WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.084
Volume 9, Issue 13, 601-615. Review Article ISSN 2277– 7105

A NOVEL APPROACH FOR VESICULAR DELIVERY OF PHYTOMEDICINES USING PHYTOSOMES

Sruthy S. Nair[1]*, Anuroop U. P.[1], Ajith Babu T. K.[2] and Jiji Jose[3]

[1]Department of Pharmaceutics, Malik Deenar College of Pharmacy, Kasaragod, Kerala.

[2]Department of Pharmaceutical Chemistry, Malik Deenar College of Pharmacy, Kasaragod, Kerala.

[3]DMWims, Mepady, Wayanad, Kerala.

Article Received on
03 Sept. 2020,

Revised on 24 Sept. 2020,
Accepted on 14 Oct. 2020

DOI: 10.20959/wjpr202013-19035

***Corresponding Author**
Sruthy S. Nair
Department of Pharmaceutics, Malik Deenar College of Pharmacy, Kasaragod, Kerala.

ABSTRACT

Phytomedicines, complex chemical mixtures prepared from plants, have been used for health maintenance since ancient times. Over the past century, chemical and pharmaceutical science established the compositions, biological activities and health giving benefits of numerous plant extracts. But often when individual components were separated from the whole there was loss of activity—the natural ingredient synergy became lost. And also many phytomedicines are limited in their effectiveness because they are poorly absorbed when taken orally. 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, and so vastly improve their absorption and bioavailability. Phytosomes are novel phospholipid based drug delivery system, which offer improved bioavailability of hydrophilic flavonoids and other similar compounds through the skin or gastrointestinal tract. They are better able to transition from a hydrophilic environment into the lipid-friendly environment of the enterocyte cell membrane and from there into the cell, finally reaching the blood. They have many distinctive advantages over other conventional formulations. The formulation methodology for phytosome is simple and can be easily upgraded to a commercial scale. The characterization methodologies and analytical techniques are well established for this type of novel formulation. Many patents are already approved for innovative formulations, processes and applications of phytosomes.

KEYWORDS: Phytosomes, Phytomedicines, Phospholipids, Bioavailability.

1. INTRODUCTION

1.1. Herbal medicines

Herbal medicines are the synthesis of therapeutic experiences of generations of practicing physicians of indigenous systems of medicines for over hundreds of years. The World Health Organization (WHO) has recently defined traditional medicines including herbal drugs as therapeutic practices that have been in existence for hundreds of years before the development and spread of modern medicine and are still in use today. The traditional preparations comprises of medicinal plant, minerals and organic matter. Herbal drugs constitute only those traditional medicines which are primarily used as medicinal plant preparation for therapy. Herbal medicines are also termed as phytotherapeutic agents or phytomedicines. These phytomedicines are also available as standardized herbal preparations consisting of complex mixtures of one or more plants, which are used in many countries.[1]

1.2. Importance of herbal medicine

The use of medicinal plants for health reasons started thousands of years ago and is still a part of medicinal practice in China, Egypt, India and other developing countries. Over the centuries, the use of medicinal herbs has become an important part of daily life in the western world despite significant progress in modern medicine and pharmaceutical research. Increasing knowledge of metabolic processes and effects of plants on human physiology has enlarged the range of application of medicinal plants. WHO estimates that 4 billion people, i.e. about 80 % of the world population, presently use herbal medicine for some aspect of primary health care. Major pharmaceutical companies are currently conducting extensive research on plant materials gathered from the rain forests and other places for their potential medicinal value.

Substances derived from the plants remain the basis for a large proportion of commercial medications used today for the treatment of heart disease, high blood pressure, pain, asthma and other problems. For example, Ephedra is a herb used in traditional Chinese medicine for more than two thousand years to treat asthma and other respiratory problems. Ephedrine, an active ingredient in Ephedra, is used in the commercial pharmaceutical preparations for the relief of asthma symptoms and other respiratory problems. It helps the patients to breathe more easily. Another example of the use of the herbal preparation in modern science is the foxglove plant. This herb had been in use since 1775. At present the powdered leaf of this plant is known as the cardiac stimulant digitalis to the millions of heart patients.[1,3]

Herbal medicines can be broadly classified into various basic system: Traditional Chinese herbalism, which is part of traditional oriental medicine, Ayurvedic herbalism, which is derived from Ayurveda and Western herbalism which originally came from Greece and Rome to Europe and then spread to North and South America.

There are some Ayurvedic herbs that are use full for reducing cholesterol, diabetes etc. Similarly the popularity of Gingseng and *Ginkgo biloba* (Ginkgo) is rising due to its effects like immunomodulatory. Herbal medicines have stood the test of time for their safety, efficacy, cultural acceptability and lesser side effect.

In comparison to well defined synthetic drugs, herbal medicines exhibit some marked differences viz.

1. Long history of use and better patient tolerance
2. Renewable resource
3. Environment friendly
4. Local availability
5. Important recent breakthrough
6. Major source new lead generation

Apart from this, they also offer therapeutics for age related disorders like memory loss, osteoporosis, immune disorders, diabetes, cancer etc; for which modern medicine has no complete cure. Herbals mainly in developing countries are known for their better cultural acceptability and lesser side effects.[1,14]

1.3. Phytosomes: a novel approach to improve the bioavailability of phytoconstituents

Most of bioactive constituents of phyto-medicines are water soluble molecules (e.g. phenolics, glycosides, flavanoids etc.). However, water soluble phytoconstituents are limited in their effectiveness because they are poorly absorbed when taken orally or when applied topically. Many approaches have been developed to improve the oral bioavailability, such as inclusion of solubility and bioavailability enhancer, structural modification and entrapment with the lipophilic carriers and thus extensive research in the field of herbal drug delivery systems as a means of improving therapeutic indices of drug is inevitable. The use of formulation technology to deliver herbal products and drugs by improved absorption and, as a consequence, produce better result than those obtained by conventional herbal extract.[2]

Phytosome is a patented technology developed by a leading manufacturer of drugs and neutraceuticals, to incorporate standardized plant extracts or water soluble phytoconstituents into phospholipids to produce lipid compatible molecular complexes, called as phytosomes and so vastly improve their absorption and bioavailabilty.[3]

Phytosome technology is a break through model for marked enhancement of bioavailability, significantly greater clinical benefit, assured delivery to the tissues, without comprising nutrient safety.[2] The phytosomes process produces a little cell because of that the valuable components of the herbal extracts are protected from destruction by digestive secretions and gut bacteria. Phytosomes are better able to transition from a hydrophilic environment into the lipid-friendly environment of the enterocyte cell membrane and from there into the cell finally reaching the blood. Phytosomes have improved pharmacokinetic and pharmacological parameter which in result can advantageously be used in the treatment of the acute and chronic liver disease of toxic metabolic or infective origin or of degenerative nature. It can also be used in anti-inflammatory activity as well as in pharmaceutical and cosmetic compositions.[3]

2. Novel drug delivery systems

Novel drug delivery system aims to deliver the drug at a rate directed by need of body the 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]

2.1. Novel vesicular drug delivery systems

Novel vesicular drug delivery systems aim to deliver the drug at a rate directed by need of body during the period of treatment, and channel the active entity to the site of action. A number of novel vesicular drug delivery systems have been emerged encompassing various routes of administration, to achieve targeted and controlled drug delivery.

Targeted drug delivery is a mode of delivering the therapeutic agent to the tissues of interest while reducing the relative concentration of therapeutic agent in remaining tissues which improves the therapeutic efficacy and reduces the side effects. Drug targeting means the delivery of drugs to receptor, organs or any other specific part of body to which one wishes to deliver the entire drug.

2.2. Novel approaches for the delivery of herbal constituents

Many approaches have been developed for improving the bioavailability such as inclusion of solubility and bioavailability enhancers, structural modification and entrapment with carriers. One such approach is the phytosome technology. The phytosome technology is a novel approach developed by Indena in an attempt to combat the issue of poor bioavailability.

2.2.1. Liposomes

Liposomes are artificial microscopic vesicles consisting of an aqueous core enclosed in one or more phospholipid layers, used to convey vaccines, drugs, enzymes or other substances to target cells or organs.

2.2.2 Nanoparticles

Nanoparticles are particles of less than 100nm in diameter that exhibit new or enhanced size dependent properties compared with large paricles of same material.

2.2.3. Microemulsion

A thermodynamically stable dispersion of two immiscible liquids, stabilised by surfactants. A microemulsion is an emulsion whose particles are less than 1 micron in size.

2.2.4. Phytosomes

It is a newly introduced patented technology developed to incorporate standardized plant extracts or water soluble phytoconstituents into phospholipids to produce lipid compatible molecular complexes they are also known as herbosome.

2.2.5. Transferosomes

A transferosomes carrier is an artificially designed to be like cell vesicle or a cell engaged in exocytosis and thus suitable for controlled and potentially targeted drug delivery. Transfersome consist of phophatidylcholine and are ultra deformable vesicles with enhance skin penetrating properties.[5,15]

3. Method of preparation

Phytomedicines, complex chemical mixtures prepared from plants, have been used for health maintenance since ancient times. Over the past century, chemical and pharmaceutical science established the compositions, biological activities and health giving benefits of numerous plant extracts. But often when individual components were separated from the whole there was loss of activity—the natural ingredient synergy became lost. And also many phytomedicines are limited in their effectiveness because they are poorly absorbed when taken orally.

The "Somes" are the cell like formulations belongs to novel drug delivery system. There are different types of somes like phytosomes, which encapsulate water and lipid-soluble pharmacologically and cosmetically active components. The phytosome technology, developed by Indena S.p.A. of Italy, markedly enhances the bioavailability of select phytomedicines, by incorporating phospholipids into standardized extracts and so vastly improves their absorption and utilization.

Numerous research works is being conducted by the researchers and the recent researches reveals that the phytosome technology is a novel method for improving the absorption and bioavailability of plant extracts significantly reducing the dose level. The suitability of this technique and increased demand of herbal medicines for various disease management in current scenario, has paved the way of newer researches. The objective of this review is to provide an update on the most promising advances in phytosome delivery of phytocostotuents. Authenticated reports regarding phytosomes and its preparation and characterization were collected from text books, scientific journals, magazines and official websites of various organizations and pharmaceutical companies involved in the research and development of phytosomes. The newly registered patent applications and clinical research studies about phytosome were also referred and scrutinized. Finally all the data obtained were compiled and presented according to their indication and a detailed report is prepared. Phytosomes are formulated by patented processes in which the standardized extract (having a stazdardized content of active principles) and/or active ingredients of herbs (like flavoliganans and terpenoids) are bound to the phospholipids like phosphatidylcholine (PC) through a polar end. The phytosome process produces small cells which protect the valuable components of the herbal extract from destruction by digestive secretions and gut bacteria. They improve transition of constituents from the water phase to the enterocytes of the gut

wall and ultimately they reach the circulation. The phytoactive components of these herbal extracts are well suited to direct binding to phosphatidylcholine from soy. PC is also the principle molecular building block of cell membranes and is miscible with both water and oil/lipid mixtures, and is well absorbed orally. Phospholipids are small lipid molecules in which the glycerol is bound to only two fatty acids, instead of three as in triglycerides, with the remaining site is occupied by a phosphate group. Specifically, the choline head of the phosphatidylcholine molecule binds to phytoconstituents while the fat-soluble phosphatidyl portion, comprising the body and tail, then envelopes the choline bound material. This results in small microspheres or the production of cells known as phytosomes. Thus, phytosomes are also considered as a phytolipid delivery system.

Phytosomes are prepared by reacting 3–2 moles (preferably with one mole) of a natural or synthetic phospholipid, such as phosphatidylcholine, phosphatidylethanolamine or phosphatidylserine, with one mole of phytoconstituents either alone or in the natural mixture in an aprotic solvent, such as dioxane or acetone, in a 1:2 or 1:1 ratio.[7] The optimum ratio of phospholipid to phytoconstituent is 1:1. The complex thus formed can be isolated by precipitation with an aliphatic hydrocarbon or lyophilization or spray drying. 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.

Mareno and Lampertico, Jiang *et al.* and Maiti *et al.* have described the methods used for phytosome preparation. Jiang *et al*. (2001) have optimized the preparation conditions using a uniform design and step regression and have prepared *Herba Epimedii* total flavonoid phytosomes (EFP) by means of solvent evaporation and investigated the cumulative dissolution of different ratios of EFP- PVP precipitates by means of dissolution release. The optimized preparation conditions are as follows: solvent-tetrahydrofuran, lecithin to PVP ratio 2:5, temperature 40˚C and reaction time 3 h. The oil/water apparent partition coefficient of icariin was enhanced more than 4 fold by phospholipid. The cumulative dissolution of *Herba Epimedii* flavonoids of the EFP-PVP precipitate was significantly higher than that of its physical mixture and a *Herba epimedii* extract tablet. Yanyu *et al* (2006) prepared a 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 and a silybin- phospholipid complex was formed.

4. Charecterization and evaluation of phytosomes

The behavior of phytosomes in both physical and biological systems is governed by factors such as the physical size, membrane permeability, percentage of entrapped solutes, and chemical composition as well as the quantity and purity of the starting materials. Therefore, phytosomes can be characterized in terms of their physical attributes i.e. shape, size, distribution, percentage drug captured, entrapped volume, percentage drug released and chemical composition.[7,10]

4.1 Different characterization techniques used for phytosomes

4.1.1. Visualization

Visualization of phytosomes can be achieved using transmission electron microscopy (TEM) and by scanning electron microscopy (SEM).

4.1.2. Vesicle size and zeta potential

The particle size and zeta potential can be determined by dynamic light scattering (DLS) using a computerized inspection system and photon correlation spectroscopy (PCS).

4.1.3. Entrapment efficiency

The entrapment efficiency of a drug by phytosomes can be measured by the ultracentrifugation technique.

4.1.4. Transition temperature

The transition temperature of the vesicular lipid systems can be determined by differential scanning calorimetry.

4.1.5. Surface tension activity measurement

The surface tension activity of the drug in aqueous solution can be measured by the ring method in a Du Nouy ring tensiometer.

4.1.6. Vesicle stability

The stability of vesicles can be determined by assessing the size and structure of the vesicles over time. The mean size is measured by DLS and structural changes are monitored by TEM.

4.1.7. Drug content

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

4.1.8. Spectroscopic evaluation

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

4.1.9.1H-NMR

The NMR spectra of (+)-catechin and its stoichiometric complex with distearoylphosphatidylcholine have been studied by Bombardelli *et al*. In nonpolar solvents, there is a marked change of the 1H-NMR signal originating from the atoms involved in the formation of the complex, without any summation of the signal peculiar to the individual molecules. The signals from the protons belonging to the flavonoids are to be broadened that the proton cannot be relieved. In phospholipids, there is broadening of all the signals while the singlet Corresponding to the N-$(CH3)_3$ of choline undergoes an uplift shift. Heating the sample to 60˚C results in the appearance of some new broad bands, which correspond mainly to the resonance of the flavonoid moiety.

4.1.10.C_{13}-NMR

In the C_{13}-NMR spectrum of (+)-catechin and its stoichiometric complex with distearoylphosphatidylcholine, particularly when recorded in C_6D_6 at room temperature, all the flavonoid carbons are clearly invisible. The signals corresponding to the glycerol and choline portion of the lipid (between 60–80 ppm) are broadened and some are shifted, while most of the resonances of the fatty acid chains retain their original sharp line shape. After heating to 60˚C, all the signals belonging to the flavonoid moieties reappear, although they are still very broad and partially overlapping.

4.1.11.FT-IR

The formation of the complex can be also be confirmed by IR spectroscopy by comparing the spectrum of the complex with the spectrum of the individual components and their mechanical mixtures. FT-IR spectroscopy is also a useful tool for the control of the stability of phytosomes when micro-dispersed in water or when incorporated in very simple cosmetic gels. From a practical point of view, the stability can be confirmed by comparing the spectrum of the complex in solid form (phytosomes) with the spectrum of its micro-dispersion in water after lyophilization, at different times. In the case of simple formulations, it is necessary to subtract the spectrum of the excipients (blank) from the spectrum of the cosmetic form at different times, comparing the remaining spectrum of the complex itself.[7,10,12]

4.1.12. In vitro and in vivo evaluation

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. 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 thioacetamide, paracetamol or alcohol induced hepatoxicity can be examined. Skin sensitization and tolerability studies of glycyrrhetinic acid Phytosome ointment, a commercial product, describe the *in vivo* safety evaluation methodology. Filburn *et al*, studied the bioavailability of a silybinphosphatidylcholine complex in dog models to examine the pharmacokinetic parameters of this new complexed form.[7,10,11]

5. Formulation of phytosomes

Phytosome complexes can be formulated both orally and topically. In order to obtain the best performances of this technological innovation both in terms of formulating manageability and enhanced bioavailability (as appropriate disintegration and dissolution time of oral forms, for instance).

5.1. Soft gelatin capsules

Soft gelatin capsules represent an ideal solution to formulate phytosome complexes. The phytosome complex can be dispersed in oily vehicles to obtain suspensions to be filled in soft gelatin capsules. Vegetable or semi-synthetic oils can be used to this purpose. Indena recommend a granulometry of 100% < 200 μm to best perform capsule production. According to Indena experience, not all the phytosome complexes behave in the same way when dispersed in oily vehicles and when the oily suspension is filled in the soft gelatin capsules; for this reasons preliminary feasibility trials should be performed to select the most suitable vehicle.

5.2. Hard gelatin capsules

The Phytosome complex can be formulated in hard gelatin capsules as well. A direct volumetric filling process (without precompression) can be applied, even if the apparently low density of the phytosome complex seems to limit the maximum amount of powder that can be filled into a capsule (usually not more than 300 mg for a size 0 capsule). With a pistontamp capsule filling process, however, it is possible to increase the amount of powder which can be filled in a capsule, but precompression might affect the disintegration time.

Indena recommend to carefully monitoring the related parameters during product/ process development. A preliminary dry granulation process is advisable define the best manufacturing process.[27]

5.3. Tablets

Dry granulation represents the ideal manufacturing process to obtain tablets with higher unitary doses and with suitable technological and biopharmaceutical properties. However, due to the limited flowability, potential stickiness and low apparent density of the phytosomecomplex, a direct compression process can be applied only for low unitary doses; note that whenever a direct compression process is applied, the phytosome complex should be diluted with 60-70% of excipients to optimize its technological properties and to obtain tablets with appropriate technological and biopharmaceutical characteristics. On the other hand, wet granulation should be avoided due to the negative effect of water and heat (granulation/ drying) on the stability of the phospholipid complex.[28]

5.4. Topical dosage forms

The phytosome complex can be formulated topically as well. The ideal process to incorporate the phytosome complex in emulsion is to disperse the phospholipidic complex in a small amount of the lipidic phase and add it to the already created emulsion at low temperatures (not higher than 40°C). The phytosome complexes are dispersible in the main lipidic solvents employed in topical formulations. In case of formulations containing a limited amount of lipids, the phytosome complex might also by dispersed into the watery phase, and again added to the final formulation at temperature lower than 40°C.[29]

6. PHYTOSOMES v/s LIPOSOMES

Phytosome products, after numerous studies prove that they are markedly better absorbed and have substantially greater clinical efficacy over niosomes and now a day's companies have successfully applied this technology to a number of standardized flavonoid preparations. The following table shows the major differences between phytosome and liposome.[30]

Table 1: Difference between Phytosomes and Liposomes.[3]

Property	Phytosome	Liposome
Bonding	It is a unit of few molecules bonded together	It is an aggregation of many phospholipid molecule that encloses other phtyo active molecules without specifically bonding to them
Bioavailability and Absorption	It has better bioavailability and absorption	Its bioavailability and absorption is lesser than phytosomes
Arrangement of Molecules	In phytosomes, Phospholipid (phosphatidylcholine) and individual phytoconstituents are present in 1:1 or 1:2 ratio depending on thesubstance	In liposomes hundreds and thousands of Phosphatidylcholine molecules surround the water soluble molecule

7. Pharmaceutical scope of phytosomes

- 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 improves their percutaneous absorption and act as functional cosmetics.
- Added nutritional benefit of phospholipids.[6]

8. CONCLUSION

Despite the wide therapeutic potential of phytoconstiuents, especially those containing flavonoids and other phenolic compounds, their phenolic nature renders them polar but has poor solubility in water and most of the organic solvents as well. Poor drug dissolution is responsible for scarce absorption and poor bioavailability. These aspects constitute a handicap against the widespread use of flavonoids in the pharmaceutical field. These hindrances can be tackled by formulating an appropriate drug delivery system. Phospholipid

based drug delivery system has been found promising for better and effective delivery of natural drug and can enhance the rate and extent of drug absorption across the lipoidal biomembrane. Phytosomes are novel phospholipid based drug delivery system, which offer improved bioavailability of hydrophilic flavonoids and other similar compounds through the skin or gastrointestinal tract. They have many distinctive advantages over other conventional formulations. The formulation methodology for phytosome is simple and can be easily upgraded to a commercial scale. The characterization methodologies and analytical techniques are well established for this type of novel formulation. Many patents are already approved for innovative formulations, processes and applications of phytosomes.

As far as the potential of phytosome technology is concerned, it has a great future for use in formulation technology and applications of hydrophilic plant compounds. Many areas of phytosome are to be revealed in future in the prospect of pharmaceutical, neutraceutical and cosmetic application. Phytosomes forms a bridge between the conventional delivery system and novel delivery system.

REFERENCES

1. Sandip S. Phytosomes- A new herbal drug delivery system. International journal of research in pharmaceutical and biomedical science, 2012; 3(4): 1709.
2. Harshal AP, Bhagyashree D. Phytosomes as a novel biomedicine: A microencapsulated drug delivery system. Bioanalysis and biomedicine, 2015; 7(1): 6-11.
3. Arijit Gandhi, Avik Dutta, Avijit Pal, Paromita Bakshi. Recent trends of phytosomes for deliveri herbal extract with improved bioavailability. Journal of pharmacognosy and phytochemistry, 2012; 1(4): 6-10.
4. Babita Rani, Vandana, Manju Nagpal, Sandeep Arora.Phytosomes: potential carrier of herbal drugs. International journal of research and reviews in pharmacy and applied science, 2012; 2(3): 568, 571-572.
5. Joseph AK, Praveen H, Aruna P, Vilasrao J. Phytosomes: A novel revolution in herbal drugs. International journal of research in pharmacy and chemistry, 2012; 2(2): 304.
6. Vinod KR, Sandhya S, Chandrasekar J, Swetha R, Rajeshwar T, David Banji, Anbuazhaghan S. A review on gensis and characterization of phytosomes. International journal of pharmaceutical sciences review and research, 2010; 4(3): 70.

7. Jagruti Patel, Rakesh Patel, Kapil Khambholja, Nirav Patel. An overview of phytosomes as an advanced herbal drug delivery system. Asian journal of pharmaceutical sciences, 2009; 4(6): 365-368.
8. Sindhumol PG, Maria Thomas, Mohanachandran PS. Phytosomes: A novel dosage form for enhancement of bioavailability of botanicals and neutraceuticals. International journal of pharmacy and pharmaceutical sciences, 2010; 2(4): 11-12.
9. Ravi GS, Chandur V, Shabaraya AR, Sanjay K. Phytosomes: An advanced herbal drug delivery system. International journal of pharmaceutical research and biomedicine, 2015; 4(3): 420- 421.
10. Tripathy S, Patel D, Baro L. Nair S. A review n phytosomes,their characterization, advancement and potential for transdermal application, Journal of drug delivery and therapeutics, 2013; 3: 147-152.
11. Bhattacharya S. Phytosomes: emerging strategy in delivery of herbal drugs and neutraceuticals. Pharma Times, 2009; 41(3): 9- 12.
12. Patel A, Tanwar Y. Phytosomes: phytolipid drug delivery system for improving bioavailability of herbal drugs. Journal of pharmaceutical science and scientific research, 2013; 3: 51-57.
13. Bentley R, Trimet H. Medicinal plants, international book Distributors, 1992; 1: 1079.
14. Samanta MK, Mukherjee PK, Prasad NK, Suresh B. The eastern pharmacist, 2000; 23-24.
15. Mascarella S. Therapeutic and anti lipoperoxidant effect of silybin phosphitidylcholine complex in chronic liver disease preliminary results, 1993; 53(1): 98-102.
16. Giorgio P, Paola B, Veronica P, Chiara N. Clinical usefulness of oral supplementation with alpha-lipoic acid, curcumin phytosome, and B-Group vitamins in patients with carpal tunnel syndrome undergoing surgical treatment. evidence-based complementary and alternative medicine, 2014; 1-7.
17. Gianni B, Andrea L, Shu H, Maria RC, Beatrice F. Greenselect phytosome for borderline metabolic syndrome. evidence -based complementary and alternative medicine, 2013; 1-7.
18. Zaveri M, Gajjar H, Kanaki N, Patel S. Preparation and evaluation of drug phospholipid complex for increasing transdermal penetration of phytoconstituents. International journal of institutional pharmacy and life sciences, 2011; 1: 80- 93.
19. Cuomo J, Appendino G, Dern AS, Schneider E, McKinnon TP, et al. Comparative absorption of a standardized curcuminoid mixture and its lecithin formulation. Journals of natural products, 2011; 74: 664- 669.

20. Gupta NK, Dixit VK Development and evaluation of vesicular system for curcumin delivery. Arch dermatol Res, 2011; 303: 89-101.
21. Cao FH, OuYang WQ, Wang YPA combination of a microemulsion and a phospholipid complex for topical delivery of oxymatrine. Arch Pharm Res, 2011; 34: 551-562.
22. Forster M, Bolzinger MA, Fessi H, Briançon S Topical delivery of cosmetics and drugs. Molecular aspects of percutaneous absorption and delivery. Eur journals of dermatology, 2009; 19: 309-323.
23. Kidd PM. Bioavailability and activity of phytosome complexes from botanical polyphenols: the silymarin, curcumin, green tea, and grape seed extracts, 2009; 14: 226- 246.
24. Yanyu X, Yunmei S, Zhipeng C, Qineng P. The preparation of silybinphospholipid complex and the study on its pharmacokinetics in rats. International journal of pharmaceutical science, 2006; 307: 77-82.
25. Maiti K, Mukherjee K, Gantait A, Ahamed HN, Saha BP. Enhanced therapeutic benefit of quercetin-phospholipid complex in carbon tetrachloride induced acute liver injury in rats: a comparative study. Iranian journal of pharmacology and therapeutics, 2005; 4: 84-90.
26. Busby A, La Grange L, Edwards J, King J. The use of a silymarin/ phospholipid compound as a fetoprotectant from ethanol-induced behavioral deficits, 2002; 2: 39-47.
27. Grange L, Wang M, Watkins R, Ortiz D, Sanchez ME. Protective effects of the flavonoid mixture, silymarin, on fetal rat brain and liver. Journal of Ethnopharmacol, 1999; 65: 53- 61.
28. Mascarella S, Guisti A, Marra F, Marena C, Relli P, et al. Therapeutic and antilipoperoxidant effects of silybin phosphatidylcholine complex in chronic liver disease, Preliminary results. Current Therapeutic Research, 1992; 53: 98-102.
29. Sandeep Arora. Preparation and Characterization of Phytosomal-Phospholipid Complex of P. Amarus and its Tablet Formulation. Journals of pharmaceutical technology research and management, 2013; 1: 1-8.
30. Jain NK. Liposomes as drug carriers, controlled and novel drug delivery, 1st edition, CBS publisher, 2005; 321-326.