Phytosomes: the Emerging Technology for Enhancement of Bioavailability of Botanicals and Nutraceuticals

S Bhattacharya, A Ghosh

Citation

S Bhattacharya, A Ghosh. *Phytosomes: the Emerging Technology for Enhancement of Bioavailability of Botanicals and Nutraceuticals*. The Internet Journal of Aesthetic and Antiaging Medicine. 2008 Volume 2 Number 1.

Abstract

Phytosomes are recently introduced herbal formulations that are better absorbed, and as a result produce better bioavailability and actions than the conventional phytomolecules or botanical extracts. Phytosomes are produced by a process whereby the standardized plant extract or its constituents are bound to phospholipids, mainly phosphatidylcholine producing a lipid compatible molecular complex. This phyto-phospholipid complex, phytosome resembles a little cell. The term “phyto” means plant while “some” means cell-like. It is also often known as herbosomes. Phytosomes exhibit better pharmacokinetic and pharmacodynamic profile than conventional herbal extracts. The phytosome technology has been effectively enhanced the bioavailability of many popular herbal extracts including milk thistle, Ginkgo biloba, grape seed, green tea, hawthorn, ginseng etc and can be developed for various therapeutic uses or as dietary supplements.

INTRODUCTION

Over the past century, phytochemical and phyto-pharmacological sciences established the compositions, biological activities and health promoting benefits of numerous botanical products. Most of the biologically active constituents of plants are polar or water soluble molecules. However, water soluble phytoconstituents (like flavonoids, tannins, glycosidic aglycones etc) are poorly absorbed either due to their large moleculer size which can not absorb by passive diffusion, or due to their poor lipid solubility; severely limiting their ability to pass across the lipid-rich biological membranes, resulting poor bioavailability.[1] It has often been observed that the isolation and purification of the constituents of an extract may lead to a partial or total loss of specific biological activity for the purified constituent - the natural constituent synergy becomes lost probably due to the removal of chemically related substances contributing the synergistic effect of the active principle(s).[2] Very often the chemical complexity of the crude or partially purified extract seems to be essential for the bioavailability of the active constituents. Extracts when taken orally some constituents may get destroyed in the gastric environment. As standardized extracts are established, poor bioavailability often limits their clinical utility due to above said reasons.

Plants are endowed with a multitude of medicinal and health giving substances, most of them are secondary metabolites, prominent among these being the flavonoids. First recognized for their antioxidant properties, flavonoids are widely distributed in plants. To date, more than 4,000 naturally occurring flavonoids have been identified from plant source having diverse biological activities.[3] The hypothesis of an interaction of flavonoids with phospholipids, which are ubiquitous in plants and animals, originated from the histochemical finding indicating that anthocyanosides from Vaccinium myrtillus L. show a strong affinity for specific cellular structures rich in phospholipids.[4] Phytosome is a newly introduced patented technology developed to incorporate standardized plant extracts or water soluble phytoconstituents into phospholipids to produce lipid compatible molecular complexes, called as phytosomes (also often referred as herbosome in certain literature) and so vastly improve their absorption and bioavailability.[2]

Phospholipids are complex lipid molecules that are used in all known life forms to make cell membranes. In humans and other higher animals the phospholipids are also employed as natural digestive aids and as carriers for both fat soluble and water soluble nutrients. They are miscible both in water and in lipid environments, and are well absorbed orally. The phospholipid mainly employed to make

phytosomes, is phosphatidylcholine, derived form soybean (Glycine max).[5] Phytosomes become more bioavailable as compared to conventional herbal extracts owing to their enhanced capacity to cross the lipoidal biomembrane and finally reaching the systemic circulation. Hence, phytosome has been an emerging trend in delivery of herbal drugs and nutraceuticals. The present review attempts to discuss a brief account on the recent research trends in phytosome technology along with specific illustrations of improved bioavailability and actions of plant products by this means.

THE PHYTOSOME TECHNOLOGY

The flavonoid constituents of plant extracts lend themselves quite well for the direct binding to phosphatidylcholine. Phytosomes results from the reaction of a stoichiometric amount of the phospholipid (phosphatidylcholine) with the standardized extract or polyphenolic constituents (like simple flavonoids) in an aprotic solvent.[2] Phosphatidylcholine is a bifunctional compound, the phosphatidyl moiety being lipophilic and the choline moiety being hydrophilic in nature. Specifically the choline head of the phosphatidylcholine molecule binds to these compounds while the lipid soluble phosphatidyl portion comprising the body and tail which then envelopes the choline bound material. Hence, the phytomolecules produce a lipid soluble molecular complex with phospholipids, also called as phyto-phospholipid complex. Molecules are anchored through chemical bonds to the polar choline head of the phospholipids, as can be demonstrated by specific spectroscopic techniques.[67] Precise chemical analysis indicates the unit phytosome is usually a flavonoid molecule linked with at least one phosphatidylcholine molecule. The result is a little micro sphere or cell is produced. The term “phyto” means plant while “some” means cell-like. The phytosome technology produces a little cell, whereby the plant extract or its active constituent is protected from destruction by gastric secretions and gut bacteria owing to the gastroprotective property of phosphatidylcholine.[8]

{image:1}

DIFFERENCE FORM LIPOSOME

Likewise phytosomes, a liposome is formed by mixing a water soluble substance with phosphatidylcholine in definite ratio under specific conditions. Here, 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. In contrast, with the phytosome process the phosphatidylcholine and the plant components actually form a 1:1 or a 2:1 molecular complex depending on the substance(s) complexed, involving chemical bonds (hydrogen bonds). This difference results in phytosome being much better absorbed than liposomes showing better bioavailability. Phytosomes have also been found superior to liposomes in topical and skin care (cosmetic) products.[9]

{image:2}

METHODS OF PREPARATION

Phytosomes are novel complexes which are prepared by reacting from 3-2 moles but preferably with one mole of a natural or synthetic phospholipid, such as phosphatidylcholine, phosphatidylethanolamine or phosphatidyiserine with one mole of component for example- flavolignanans, either alone or in the natural mixture in aprotic solvent such as dioxane or acetone from which complex can be isolated by precipitation with non solvent such as aliphatic hydrocarbons or lyophilization or by spary drying. In the complex formation of phytosomes the ratio between these two moieties is in the range from 0.5-2.0 moles. The most preferable ratio of phospholipid to flavonoids is 1:1.[10]

In the phytosome preparations, phospholipids are selected from the group consisting of soy lecithin; phosphatidylcholine, phosphatidylethanolamine, phosphatidyiserine, in which acyl group may be same or different and mostly derived from palmitic, stearic, oleic and linoleic acid. Selection of flavonoids are done from the group consisting of quercetin, kaempferol, quercretin-3, rhamnoglucoside, quercetin-3-rhamnoside, hyperoside, vitexine, diosmine, 3- rhamnoside, (+) catechin, (-) epicatechin, apigenin-7-glucoside, luteolin, luteolinglucoside, ginkgonetine, isoginkgonetine and bilobetine.[11]

Marena and Lampertico, Jiang et al, Maiti et al. reported the methods of phytosome prepration.[12131415] Yanyu et al prepared silybin-phospholipid complex using ethanol as a reaction medium. Silybin and phospholipids were resolved into the medium, after the organic solvent was removed under vacuum condition, silybin-phospholipid complex was formed.[16]

PHYSICO-CHEMICAL PROPERTIES OF

PHYTOSOMES

Phytosome is a complex between a natural product and natural phospholipids, like soy phospholipids. Such a complex is obtained by reaction of stoichiometric amounts of phospholipid and the substrate in an appropriate solvent. Their sizes vary between 50 nm to a few hundred μm. 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 head of phospholipids (i.e. phosphate and ammonium groups) and the polar functionalities of the substrate. These phyto-phospholipid complexes are often freely soluble in aprotic solvents, moderately soluble in fats, insoluble in water and relatively unstable in alcohol. When treated with water, phytosomes assume a micellar shape forming liposome-like structures. In liposomes the active principle is dissolved in the internal pocket or it is floating in the layer membrane, while in phytosomes the active principle is anchored to the polar head of phospholipids, becoming an integral part of the membrane for example in the case of the catechindistearoylphosphatidylcholine complex, in this there is the formation of H-bonds between the phenolic hydroxyl ends of the flavonoid moiety and the phosphate ion on the phosphatidylcholine moiety. Phosphatidylcholine can be deduced from the comparison of the ^{1}H-NMR and ^{13}C-NMR spectra of the complex with those of the pure precursors. The signals of the fatty chain remain almost unchanged. Such evidences inferred that the two long aliphatic chains are wrapped around the active principle, producing a lipophilic envelope, which shields the polar head of the phospholipid and the flavonoid molecule and enables the complex to dissolve in low polarity solvents.[17]

CHARACTERIZATION OF PHYTOSOMES

The behavior of phytosomes in both physical and biological system is governed by the factors such as physical size membrane permeability; percent entrapped solutes, chemical composition as well as the quantity and purity of the starting materials. Therefore, the phytosomes are evaluated for their organoleptic properties i.e. shape, size, its distribution and physico-chemically characterized by UV, IR, NMR, DSC, SEM etc. Percentage drug entrapment, percentage drug release profile are also studied accordingly.[18]

ADVANTAGES OF PHYTOSOMES

Phytosomes have the following advantages.[192021]

It enhances the absorption of lipid insoluble polar phytoconstituents through oral as well as topical route showing better bioavailability, hence significantly greater therapeutic benefit.

Appreciable drug entrapment.

As the absorption of active constituent(s) is improved, its dose requirement is also reduced.

Phosphatidylcholine used in preparation of phytosomes, besides acting as a carrier also acts as a hepatoprotective, hence giving the synergistic effect when hepatoprotective substances are employed.

Chemical bonds are formed between phosphatidylcholine molecule and phytoconstituent, so the phytosomes show better stability profile.

Appilcation of phytoconstituents in form of phytosome improve their percutaneous absorption and act as functional cosmetics.

Added nutritional benefit of phospholipids.

ENHANCED BIOAVAILABILITY: BETTER RESULTS

Recent research shows improved absorption and bioavailability with phytosomes as compared to the conventional means. Most of the phytosomal studies are focused to Silybum marianum (milk thistle) which contains premier liver-protectant flavonoids. The fruit of the milk thistle plant contains flavonoids known for hepatoprotective effects.[2223] Silybin is the chief and most potent constituent of silymarin, the flavonoid complex from milk thistle. A standardized extract from Silybum marianum (milk thistle) is an excellent liver protectant but very poorly absorbed orally.

Yanyu et al. prepared the silymarin phytosome and studied its pharmacokinetics in rats. In the study the bioavailability of silybin in rats was increased remarkably after oral administration of prepared silybin-phospholipid complex due to an impressive improvement of the lipophilic property of silybin-phospholipid complex and improvement of the biological effect of silybin.[16]

Tedesco et al. reported silymarin phytosome show better anti-hepatotoxic activity than silymarin alone and can provide protection against the toxic effects of aflatoxin B1 on performance of broiler chicks.[24] Busby et al reported that the use of a silymarin phytosome showed a better

fetoprotectant activity from ethanol-induced behavioral deficits than uncomplexed silymarin.[25] Grange et al. conducted a series of studies on silymarin phytosome, containing a standardized extract from the seeds of S. marianum, administered orally and found that it could protect the fetus from maternally ingested ethanol.[26]

Bombardelli et al. reported Silymarin phytosomes, in which silymarin (a standardized mixture of flavanolignans extracted from the fruits of S. marianum) was complexed with phospholipids. Phytosomes showed much higher specific activity and a longer lasting action than the single constituents, with respect to percent reduction of odema, inhibition of myeloperoxidase activity, antioxidant and free radical scavenging properties.[20]

In the human subjects silybin from phytosomes effectively reaches the intended target organ, the liver. This was proven by Schandalik et al. using nine volunteer patients who had earlier undergone surgical gall bladder removal necessitated by gallstones. They received single oral doses of 120 mg silybin as silybin phytosome, and bile was accessed for silybin levels. Silybin appeared in the bile and peaked after 4 hours. In the case of phytosomal silybin, the total amount recovered in the bile after 48 hours accounted for 11 per cent of the total dose. In the case of silymarin, approximately 3 per cent of the silybin was recovered. These data demonstrate a four times greater passage through the liver for phytosomal silybin.[2728]

Barzaghi et al. conducted a human study designed to assess the absorption of silybin when directly bound to phosphatadylcholine. Plasma silybin levels were determined after administration of single oral doses of silybin phytosome and a similar amount of silybin from milk thistle in healthy volunteers. The results indicated that the absorption of silybin from silybin phytosome is approximately seven times greater compared to the absorption of silybin from regular milk thistle extract (70-80 % silymarin content).[29]

Moscarella et al. investigated in one study of 232 patients with chronic hepatitis (viral, alcohol or drug induced) treated with silybin phytosome at a dose of 120 mg either twice daily or thrice daily for up to 120 days, liver function returned to normal faster in patients taking silybin phytosome compared to a group of controls (49 treated with commercially available silymarin, 117 untreated or given placebo).[30]

Studies have shown ginkgo phytosome (prepared from the standardized extract of Ginkgo biloba leaves) produced better results compared to the conventional standardized extract from the plant (GBE, 24 % ginkgo flavone glycoside and 6 % terpene lactones). In a bioavailability study conducted with healthy human volunteers the levels of GBE constituents (flavonoids and terpenes) from the phytosomal form peaked after 3 hours and persisted longer for at least 5 hours after oral administration. It was found that the phytosomal GBE produced a 2-4 times greater plasma concentration of terpenes than did the non-phytosomal GBE. Its major indications are cerebral insufficiency and peripheral vascular disorders, and it also can ameliorate reduced cerebral circulation. Its improved oral bioavailability and good tolerability makes it the ideal Ginkgo product even for long term treatment. In studies with ginkgo phytosome in patients with peripheral vascular disease (e.g. Raynaud's disease and intermittent circulation) it was shown to produce a 30-60 % greater improvement compared to regular standardized GBE.[931]

Grape seed phytosome is composed of oligomeric polyphenols (grape proanthocyanidins or procyanidins from grape seed extract, Vitis vinifera) of varying molecular size, complexed with phospholipids. The main properties of procyanidin flavonoids of grape seed are an increase in total antioxidant capacity and stimulation of physiological antioxidant defenses of plasma, protection against ischemia/reperfusion induced damages in the heart, protective effects against atherosclerosis thereby offering marked protection for the cardiovascular system and other organs through a network of mechanisms that extend beyond their great antioxidant potency.[32]

In a study where rabbits were fed a high cholesterol diet for 6 weeks, to markedly elevate their blood cholesterol and induce atherosclerotic lesions in their aortas and carotid arteries. One group of rabbits received grape seed phytosome in their feed for the first 6 weeks, then 4 weeks of the high-cholesterol diet. These developed significantly less aortic plaque than did the control groups which received conventional standardized grape seed extract in similar regimen. In a randomized human trial, young healthy volunteers received grape seed phytosome once daily for 5 days. The blood TRAP (Total Radical-trapping Antioxidant Parameter) was measured at several time intervals during 1st day, then also on 5th day. Already by 30 mins after administration on 1st day, blood TRAP levels were

significantly elevated over the control which received conventional standardized grape seed extract.[33]

Green tea extract generally contains a totally standardized polyphenolic fraction (not less than 66.5 %, containing epigallocatechin and its derivatives) obtained from green tea leaves (Thea sinensis) and mainly characterized by the presence of epigallocatechin 3-O-gallate, the key compound. These compounds are potent modulators of several biochemical processes linked to the breakdown of homeostasis in major chronic-degenerative diseases such as cancer and atherosclerosis. Green tea has got several long term benificial activities such as antioxidant, anticarcinogenic, antimutagenic, antiatherosclerotic, hypocholesterolemic, cardioprotective, antibacterial and anticariogenic effects. Despite such potential actions green tea polyphenols have very poor oral bioavailability from conventional extracts. The complexation of green tea polyphenols with phospholipids strongly improves their poor oral bioavailability. A study on absorption of phytosomal preparations was performed in healthy human volunteers along with non complexed green tea extract following oral administration. Over the study period of 6 hours the plasma concentration of total flavonoids was more than doubled when coming from the phytosomal versus the non-phytosomal extract. Antioxidant capacity was measured as TRAP (Total Radical-trapping Antioxidant Parameter). The peak antioxidant effect was a 20% enhancement and it showed that the phytosome formulation had about double the total antioxidant effect.[934]

Maiti et al. developed the quercetin-phospholipid phytosomal complex by a simple and reproducible method and also showed that the formulation exerted better therapeutic efficacy than the molecule in rat liver injury induced by carbon tetrachloride.[35]

Maiti et al. developed the phytosomes of curcumin (flavonoid from turmeric, Curcuma longa) and naringenin (a flavonoid from grape fruit, Vitis vinifera) in two different studies.[1415] The antioxidant activity of the complex was significantly higher than pure curcumin in all dose levels tested. In the other study the developed phytosome of naringenin produced better antioxidant activity than the free compound with a prolonged duration of action, which may be due to decrease in the rapid elimination of the molecule from body.

Hesperetin is a potent phytomolecule abundant in citrus fruits, such as grapefruit and oranges. In spite of several therapeutic benefits viz. antioxidant, lipid-lowering, anti-carcinogenic activities their shorter half life and lower clearance from the body restricts its use. To overcome this limitation, recently Mukerjee et al. deleloped a novel hesperetin phytosome by complexing hesperetin with hydrogenated phosphatidyl choline. This complex was then evaluated for antioxidant activity in CCl_4-intoxicated rats along with pharmacokinetic studies. It was found that the phytosome had a sustained release property for over 24 h and enhanced antioxidant activity. Pharmacokinetic study revealed that the phytosome had higher relative bioavailability than that of parent molecule at the same dose level.[36]

In this way different phytosome products have demonstrated significant therapeutic or health giving effects when compared with the conventional plant extracts. Some commercially available phytosome products are summarized in the Table 1.

CONCLUSION

In recent times the emerging technology of drug delivery and drug targeting is also being applied to phytopharmaceuticals. Botanicals have enormous therapeutic potential which should be explored through some value added drug delivery systems. Lipid solubility and molecular size are the major limiting factors for drug molecules to pass the biological membrane to be absorbed systematically following oral or topical administration. Several plant extracts and phytomolecules, despite having excellent bio-activity in vitro demonstrate less or no in vivo actions due to their poor lipid solubility or improper molecular size or both, resulting poor absorption and poor bioavailability. Standardized plant extracts or mainly polar phytoconstituents like flavonoids, terpenoids, tannins, xanthones when complexed with phospholipids like phosphatidylcholine give rise to a new drug delivery technology called phytosome (or herbosome) showing much better absorption profile following oral administration owing to improved lipid solubility which enables them to cross the biological membrane, resulting enhanced bioavailability i.e. more amount of active principle in the systemic circulation. This means more amount of active constituent becomes present at the site of action (liver, brain, heart, kidney etc) at similar or less dose as compared to the conventional plant extract or phytomolecule. Hence, the therapeutic action becomes enhanced, more detectable and prolonged. Several

excellent phytoconstituents have been successfully delivered in this way exhibiting remarkable therapeutic efficacy in animal as well as in human models. Recently Mukherjee et al. has regarded phytosomes as a value added drug delivery system.[37] Phytosomes also have wide scope in cosmetology.[638]

Thorough study of literature reveals that several plant extracts (crude, partially purified or fractionated) are reported to possess different significant pharmacological or health promoting properties. These extracts can be standardized accordingly and may be formulated as phytosomes for systematic investigation for any improved potential to be used rationally. In this way after screening and selection of potential extracts or constituents from plants, phytosomes can be developed for different therapeutic purposes like cardiovascular, anti-inflammatory, immunomodulator, anticancer, antidiabetic etc or for prophylactic and health purposes as nutraceuticals, in due course. Many areas of phytosome are to be revealed in future in the prospect of pharmaceutical application.

{image:3}

References

1. Manach C, Scalbert A, Morand C. Polyphenols: food sources and bioavailability, Am J Clin Nutr 2004; 79:727-47.
2. Bombardelli E, Curri SB, Loggia Della R, Del NP, Tubaro A, Gariboldi P. Complexes between phospholipids and vegetal derivatives of biological interest. Fitoterapia 1989; 60:1-9.
3. Middleton E, Kandaswami C. The impact of plant flavonoids on mammalian biology: implications for immunity, inflammation, and cancer. In: Harborne JB, editor. The Flavonoids: Advances in Research Since 1986. 1st Ed. London: Chapman and Hall; 1994. p. 619-652.
4. Bombardelli E. Curri SB. Anthologia Medica Santoriana 1976; 5: 177.
5. Citernesi U, Sciacchitano M. Phospholipids/active ingredient complexes. Cosm & Toil 1995; 110 (11): 57-68.
6. Bombardelli E. Phytosome: new cosmetic delivery system. Boll Chim Farm 1991; 130 (11): 431-38.
7. Bombardelli E, Spelta M. Phospholipid-polyphenol complexes: A new concept in skin care ingredients. Cosm & Toil 1991; 106 (3): 69-76.
8. Murray D. Phytosomes- Increase the absorption of herbal extract, Available at: www.doctormurray.com/articles/silybin.htm Accessed- Sept. 28, 2008.
9. Phytosomes: A technical revolution in phytomedicine. Available at: http:// www.indena.com Accessed- Oct. 2, 2008.
10. Magistretti Maria Jose, Bombardelli Ezio, 1987, U.S. Patent No-EPO209037 Pharmaceutical compositions containing flavanolignans and phospholipida active principles.
11. Sharma S, Sikarwar M. Phytosome: a review. Planta Indica 2005; 1(2): 1-3.
12. Marena C, Lampertico M. Preliminary clinical development of silipide: a new complex of silybin in toxic liver disorders. Planta Med 1991; 57: A 124-25.
13. Jiang YN, Yu ZP, Yan ZM, Chen JM. Studies on preparation of herba epimedii flavanoid phytosomes and their pharmaceutics. Zhongguo Zhong Yao Za Zhi 2001; 26 (2): 105-8.
14. Maiti K, Mukherjee K, Gantait A, Saha BP, Mukherjee PK. Curcumin-phospholipid complex: Preparation, therapeutic evaluation and pharmacokinetic study in rats. Int J Pharm 2007; 330 (1-2): 155-163.
15. Maiti K, Mukherjee K, Gantait A, Saha BP, Mukherjee PK. Enhanced therapeutic potential of naringenin-phospholipid complex in rats. J Pharm Pharmacol 2006; 58 (9):1227-33.
16. Yanyu X, Yunmei S, Zhipeng C, Quineng P. The preparation of silybin-phospholipid complex and the study on its pharmacokinetics in rats. Int J Pharm 2006; 307 (1):77-82.
17. Bombardelli E, Mustich G. 1991, U.S. Patent No. EPO-275005 Bilobalide phospholipid complex, their uses and formulation contaning them.
18. Jain NK. Controlled and novel drug delivery, 1st ed. New Delhi: CBS Publishers; 2005. p. 321-326.
19. Kidd P, Head K. A review of the bioavailability and clinical efficacy of milk thistle Phytosome: a silybin-phosphatidylcholine complex. Altern Med Rev 2005; 10 (3):193-203.
20. Bombardelli E. Phytosomes in functional cosmetics. Fitoterapia 1994; 65 (5): 320-27.
21. Bombardelli E, Spelta M, Loggia Della R, Sosa S, Tubaro A. Aging Skin: Protective effect of silymarin-PHYTOSOME. Fitoterapia 1991; 62(2): 115-22.
22. Hikino H, Kiso Y, Wagner H, Fiebig M. Antihepatotoxic actions of flavonolignans from Silybum marianum fruits. Planta Med 1984; 50:248-250.
23. Wellington K, Jarvis B. Silymarin: a review of its clinical properties in the management of hepatic disorders. Bio Drugs 2001; 15: 465-89.
24. Tedesco D, Steidler S, Galletti S, Tameni M, Sonzogni O, Ravarotto L. Efficacy of silymarin-phospholipid complex in reducing the toxicity of aflatoxin B1 in broiler chicks. Poult Sci 2004; 83 (11):1839-43.
25. Busby A, La Grange L, Edwards J, Kings J. The use of a silymarin/phospholipids compound as a fetoprotectant from ethanol-induced behavioral deficits. J Herb Pharmacother 2002; 2 (1):39-47.
26. La Grange L, Wang M, Watkins R, Ortiz D, Sanchez ME, Konst J, Lee C, Reyes E. Protective effects of the flavonoids mixture, silymarin, on fetal rat brain and liver. J. Ethnopharmacol 1999; 65: 53-61.
27. R. Schandalik, G. Gatti, E. Perucca. Pharmacokinetics of silybin in bile followingadministration of silipide and silymarin in cholecystectomy patients. Arzneimittelforschung. 42:964-68 (1992).
28. R. Schandalik, E. Perucca. Pharmacokinetics of silybin following oral administration of silipide in patients with extrahepatic biliary obstruction. Drugs Exp. Clin. Res. 20:37-42 (1994).
29. Barzaghi N, Crema F, Gatti G, Pifferi G, Perucca E. Pharmacokinetic studies on IdB 1016, a silybin phosphatidylcholine complex in healthy human subjects. Eur. J Drug Metab Pharmacokinet 1990; 15:333-38.
30. Moscarella S, Giusti A, Marra F, Marena C, Lampertico M, Relli P, Gentilini P, Buzzelli G. Therapeutic and antilipoperoxidant effects of silybin phosphatidylcholine

complex in chronic liver disease: preliminary results, Curr Ther Res 1993; 53:98-102.
31. Vitamedics, Phytosome Products, Available at http://www.vitamedics.com. Accessed – Sept. 19, 2008.
32. Schwitters B, Masquelier J. OPC in practice: Biflavanals and their application. Alfa Omega, Rome, Italy, 1993.
33. Facina RM, et al. Free radicals scavenging action and anti-enzyme activities of procyanidins from Vitis vinifera. A mechanism for their capillary protective action. Arzneim Forsch 1994; 44: 592-601.
34. Phospholipids: The vital lipids. Available at: www.phospholipidsonline.com Accessed- Sept 26, 2008.
35. Maiti K, Mukherjee K, Gantait A, Ahamed HN, Saha BP, Mukherjee PK. Enhanced therapeutic benefit of quercetin-phospholipid complex in carbon tetrachloride induced acute liver injury in rats: a comparative study. Iran J Pharmacol Ther 2005; 4: 84–90.
36. Mukherjee K, Maiti K, Venkatesh M, Mukherjee PK. Phytosome of hesperetin, a value added formulation with phytomolecules. 60th Indian Pharmaceutical Congress; 2008 Dec 12-14; New Delhi, India. p. 287.
37. Mukherjee PK, Maiti K, Kumar V. Value added drug delivery systems with botanicals: Approach for Dosage development from natural resources. Pharma Rev 2007; 6: 57-60.
38. Gupta A, Ashawat MS, Saraf S, Saraf S. Phytosome: a novel approach towards functional cosmetics. J Plant Sci 2007; 2 (6): 644-649.

Author Information

Sanjib Bhattacharya, M.Pharm.
Bengal School of Technology

Ashoke K. Ghosh, Ph.D.
Bengal School of Technology