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Review Article

PHYTO-PHOSPHOLIPID COMPLEXES (PHYTOSOMES): A NOVEL APPROACH TO IMPROVE THE BIOAVAILABILITY OF ACTIVE CONSTITUENTS

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ABSTRACT

The primary objective of any pharmacotherapeutics approach entirely lies with the effectiveness of the rationally designed delivery system to effectually deliver the suitable drug at the appropriate concentration at the proper site. Phytopharmaceuticals are healing the world from millions and billions of years even though their clinical validation is questioned by virtue of their impediments like low lipid solubility, poor stability, large size moiety and needless metabolism in gut. A strategy of using phyto-phospholipid complexes represents a promising approach to increase the oral bioavailability of active constituents, which is consist of label-friendly phospholipids and active constituents. Hydrogen bond interactions between active constituents and phospholipids enable phospholipid complexes as an integral part. The term 'phyto' means plant while 'some' means cell-like. Phytosome is a novel emerging technique applied to phyto-pharmaceutical which contains phytoconstituents of herbal extract surrounds and bound by lipid. Most of bioactive constituents of phyto-medicine are water soluble compounds like flavonoids. Because of water solubility and lipophilic outer layer, phytosome shows better absorption, hence produces better bioavailability, reduction in the clearance rate, providing higher dissolution and amplification of solubility by several folds of various natural products than the conventional herbal extracts. Phytosomes can be used to treat acute and chronic liver failure and therapeutically used as dietary supplements due to improved pharmacological and pharmacokinetic property. In market, many products based on phytosome technology are available which include herbal extracts and phytochemicals with great therapeutic potential such as curcumin, ginkgo biloba, grape seed, silymarin, and many more. The present review highlights the method of preparation, properties, advantages, characterization, applications 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.

Keywords: Phytosome, Phyto-phospholipid complexes, Active constituents, Herbal drug delivery, Bioavailability

1. INTRODUCTION

The therapeutic effectiveness of any drug obtained from plant, animals or synthetic, depends upon the ability of the dosage form to deliver the medicament to its site of action at a rate and amount sufficient to elicit the desired pharmacological response [1]. Novel drug delivery system aims to deliver the drug at a rate directed by the needs of the body during the period of the treatment and channel the active entity to the site of action. A number of novel drug delivery systems have been emerged encompassing various routes of administration, to achieve controlled and targeted drug delivery by encapsulation of the drug in systemic circulation which reduces the tonicity and selective uptake of drug. Consequently a number of vesicular drug delivery systems such as liposomes, niosomes, transferosomes and pharmacosomes were developed. Advances have since been made in the area of vesicular drug delivery, leading to development of systems that allow drug targeting, and the sustained or controlled release of conventional medicines [2, 3]. Active constituents extracted from plants have been used to treat various diseases since ancient times [4, 5]. Silybin extracted from milk thistle fruit has been used to provide liver support for 2000

years [6]. Curcumins extracted from turmeric have been reported to exhibit antioxidant and anticancer properties [7, 8]. Moreover, some of the most widely studied active constituents are polyphenols, such as flavonoids, terpenoids, and phenolics [9, 10]. However, many active constituents extracted from plants are poorly absorbed when administered orally, which limits their widespread application [11, 12]. The poor absorption of these compounds results from two properties. First, the multi-ring structures of polyphenols are too large to be absorbed by passive diffusion or non-active absorption. Second, the poor water or lipid solubility of these compounds prevents them from passing across the outer membrane of gastrointestinal cells [13, 14]. Active constituents extracted from natural plants have been shown to exhibit robust in vitro pharmacological effects, but poor in vivo absorption. A variety of solutions have been proposed to counter the problem of poor absorption [15], such as the preparation of emulsions [16], liposomes [17] and nanoparticles [18], as well as the modification of chemical structures [19] and delivery as prodrugs [20]. Among the potential strategies, phyto-phospholipid complexes (known as phytosomes) have emerged as a promising strategy to enhance the bioavailability of active constituents [14]. Phytosomes are prepared by complexing active constituents at defined molar ratios with phospholipids under certain conditions [21]. Amphipathic phospholipids mainly act as "ushers" of active constituents to help them pass through the outer membrane of gastrointestinal cells, eventually reaching the blood [14]. After forming phospholipid complexes, the membrane permeability and oil-water partition coefficient of constituents are greatly improved. Thus, phytosomes are more readily absorbed and generate higher bioavailability compared to free active constituents [22, 23]. Encouragingly, the technique of phospholipid complexes has overcome the obstacle of poor bioavailability for many active constituents [24, 25]. Therefore, the preparation of phytosomes has recently received increased attention [23]. Based on the literature, we review various aspects of phytophospholipid complexes, method of preparation, properties, advantages, characterization and applications; we also highlight recent advances in the types of active constituents, phospholipids, solvents and stoichiometric ratios.

2. PHYTOSOMES

Indeed, in 1989, Indena an Italian pharmaceutical and Neutraceutical Company have developed phospholipid complexation technique by chemically reacting polyphenolic plant actives with phospholipids containing phosphatidylcholine (PC) and later patented the technology with the name Phytosome [26]. Phytosome technology had improved the absorption which produces better bioavailability and improved pharmacological and pharmacokinetic properties than conventional herbal extract by incorporating phospholipids into standardized plant extracts [27]. When a stoichiometric amount of phospholipid (phosphatidylcholine) reacted with standardized extract in nonpolar solvent [28]. 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 [29]. Phytosome is vesicular drug delivery system in which phytoconstituents of herb extract surround and bound by lipid (one phyto-constituent molecule linked with at least one phospholipid molecule). Phytosome protect valuable component of herbal extract from destruction by digestive secretion and gut bacteria and because of which they shows better absorption. Phosphatidylcholine is bi-functional compound, where the nature of choline moiety is hydrophilic and phosphatidyl moiety is lipophillic. In phyto-phospholipid complex, the choline head of phosphatidylcholine molecule bind to the phytoactive constituent while the lipid-soluble portion wraps the choline bound material. Hence, it produces phytophospholipid complex. Through spectroscopic techniques, it was analyzed that molecules are hooked through chemical bonds to the choline head of phosphatidylcholine [27, 30]. For enhancement of bioavailability, greater clinical benefit assured delivery to the tissue phytosome technology has been useful.

2.1. Structure of phytosome

Phytosome are formed by interactions between active constituents and the polar head of phospholipids [31]. Interactions between active constituents and phospholipids enable phospholipid complexes to be an integral part in which the phospholipids head group is anchored, but the two long fatty acid chains do not participate in complex formation. The two long fatty acid chains can move and encapsulate the polar part of complexes to form a lipophilic surface. Phytosome form agglomerates when diluted in water, which resemble a small cell that shows some similarity to liposomes; the differences between liposomes and complexes are shown in Figure 1 [32]. As can be seen from Figure 1, the

biggest difference between phytosomes and liposomes is that, in liposomes, the active ingredient is distributed in the medium contained the cavity or in the layers of the membrane, whereas in phytosomes, it is an integral part of the membrane, being the molecules stabled through hydrogen bonds to the polar head of the phospholipids. Liposomes are closed vesicles formed by lipid bilayers that can encapsulate compounds within an aqueous compartment or multiple lipid bilayers, but do not mix with compounds [28].

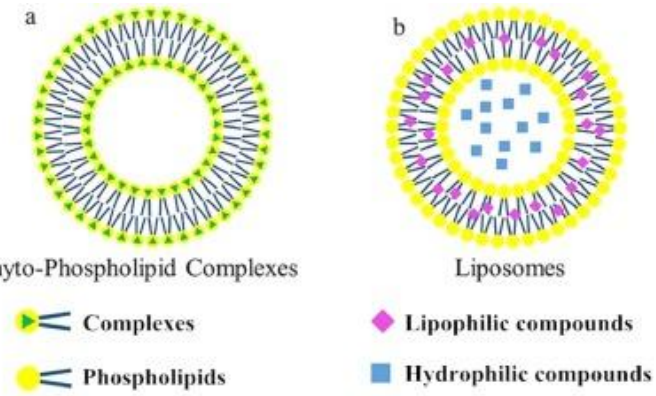

Fig. 1: Structure of phyto-phospholipid complexes and liposomes

2.2. Phytosome components

Bombardelli proposed that phyto-phospholipid complexes can be created from the reaction of phospholipids at a stoichiometric ratio with active constituents that are extracted from plants [33]. Based on subsequent studies, this initial description of phyto-phospholipid complexes has been challenged. According to the literature, we have proposed an updated list of the four essential components needed: phospholipids, phyto-active constituents, solvents and the stoichiometric ratio involved in the formation of phyto-phospholipid complexes [32].

2.2.1. Phospholipids

The phospholipids are amphiphilic and zwitterionic molecules and are considered to be an important component of cell plasma membrane [34]. It gains its amphiphilic nature due to the presence of hydrophilic (head region) region composed of phosphate group which is negatively charged and a hydrophobic region (tail region) composed of long chain fatty acids. These head and tail regions are connected by glycerol or alcohol group, thereby allowing them to form a lipid bilayer in biological systems. Broadly, the phospholipids can be bifurcated in two types, i.e., glycerophospholipids and sphingophospholipids based on the alcohol it possesses. Glycerophospholipids possess glycerol in the neck region whereas sphingomyelins possess sphingosine as their alcoholic moiety [35]. Phospholipids are abundant in egg yolk and plant seeds. Currently, industrially produced phospholipids are available [31]. Additionally, glycerophospholipids include phosphatidylcholine (PC), phosphatidylethanolamine (PE), phosphatidylserine (PS), phosphatidic acid (PA), phosphatidylinositol (PI), and phosphatidylglycerol (PG) [36]. PC, PE, and PS are the major phospholipids used to prepare complexes that are composed of a hydrophilic head group and two hydrophobic hydrocarbon chains [37]. Among these phospholipids, PC is the most frequently used to prepare phospholipid complexes. The benefits of PC include its amphipathic properties that give it moderate solubility in water and lipid media. Moreover, PC is an essential component of cell membranes, and accordingly it exhibits robust biocompatibility and low toxicity. PC molecules exhibit hepatoprotective activities, and have been reported to show clinical effects in the treatment of liver diseases, such as hepatitis, fatty liver, and hepatocirrhosis [38]. *Patel et al.* prepared high-affinity small moleculephospholipid complexes of siramesine and PA [28]. To date, the use of PG and PI to prepare phospholipid complexes has not yet been reported.

2.2.2. Phyto-active constituents

Basically, either active constituents or standardized extract were selected for phospholipid complex formulation. However, natural products after isolation and purification may lead to a limited or total loss of specific biological activity so, in such cases whole plant extracts are selected. Usually, phospholipid complex formulations are prepared according to weight basis for standardized extract, whereas molar ratios for active constituent. Selection of plant extract depends on its phytochemical (such as polyphenols, triterpenoids, tannins, alkaloids and saponins) and pharmacokinetic profile. Usually they have multiple ring molecules which are too large to be absorbed by simple diffusion and have low permeability across the cellular lines of the intestine. A drug which contains an active hydrogen atom like –COOH, -OH, -NH2, -NH etc., which have the ability to form hydrogen bond between the drug and N-(CH3) of PC molecules. Any drugs which possess π electrons can be formulated into different complexes with phospholipid molecules. Both hydrophilic and lipophilic

actives can be complexed to improve bioavailability [39-42].

2.2.3. Solvents

In phospholipid complexation technique the selection of solvent depends on the solubility of both drug and phospholipids. Different solvents have been utilized by different researchers as the reaction medium for formulating phytosome. Traditionally, aprotic solvents, such as aromatic hydrocarbons, halogen derivatives, methylene chloride, ethyl acetate, or cyclic ethers etc. have been used to prepare phytosome but they have been largely replaced by protic solvents like ethanol [29, 43]. Indeed, protonic solvents, such as ethanol and methanol, have been more recently been successfully utilized to prepare phospholipid complexes. For example, Xiao prepared silybin-phospholipid complexes using ethanol as a protonic solvent; subsequently, the protonic solvent was removed under vacuum at 40°C [25]. Various types of solvents have been successfully studied. When the yield of phospholipid complexes is sufficiently high, ethanol can be a useful and popular solvent that leaves fewer residues residual and causes minimal damage. Some liposomal drug complexes operate in the presence of water or buffer solution, where the phytosomes interact with a solvent with a reduced dielectric constant [28]. Recently, many studies have used the supercritical fluid (SCF) process to control the size, shape, and morphology of the material of interest. Supercritical anti solvent process (SAS) is one of the SCF technologies that are becoming a promising technique to produce micronic and submicronic particles with controlled size and size distribution [44]. In this technique, a supercritical fluid (usually CO2) will be chosen as an anti-solvent to reduce the solute's solubility in the solvent.

2.3. Stoichiometric ratio of active constituents and phospholipids

Normally, phytosomes are employed by reacting a synthetic or natural phospholipid with the active constituents in a molar ratio ranging from 0.5 to 2.0 [45]. Whereas, a stoichiometric ratio of 1:1 is considered to be the most efficient ratio for preparing phospholipid complexes [46]. For example, quercetin-phospholipid complexes were prepared by mixing lipoid S 100 and quercetin at a molar ratio of 1:1 [47]. However, different stoichiometric ratios of active constituents and phospholipids have been used. *Maryana et al.* prepared silymarin-phospholipid complexes with different stoichiometric ratios of 1:5, 1:10, and 1:15; they found that the complexes with a stoichiometric ratio of 1:5 showed the best physical properties and the highest loading capacity of 12.18% ± 0.30% [48]. *Yue et al.* conducted a comparative study using the stoichiometric ratios of 1:1, 1.4:1, 2:1, 2.6:1, and 3:1 to generate oxymatrine-phospholipid complexes; they determined that optimal quantity was obtained at a ratio of 3:1 [23]. Therefore, a stoichiometric ratio of 1:1 is not always optimal for the formulation of phospholipid complexes. For different types of drugs, we should experimentally adjust the stoichiometric ratio of active constituents and phospholipids according to distinct purposes, such as the highest drug loading.

2.4. Properties of phytosomes

Following are some of the important properties of phytosomes:

2.4.1. Physico-chemical properties

- Phytosome is prepared by reaction of stoichiometric amount of phospholipid with the standardized plant extracts as substrate. The spectroscopic data reveals that the phospholipid substrate interaction is due to the formation of hydrogen bond between the polar head (i.e., phosphate and ammonium group) and the polar functionalities of the substrate [49].
- The size of phytosome varies from 50 nm to a few hundred μm [50].
- Phytosome when treated with water assumes a micellar shape resembling liposome and photon correlation spectroscopy (PCS) reveals this liposomal structures acquired by phytosome [51].
- The H_1 NMR and C_{13} NMR data deduced that the fatty chain gives unchanged signals both in free phospholipid and in the complex, which indicates that long aliphatic chains are wrapped around the active principle producing lipophilic envelope [52].
- 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 [53].

2.4.2. Biological properties

Phytosome are novel complexes which are better absorbed and utilized; hence they produce more bioavailability and better result than the conventional herbal extract or non-complex extracts, which has been demonstrated by pharmacokinetic studies or by

pharmacodynamic tests in experimental animals and in human subjects [53, 54].

2.5. Methods for the preparation of phytosome

There are three primary methods for preparation of phytosome complexes, including solvent evaporation, freeze-drying, and anti-solvent precipitation. The common stages for preparation of phytosomes are shown in Figure 2.

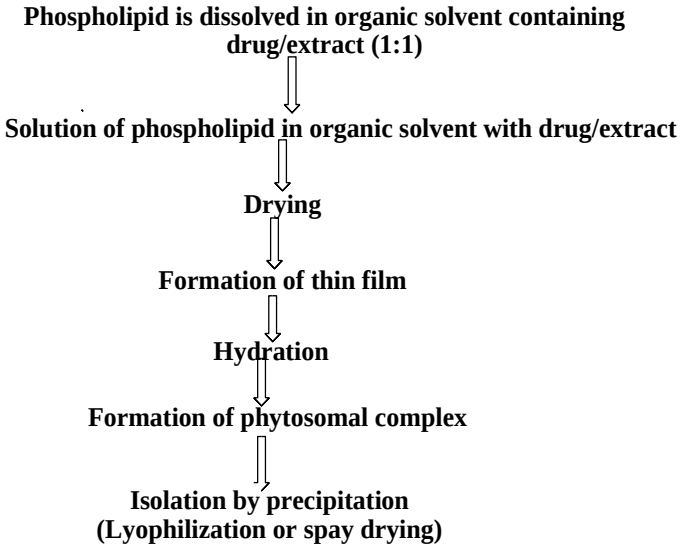

Fig. 2: Common stages for preparation of phytosomes [28]

2.5.1. Solvent evaporation method

Widely used preparation method for drug phospholipid complex is solvent evaporation method. In this method, the compound of interest and phospholipid are dissolved in solvent or mixture of solvents which are then refluxed for a certain period of time and then evaporated by using rota evaporator [55]. The solvent evaporation by rota evaporator works on the principle of boiling point reduction by application of vacuum, followed by rotation to increase the heating surface area to the solution. Its speed and ability to handle a large volume of solvents make rota evaporator a suitable method to cause complex formation. However, for evaporating high boiling point solvents like DMSO and DMF etc., high pressure vacuum system is required to get desired boiling point depression.

2.5.2. Co-grinding

This method mainly involves external mechanical force to knead the drug and phospholipid together for complex formation. An elucidation for this is probucol phospholipid complex which was prepared by co-grinding method and was compared with solvent evaporation method. It was observed that solvent evaporation gave a high degree of drug complexation as compared to co-grinding method. Nevertheless, this method was found suitable for scale-up production [56].

2.5.3. Mechanical dispersion method

In mechanical dispersion method, the phospholipid is dissolved in solvent and is subjected for sonication for few to several minutes. Then, the drug solution is added drop wise into the solution continuously while sonication. The example illustrating the application of mechanical dispersion to form drug-phosphoipid is well depicted in an investigation done by *Sikarwar et al.* [57]. The authors developed marsupin phospholipid complex using mechanical dispersion which proved to be stable and efficient in improving the bioavailability.

2.5.4. Super critical fluid process

SCF technologies are a promising technique as they can be used to produce particles of controlled size and distribution. This process can be performed at mild conditions of temperature and pressure. Apart from this, it is also environment friendly as compared to the process involving organic solvents. Carbon dioxide is the most widely used supercritical fluid because it has critical temperature of 31°C and critical pressure of 74 bar, allowing it to be used at mild temperature conditions (40–60°C). However, this technology has certain limitations like limited solubility of polar compounds in supercritical CO_2. *Li et al.* [58] reported puerarin phospholipid complex by this method and compared it with conventional methods like solvent evaporation, freeze drying and gas anti-solvent crystallization. They claimed that the phospholipid complex formed by supercritical fluid technology showed more dissolution efficiency as compared to the other three methods due to their higher ability to cause amorphization of the drug.

2.5.5. Co-solvent lyophilization

The principle involved in the lyophilization method is sublimation (removal of water from the frozen state without liquid phase). Lyophilization performed at temperature and pressure conditions below triple point, which enables sublimation of ice. Three steps involved in lyophilization process include freezing stage, primary drying, and secondary drying. An example describing the use of co-solvent lyophilization to form drug-

phospholipid complex is explained in a study conducted by *Cui et al.* [59]. In their investigation, authors developed insulin phospholipid complex which was then characterized by solubilization, IR, and X-ray diffraction. These mentioned characterization studies cumulatively helped in confirming the formation of drug-phospholipid complex.

2.5.6. Anti-solvent precipitation

In anti-solvent method, the drug and the phospholipid are dissolved in solvent and refluxed for particular time followed by precipitation using anti-solvent, which has limited solubility for the formed complex. Anti-solvent precipitation method can be performed at ambient temperature and pressure without using expensive equipment. This process is well elaborated in a study reported by *Murugan et al.* [60]. The authors reported ellagic acid phospholipid complex by anti-solvent precipitation method using DCM as solvent and n-hexane as anti-solvent to precipitate complex. Both DSC and TEM analysis collectively confirmed the formation of drug-phospholipid complex.

2.5.7. Solvent ether-injection process

This technique involves reaction of lipids dissolved in organic solvent with herbal extracts in aqueous phase. Phospholipids solubilised in diethyl ether are slowly injected drop wise in an aqueous solution of the phytoconstituents which is to be encapsulated. It results in the formation of cellular vesicles on subsequent solvent removal, leading to complex formation [31]. Structure of phytosomes depends upon concentration, amphiphiles in mono state are produced when the concentration is less, but variety of structures with different shapes viz. round, cylindrical, disc and cubic or hexagonal vesicles may be formed on increasing the concentration.

2.6. The factors influencing the phytosome formation

The factors that influence the formation of phyto phospholipid complexes are mainly included solvent, stoichiometric ratio of active constituents, reaction temperature and reaction time. Depending on the desired target, different process variables can be selected. For maximum yield, *Saoji et al.* studied the influence of process variables such as the phospholipid-to-drug ratio, the reaction temperature and the reaction time, and used a central composite design to acquire the optimal formulation [61]. For best solubility and skin permeation, *Das and Kalita* prepared a rutin phytosome in different stoichiometric ratios [62]. According to a recent report [63], by changing stoichiometric ratios and reaction temperature, the highest yield apigenin-phospholipid complexes are prepared by *Telange and his colleagues.*

2.7. Characterization of phytosomes

2.7.1. Solubility and partition coefficient

Determining solubility in either water or organic solvents and the n-octanol/water partition coefficient (P) is necessary to characterize active constituents, active constituent phytophospholipid complexes and physical mixtures. Generally, phyto-phospholipid complexes have better lipophilicity and hydrophilicity than active constituents, and typically exhibit improved lipophilicity [32]. *Rahila* confirmed that embelin in complex has greater solubility in n-octanol and water than embelin and its respective physical mixtures [64].

2.7.2. Particle size and zeta potential

Particle size and zeta potential are important properties of complexes that are related to stability and reproducibility. In general, the average phospholipid complexes particle size ranged from 50 nm to 100 μm. *Mazumder* prepared sinigrin phytosome complexes, and the average particle size and zeta potential of the complex were 153±39 nm and 10.09±0.98 mV, respectively [65].

2.7.3. Scanning electron microscopy (SEM) and transmission electron microscopy (TEM)

SEM has yielded important insights into the solid state properties and surface morphology of complexes. TEM is often used to study the crystallization and dispersion of nano-materials and to measure the particle size of nanoparticles. SEM has shown that active compounds can be visualized in a highly crystalline state, but the shaped crystals disappeared aftercomplexation. When diluted in distilled water under slight shaking, TEM showed that phyto-phospholipid complexes exhibit vesicle-like structures [65].

2.7.4. Spectroscopic evaluation

To confirm the formation of a complex or to study the reciprocal interaction between the phytoconstituents and the phospholipid, the following spectroscopic methods are used.

2.7.4.1. Ultraviolet spectra (UV-spectra)

Samples that reflect different absorption in the UV wavelength range can be used to characterize own

structural properties. Most studies have revealed no differences in the UV absorption characteristics of constituents before and after complexation. *Xu et al.* prepared luteolin-phospholipid complexes and found that the characteristic peaks of luteolin remained present [66]. Therefore, we conclude that the chromophores of compounds are not affected by being complexed with phospholipids.

2.7.4.2. Differential scanning calorimetry (DSC)

In DSC, interactions can be observed by comparing the transition temperature, appearance of new peaks, disappearance of original peaks, melting points, and changes in the relative peaks area [67]. Phyto-phospholipid complexes usually display radically different characteristic peaks compared to those of a physical mixture. It is assumed that, in addition to the two fatty chains of phospholipids, strong interactions occur in the active ingredients and the polar part of phospholipids also inhibits free rotation. *Das and Kalita* prepared phyto-phospholipid complexes that contained rutin and the resulting DSC thermogram showed two characteristic peaks that were lower than that of the physical mixture and the peaks of rutin and PC disappeared [62].

2.7.4.3. Fourier transforms infrared spectroscopy (FTIR)

FTIR is a powerful method for structural analysis, and yields different functional groups that show distinct characteristics in band number, position, shape, and intensity. The formation of phyto-phospholipid complexes can be verified by comparing the spectroscopy of phospholipid complexes to that of physical mixtures. Separate studies may show different results. Indeed, *Das and Kalita* prepared phyto-phospholipid complexes composed of rutin. The FTIR of a physical mixture of rutin and phyto-phospholipid complexes was superimposable with that of pure tutin [62]. When *Mazumder et al.* prepared sinigrin-phytosome complexes, the FTIR of phytosome complex showed different peaks from that of sinigrin, phospholipids and their mechanical mixtures [65].

2.7.4.4. X-ray diffraction

Currently, X-ray diffraction is an effective method to examine the microstructure of both crystal materials and some amorphous materials. X-ray diffraction is usually performed on either active constituents or active constituent phytophospholipid complexes, PCs and their physical mixtures. X-ray diffraction of an active constituent and physical mixture shows intense crystalline peaks that indicate a high crystal form. By contrast, active constituent phyto-phospholipid complexes do not exhibit crystalline peak, which suggests that the constituents in complex with phospholipids exhibit a molecular or amorphous form. That may account for the observation that phyto-phospholipid complexes have better lipophilicity and hydrophilicity than active constituents [32].

2.7.4.5. Nuclear magnetic resonance (NMR)

The ^{1}H NMR and ^{13}C NMR techniques play an important role in the identification of the structures of the complexes. As noted above, interactions between polyphenols and phospholipids are created by hydrogen bonds rather than chemical bonds. Angelico et al. established based on NMR data that hydrogen bonds can form between some polar phenolic functional groups of silybin A and phospholipids [68]. The spectra of different phyto-phospholipid complexes suggest that the hydrophobic side of lipids can act to cover the envelope on the central choline-bioactive parts of these complexes.

2.8. Oral bioavailability enhancement using a phospholipid complex: a mechanistic outlook

Generally, drugs with poor solubility (BCS class II) or with poor permeability (BCS classes III and IV), when given orally, show relatively low bioavailability [69]. Additionally, other reasons for low bioavailability are presence of P-gp pump which causes the efflux of naked drugs, the presence of metabolizing enzymes, and the environmental pH-mediated degradation [70]. Thus, delivery vehicles are essential for drugs so as to attain a desired level in the systemic circulation [71]. Phospholipid-drug complex could be used for the same, in which the absorption process is similar to the process through which the triglycerides and essential phospholipids are absorbed. The mechanism for absorption of the phospholipid-drug complex is similar to that of the endogenous absorption of phospholipids through enterocytes [72]. Structurally, the phospholipid comprises two fatty acid chain attached to the glycerol (diacyl glycerol) moiety, which undergoes hydrolysis to release fatty acid, which triggers its absorption. Similarly, the drug-diacyl glycerol complex when taken via oral route undergoes hydrolysis. Minor hydrolysis occurs in the stomach at pH of ~ 1.5, and majority of it occurs in the intestine starting from duodenum in which secretions from the liver, bile bladder, and pancreas in the form of juice are secreted [73,74]. In the intestine, the hydrolysis

of drug-diacyl glycerol occurs due to the presence of phospholipases (particularly phospholipase A2) which leads to release of fatty acid and form drug-monoacyl glycerol. The former drug-monoacyl glycerol along with the bile salts then forms micellar vehicles. For these micelles to form, excretion of bile into the duodenum is crucial which is regulated by a hormone called cholecystokinin (CCK) which is released when a higher concentration of fatty acids are formed by hydrolysis of diacyl-glycerophospholipids and triglycerides [73, 75]. However, the minor hydrolysis which occurs in the stomach tends to release the fatty acid which initially triggers the CCK release which further regulates the release of bile acids and salts. Once the hydrolysis is done, the drug-monoacyl phospholipid vesicles are then taken up by passive diffusion by enterocytes. The enzymes in smooth endoplasmic reticulum of enterocytes, i.e., acyl-CoA convert drug-monoacyl phospholipids and endogenous diglycerides to diacyl phospholipids and triglycerides, respectively. Further, in golgi apparatus, apoportein B-48 is integrated into the phospholipid vesicle to form nascent chylomicron [76]. The chylomicron exits enterocyte via exocytosis through the basal membrane and enters lacteal (lymph capillary) which then transports it away from the intestine and bypasses the first pass metabolism. The chylomicrons deliver the drug complex into systemic circulation at thoracic duct connection with a left subclavian vein [77]. Once nascent chylomicron enters the systemic circulation, it is converted to mature chylomicron when high density lipoprotein transfers apolipoprotein C-II and apolipoprotien E to the nascent one. After the triglycerides are stored, the matured chylomicron returns back the apolipoprotein C-II, and then, they are termed as chylomicron remnant, which is generally present in the liver for endocytosis and breakdown [78]. Hence, through the chylomicron, the drug phospholipid complex enters the systemic circulation and bypasses the first pass metabolism. This mechanism of the drugphospholipid complex allows the absorption of drugs which are either not soluble or has shown extensive first pass metabolism. The schematic illustration of the same is depicted in Figure 3.

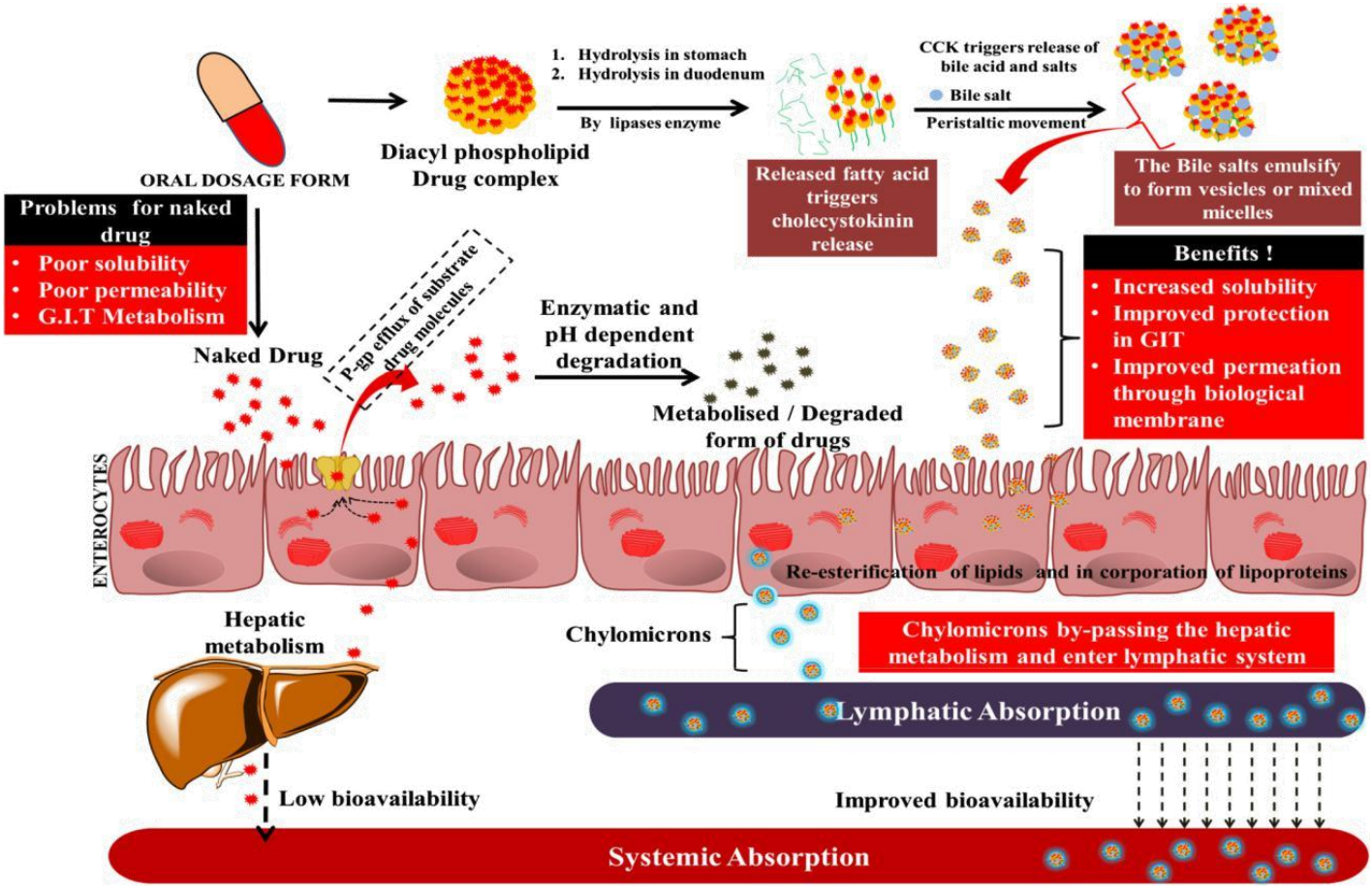

Fig. 3: The general mechanism of drug phospholipid complex to enhance bioavailability [79]

2.9. Potential of phytosomes as a novel drug delivery system: applications

Phytosomes are used in curing various diseases like liver disease, heart disease, etc. Many other uses of phytosomes include anti-inflammatory, lipolytic, vasokinetic, anti-edema agent, etc. In addition, it is used as a nutraceutical, immunomodulator, antioxidant, etc. *Yanyu et al.* [80] demonstrated that bioavailability of silybin in rat was increased extraordinarily after oral administration of prepared silybinphospholipid complex. Similarly, *Tedesco et al.* [81] showed that in protection against the toxic effect of aflatoxin B, silymarin phytosome shows better antihepatotoxic effect than silymarin alone. Similarly, quercetin phospholipids complex exerted better therapeutic efficacy than the molecule in rat liver injury induced by carbon tetrachloride [82]. The various advantages and applications of phytosomes are mentioned below:

1. Phytosome permeates the nonlipophillic botanical extract, making botanical extracts better bioavailable.
2. Phytosome works in small quantity to give desired results and is widely used in cosmetics due to their better skin penetration.
3. Phytosome finds applications in giving liver-protectant flavonoids due to their easy bioavailability.
4. The phytosome process gives rise to little cells whereby the costly components of the herbal extract are protected from damage by digestive secretions and gut bacteria.
5. Phytosomes are used in anti-inflammatory formulations, pharmaceuticals, and cosmetic formulations. Phytosomes are also used to treat acute and chronic liver disease.
6. Phytosomes are also used as cancer chemopreventive agent, antioxidant, brain stimulant, immunomodulator, skin-improving agent, anti-wrinkle and antiaging supplement, antihypertensive agents, etc [83]. Phyto-phospholipid complexes on the market are shown in Table 1.

Table 1: Therapeutic application of different phyto-phospholipid complexes on the market [84]

S. no.	Trade name	Phytoconstituents complex	Indication
1	Greenselct®	Epigallocatechin 3-O-gallate from cameliasinensis (green tea)	Systemic antioxidant, protect against cancer and damage to cholesterol.
2	Ginkgoselect®	Ginkgo flavono glycosides from ginkgo biloba	Protects brain and vascular lining
3	Silybin	Silybin from silymarin	Antioxidant protection for the liver and skin.
4	Glycyrrhiza	18-beta glycyrrhetinic acid	Anti-inflammatory activity
5	Grape seed (Leucoselect)	Procyanidins from vitis vinifera	Anti oxidant, anticancer
6	Curcumin (Merinoselect)	Polyphenol from curcuma longa	Cancer chemopreventive agent improving the oral bioavailability of curcuminoids and the plasma.
7	OleaselectTM	Polyphenols from olive oil	Inhibit harmful oxidation of LDL cholesterol, and anti-inflammatory effect.
8	Sabalselect®	An extract of saw palmet to berries through supercritical CO2 (carbondioxide) extraction	It is beneficial to the normal functioning of the prostate
9	PA2	Proanthocyanidin A2 from horse chestnut bark	Anti-wrinkles, UV protestant
10	Zanthalene	Zanthalene from zanthoxylum bungeanum	Soothing, anti-irritant, anti itching
11	Centella	Terpenes	Vein and skin disorders
12	Hawthorn TM	Flavonoids from crataegus sp.	Nutraceutical, antihypertensive, cardio-protective,

3. CONCLUSION

Herbal medicines have been widely accepted globally since ancient times and have been recognized for their better therapeutic value and extremely lesser adverse effects as compared with modern allopathic medicines. At the same time, there are many challenges associated with herbal drugs like biological standardization; pharmacological and toxicological evaluation; investigation of sites of action/absorption, safety, toxicity, legal, and regulatory aspects of herbal drugs; etc. Moreover, Ayurvedic drugs/phytotherapeutics need a suitable delivery system for the active components to the target site to increase efficacy for which novel drug delivery systems are the most desirable one. Novel drug delivery systems like phytosomes not only reduce the repeated administration of drugs but also help to increase the therapeutic value by reducing toxicity and increasing bioavailability. Phytosomes form a connection between the conventional drug delivery system and novel drug delivery system. Phytosomes are used as a medicament and have wide scope in medical sciences, and many more areas of phytosome applications are to be revealed in the future in the view of pharmaceutical application.

4. REFERENCES

1. Brahmankar DM, Jaiswal SB. Biopharmaceutics and pharmacokinetics-a treatise.1st ed. Delhi:Vallabh Prakashan Publisher; 1995.
2. Dhiman A, Nanda A, Ahmad S. *Int Conf Envi Chem Biol,* 2012; **49**:171-175.
3. Pawar HA, Bhangale BD. *J Bioanal Biomed,* 2015; **7**:006- 012.
4. Saller R, Meier R, Brignoli R. *Drugs,* 2001; **61(14)**:2035-2063.
5. Kidd PM. *Altern Med Rev,* 2009; **14(3)**:226-246.
6. Celik HT, Guru M. *J Supercrit Fluids,* 2015; **100**:105-109.
7. Namratha K, Shenai P, Chatra L. *Cagdas Tıp Dergisi,* 2013; **3(2)**:136-143.
8. Ramsewak RS, Dewitt DL, Nair MG. *Phytomedicine,* 2000; **7(4)**:303-308.
9. Apostolova E, Spaseska B, Crcarevska MS, Dodov MG, et al. *Int Symp Med Sci,* 2015; **1(1)**:95-96.
10. Dai J, Mumper RJ. *Molecules,* 2010; **15(10)**:7313-7352.
11. Teng Z, Yuan C, Zhang F, et al. *PLoS One,* 2012; **7(1)**:e29647.
12. Manach C, Scalbert A, Morand C, Remesy C, et al. *Am J Clin Nutr,* 2004; **79(5)**:727-747.
13. Bhattacharya S. *Int J Health Res,* 2009; **2(3)**:225-232.
14. Kidd P, Head K. *Altern Med Rev,* 2005; **10(3)**:193-203.
15. Ting Y, Jiang Y, Ho CT, Huang Q. *J Funct Foods,* 2014; **7**:112-128.
16. Wei L, Kelly AL, Song M. *Trends Food Sci Tech,* 2016; **47**:1-9.
17. Aude M, Florence EL. *Pharmaceutics,* 2011; **3(4)**:793-829.
18. He JL, Luo LY, Zeng L. *Food Sci,* 2011; **32**:317-22.
19. Lambert J, Sang S, Hong J, et al. *Drug Metab Dispos,* 2006; **34**:2111-2116.
20. Mulholland PJ, Ferry DR, Anderson D, et al. *Ann Oncol,* 2001; **12(2)**:245-248.
21. Hostettmann K. *Int J Pharma Sci* 2010; **36(1)**:S1-S3.
22. Chen ZP, Sun J, Chen HX, et al. *Fitoterapia* 2010; **81(8)**:1045-1052.
23. Yue PF, Yuan HL, Ming Y, et al. *Drug Dev Ind Pharm,* 2009; **1**:99-102.
24. Maiti K, Mukherjee K, Gantait A, Saha BP, et al. *Int J Pharma,* 2007; **330(1-2)**:155-163.
25. Xiao Y, Song Y, Chen Z, Ping Q. *Int J Pharma,* 2006; **307(1)**:77-82.
26. Amin T, Bhat SV. *Int J Adv Res Technol,* 2012; **1(3)**:1-5.
27. Bombardelli E, Spelta M. *Cosmet Toiletries,* 1991; **106**:69-76.
28. Patel J, Patel R, Khambholja K, Patel N. *Asian J Pharm Sci,* 2009;**4**:363-371.
29. Amit P, Tanwar YS, Rakesh S, Poojan P. *J Pharm Sci Biosci Res,* 2013; **3**:51-57.
30. Bombardelli E. *Boll Chim Farm,* 1991; **130**:431-438.
31. Khan J, Alexander A, Saraf S, Saraf S. *J Control Release,* 2013; **168(1)**:50-60.
32. Ghanbarzadeh B, Babazadeh A, Hamishehkar H. *Food Biosci,* 2016; **15**:126-135.
33. Bombardelli E, Sabadie M. 1990; US Patent No. 4963527.
34. Singh RP, Gangadharappa H, Mruthunjaya K. *J Drug Deliv Sci Technol*, 2017; **39**:166-179.
35. Marsh D. *Chem Phys Lipids*, 1991; **57(2-3)**:109-120.
36. Li J, Wang X, Zhang T, et al. *Asian J Pharma Sci,* 2015; **10(2)**:81-98.
37. Suriyakala PC, Babu NS, Rajan DS, Prabakaran L. *Int J Pharm Pharm Sci,* 2014; **6(1)**:8-11.
38. Duric M, Sivanesan S, Bakovic M. *Eur J Lipid Sci Tech,* 2012; **114(4)**:389-398.
39. Bombardelli E, Cristoni A, Morazzoni P. *Fitoterapia,* 1994; **65(5)**:387-401.

40. Sarika D, Khar RK, Chakraborthy GS, Saurabh M. *J Pharm Res,* 2016; **15(2)**:56-62.
41. Afanaseva YG, Fakhretdinova ER, Spirikhin LV, Nasibullin RS. *Pharm Chem J,* 2007; **41(7)**:354-356.
42. Semalty A, Semalty M, Rawat BS, singh D, et al. *Expert Opin Drug Deliv,* 2009; **6(6)**:599-612.
43. Shakeri A, Sahebkar A. *Recent Pat Drug Deliv Form,* 2016; **10(1)**:7-10.
44. Semalty A. *Expert Opin Drug Deliv,* 2014; **11(8)**:1255-1272.
45. Tripathy S, Patel DK, Barob L, Naira SK. *J Drug Deliv Ther,* 2013; **3(3)**:147-152.
46. Chauhan NS, Rajan G, Gopalakrishna B. *J Pharm Res,* 2009; **2(7)**:1267-1270.
47. Zhang K, Zhang M, Liu Z, et al. *Fitoterapia,* 2016; **113**:102-109.
48. Maryana W, Rachmawati H, Mudhakir D. *Mater Today Proc,* 2016; **3(3)**:855-866.
49. Tripathy S, Patel D, Baro L, Nair S. *J Drug Deliv Ther,* 2013; **3**:147-152.
50. Patel A, Tanwar Y, Rakesh S, Patel P. *J Pharm Sci Bio Sci Res*, 2013; **3**:51-57.
51. Jain NK. Liposomes as drug carriers, controlled and novel drug delivery, 1st ed., New Delhi: CBS publisher; 321-326.
52. Dayan N, Touitou E. *Biomaterials,* 2000; **21**:1879-1885.
53. Maffei Facino R, Carini M, Aldini G, Bombardelli E, et al. *Arzneimittelforschung,* 1994; **44**:592-601.
54. Jain N, Jain R, Jain DK, Jain S. *Int J Pharm Sci Drug Res* 2010; **2(4)**:224-228
55. Dora CP, Kushwah V, Katiyar SS, Kumar P, et al. *Int J Pharm,* 2017; **534(1-2)**:1-13.
56. Guo B, Liu H, Li Y, Zhao J, et al. *Int J Pharm*, 2014;**474(1–2)**:50-56.
57. Sikarwar MS, Sharma S, Jain AK, Parial S. *AAPS Pharm Sci Tech*, 2008;**9(1)**:129-137.
58. Li Y, Yang D-J, Chen S-L, Chen S-B, et al. *Pharm Res*, 2008; **25(3)**:563-577.
59. Cui F, Shi K, Zhang L, Tao A, et al. *J Cont Rel,* 2006; **114(2)**:242-250.
60. Murugan V, Mukherjee K, Maiti K, Mukherjee PK. *J Agric Food Chem*, 2009; **57(11)**:4559-4565.
61. Saoji SD, Raut NA, Dhore PW, Borkar CD, et al. *AAPS J,* 2016; **18(1)**:102-114.
62. Das MK, Kalita B. *J Appl Pharm Sci,* 2014; **4(10)**:51-57.
63. Telange DR, Patil AT, Pethe AM, Fegade H, et al. *Eur J Pharm Sci,* 2017; **108**:36-49.
64. Pathan RA, Bhandari U. *J Incl Phenom Macrocycl,* 2011; **69(1-2)**:139-147.
65. Mazumder A, Dwivedi A, Preez JLD, Plessis JD. *Int J Pharm,* 2015; **498(1-2)**:283-293.
66. Xu K, Liu B, Ma Y, et al. *Molecules,* 2009; **14(9)**:3486-3493.
67. Hao H, Jia Y, Han R, Amp IA. *J Chin Pharm Sci,* 2013; **22(5)**:385-392.
68. Angelico R, Ceglie A, Sacco P, Colafemmina G, et al. *Int J Pharm,* 2014; **471(1-2)**:173-181.
69. Bhingare U, Khadabadi S, Shinde N. *Int J,* 2014; **3(1)**:14-20.
70. Gavhane YN, Yadav AV. *Saudi Pharm J*, 2012; **20(4)**:331-44.
71. Jena SK, Singh C, Dora CP, Suresh S. *Int J Pharm*, 2014; **473(1-2)**:1-9.
72. Van Hoogevest P. *Eur J Pharm Sci*, 2017; **108:**1-12.
73. Chaudhri O, Small C, Bloom S. *Phil Trans R Soc London B: Biol Sci.*. 2006; **361(1471)**:1187-1209.
74. Marieb EN, Hoehn K. Human anatomy and physiology. 8th ed. San Francisco: Benjamin Cummings; 2010.
75. Kossena GA, Charman WN, Wilson CG, O'Mahony B, et al. *Pharm Res*, 2007; **24(11)**:2084-2096.
76. Higgins J, Fielding C. *Biochemistry*, 1975; **14(11)**:2288-2293.
77. Harde H, Das M, Jain S. *Expert Opin Drug Deliv*, 2011; **8(11)**:1407-1424.
78. Nestel P, Havel R, Bezman A. *J Clin Invest*.. 1962; **41(10)**:1915-1921.
79. Kuche K, Bhargavi N, Dora CP, Jain S. *AAPS PharmSciTech,* 2019; **20**:43.
80. Yanyu X, Yunmei S, Zhipeng C, Quineng P. *Int J Pharm*, 1998; **307**:77-82.
81. Tedesco D, Steidler S, Galletti S, Tameni M, et al. *Poult Sci,* 2004; **83**:1839-1843.
82. Maiti K, Mukherjee K, Gantait A, Ahamed HN, et al. *Iran J Pharmacol Ther*, 2005; **4**:84-90.
83. Dhyani A, Juyal D. *Curr Trends Biomedical Eng Biosci,* 2017; **3(5)**; 5555621.
84. Lua M, Qiu Q, Luo X, Liu X, et al. *Asian J Pharm Sci*, 2019; **14:**265-274.