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Review On Phytosomes: As A Emerging Strategy To Improve The Bioavailability Of Phytoconstituents

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ABSTRACT

Phytoconstituents, in modern time phytosomes are being increase the level of natural remedies. It is recently introduced system to have used as a novel drug delivery. However nowadays it has been developed into the most well-turned and self assembled system to raise the oral bioavailability of phyto-drugs. That generally recognized as phytosomes. Phytoconstituents have a benignant moderation between hydrophilic and lipophilic in nature molecules which is helps in breakdown of gastro-intestinal sap to pass the lipid rich bio-membrane of cells. It can just be achieved as a result of phytosomes technique. But the delivery of herbal drugs is turn into the challenges owing to reduced aqueous dissolubility, poor permeations and foremost metabolite rate. Therefore, phytosome works as linkage for retain the efficiency toward develop the incorporation of numerous well-liked herbal drugs. E.g. - Ginkgo biloba, grape seeds, green tea etc. it can merely be evolved for a variety of remedial use.

Keyword: Phyto-constituents, Phytosomes, Bioavailability, Novel drug delivery.

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INTRODUCTION

From ancient times, phyto-chemical and phyto-pharmacological studies have been well establish the various creations in natural behavior and their numerous health promising advantages of botanical herbs. Some of the biologically active phyto-constituents are consist in the nature of polar solvents (water). [1] However, water-soluble phyto-constituents are weakly absorbed when it takes orally or after applied topically. Owing to their big molecular mass and reduced lipid solubility profile it cannot be wrapped by passive distribution. Thus, there are many phyto-constituents which possibly will have various rings system and therefore, they could not be immersed from the intestinal fluid into the blood through basic dispersion course. Also, a small number of phyto-molecules are originated in broke environment which is soluble in lipids along with added oils as well as and it repeatedly show the inhibition to pass the small intestine owing to its diploid characters. The efficiency of every natural product is based on release of complexes. So it resultant shows the lower bioavailability over the herbal drugs [2]. Phytosomes are consist of lipid molecular complex along with have small cell like structures which is composed of "phyto" which means plant and "some" meaning cell-like. Phytosome is innovative approach which is involved the incorporation of phospholipids layer into standardized extracts for improving absorption and bioavailability [3]. This type of phytosomal technology can be marked the model to increase the bioavailability of phyto-molecules. Significantly, it can increase the greater clinical advantage and also ensured the delivery to the tissues site, and without conciliate nutrient protection. Few of the water-soluble phyto-molecules can be modified into lipid-friendly nature by reacting herbal drugs with phospholipids complex, therefore, it is called phytosomes technology [4]. Phytosomes technology was come in 1989, which is set on the plant chemical analysis examination of definite polyphenolics compounds. These are usually combination of polyphenols and extraction of its own plant genus, in addition, these complexes is experienced for the development of phytosome to mark the superior bioavailability and its effectiveness in straight assessment to its non-phytosomes drugs [5].

PROPERTIES OF PHYTOSOMES

Chemical Properties

Phyto-complexes are prepared as a result of reaction among substrate and polymer (phospholipids) generally in ration 1:1 and 1:2 or based on the essential quantity of phospholipids and substrate [6]. For the period of contact of both there is demonstrates the development of hydrogen bond linking in the polar part of phospholipids and substrate molecules as well as. It can be examined by way of spectroscopic system [7].

While phytosomes is attached to the glacial top of phospholipids, it can become an interior division of the molecular film for the creation of OH bonding involving to the phenol hydroxyls of the flavones moiety [8].

It can be able to induce the similarity of the NMR of the phytosomes by individuals of the untainted precursor after that the signals of the fatty sequence are about unaffected, such confirmation with the intention of complex were show the accessibility of the phytosomes by means of the assessment of substance property [9].

Biological properties

Phytosomes are the sophisticated as a natural world for herbal crops with the aim of these products are make the superior absorption and consumption as improved domino effect over the entire predictable herbal drugs [10].

Phytosomes is helpful to build the bioavailability of the phytosomes rather than the non-complexes botanical herbs it has been established as a result of *in-vitro* and *in-vivo* studies for better invention of herbs in living thing [11].

Advantages

1. There is a greatly increase the bioavailability and reforms the absorption of herbal drugs owing to their combination with phospholipids and botanical herbs in the intestinal tract [12].
2. Phytosomes have been used to convey the hepatic caring flavonoids moiety since they can also be capable of become bioavailable in the biological environment by acting as liver protective substances [13].
3. Phytosomes may be too make the improvement of the distribution of drug in the course of skin via transdermal route at the same time they can act as bridge for the release of enormous mixed collection of drugs such as peptides and protein [14].
4. Phytosomes can be adopted as systemic targeting agents to the transition of biological material from the hydrophilic nature into lipophilic nature of enterocyte cell and from nearby into cell [15].
5. Phytosomes have low risk report over the toxicological outline of the phospholipids are maintain in well form in the systematic text [16].
6. Phytosomes do not have the difficulty with drug entrapment throughout formulation development. In addition, the entrapment effectiveness is elevated besides predetermined form, for the reason that the drug itself forms vesicles subsequent to conjugation with lipid [17].

Disadvantages

Although phytosomes having so many advantages instead of this technology it has few disadvantages such as phospholipids (lecithin) can provoke the proliferation on MCF-7 breast cancer cell line and it has been reported that phytosomes could rapidly eliminate the phytoconstituents [18, 19].

PREPARATION TECHNIQUE OF PHYTOSOMES

Phytosomes are novel complex which is prepared by reacting synthetic or natural phospholipids with active components of drug in a ratio ranging from 0.5 to 5. But usually taken in 1:2 for preparation of phytosomes. But this reaction is carried out alone or in the natural mixture in aprotic solvent such as a bioflavonoid, dioxane, and methylene chloride and polyphenolic constituents [20]. The complex of phytosomes thus formed it can be isolated by precipitation with an aliphatic hydrocarbon or lyophilization or spray drying. However, Solvent evaporation technique is the most generally used for the preparation of phytosomes. It can be evaporated by using rotary evaporators. Therefore, after drying the solvents, the resulting complexes are soluble in aprotic and polar solvents [21]. Which are single components of the complex are usually insoluble. For the preparation of phytosomes the phospholipids are obtained from the group consisting of soylecithin, from bovine or swine brain or dermis, and phosphatidylcholine, phosphatidylethanolamine, phosphatidylserine, in which acryl group may be same or different and mostly received from palmitic, stearic, oleic and linoleic acid [22]. Some liposomal drugs complex operate in the presence of the water or buffer solution whereas phytosomes operate with the solvent having a reduced dielectric constant [23]. Preliminary matter of component like flavonoids is insoluble in chloroform, ethyl ether or benzene. They become extremely soluble in these solvents after forming phytosomes. Subsequently, chemical and physical properties could be change is due to the formation of a precise stable complex [24].

There are different types of technique employed to formulation of phytosomes which is summarized below.

- Solvent evaporation method
- Rotary evaporation method
- Anti solvent precipitation method

Table 1: Some Patented Technologies Related To Phytosomes Formulation

S. No	Patent title	Description of innovation	Patent no.	Ref.
1.	Phospholipid complexes of olive fruits or leave extract composition	Having improved bioavailability	WO/2007/118631	25
2.	Cosmetic and dermatological compositions for the treatment of aging and photo damaged skin	Cosmetic or dermatological composition for topical treatment	EP/1640041	26
3.	Anti-oxidant preparation based on plant extracts	For treatment of circulation and adiposity problems	US/6756065	27
4.	Treatment of skin and wound repair with thymosin beta-4	Thymosin beta-4 for treatment of skin problems	US/2007/0015698	28
5.	Complexes of saponins with phospholipid and pharmaceutical and cosmetic compositions containing them	Complexes of saponins with natural or synthetic phospholipid have high lipophilic and improved bioavailability and are suitable for use as active principle in pharmaceutical, dermatologic and cosmetic compositions	EP/0283713	29
6.	Complexes of flavanolignans with phospholipids, preparation thereof and associated pharmaceutical compositions	The resulting improvement in the pharmacokinetic and pharmacological parameters and such used in the treatment of acute and chronic liver disease of toxic, metabolic or infective origin or of degenerative nature.	US/4764508	30
7.	Phospholipid complexes of proanthocyanidin A2 as antiatherosclerotic agents	treating or preventing atherosclerosis and myocardial and cerebral infarction in a patient by administering the complex of proanthocyanidin- A2	US/ 6429202	31
8.	Phospholipid complexes prepared from extracts of Vitis vinifera as anti-atherosclerotic agents	For the treatment and the pro phylaxis of atherosclerosis, and of myocardial and cerebral infarctions.	US/6297218	32
9.	Ginkgo complexes for the enhancement of cognitive functions and the alleviation of mental fatigue	For the enhancement of cognitive function and alleviation of mental fatigue, i.e. to improve the speed of memory and memory quality, to increase accuracy and attention in activities in normal healthy subjects.	US/ 8591965	33
10	Phospholipids complexes of curcumin or extracts containing	Curcumin having improved bio- availability and chemopreventive action.	US/2009/0131373	34

COMMERCIAL RESEARCHES ON PHYTOSOMES TECHNOLOGY

Jhiang *et al,* (2001) prepared Herba Epimedii flavonoid phytosome (EPF) by means of solvent evaporation technique and the accumulative dissolution of different ratios of EPF-PVP precipitate was investigated by dissolution study. The study showed that the dissolution of the precipitate was significantly higher than that of its physical mixture and Herba Epimedii extract tablets [35].

Yanyu *et al, (*2006) developed the phytosomes of silymarin and studied its pharmacokinetic rate in rats. In present study, the bioavailability of silybin in rat was markedly enhanced after oral administration of silybinphospholipid complex due to an influential reformation of the lipophilic properties of silybinphospholipid complex and improvement of biological effect of silybin 3[6]. Tedesco et al., (2004) reported the phytosomes of silymarin. This study is focused on the better Anti-hepatotoxic Activity than silymarin alone and can provide the protection against the toxic effect of aflatoxin B1 on performance of broiler chicks [37].

Maiti *et al,* (2006) prepared the phytosomes of curcumin (flavonoid from turmeric, Curcuma longa) and naringenin (flavonoid from grape fruit, Vitis vinifera) in two different studies. 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 [38].

Maiti *et al,* (2005) developed the quercetin phospholipid complex in carbon tetrachloride to overcome the absorption of herbal formulation and it exerted better therapeutic efficacy to induced acute liver injury in rats [39].

Keyong Xu *et al,* (2009) formulated luteolin - phospholipid complex and suggest that results showed the luteolin and phospholipid complex joined by non-covalent-bonds and didnot form a new compound.They were reported that the complex has an efficient scavenger of DPPH radicals and powerful inhibitor activity within the Rancimat antioxidant test using animal oil as substrate [40].

Mukerjee *et al,* (2008) developed a novel hesperetin phytosome by complexing hesperetin with hydrogenated phosphatidyl choline. This complex was then evaluated for antioxidant activity in CCl4 intoxicated rats along with pharmacokinetic studies. It was found that the phytosome had 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 [41].

Cao *et al,* (2010) prepared Oxymatrine-phospholipid complex (OMT-PLC) to reform the lipid solubility of oxymatrine-phospholipid. The purpose of this study was to recognize the utility of the

combination of a micro emulsion and an OMT-PLC as topical delivery vehicle for increasing the absorption and efficacy of OMT. The solubility of OMT-PLC was determined and phase diagram of micro emulsion were constructed. Subsequently it is concluded that the combination of a micro emulsion and phospholipids complex show the effective vehicle for topical delivery of OMT [42].

Table 2: Commercially Available Marketed Phytosomes

S. No	Marketed Phytosomes	Sources	Biological Activity	Application of technology	Route of Administration	Dose	Ref
1.	Silybin Phytosome	Silybummarianum	Hepatoprotective and antioxidant	Increase in therapeutic effect	Subcutaneous	120mg	43
2.	Ginkgo Phytosome	Ginkgo biloba	Cardioprotective, anti-asthmatic and anti-diabetic	Induced hepatoprotective effect	Oral	120mg	44
3.	Ginseng Phytosome	Panax ginseng	Nutraceutical, immunomodulator	Increase absorption	Oral	150 mg	45
4.	Green tea Phytosome	Camellia sinensis	Nutraceutical, antioxidant, anticancer	Increase absorption	Oral	50-100 mg	45
5.	Grape seed phytosome	proanthocyanidins	Systemic antioxidant, cardio-protective	The blood TRAP nTotal Radical-trapping Antioxidant Parameter) were significantly elevated over the control	Oral	50-100 mg	45
6.	Curcumin phytosomes	Curcuma longa	Antioxidant, anticancer	Increase antioxidant activity and Increase bioavailability	Oral	360 mg/ kg	45
7.	Echniacea Phytosomes	Echniacea angustifolia	Nutraceutical, immunomodulator	Used to stimulate cellular and hormonal immune defenance, activates B, and T, lymphatocytes and stimulate tissue necrosis factor.	Oral	-	46
8.	Naringenin phytosomes	Citrus aurantium	Antioxidant	Increase the activity of glutathione peroxides, superoxide dismutase, catalase	Oral	100 mg	47
9.	Glycyrrhetinic acid (Mulethi)	Glycyrrhiza glabra	Anti-inflammatory, used in dermatitis, Anti- irritant	Glycyrrhetinic acid is structurally similar to cortisol, it pontentiates the anti-inflammatory activity of cortisol by inhibiting its intracellular inactivation	Oral, Topical	-	48
10.	Bilberry Phytosome	Vaccinium myritillus	Antioxidant, Improvement of Capillary Tone	Reduces capillary permeability and increase capillary resistance and also inhibits proteolytic enzymes.	Oral	-	49

SELECTION OF PHYTOSOMES CONTAINING DOSAGE FORM

Phytosomes formulation can be delivered by both routes like oral and topically, to obtained the best output regarding bioavailability of the phytosomes. There are different types of dosage form containing phytosomes are depicted below [50].

Soft gelatin capsule:

These types of phytosomes are developed in form of heterogeneous mixture (suspensions) with phytoconstituents as dispersed phase such as vegetable oils or semi synthetic oils as dispersion medium it is use to make a soft gelatin phytosomes capsules for oral drug delivery [51]. Example- Curcumin phytosome

Hard gelatin capsule:

Phytosomes can be used with direct volumetric process. It can be filled into hard gelatin capsules in powder form itself. Capsule size may not have increase 300 mg for low density phytosomes it is should be in zero size [52].

Tablet:

An ideal Phyto-phospholipid complex powder could not have got better technological properties due to their potential stickiness, flow ability, and low apparent density. When applying the direct compression process for material, it should be diluted with 60 to 70% of excipients and to optimize its physical & chemicals characteristics. For major process, dry granulation process can be most suitable to find the dose uniformity and convenient bioavailability. In other way, wet granulation process should be avoided owing to the negative effect of water and heat (used for granulation/drying) on the stability of the phospholipids complex [53].

Topical dosage form:

Phyto-phospholipid complex can be formulated topically in form cream, gel ointment as well. It is innovative process to incorporate the phytosomes complex is dispersed in the small amount of oily phase and then added already created emulsion at less temperature (not more than 40°C). In case outer phase is water containing phase then the phytosomes complex might also by dispersed into the watery phase and again added final formulation under 40°C [54].

CONCLUSION

Phytosomes are newly introduced technology in drug delivery. It is being applied to phytoconstituents for the improvement of bioavailability of herbal drug. Phytosomes have both properties like pharmacokinetics and pharmacodynamics and have wide range of cosmeticology but this technology is not limited to polyphenolic, alkaloids. In that, any molecules are eligible for the conversion. Phytosomal formulations are simple and reproducible as a part of that phospholipid

that is used in preparation of phytosomes. They have own beneficial effects in the body and markedly enhance the bioavailability of oral phyto constituents drug.

REFERENCES

1. Amit Kumar B, Habbu Prasanna, prabha Hullatti , Ravi Kumar S. Phytosomes as novel drug delivery system for herbal medicine-A review. Systematic Reviews in Pharmacy. 2017:8(1); 5-7.
2. Jagruti Patela, Rakesh Patelb, Kapil Khambholjab, Nirav Patel. "An overview of phytosomes as an advanced herbal drug delivery system". An overview of phytosomes/Asian Journal of Pharmaceutical Sciences 2009: 4(6); 363-371.
3. Tawheed Amin, Suman Vikas Bhat. "A Review on Phytosome Technology as a Novel Approach to Improve the Bioavailability of Nutraceuticals". International Journal of Advancements in Research & Technology. 2012:1(3); 1-15.
4. Abhishek Bhattacharjee. "An overview on Phytosome as a novel drug delivery system for herbal drugs". International journal of innovative pharmaceutical sciences and research 2015:3(6); 730-739.
5. Kidd, Parris M. "Bioavailability and activity of phytosome complexes from botanical polyphenols: the silymarin, curcumin, green tea, and grape seed extracts." Altern Med Rev 2009:14(3); 226-46
6. Keshwani, Bhawana, Divyanshu Sharma, Arindam Chatterjee, and Manish Jaimini. "Phytosomes: A promising system of herbal drug delivery." Journal of Chemical and Pharmaceutical Research 2016:8(1); 804-808.
7. Shyam baboo Prasad, Bhatia Sonam, Singh Shaminder. Phytosome: Phytoconstituent based lipid derived drug delivery system. Journal of Chemical and Pharmaceutical Research 2016:8(5); 664-67.
8. Roy Chowdhury Santanu, Bhandari Neeraj, Verma pooja. "Phytosomes an emerging technology in phytomedicine: A review". International Research Journal of Pharmacy 2012:3(10); 61-64
9. Arpita Singh, Anil Pratap Singh, Neeraj Verma. Phytosome: "A Revolution in Herbal Drug Delivery Systems". Asian Journal of Chemistry 2011:23(12); 5189-5193.
10. Amit Patel, Tanwar Y.S., Suman Rakesh, Patel poojan. "Phytosome: Phytolipid Drug delivery Systems for improving Bioavailability of Herbal Drug". Journal of pharmaceutical Science and Bioscientific Research 2013:3(2); 51-7

11. Jain N, Gupta BP, Thakur N, Jain R, Banweer J, Jain DK, Jain S. Phytosome: a novel drug delivery system for herbal medicine. International Journal of Pharmaceutical Science Drug and Research 2010:2(4); 224-8.
12. Pawar, Harshal Ashok, and Bhagyashree Dilip Bhangale. "Phytosome as a novel biomedicine: a microencapsulated drug delivery system." Journal of Bioanalysis & Biomedicine 2015:7(1); 06-12.
13. Saraf S, Kaur CD. Phytoconstituents as photoprotective novel cosmetic formulations. Pharmacognosy reviews. 2010:4(7); 1-11
14. Kumar S, Baldi A, Sharma DK. Phytosomes: A Modernistic Approach for Novel Herbal Drug Delivery-Enhancing Bioavailability and Revealing Endless Frontier of Phyto pharmaceuticals. Journal of Developing Drugs. 2019:8(1); 1-8.
15. Anitha V, Reddy Dwarakanadha D, Ramkanth S. Phytosomes: a Promising Technology in Novel Herbal Drug Delivery System. PharmaTutor 2019:1.7(6); 18-25.
16. Rathore, Priyanka, and Gaurav Swami. "Planterosomes: A potential phyto-phospholipid carriers for the bioavailability enhancement of herbal extracts." International Journal of pharmaceutical sciences and research 2012:3(3); 737-755.
17. Bhise Jayashree J, Bhusnure Ompraksh G, Jagtap R Sneha, Gholve Sachine B, Wale RR. Phytosomes: A Novel Drug Delivery for Herbal Extracts. Journal of Drug Delivery and Therapeutics. 2019:15.9(3-s); 924-30.
18. Singh, Bhuwanendra, Rajendra Awasthi, Arshad Ahmad, and Asif Saifi. "Phytosome: Most Significant Tool for Herbal Drug Delivery To Enhance The Therapeutic Benefits Of Phytoconstituents." Journal of Drug Delivery and Therapeutics 2018:8(1); 98-102.
19. Saha S, Sarma A, Saikia P, Chakrabarty. "Phytosome: A Brief Overview". Scholars Academic Journal of Pharmacy 2013:2(1); 12–20.
20. Sharma, Shalini, and Ram Kumar Roy. "Phytosomes: an emerging technology." International Journal of Pharma. Research and Development 2010:2(5); 1-7.
21. Tripathy, Surendra, Dilip K. Patel, Lipika Barob, and Suresh K. Naira. "A review on phytosomes, their characterization, advancement & potential for transdermal application." Journal of Drug Delivery and Therapeutics 2013:3(3); 147-152.
22. Chauhan, Nitesh S., Rajan Gowtham, and B. Gopalkrishna. "Phytosomes: potential Phytophospholipid carriers for herbal drug delivery." Journal of Pharmaceutical Research 2009:2(7); 1267-70.

23. Mahajan, Raghunath T., and Gunjan M. Chaudhari. "A novel approach towards phytosomal flavonoids." Pharma Science Monitor Pharma Science Monitor An International Journal Of Pharmaceutical Sciences 2012:3(4); 2079-2105.
24. Shelke, Sandip Sarjerao. "Phytosomes-A new herbal drug delivery system." International Journal of Research in Pharmaceutical and Biomedical (2012):3(4); 1710-1715.
25. Franceschi F, Giori A, inventors; Indena SPA, assignee. Phospholipid complexes of olive fruits or leaves extracts having improved bioavailability WO2007118631:2007.
26. Doering T, Traeger A, Waldmann-Laue M. Cosmetic and dermatological composition for the treatment of aging or photodamaged skin. EP1640041:2006.
27. Merizzi G, inventor; Ceteris Holding BV, assignee. Anti-oxidant preparation based on plant extracts for the treatment of circulation and adiposity problems. United States patent US 6,756,065: 2004.
28. Kleinman H, Goldstein A, Malinda K, Sosne G, inventors; US Department of Health, Human Services (HHS), RegeneRx Biopharmaceuticals Inc, assignee. Treatment of skin, and wound repair, with thymosin beta 4. United States patent application US 11/284,408: 2007.
29. Bombardelli E, Patri GF, Pozzi R. Complexes of saponins with phospholipids and pharmaceutical and cosmetic compositions containing them. EP0283713. 1988; 198.
30. Gabetta B, Bombardelli E, Pifferi G, inventors; Inverni Della Beffa SpA, assignee. Complexes of flavanolignans with phospholipids, preparation thereof and associated pharmaceutical compositions. United States patent US 4,764,508:1988.
31. Bombardelli E, Morazzoni P, inventors; Indena SpA, assignee. Phospholipid complexes of proanthocyanidin A2 as antiatherosclerotic agents. United States patent US 6,429,202:2002.
32. Morazzoni P, Bombardelli E, inventors; Indena SpA, assignee. Phospholipid complexes prepared from extracts of Vitis vinifera as anti-atherosclerotic agents. United States patent US 6,297,218:2001.
33. Morazzoni P, Petrini O, Scholey A, Kennedy D, inventors; Indena SpA, assignee. Use of Ginkgo complexes for the enhancement of cognitive functions and the alleviation of mental fatigue. United States patent US 8,591,965:2013.
34. Giori A, Franceschi F, inventors; Indena SpA, assignee. Phospholipids complexes of curcumin having improved bioavailability. United States patent application US 12/281,994:2009.

35. 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.
36. Raju, Thurapati Pandu, Mettu Srikanth Reddy, and Veerareddy Prabhakar Reddy. "Phytosomes: a novel phyto-phospholipid carrier for herbal drug delivery." International Research Journal of Pharmacy 2011:2(6); 28-33.
37. 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. Poultry science 2004:83(11); 1839-43.
38. Kumar, Prashant, S. Yadav, Anant Agarwal, and Nitin Kumar. "Phytosomes: Novel phyto-phospholipid carriers: an overview." International J Pharma Res 2010:2(6); 1-7.
39. Maiti, Kuntal, Kakali Mukherjee, Arunava Gantait, Haja Nazeer Ahamed, Bishnu Pada Saha, and Pulok Kumar Mukherjee. "Enhanced therapeutic benefit of quercetinphospholipid complex in carbon tetrachloride-induced acute liver injury in rats: a comparative study." Iranian Journal of Pharmacology & Therapeutics 2005:4(2); 84-90.
40. Xu, Keyong, Benguo Liu, Yuxiang Ma, Jiquan Du, Guanglei Li, Han Gao, Yuan Zhang, and Zhengxiang Ning. "Physicochemical properties and antioxidant activities of luteolin-phospholipid complex." Molecules 2009:14(9); 3486-3493.
41. Venkatesh, M., K. Mukherjee, K. Maiti, and P. K. Mukherjee. "Enhancement of bioavailability of phytomolecules with value added formulation." Planta Medica 2008:74(9); PC11.
42. Cao Fa-Hao, OuYang W, Wang Y, Yue P, Li S, A combination of a microemulsion and a phospholipid complex for topical delivery of Oxymatrine, Archieves of Pharmcal Research, 2010:34(4); 551-562.
43. Chaturvedi, Mayank, Manish Kumar, Amit Sinhal, and Alimuddin Saifi. "Recent development in novel drug delivery systems of herbal drugs." International Journal of Green Pharmacy (IJGP) 2011:5(2); 87-94.
44. Panda, Vandana S., and Suresh R. Naik. "Evaluation of cardioprotective activity of Ginkgo biloba and Ocimum sanctum in rodents." Alternative Medicine Review 2009:14(2); 161-171.
45. Saraf S. Applications of novel drug delivery system for herbal formulations. Fitoterapia. 2010:81(7); 680-9.

46. Singh, Anupama, Vikas Anand Saharan, Manjeet Singh, and Anil Bhandari. "Phytosome: drug delivery system for polyphenolic phytoconstituents." Iranian Journal of Pharmaceutical Sciences 2011:7(4); 209-219.
47. Maiti K, Mukherjee K, Gantait A, Saha B, PK M. Enhanced therapeutic potential of naringeninphospholipid complex in rats. J Pharm Pharmacol 2006:58; 1227-33.
48. L.A. Baltina, Chemical Modification of Glycyrrhizic Acid as A Route to New Bioactive Compounds for Medicine. Current Medicinal Chemistry 2003:10; 155-171
49. Dewan, Nazneen, Debaprotim Dasgupta, Suravi Pandit, and Prince Ahmed. "Review on-Herbosomes, A new arena for drug delivery." Journal of Pharmacognosy and Phytochemistry 2016:5(4); 104.
50. Bhuwanendra singh, Rajendra Awasthi, Arshad Ahmed Asif saif. "Phytosome: most significant tool for herbal drug delivery to enhance the therapeutic benefits of phytoconstituents". journal of drug delivery and therapeutics 2018:8(1); 98-102
51. TappetaJoshi Anand, Sandhya Vangara, Vaishnavi Vetsa, and Uppuluri Spandana. "Amphiphilic Drug Delivery System-Phytosomes". Research and Reviews: Journal of Pharmacognosy and Phytochemistry 2019:7(1); 8-14.
52. Karataş, Ayşegül, and Fatih Turhan. "Phyto-Phospholipid Complexes as Drug Delivery System for Herbal Extracts/Molecules." Turkish Journal of Pharmaceutical Science 2015:12(1); 93-102.
53. Amudha, Prabal Kumar Manna, Jeganathan N, Anbazhagan. Phytosomes: An Emerging Nanotechnology for Improved Bioavailability of Phytomedicines – A Review. Asian Journal of Pharmaceutical Technology & Innovation 2016:4(17); 83-94
54. Sachin, Ks, Jino Nesalin J. Adlin, and Mani T. Tamizh. "Phytosome; "A Promising Drug Delivery System". Int J Pharm Pharma Analysis 2018:1(2); 10-16.