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PHYTOSOME: A NOVEL DRUG DELIVERY CARRIER

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ABSTRACT

Novel drug delivery system aims to improve the shortcomings of conventional and traditional delivery systems. The novel delivery approach towards plant based drugs is gearing up and tremendous success have achieved in making phytoconstituent more bioavailable and stable. Polyphenolic phytoconstituent of flavonoid class have been known for centuries possessing diverse health giving properties but not extensively formulated to modern dosage forms due to problem in gastrointestinal absorption. A covalent complex of such phytoconstituent with phosphatidylcholine – the principle phospholipid of biological membrane makes them significantly bioavailable and stable. The complex such developed is a patented technology and given the name Phytosome. The phytosome technology markedly enhances the bioavailability of phytomedicine by making them soluble in GI fluid and enhancing lipid solubility. Important herbs including *Milk thistle, Ginkgo biloba, Grape seed, Green tea, Hawthorn, Ginseng, etc*. are currently available in phytosome form in the market. Phytosomal delivery is not restricted to flavonoids (polyphenol) class of phytoconstituents only, but any beneficial molecule possessing structural requirement for direct binding with phosphatidylcholine can be converted to phytosome, e.g. Androrgrapholide Phytosome, clarithromycin-phospholipid complex, glycerrhetinic acid-phospholipid complex, aceclophenac-phospholipid complex. Knowing the underlying objective, potentiality and diverse application of this novel phytosome technology, an attempt is accomplished to review the available literatures with research related to clinical aspect and formulation as well as success of this newer approach.

Keywords: Phospholipid complex, polyphenolic, phosphatidylcholine, flavonoid, bioavailability, solubility.

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INTRODUCTION

Herbs are known to be the oldest remedies used by mankind. Throughout history India has well known for oldest, richest and most diverse cultural living traditions associated with the folk knowledge of use of medicinal plant (Tandon *et al* 2004). Ancient Chinese and Egyptian Papyrus writings describe medicinal uses of plants. Researchers found that people in different parts of the world tended to use the same or similar plants for the same purposes (Altschuler *et al* 2007). Side effects of allopathic medicines (Dandiya *et al* 1974), efficacy of plant derived drugs (Bhatt 1999) and growing interest in natural products has increased scientific interest in medicinal plants and it seems that plant derived products will continue to play an important role in human health (Patwardhan 2000). As per WHO estimates, 80 percent of about 4000 million inhabitants on this planet rely on plant products. It is estimated that the global traditional medicine market is growing at the rate of 7 - 15 % annually (Chaudhari 1996). The medicinal plant value is about 5000 INR crores in India and it is estimated that the country exports about 550 INR crores worth of herbal drugs. But with the rich and diverse botanical resources in our country, this is not an impressive export performance considering the worldwide herbal market worth US 60 billion dollars (Satish 2006).

Plants are the rich source of numerous medicinal and health giving substances, most of them are secondary metabolites, prominent among these are the flavonoids. Flavonoids are a class of secondary plant phenolic with significant antioxidant and chelating properties (Catherine *et al* 1996). Flavonoids are first recognized for their anti-oxidant properties and are widely distributed in plants. To date more than 4000 naturally occurring flavonoids have been identified from plant source having diverse biological activities (Kelly *et al* 2002). A diet containing antioxidant substances such as flavonoids or polyphenols has been recognized to hinder degenerative processes that are principal cause of chronic diseases. Since the thirties, flavonoids and other polyphenols have been known for their capillary protective activity. In the recent past epideminological studies in the southern France revealed that mortality rates from heart diseases were lower than expected, despite very high intake of lipids and the tendency to smoke cigarettes. The phenomena, known as French Paradox is probably

due to concomitantly elevated consumption of red wine which contain flavonoids. Flavonoids are chemically polyphenolic and are less absorbed from GIT. The less absorption of polyphenolics is due to multiple ring arrangement of the molecules and high water solubility which is a hindrance in passage through biomembrane. Some of the polyphenolics are highly lipophilic and possess inadequate dissolution in aqueous GI fluids (Jiang *et al* 2001).

In the recent past, considerable scientific works targeted on the development of novel drug delivery system (NDDS) for herbal drugs. NDDS approaches toward phytochemicals to develop polymeric nanoparticles and nanocapsules, liposomes, solid-lipid nanoparticles, transferosome, pharmacosome, phytosomes and nanoemulsions have a number of advantages for herbal drugs, including enhancement of solubility and bioavailability, protection from toxicity, enhancement of pharmacological activity, enhancement of stability, improved tissue macrophages distribution, sustained delivery and protection from physical and chemical degradation. Thus novel drug delivery of herbal drugs have significant scope for enhancing the activity and overcoming problems associated with plant medicine of conventional type (Ajazuddin *et al* 2010). Liposomes, which are biodegradable and essentially nontoxic vehicles, can encapsulate both hydrophilic and lipophilic materials including phtyoconstituent (Medina *et al* 2004). On human body herbal cosmetic formulations can be made more efficient through NDDS approach (Chanchal *et al* 2008). Liposomal as well as niosomal systems are not efficient enough for transdermal delivery (Cevc *et al* 1997). A new type of carrier system called transferrosome has recently been introduced, which is capable of transdermal delivery of low as well as high molecular weight drugs (Schatzlein *et al* 1995). Transferosomes are chemically unstable and expensive. The limitations of transferosome can be overcome by the pharmacosome approach. They are amphiphillic in nature. These are colloidal dispersions of drug covalently bound to lipids, and exist as ultrafine vesicular, micellar, or hexagonal aggregates depending on the chemical structure of drug lipid complex (Vaizoglu *et al* 1986). In pharmacosome process any drug possessing an active hydrogen atom (-COOH, -OH, $-NH_2$) can be esterified to lipid, with or without spacer chain and synthesis is so guided to result in an amphiphillic compound which facilitate tissue transfer (Biju *et al* 2006).

The bioavailability of some orally administered botanical extracts is erratic and poor due to sub optimal gastro intestinal absorption. Bioavailability can be improved by using new delivery systems which can enhance the rate and the extent of solubilization into aqueous intestinal fluids and the capacity to cross biomembrane (Semalty *et al* 2010).

Most of the phytoconstituents possess complex ring structure with hydrophilicity which leads to poor absorption through lipid membranes. At the same time highly lipophilic phytoconstituents have poor dissolution in aqueous gastric fluid leading to limited gastro-intestinal absorption. These phytoconstituents can be associated with lipid moieties like phosphatidylcholine to absorb better. Indena Inc. (Italy) has developed a new series of non-covalent supramolecular adducts named 'phytosomes' by complexing the phytoconstituents in a molar ratio with phosphatidylcholine (Vasanti 2008). The problem of lesser absorption associated with polyphenol can be minimized by complexing with phospholipids. In higher animals the phospholipids are also employed as natural digestive aids and as carrier for both fat soluble and water soluble nutrients. They are miscible both in water and in lipid environment and are well absorbed orally. Phytosomes become more bioavailable as compared to conventional herbal extract owing to their enhanced capacity to cross the lipoidal biomembrane and finally reaching the systemic circulation. Hence phytosome is fastly growing attractive way of delivering botanicals based drugs and nutraceuticals (Bhattacharya and Ghosh 2009).

The phytosome process has been applied to many useful herbal extracts such as Ginkgo biloba, grape seed, hawthorn, milk thistle, green tea, and ginseng (Barzhagi 1990). The usual scheme to produce phytosome through binding individual components of herbal extracts to phosphatidylcholine, which results in a dosage form that is better absorbed and thus leads to better results than conventional herbal extracts (Murray 2006). The results are encouraging and indicate that the absorption of silybin from silybin phytosome is approximately seven times greater compared to the absorption of silybin from regular milk thistle extract (Barzhagi 1990). Drug can be embedded or dissolved in carrier and can also be adsorbed or coupled on the surface (Yuan *et al* 2003). Encapsulating drug within nanoparticulate carrier can improve the solubility and pharmacokinetics of drugs, and in some cases enable further clinical development

of new chemical entities that have limited applicability because of poor pharmacokinetic properties (Alexis *et al* 2008).

Phospholipids are small lipid molecule in which the glycerol is bound to only two fatty acids instead of three as in tryglyceride, with the remaining site is occupied by a phosphate group (Citernesi *et al* 1995). Phosphatidylcholine (PC), used to be called lecithin, is the most abundant constituent in human body and has many important functions. PC is the most important building block to furnish replacement membrane mass when any membrane is damaged. PC also has excellent emulsifying properties which are drawn upon by the liver to produce the bile fluid. PC also has excellent surfactant properties, on which the lung and intestinal lining cells depend for their gas and fluid exchange functions (Dubey 2007). Likewise, several studies have indicated the beneficial role of soy lecithin containing phospholipids in maintaining the concentration of the drug in plasma for a longer time and also in enhancing the therapeutic efficiency of some molecules having poor oral absorption. Several phospholipids are reported to be employed for this purpose such as hydrogenated soy phosphatidylcholine, dipalmitoylphosphatidylcholine, distearoylphosphatidylcholine (Murray 2006).

The core of the phytosome technology

Flavonoids are chemically polyphenolic and provide the necessary structural framework for the direct binding with phosphatidylcholine molecule. When a stoichiometric amount of the phospholipid react with purified herbal extract in an aprotic solvent, phytosomes come to existence. Phosphatidylcholine is an amphoteric compound. The phosphatidyl part is lipophilic and the choline part bear hydrophilic properties. The polyphenolics bind with the choline portion of phosphatidylcholine whereas the lipoidal phosphatidyl portion constructs the body and tail of the complex and envelop the hydrophilic choline based core. Molecules are tied by chemical bonds to the polar choline head of the phospholipid, as can be characterized by specific spectroscopic techniques (Parris 2009). This results in small microsphere or the production of cells known as phytosome (Dubey *et al* 2007).

Preparation of phytosomes

Phytosomes are prepared by reacting one to three moles of a natural or synthetic phospholipid such as phosphatidylcholine with one mole of polyphenolic constituent, either alone or in the natural mixture in aprotic solvent such as dioxin or aceton from which complex can be isolated by precipitation with non solvent such as aliphatic hydrocarbon or lyophilization or by spray drying. In the complex formation of phytosomes the ratio between these two moieties is in the range from 0.5-2 moles. The most preferable ratio of phospholipid to flavonoids is 1:1 (Marena *et al* 1991).

Yan *et al* 2009, prepared clarithromycin-phospholipid complex. The method they followed is as the required amount of clarithromycin and phospholipid were put in a 50 ml round bottomed flask and 20 ml reaction solvent was added. The mixture was refluxed at 65°C for 3 hours. Then the settled solution was evaporated to obtain the dried clarithromycin-phospholipid complex. The reaction solvent used was acetone, acetic ether and dehydrated alcohol. The ratios of clarithromycin to soybean lecithin were 1:1, 1:8 and 1:10. Quercetin-phytosome (Maiti 2005) developed by refluxing 1 mole of Quercetin with 1 mole of hydrogenated soy phosphatidylcholine (HSPC) in 20 ml of dichloromethane till all the quercetin dissolved. The volume of the resulting solution was reduced to 2-3 ml and 10 ml of n-hexane was added to above solution to get the complex as precipitate. The complex was then filtered, dried under vacuum and stored in air tight container. In a similar way poorly aqueous soluble curcumin was also transformed to phospholipid complex (Maiti *et al* 2007).

Yanyu *et al* 2006 prepared a silybin-phospholipid complex using ethanol as a reaction medium. Silybin and phospholipid were resolved into the medium, after that the organic solvent was removed under vacuum condition, and a silybin-phospholipid complex was formed.

Various preparation methods results in different phytosome complexes depending on the protocol employed. Thus, the phospholipid complex of curcumin prepared in an aprotic solvent (Liu et al 2006) showed remarkable difference from the one prepared in a protic solvent (Franceschi *et al* 2007). Different phospholipids afford different complexes, as found for Ginko biloba phytosomes, commercially known as Virtiva

and Ginkoselelct-phytosome prepared with phosphatidylserine and phosphatidylcholine, respectively (Morazzoni *et al* 2005).

Physicochemical characteristics

Phytosomes are obtained by reaction of molar equivalent amount of phospholipids and the substrate in an appropriate solvent. On the basis of spectroscopic data it has been shown that the main phospholipid-substrate interaction is due to the formation of hydrogen bonds between the polar heads of phospholipid (i.e. phosphate and ammonium groups) and the polar functionalities of the substrate. When treated with water phytosomes acquire a micellar shape forming liposome like structures but still there exist some fundamental difference between phytosome and liposome. In liposomes the active drugs are dissolved in the core of the complex and there is no molecular bonding between the lipid and the guest substance. But in case of phytosome the polar groups of the lipophilic or hydrophilic guest interact through hydrogen bonding with the polar groups of phospholipid, forming a unique arrangement that have been confirmed by spectroscopy (Bombardelli *et al* 1989, Gabetta *et al* 1989). In general phytosomes are amphiphillic substance having definite melting point, commonly soluble in lipids. The low solubility in aqueous media makes the formation of stable emulsions and creams possible, improving the biopharmaceutical properties of both highly lipophilic and hydrophilic phytoconstituents (Semalty *et al* 2010).

Evaluation of physical, chemical and biological parameters of phytosome

Visualization of phytosomes can be achieved using transmission electron microscopy (TEM) and by scanning electron microscopy (SEM) (Maghraby *et al* 2000). The particle size and zeta potential can be determined by dynamic light scattering (DLS) using a computerized inspection system and photon correlation spectroscopy (PCS) [Fry *et al* 1978]. The entrapment efficiency of a drug by phytosomes can be measured by the ultracentrifugation technique (Jain 2005). The transition temperature of the vesicular lipid systems, which is an indication of interaction due to incompatibility, can be determined by differential scanning calorimetry (DSC) (Cevc *et al* 1995). The amount of drug can be quantified by a modified high performance liquid chromatographic method or by a suitable spectroscopic method (Facino *et al* 1994). To confirm the formation of a complex or to study the reciprocal interaction between

the phytoconstituent and the phospholipids, sophisticated spectroscopic methods are used (Semalty *et al* 2006) such as FTIR, ^{1}H NMR, ^{13}C NMR (Bombardelli *et al* 1991). Researchers evaluated the biological effectiveness of phytosome based on variety of models. Models of *in vitro* and *in vivo* evaluations are selected on the basis of the expected therapeutic activity of the biologically active phytoconstituents present in the phytosomes (Semalty *et al* 2006). For example, *in vitro* antihepatotoxic activity can be assessed by the antioxidant and free radical scavenging activity of the phytosomes. For assessing antihepatotoxic activity *in vivo*, the effect of prepared phytosomes on animals against carbon tetrachloride (Maiti *et al* 2010), thioacetamide, paracetamol or alcohol induced hepatoxicity can be examined (Comoglio *et al* 1995). Skin sensitization and tolerability studies of glycyrrhetinic acid-Phytosome® ointment, a commercial product, describe the *in vivo* safety evaluation methodology (Bianchi *et al* 1989). Filburn *et al* 2007 studied the bioavailability of a silybin-phosphatidylcholine complex in dog models to examine the pharmacokinetic parameters of this new complexed form.

Cosmetic value of phytosomes

The topical use of flavonoids is restricted due to poor absorption through skin. Phytosomes are probably a system which can improve absorption of phytoconstituents through skin to regulate the physiology of skin compositions. The improvement in the functioning of skin indicates the functional cosmetic value of the phytosomes. Generally the passage of the compounds linked to phospholipids takes place through interaction with cutaneous structure, which influences the release of the phytoconstituents. The rate of absorption from the phytosome complex is dramatically enhanced without damaging the epidermis, which suggests potential use of phytoconstituents-phospholipid complex cosmetic value in skin as well as for systemic function via skin (Gupta *et al* 2007).

The phytosomes have a marked lipophilic character and facilitate topical absorption of complex molecules which show improved specific activity in the skin functions such as hydration, collagen structure and enzyme balance. Topical absorption of biologically active phytoconstituents provides local application at the site of requirement. The phytosome process intensifies herbal compounds by improving

absorption, increasing bioavailability and enhancing delivery to the tissues. By combining the emulsifying action of the phospholipids with the standardized botanical extracts, the phytosome form provides dramatically enhanced bioavailability and delivers faster and improved absorption through the skin (Bomberdelli *et al* 1994).

Dosage comparison of phytosomes and regular extract

The dosage level of a phytosome is almost close to the dosage recommendation typically given for the corresponding standardized herbal extracts. For example, Grape seed extract and Grape seed phytosome. One 50 mg capsule of grape seed phytosome is equivalent to about 50 mg of regular grape seed extract, in terms of absorption only. However, in terms of biological activity, it is estimated that one 50 mg capsule of Grape seed phytosome may be as effective as 150 mg of unbound grape seed extract. Studies with SILIPHOST and Ginko phytosomes also support that the phytosome process enhances the utilization of the key components of the plant extract (Gupta *et al* 2009).

The effectiveness of any herbal product is dependent upon delivering an effective level of the active compounds. If the absorption of the active constituent can be increased better result is expectable. Several clinical studies have shown SILIPHOST is more effective and produce better results compared to regular milk thistle extracts. In one study of 232 patients with chronic hepatitis (viral, alcohol, or drug induced) treated with SILIPHOST at a dosage either 120 mg twice daily or 120 mg thrice daily for up to 120 days, liver functions returned to normal faster in the patients taking SILIPHOST compared to a group of controls in which 49 treated with a commercially available silymarin and 117 untreated or given placebo (Mascarella 1993).

DISCUSSION AND CONCLUSION

Over the past several years, great advances have been made on development of novel drug delivery systems (NDDS) for plant actives and extracts. The variety of novel herbal formulations like polymeric nanoparticles, nanocapsules, liposomes, phytosomes, nanoemulsions, microsphere, transferosomes and ethosomes has been reported using bioactive and plant extracts. The novel formulations are reported to have remarkable advantages over conventional formulations of plant actives and extracts which include enhancement of solubility, bioavailability, protection from toxicity,

enhancement of pharmacological activity, enhancement of stability, improved tissue macrophages distribution, sustained delivery, and protection from physical and chemical degradation (Ajazuddin 2010). Over the years, vesicular systems have been investigated as a major drug delivery system, due to their flexibility to be tailored for varied desirable purposes and play an important role in the selective targeting and the controlled delivery of various drugs (Biju *et al* 2006).

Phytosome technology emerged in 1989 and sparked a revolution in delivery of herbal phytoconstituents. The scientific community has done sufficient research in this particular segment and outcome of which is distinctively visible as many phytosome based product are available commercially and Siliphos, Meriva, Ginkoselect Phytosome, Centella Phytosome, Greenselect Phytosome are a few examples.

Phosphatidylcholine is endowed with ampiphilic properties because of one positively charged head group and two neutrally charged tail groups, a rare molecular characteristic that renders PC miscible in both aqueous and nonaqueous environment. By complexing a polyphenol with PC to make a phytosome, the polyphenol comes to share some of PCs versatile solubility properties. The water miscible PC molecule enhances the dispersion of the poorly soluble polyphenol molecules into aqueous environment of the gastrointestinal lumen. Further, PC enhances transfer from the lumen into the lipid soluble environment of the outer cell membrane of the enterocytes. The enterocyte outer membrane has a lipid bilayer that consists largely of PC. It is feasible that the PC of the phytosome merges into this PC domain of the enterocytes membrane, carrying the polyphenol with it and so ushering the polyphenol into the cell (Kidd *et al* 2002).

Phytosomes can influence the functioning of the skin suggesting the functional cosmetic value of the phytosomes. The rate of absorption from the phytosome complex is dramatically enhanced without damaging the epidermis, which suggests potential use of phytosome based product in cosmetics as well as for systemic function via skin (Gupta *et al* 2007).

Plants are the rich library of many readymade molecules, and continuous review as well as research is necessary to explore new molecules for the management of complex human ailments by taking the advantage of novel and advanced drug carrier and delivery

system. Phytosome technology has brought us one step ahead in successful delivery of herbal constituent.

Ongoing development suggests that phytosomal delivery is not restricted to flavonoids (polyphenol) class of phytoconstituents only, but any beneficial molecule possessing structural requirement for direct binding with phosphatidylcholine can be converted to phytosome, e.g. androrgrapholide phytosome, clarithromycin-phospholipid complex, glycerrhetinic acid-phospholipid complex.

In the consequence of further development of phytosome technology, phytosome complexes can be combined with the patch type of novel drug delivery systems like buccal, transdermal patch. In this way pharmacokinetic of medicinal agent via skin can be manipulated and usual limitations of oral route can be eliminated with increased patient compliance.

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