorption of tripterin via buccal mucosa and have a positive effect on its bioavailability. [43]
- ***Telange D. et al (2017):*** They have been studying the different characterization parameters of apigenin phytosomes related to aqueous solubility, dissolution, *in vivo* bioavailability and antioxidant activity of a pigenin. Their results confirm that the phytosome loaded apigenin have over 36-fold higher aqueous solubility compare to the pure form of it. The formulations also demonstrated high dissolution rate and also significant enhancement in apigenin oral bioavailability. They have been proven by their research that phytosome is a promising and feasible strategy for upgrading the delivery of apigenin and other similar phytoconstituents. [44]
- ***Ayu Lestari et al (2017):*** The purpose their research was to find the best formula composition for keratin Phytosomes intended for oral administration**.** They prepared their formulation by dry fil hydration method. Each formula had evaluated and the results demonstrate that the formulas show excellent in vitro bioavailability. [45]

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- ***Abdul Azeez et al (2017):*** They investigated the formulation of economic phytosome of Allium Sativum as an alternative for cancer treatment since its phenolic compound have capable of cure and prevent the growth of cancer cells. The prepared phytosomes were evaluated for their effect against cancer cells, which demonstrated a 100% toxicity against cancer cell lines. Hence, they claimed that the allium sativum phytosome have an excellent bioavailability at the tumor site and can also be generalized to active targeting tumor site by attaching the targeting moiety on the surface of the phytosome. [46]

MECHANISM OF PHYTOSOME COMPLEX FORMATION

The active parts of botanical extracts (phytoactive) are suitable candidates to form chemical bonds with phosphatidylcholine. Phytoconstituent (mostly polyphenolics, saponin and triterpenes) which can provide site for this bond formation (polyphenol) with the phosphatidylcholine, can be changed over into Phytosomes. [48] Phosphatidylcholine is a large functional compound. [39] In the Phosphatidyl choline, the Phosphatidyl moiety bears lipophilic property, whereas the choline moiety shows hydrophilic action in nature. Particularly, the choline parts of the phosphatidylcholine molecules form bound to phytoconstituent while the lipid soluble Phosphatidyl section which include the body and tail, covers the choline-phytoconstituent complex site (choline bound materials). Consequently, creates the lipid compatible molecular complex with phospholipid, which also call as phytophospholipid complex. [48]. By encapsulating the active ingredients (phytoconstituent) into the phospholipids environment, these are protected from water-activated degradation while, in the meantime, the quick interchange of phospholipids between the biological membrane and the extracellular fluids can carry them into biological membranes, heightening its cell capitation. [47]

PREPARATION 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. [49] 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. [13] The prepared Phytosomes will be isolated then by precipitation with non-solvents, for example, aliphatic hydrocarbons or by lyophilization or by spray drying. [50.51] generally in the phytosome complexes the ratio

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between phytoconstituent and phospholipids are in the proportion 0.5-2.0 moles. The most ideal proportion of phospholipid to flavonoids is 1:1. [52]

There are different methods involves in Phytosomes preparation as follows:

ROTARY EVAPORATOR TECHNIQUE

Dissolve particular measure of phytoconstituent and phospholipid appropriate aprotic solvent in a rotating round bottom flask followed by stirring for 3 hours at a temperature not surpassing 40°C. A Thin film of the mixture sample was acquired to which n-hexane/CH3) 2CO was included and consistently blended utilizing a magnetic stirrer. The obtained precipitate was collected, set in amber colored glass bottle and stored at room temperature. [53]

SOLVENT EVAPORATION TECHNIQUE

The specific amount of plant extract, polymer and phospholipids were taken into a round bottom flask and reflux with suitable solvent at a temperature range of 50-60°C for 2 hours. The blend was concentrated to 5-10 ml to get the precipitate which can be isolated and collected for drying. The dried precipitated Phytosomes complex can be placed in an amber colored glass bottle and store at room temperature. [54]

ETHER INJECTION TECHNIQUE

In this method, the complex of phytoconstituent and phospholipids is dissolved in an organic solvent. This blend is gradually injected into a warmed aqueous solvent, bringing about the development of vesicles. The condition of amphiphilic relies upon the concentration, when the concentration is less, amphiphiles present a monomer state yet as the concentration is expanded, diversity of structures might be shaped, that is, round, tube shaped, circle, cubic, or hexagon type. [55]

ANTISOLVENT PRECIPITATION TECHNIQUE

The specific amount of drug and phospholipid taken into a round bottom flask and reflux with suitable solvent at a temperature not surpassing 60° C for 2 hours. At this point blend have to concentrated to 5-10 ml. N-hexane can added precisely with uninterrupted mixing to get the precipitate which then filtered and store in a vacuum desiccator for overnight. The dried precipitate has crushed in mortar and sieved through #100 meshes. The dried precipitate Phytosomes store in amber color glass and keep at room temperature. [56]

SUPER CRITICAL FLUIDS (SCF)

Using super critical fluid (SCF) has developed as a powerful technique for creating particles with size extending from 5 to 2000 nm.

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Diverse strategies for supercritical liquid have been used for enhancing solubility profiles of poorly soluble drug, which some of them are compress antisolvent process (PCA), supercritical antisolvent strategy (SAS), rapid development of supercritical solution (RESS), gas antisolvent technique (GAS) and solution Enhanced dispersion of supercritical liquids (SEDS).

Gas antisolvent technique (GAS)

In this procedure, a suitable supercritical antisolvent will be added to the active ingredients and phospholipids solution separately, and continue till the point that the final pressure shows up. The reaction vessel will be then keep for 3 h with no disturbance at a settled temperature of 38 °C with 10 mPa of pressure30.

Solution Enhanced scattering by supercritical liquids (SEDS)

In the SEDS system, the liquid solution and the supercritical antisolvent were constantly included in the precipitation unit. Carbon dioxide gas was permitted to go through a nozzle of 0.1 mm diameter into the blend of phospholipids and drugs in the solvent.

The test conditions were optimized with a temperature of 35 °C, a pressure of 10 mPa, 1% mass proportion of the drug to phospholipids and a 100 mg/ml concentration of drug. [57]

LYOPHILIZATION TECHNIQUE

Natural as well as manufactured phospholipid and phytoconstituent will be dissolve in various solvent. At this point phytoconstituent solution will be add to phospholipid solution and start stirring till complex development happens. The formed complex will be isolated by lyophilization. [58]

SALTING OUT METHOD

The active constituents of herbal extracts and phosphatidylcholine will be dissolved in an aprotic solvent, for example, Dioxane or CH3) 2CO then the solution will be blended overnight. The created complex is separated from by precipitation from non-solvent like n-hexane. [10]

CHARACTERIZATION AND EVALUATION OF PHYTOSOMES

The phytosome behavior in physical and/or biological environment is represented by the different factors, for example, physical size, membrane permeability, % entrapped solutes, chemical composition and also the quantity and quality of the starting materials.

A result, the Phytosomes are described for physical properties i.e. Shape, size, its distribution, % drug content, % drug release and chemical composition. [49,21].

Different methods involve in evaluation of Phytosomes to determine its properties and characterizations, these methods are as follows:

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Particle size determination

The Phyto phospholipid complex mean diameter can be estimated utilizing a Nanophox (Sympatec GmbH, Germany) at a fixed scattering angle of 90° at 25 °C. [57]

Vesicle size and zeta potential determination

Phytosome loaded phytoconstituent vesicle size and zeta potential can be determined by utilizing a Zetasizer ZEN 3600 at a fixed scattering angle of 90 °at 25°C. (56) likewise they can be measured by Dynamic Light Scattering (DLS) and Photon Correlation Spectroscopy (PCS). [49]

Differential scanning calorimetery (DSC)

It is a thermoanalytical technique in which the difference in the amount of heat required to increase the temperature of a sample and reference is measured as a function of temperature Herbal polyphenolic extract, phosphatidylcholine, a physical blend of drug extracts and Phosphatidylcholine, and the drug phospholipid complex were put in an aluminum cell and warmed to a temperature of 50-250°C/minutes from 0 to 400°C in nitrogen media. [19]

Entrapment efficacy determination

The entrapment efficacy of loaded phytosome can be determined by using the cooling centrifuge machine by diluting 1part of preparation with 10 ml of solvent and afterward centrifuge -4°C for 30 min with RPM equal to 18000. At this point The supernatant solution will be collected and analyze by UV/V spectroscopy to determine the quantity of free drug. The ultimate value of entrapment efficacy should be calculated by following formula:

Entrapment efficacy (%) = (total quantity of drug) – (quantity of free drug) ×100÷ (total quantity of drug). [56]

% yield determination

% yield of phytosome loaded phytoconstituent can be calculated by the following formula:

(%) Yield = Practical yield × 100 ÷ Theoretical yield. [59]

Drug content determination

The amount of drug can be quantified by a modified high performance liquid chromatographic method or by a suitable spectroscopic method. [6]

Spectroscopic evaluations

To support the establishment of a complex or to examine the mutual interaction between the phytoconstituent and the phospholipids, the following spectroscopic methods are used. [12]

1H-NMR

There is an obvious change of the 1H-NMR signal initiating from the atoms of the complex formulation in nonpolar solvents, and there is not swift of the signal odd to the individual

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molecules. The signals from the protons belonging to the flavonoids are to be broadened that the proton cannot be relieved. In phospholipids, there is broadening of all the signals while the singlet corresponding to the N-(CH3)3 of choline undergo an uplift shift. Heating the sample to 60˚ results in the appearance of some new broad bands, which correspond mainly to the resonance of the flavonoid moiety.

13C-NMR

In the 13C-NMR range of the greater part of phytoconstituent and their stoichiometric complex with phosphatidylcholine, especially when recorded in C6D6 at room temperature, all the flavonoid carbons are plainly imperceptible. The signs comparing to the glycerol and choline bit of the lipid (between60– 80 ppm) are widened and some are moved, while the greater part of the resonances of the unsaturated fat chains hold their unique sharp line shape. In the wake of warming to 60˚, every one of the signs having a place with the flavonoid moieties return, in spite of the fact that they are still exceptionally expansive and somewhat covering.

FTIR

The arrangement of the complex can be additionally being affirmed by IR spectroscopy by contrasting the range of the complex and the range of the individual segments and their mechanical blends. FTIR spectroscopy is likewise a helpful device for the control of the dependability of Phytosomes when small scale scattered in water or when fused in extremely basic restorative gels. From a viable perspective, the solidness can be affirmed by looking at the range of the complex in strong shape (Phytosomes) with the range of its miniaturized scale scattering in water after lyophilization, at various occasions. On account of basic definitions, it is important to subtract the range of the excipients (clear) from the range of the restorative shape at various occasions, looking at the rest of the range of the complex itself. [39]

Visualization determination

There are different methods for Visualization of Phytosomes which the two best among them are using transmission electron microscopy (TEM) and by scanning electron microscopy (SEM). [60]

Scanning electron microscopy (SEM)

For characterization and determination of particle size distribution and surface morphology of formulated complexes can use scanning electron microscopy. Samples can study by using scanning microscopes like JEOL-JSM-6360 (japan). In this technique, dry sample should be place on brass stub of an electron microscope and coated with gold in an ion sputter. The

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digital image of phytosome complexes can be taken by random stub scanning at different magnification as ,1000,5000,10000 and 3000 X. [19]

Transition electron microscopy (TEM)

Transition electron microscopy is one of the methods other than scanning electron microscopy, which can be used to characterize the size of phytosomal vesicle complexes in 1000 magnifications. [19]

Transition temperature determination

By methods such as differential scanning calorimetry techniques, can determine the lipoidal vesicles like phytosome complexes transition temperature. [60]

Surface tension measurement

The most common method for measurement the surface tension y of vesicles is by using Du Novy ring densimeter. it is used for determination of activity of drugs which can be dissolved **an aqueous solution. [61]**

Stability study

For stability study, first of all the optimized formulation should be chosen. The formulation stability should be studying for two six month depend on type of stability study by placing the products in a humidity chamber (sonar). The temperature and RH% should maintain based on the product and study. After a time of study (two to six months) is over, the formulation should be evaluated for its weight variation, hardness, friability, disintegration and percentage drug content. [61]

***In-vitro* drug release determination**

In-vitro drug release from drug carriers (phytosomal complexes) can be determined by using Franz diffusion cell. In this technique, based on drug physicochemical property, the buffer system with suitable pH. Should be chosen as dissolution medium. The complex solution will be placed on a semi permeable membrane. Finally, the concentration of the permeate drug in collecting sample will be checked by spectroscopic methods. [57]

In vitro drug release can also be evaluated by dissolution apparatus, USP II paddle type at 50 RPM. The cotton tea bag can be used to carry out the in vitro drug release. The cotton tea bag which contains phytosome can be placed in dissolution vessels and the vessels should be close to prevent media evaporation.

At predetermined time intervals, the sample should be withdrawn and same amount of buffer should replace to provide the steady state environment. The collected sample should be analyzed by spectroscopic methods. [59]

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In-vitro and In-vivo evaluation

Models of in vitro and in vivo assessments are chosen based on the normal restorative movement of the naturally dynamic phytoconstituent present in them. For instance, in-vitro hostile to hepatotoxic movement can be evaluated by the cancer prevention agent and free radical searching action of the Phytosomes. For evaluating hostile to hepatotoxic action in-vivo, the impact of arranged Phytosomes on animals against thioacetamide, paracetamol or alcohol induced Hepatotoxicity can be inspected. Skin sensitization and tolerability investigations of ointments, a business item, depict the in vivo security assessment strategy. The bioavailability of a sallying-phospholipid complex was contemplated in dog models to look at the pharmacokinetic parameters of this new complexed form. [50]

APPLICATION OF PHYTOSOME [37,62]

since Phytosomes improved absorption and bioavailability of the herbal extract, they can be use in enormous range of therapeutically and cosmetically fields, such as:

Antioxidant properties

Phytosomes loaded phytoconstituents such as Silybum marianum,Quercetin,Calendula officinalis had been revealed superior antioxidant activity in contrast with their conventional form.

Hepato protective activity

The phytoconstituents of various plants which proven to have hepatoprotective property, such as, Ginkgo biloba, Mangiferin, Andrographis paniculata Linn, were extracted and formulated as phytosome drug delivery system and their hepatoprotective activity were examine compare to traditional form of the same. The result reveals that the drug in equimolar dose in form of phytosomes have improved absorption and also demonstrated reduction in SGOT and SGPT in serum when contrasted with its conventional form measurement.

Cancer treatment

Herbal medicine, which contains phytoconstituents like flavones, isoflavones, flavonoids, anthocyanins, coumarins, Lignins, catechins, and isocatechins demonstrate antioxidant activity which contribute their anti-neoplastic prospective. Although, there are some herbal medicines phytoconstituents which shows toxic effects in increasing concentration and induce certain adverse effects. The existing conventional treatment for cancer therapy like chemotherapy and/or radiotherapy are highly expensive and also results in numerous side effects such as, myelosuppression and neurological, cardiovascular, pulmonary, and renal toxicity, which cause inevitable harm to the personal life quality of patient. Therefore, by formulating these herbal medicines with the help of bipolar moiety (like phytosomes) can upgrade its solubility,

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dispersibility and permeability and as results their bioavailability will increase and hence end up being a strong enemy of malignancy operator.

Transdermal application

Ruta graveolens, Panax ginseng M are examples of botanical medicines which have diverse therapeutically and cosmetically activities and can be use in treatment of different conditions such as, capillary fragility, hypertension, UV-induced cutaneous oxidative stress, hepatic and blood cholesterol, cataract, cardiovascular ailment and also highlighting certain activities when formulating as phytosomal delivery system such as anti-oxidant, anti-inflammatory, antithrombotic, antineoplastic and anti-platelet activity. This phytosomes formulation can be used for transdermal application and it is proven that they will be demonstrating excellent penetration through skin barriers like stratum corneum comparability to their free form.

Wound healing

Sinigrin is one of the major glucosinolate agents present in plants of the Brassicaceas family (especially in Wrightia Aborea leaves) which have excellent wound healing activity. Phytosome formulation of sinigrin demonstrated 100% recovery of wounds and injuries, whereas the sinigrin alone (conventional form) showed only 71% healing activity. Additionally, Sinigrine phytosome demonstrated upgrade in anti-cancer activity of the A-375 melanoma cells.

PHYTOSOME CONTAINING DOSAGE FORM

Phytosomes loaded phytoconstituents formulation can be administered by either oral or topical routes. To acquire the best and optimum results regarding bioavailability of these preparations, it is mandatory to study their dissolution and disintegration time. Dosage form containing phytosomes is as follows: [53]

Soft gelatin capsule

One of the ideal routes to formulate the phytosomes complexes are soft gelatin capsules. For this purpose, the loaded phytosomes will be dispersed in vegetable or semi-synthetic oily vehicles to prepare a suspension to be filled in soft gelatin capsules. For production of better perform capsules, Indena recommended that the granulometry of products be <200µm. According to Indena, an initial viability trial study has to be conducted for selection of the most suitable oily vehicle, since phytosome loaded complexes do not have the same behavior when dispersing in oily vehicles. [39]

Hard gelatin capsules

The hard gelatin capsule shell can be filled by a direct volumetric filling process. For a longer disintegration time it is recommended to fill the capsules without tapping in spite of low

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density. If the quantity of powder is more than 300 mg in size 0 capsules, then the dry granulation is recommended and necessary. [27]

Tablets

For having tablets with higher doses in each unit and with appropriate technology and biopharmaceutical possessions dry granulation process is recommended. Direct compression can be applied only in case of less unitary doses, since phytosome loaded complexes have the limited flow ability probable adhesiveness and low superficial density. To optimize the physicochemical property of tablet and obtain a tablet with suitable technology and biopharmaceutical characteristics while manufacturing it by the direct compression method, it is necessary to dilute phytosome with 60-70% of excipients before compression. Alternatively, wet granulation should be avoided due to the negative effect of water and heat (granulation/ drying) on the stability of the phospholipid complex. [31]

Topical dosages form

Phytosome complexes can formulate as topical dosage form by dispersing them in the main lipid solvent use in preparation of topical formulations. For preparation of emulsion of phytosome complexes they have to be disperse in small amount of lipid phase. The phytosome complex might also by dispersed into the watery phase, and again added to the final formulation at temperature lower than 40°C. [23]

PHYTOSOME MARKETED PRODUCTS [63,64,65]

Table 2: Marketed Phytosome Product with Their Therapeutic Application and Dose.

Sl. No.	PHYTOSOME PRODUCT NAME	DAILY DOSAGE	APPLICATION
1	*Leucoselect* ® phytosome	50–100mg	Systemic antioxidant, specific. Best choice for most people under age of fifty. Also specific for the eyes, lungs, diabetes, varicose veins, and protection against heart disease.
2	*Greenselect* ® phytosome	50–100mg	Systemic antioxidant. Best choice for protection against cancer and damage to cholesterol
3	*Ginkgoselect* ® phytosome	120 mg	Best choice for most people over the age of 50. Protects brain and vascular lining.
4	Silybinphytosome	150 mg	Best choice if the liver or skin needs additional antioxidant protection
5	*Panax ginseng*phytosome	150mg	As a Food Product
6	*Mirtoselect* ® phytosome	__	It delivers fatty acids, alcohols and sterols that benefit prostatehealth.Also beneficial for non-cancerous prostate enlargement
7	*Sabalselect* ®phytosome	__	It enhances immune function in response to a toxic challenge

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CONCLUSION AND FUTURE PROSPECT

Herbal drug extract (phytoconstituent) has massive benefits over synthetic medicine without any adverse effect, but they show low absorption, which consequently will lead to less bioavailability in biological systems. Phytosome is a complex between polar polyphenolics and dietary phospholipids that shows clear physicochemical and spectroscopic highlights. Later innovation of medication conveyance when connected to botanicals open new roads to investigate the most extreme helpful capability of plant substances of polar nature. Phytosomal buildings were first researched for restorative applications, however, mounting confirmation of potential for sedate conveyance has been cumulated in the course of recent years, with valuable movement in the domains of cardiovascular, mitigating, hepatoprotective and anticancer applications. Institutionalized plant separates or for the most part polar phytoconstituents like flavonoids, terpenoids, tannins, xanthones when complexed with phospholipids phosphatidylcholine offer ascent to another medication conveyance innovation called phytosome indicating much better ingestion profile following oral organization attributable to moved forward lipid dissolvability which empowers them to cross the organic film, coming about upgrading bioavailability. Phytosomes have enhanced pharmacokinetics and pharmacological parameter, which in result can favorably be utilized in the treatment of different intense maladies as more a measure of dynamic constituent ends up introduce at the site of activity (liver, cerebrum, heart, kidney and so on) at comparative or less measurement when contrasted with the customary plant extract.

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