Available online www.jocpr.com

Journal of Chemical and Pharmaceutical Research, 2016, 8(5):664-670

Review Article

ISSN : 0975-7384
CODEN(USA) : JCPRC5

Phytosome: Phytoconstituent based lipid derived drug delivery system

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ABSTRACT

Polyphenolic plant secondary metabolite have antioxidant, anti-inflammatory, anti cancer, antiobesity and hepatoprotective properties but owing to their polar nature they have poor absorption which ultimately lead to their poor systemic bioavailability, thereby their therapeutic efficacy gets reduced. Phytosome: a phytoconstituent based lipid derived drug delivery system can surpass these drawbacks .phytosomes are phospholipid-substrate complex in which there occurs the formation of weak hydrogen bonds between the polar portion while the non polar tail of phospholipid wraps over the complex thereby imparting lipophilic character to it and hence increases its absorption.

Key words: Phytosomes, Herbal drug delivery system, Herbal delivery, flavonoids, Polyphenolics.

INTRODUCTION

Since many years back, medicinal plants and/or their constituents are known to treat aliments and even today they are used for the same. At present due to the availability of various sophisticated techniques isolation of particular constituent from a plant is possible which can experimentally demonstrate to have particular therapeutic or nutritional benefit[1]. Many phytoconstituents such as flavonoids and various phenolic compounds are known to have antioxidant, anti-inflammatory, anti cancer and weight loss effect but their full therapeutic efficacy cannot be obtain due their poor systemic bioavailability own to their poor absorption from the GIT tract . Many reasons are there which are responsible for the same e.g. some have multiple ring system due to which they cannot be passively diffuse through the GIT membrane(as molecular weight of the molecule increases), some have poor lipid phase miscibility[2-4]. Due to these drawbacks a need of such a drug delivery system had always been felt which can made these constituents to available in high concentration in the systemic circulation so that proper therapeutic or nutritional efficacy can be obtain. After using many techniques like solubility and bioavailability enhancers which couldn't met the requirement, the "phytosome technology" was invented by Indena in 1989[5]. The word "phytosome" comprises of two words "phyto" means "plant" "some" means "cell like"[6]. With the advent of this technology more drug delivery to systemic circulation and tissues and nutritional safety can be assured. In phytosome there is the formation of lipid-miscible complexes of hydrophilic phytoconstituents with phospholipids obtained from various natural and synthetic sources e.g. phosphatidylcholine (PC), phosphatidylethnolamine phospholipids are amphipathic molecule which have both polar as well as non polar ends[7, 8]. With the use of phytosome technology

bioavailability, various pharmacokinetic and pharmacodynamic parameters can be improved[9-11]. With the use of this technology phytosome of many herbal extracts have already been made e.g. *Ginkgo biloba*, grape seed, *Silybum marianum*, *Thea sinensis*, *Panax ginseng.*

Nature of phytosome

As discussed earlier, a phytosome is a complex formed between herbal drug extract/molecule with phospholipids, brief account on their chemical and biological properties are given below:

Chemical properties

- These complexes are made by reaction between herbal extract/molecules with phospholipids in a stoichiometric ratio generally in 1:1 or 2:1[12].
- During the interaction there occur formation of hydrogen bonds between the polar groups of phospholipids and polar portion of the substrate molecule. This can be verified with the help of various spectroscopical techniques[13].
- Melting point – Clear

Solubility- non-polar solvent: freely soluble
Polar solvent (water): micelle formation
Fats: intermediate solubility[14-17]

Biological properties

This involves the determination of various pharmacokinetic and pharmacodynamic parameters associated with herbal exact/ molecule alone and their phytosome preparation in animal models and human subjects and the comparison of the result obtained. It has been demonstrated that phytosome offers better bioavailability with respect to botanical derivatives alone[18].

Advantages of phytosomes

Phytosome offers various advantages over conventional drug delivery system. They are as follow:

- They are proved to be beneficial for botanical derivatives in by passing the GIT barrier. Hence they increase their absorption and ultimately increase their systemic bioavailability.
- They offer increased permeation through the enterocytes which otherwise is not possible.
- They involve the usage of such components which are already proven for their safety.
- Phospholipids used in them provides 2 advantages:

1. They have synergistic effect for flavonoids.
2. They themselves have hepatoprotective action.

- They offer better permeation through skin (both dermal as well as transdermal). Hence they are very effective in cosmetic preparations which are meant for protection of skin.
- Phosphatidylcholine is a part of cell membrane which made it a suitable carrier for nourishment of skin.
- %entrapment efficacy of phytosome is very high and sometimes found to be more than theoretically determined.
- Stability of phytosome is more due to the formation of hydrogen bonds
- Phytosome are effective via oral route. Therefore, it is a noninvasive technique of drug delivery.
- Their commercial scale production is easy.
- They also have application in veterinary field[19-24].

Difference between phytosome and liposome[25]

Main points of difference are listed in table 1.

Table 1: Difference between phytosome and liposome [25]

S. no.	Phytosome	Liposome
1	There is the formation of hydrogen bonds.	No hydrogen bonds are formed during liposome formation.
2	Complexation generally occurs in ratio 1:1 or 2:1.	During complexation ratio is very high (e.g. 1:500 or1:1000).
3	They are prepared in the solvent having low dielectric constant.	They are prepared in the presence of solvent having high dielectric constant.
4	They are suitable to increase bioavailability by non invasive route (e.g. oral route).	They are not effective via non invasive route.
5	They offer more physical stability due to the formation of weak chemical bonds.	They have lesser stability as compare to phytosome.
6	They are suitable for the dietary supplements.	They are not suitable for dietary supplements.
7	They are more superior to liposome in cosmetic products.	They are less superior.

Mechanism of working (Figure 1)

Phospholipids are amphipathic in nature they have both polar as well as non Polar Regions. Their polar end consists of amine or phosphate groups which bound to the substrates polar group via weak hydrogen bonds and the remaining non polar chain of the phospholipid warps itself over the formed complex thereby imparting a lipophilic character to the complex. Now it can easily pass through the lipophilic enterocyte membrane and the passage of the botanical derivative (in the form of complex with phospholipid) through the GIT barrier become easy (water phase > enterocyte> systemic circulation) [26,27].

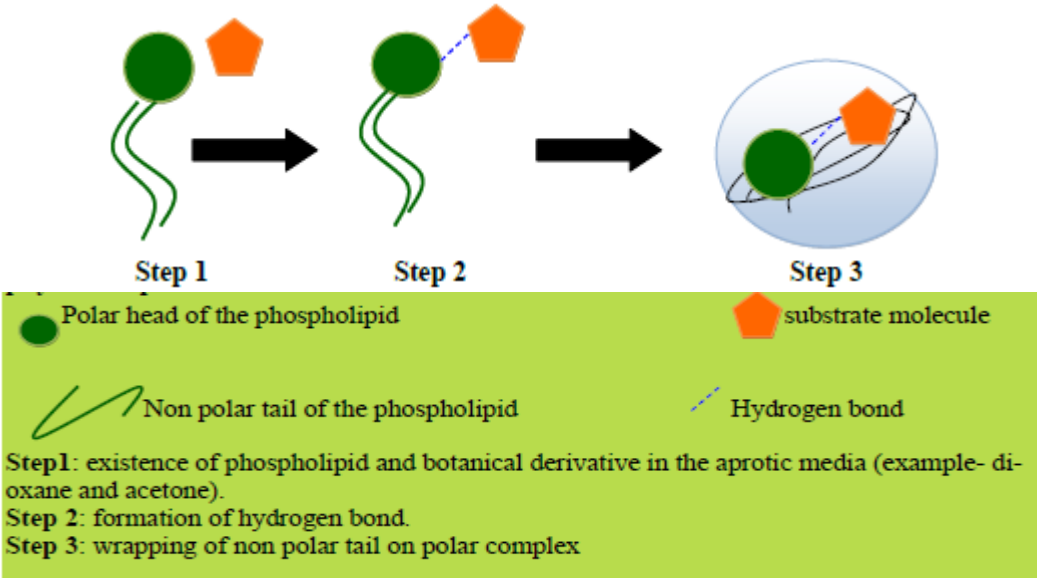

Figure 1: Schematic representation of the steps involved in formation of complex during phytosome production[26]

Method of preparation

General method of preparation of phytosome involves following steps:

1. Phospholipids and substrate is mixed in an appropriate ratio (preferably 1:1) in the presence of aprotic solvent (example- dioxane and acetone).
2. Isolation of the complex is done by precipitation method. Precipitation can be done by any of the following :

- Lyophilization
- Aliphatic hydrocarbons
- Spray drying method.

3. Drying of phytosomes
4. Hydration of prepared phytosomes to obtain phytosomal suspension[28,29].

Various scientists develop various methods for the preparation of phytosomes. Some of the scientists are Jiang, *et al* (2001), Yanyu *et al* (2006) and Maiti *et al* (2006).

Jiang, *et al* (2001) prepared phytosomes of *Herba Epimedii* flavonoids using different ratios of phospholipids and compare their cumulative dissolution profile with the tablets formed with normal extract tablets. He found that there is remarkable increase in cumulative dissolution rate. The phytosomes were prepared by spay drying method. The conditions of the experiment were as follow:

Solvent used- tetrahydrofuran
Lecithin: PVP- 2.5:1
Temperature-40^0C
Time period of experiment- 3hrs[30-32].

Yanyu *et al* (2006) prepared Silybin phytosome using vacuum drying method and ethanol as solvent[33].

Table 2 shows some herbal drugs whose phytosomal preparations are available in the market[34].

Table 2: some herbal drugs (along with their uses) whose phytosomes are available in market[34]

S. no.	Herbal drug	Use
1	*Ginkgo biloba*	Anti-ageing, Protects brain, Protects vascular lining
2	Olive Oil	In treatment of inflammation, In treatment of Hyperlipidemia
3	*Silybum marianum*	Antioxidant, Anti ageing, Anti inflammatory, Liver protective
4	*Panax ginseng*	Anti ageing, Immunomodulators
5	Green Tea	Anti oxidant, Anti neoplastic, Protection of heart
6	Bilberry	Anti oxidant
7	*Curcuma longa*	Anti oxidant, Anti neoplastic
8	Visnadine	In improvement of blood circulation

Patents related to phytosomes

In different parts of the world many academic scientists and industrialists are working on phytosome technology and bring about many innovations. Title of some patents and there patent numbers are mentioned in table 3[35- 42].

Table 3: Patents related to phytosomes

S. no.	Patent	Patent no.
1	Compositions comprising *Ginkgo biloba* derivatives for the treatment of asthmatic and allergic conditions	EP1813280
2	Complexes of saponins with phospholipids and pharmaceutical and cosmetic compositions containing them	EP0283713
3	Treatment of skin, and wound repair, with thymosin beta 4	US/2007/0015698
4	Soluble isoflavone compositions	WO/2004/045541
5	Phospholipid complexes of olive fruits or leaves extracts having improved bioavailability	EP/1844785
6	Cosmetic and dermatological composition for the treatment of aging or photodamaged skin	EP1640041
7	An anti-oxidant preparation based on plant extracts for the treatment of circulation and adiposity problems	EP1214084
8	Fatty acid monoesters of sorbityl furfural and compositions for cosmetic and dermatological use	EP1690862

Methods of characterization

Various characters of phytosome include:

- Size
- Membrane permeability
- Percentage entrapment of drug
- Chemical characteristics
- Amount of starting material taken
- Purity of starting material
- Release profile
- Spectroscopical evaluation
- *In vitro* and *in vivo* evaluation[43]

Various techniques to analyze these characters are listed in table 4 [44-53].

Table 4: techniques used for the determination various characteristics of phytosomes

S. no.	Character	Technique for determination
1	Microscopy	• Scanning electron microscopy(SEM) • Transmission electron microscopy(TEM)
2	Particle size and zeta potential	• Dynamic light scattering • Photon correlation spectroscopy(PCS)
3	% entrapment	• Ultracentrifugation equipment
4	Transition temperature	• Differential scanning calorimetry
5	Surface tension	• DuNouy tensiometer
6	Drug content	• High performance liquid chromatography (HPLC)
7	Spectroscopical evaluations	• ^{1}H-NMR • ^{13}C-NMR • FTIR
8	*In vitro* and *in vivo* evaluation	E.g. anti hepatotoxic activity determination and skin sensitization studies[1].

Applications of phytosome technology

Phytosome are supposed to increase the systemic bioavailability of the hydrophilic phytoconstituents and there by increases their therapeutic efficacy. The applicability of this property is tested by many scientists by comparing the bioavailability of the phytoconstituents alone as well as their phytosomal complex with phospholipids (table 2).

Quercetin phytosomes were prepared by Maiti *et al* (2005) and its hepatoprotective activity is tested against carbon tetrachloride induced hepatotoxicity in rats. They are food to be much more efficient than the native formulation[54]. These positive results inspire Maiti et al to carry out further work in this field and in 2006 they carried out two independent studies on curcumin and naringenin the former is tested for its hepatoprotective and antioxidant activity while the latter has only the antioxidant activity for which it was tested. In both the cases positive results was obtained[31, 32].

Many studies have been performed on *Silybum marianum* by Tedesco *et al*, Grange *et al*, Yanyu *et al*, Barzaghi *et al*, Mascarella *et al* and Bombardelli *et al* for testing its hepatoprotective, fetoprotective and antioxidant activity and a comparison of therapeutic efficacy of drug extract alone and their phytosomal preparation was also done which yield positive results[55,56,57,58,59,60,61,62,63].

CONCLUSION

Many plant derived products especially flavonoids and other phenolic compounds are found to have immense therapeutic importance but owing to their polar nature they have low absorption rate which ultimately decreases their therapeutic efficacy. Therefore such delivery system was desired which can overcome these drawbacks – "phytosome" a phytolipid delivery system is a novel approach in this regard. Its commercial scale production is easy. Characterization can easily be done. Percentage entrapment efficacy is high. Many phytosomes have already been made and marketed. Many patents associated with phytosomes are available. Phytosomes have application in pharmaceutical, cosmetics as well as in veterinary field.

REFERENCES

[1] C Manach; A Scalbert; C Morand; Polyphenols. *Am. J. Clin. Nutr*., **2004**, 79, 727-747.
[2] H Verma; SB Prasad; H Singh; Yashwant. *Int J Current Pharma Rev Res*., **2013**, 4, 88-101.
[3] MA Longer; HS Ching; JR Robinson. *J. Pharm. Sci.*, **1985**, 74, 406-411.
[4] S Sharma; M Sikarwar. *Planta Indica*., **2005**, 1, 1-3.
[5] Prasad SB; Aeri V. *American Journal of Phytomedicine and Clinical Therapeutics*., **2013**, 1(7), 536-47.
[6] E Bombardelli; SB Curri; R Loggia Della. *Fitoterapia*., **1989**, 60, 1-9.
[7] E Bombardelli; A Cristoni; P Morazzoni. *Fitoterapia*., **1994**, 95, 387-401.
[8] http://www.pharmainfo.net/reviews/phytosome-novel-dosage-structure (Cited on 15th Jan **2016**).
[9] S. Mascarella. *Curr. Ther. Res* **1993**; 53: 98-102.
[10] A. Gupta, M. S. Ashawal, S. Saraf. J. *Plant Science* **2007**: 644-649.
[11] Pandey S, Patel K. *Int J Pharma Tech Res* **2010**; 2:627-631.

[12] S. Vasanti. Phytosomes: a short review. available at http://www.biology-online.org/articles/phytosomes-short-review.html. (**2008**).
[13] A. Semalty, M. Semalty, M. S. M. Rawat. *Pharmacognosy Reviews* **2007**;1: 369-374
[14] E. Bombardelli. *Boll. Chim. Farm* **1991**;130: 431-438.
[15] E. Bombardelli, M. Spelta. *Cosm. & Toil* **1991**; 106: 69-76.
[16] Sharma S, Sikarwar M. *Plant Indica* **2005**;1:1-3.
[17] Chauhan NS, Gowtham R, Gopalkrishna B. *J Pharm Res* **2009**;2:1267-1270.
[18] P. G. Franco, E. Bombardelli. Complex coppouns of bioflavonoids with phospholipids, their preparation and uses and pharmaceutical and cosmetic compositions containing them. U.S. Patent No: EPO 275005, **1998**.
[19] P. Kidd, K. Head. *Altern. Med. Rev* **2005**; 10: 193-203.
[20] E. Bombardelli. *Fitoterapia* **1994**; 65: 320-327.
[21] E. Bombardelli, M. Spelta, R. L. Della, S. Sosa, A. Tubaro. *Fitoterapia* **1991**; 62: 115-122.
[22] A. D. Kingdom, *J. Pharmacog. Pharmacol* **2001**;53: 135- 148.
[23] B. Gabetta, E. Bombardelli, G. Pifferi. Complexes of flavanolignans with phospholipids preparation, thereof and associated pharmaceutical compositions. U. S. patent No. 4764508, **1986**.
[24] C. Marena, M. Lampertico. *Planta Med* **1991**; 57: A124-A125.
[25] www.indena.com/pdf/ephytosome.pdf (July28, **2011**).
[26] U. Citernesi, M. Sciacchitano. Phospholipids active ingredient complexes. Cosm. & Toil **1995**;110: 57-68.
[27] .M. T. Murray. Phytosomes: Herbal Support – Increase the Absorption of Herbal Extracts, Available at www.doctomurray.com/articles/silybin.htm (**2004**).
[28] Battacharya S. Phytosomes: Emerging strategy in delivery of herbal drugs and nutrceuticals. Pharm Times **2009**;41:3.
[29] N. K. Jain. Liposomes as drug carriers, controlled and novel drug delivery, 1st edition, CBS publisher 2005: 308.
[30] Y. N. Jiang, Z. P. Yu, Z. M. Yan, *et. al*. Preparation of herba epimedii flavanoid and their pharmaceutics. Zhongguo Zhong Yao **2001**; 26: 105-108.
[31] K. Maiti, K. Mukherjee, A. Gantait, *et al. Int. J. pharm., Sept*. **2006**.
[32] K. Maiti, K. Mukherjee, A. Gantait, *et al*. *J. Pharm. Pharmacol* **2006**; 58: 1227-1233.
[33] X. Yanyu, S. Yunmei, C. Zhipeng, *et al*. *Int. J. Pharm* **2006**; 307: 77-82.
[34] Bhattachrya S. Phytosomes: *Int J Health Res* **2009**;2:225
[35] F. Franceschi, A. Giori. A phospholipid complex of olive fruits or leaves extracts having improved bioavailability. EP1844785, **2007**.
[36] F. Di Pierro. Compositions comprising *Ginko biloba* derivatives for the treatment of asthmatic and allergic conditions. EP1813280, **2007**.
[37] .V. Bertelli. Fatty acid monoesters of sorbityl furfural and compositions for cosmetic and dermatological use. EP1690862, **2006**.
[38] T. Doering, A. Traeger, M. Waldmann-Laue, *et al*. Cosmetic and dermatological composition for the treatment of aging or photodamaged skin. EP1640041, **2006**.
[39] H. K. Kleinman, A. L. Goldstein, *et al*. Treatment of skin, and wound repair, with thymosin beta 4. U. S. Patent No-20070015698, **2007**.
[40] A. B. Khare. Soluble isoflavone compositions. WO/2004/045541, **2004**
[41] G. Merizzi. An anti-oxidant preparation based on plant extracts for the treatment of circulation and adiposity problems. EP1214084, **2002**.
[42] E. Bombardelli, G. F. Patri, R. Pozzi. Complexes of saponins with phospholipids and pharmaceutical and cosmetic compositions containing them. EP0283713, **1988**.
[43] N. K. Jain. Liposomes as drug carriers, controlled and novel drug delivery, 1st edition, CBS publisher **2005**: 321-326.
[44] GMM Maghraby El, A. C. Williams, B. W. Barry. *Int. J. Pharm*. **2000** ;196: 63-74.
[45] D. W. Fry, J. C. White, I. D. Goldman. *Anal. Biochem*. **1978**; 90: 809-815.
[46] Liposomes: A Practical Approach, Preparation of liposomes and size determination, New RRC (Ed.), Oxford University Press **1990**: 36-39.
[47] G. Cevc, A. Schatzlein, G. Blume. *J. Control. Release* **1995**; 36: 3-16.
[48] BAI V. Berge, VAB Swartzendruber, J. Geest. *J. Microsc*. **1997**;187: 125-133.
[49] N. Dayan, E. Touitou. *Biomaterials* **2002**; 21:1879-1885.
[50] R. M. Facino, M. Carini, G. Aldini, *et al*. *Arzneim. Forsch*. **1994**;44: 592-601.
[51] A. Semalty, M. Semalty, R. Singh, M. S. M. Rawat. *Indian drugs* **2006**;43: 937-946.

[52] E. Bombardelli, G. Mustich. Bilobalide-phospholipid comlex, their uses and formulation containing them. U. S. Patent No. EPO-275005, **1991**.
[53] S. Abrol, A. Trehan, O. P. Katare. *Current Drug Delivery* **2005**;2: 45-51.
[54] A. Comoglio, A. Tomasi, S. Malandrino, *et al*. *Biochem. Pharmacol*. **1995**;50: 1313-1316.
[55] U. Delgi, S. D. Urbino. Tolerability and cutaneous sensitization study in healthy volunteers after topical application of the product glycyrrhetinic acid-Phytosome® ointment. Unpublished data submitted by CTFA **2004**; 36: 2.
[56] C. R. Filburn, R. Kettenacker, D. W. *J. Vet. Pharmacol. Ther.* **2007**; 30: 132-138.
[57] Maiti K, Mukherjee K, Gantait A, Ahmed HN, Saha BP, Mukherjee PK. *Iran J Pharmacol Ther* **2005**;4:84-90.
[58] Hikino H, Kiso Y, Wagner H, Fiebig M. *Planta Med* **1984**;50:248-250.
[59] Kidd PM. *Altern Med Rev* **1996**;1:258-274.
[60] Tedeco D, Steidler S, Galletti S, Tameni M, Sonzogni O, Ravarotto L. *Poult Sci* **2004**;83:1839-1843.
[61] Busby A, La Grange L, Edwards J, King J. *J Herb Pharmacother* **2002**;2:39-47.
[62] Bomberdelli E, Spelta M, Della Loggia R, Sossa S, Tubaro A. *Fitoteapia* **1991**;62:115-122.
[63] Grange LL, Wang M, Watkins R, Ortiz D, Sanchez ME, Konst J, Lee C, Reyes E. *J Ethnopharmacol* **1999**;65:53-61.