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PHYTOSOMES: A NOVEL APPROACH FOR PHYTOMEDICINE

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ABSTRACT

In the recent days, most of the prevailing diseases and nutritional disorders are treated with natural medicines. The effectiveness of any herbal medication is dependent on the delivery of effective level of the therapeutically active compound. Phytosomes are recently introduced in herbal formulations that are better absorbed and as a result produced better bioavailability and actions than the conventional phyto molecules or botanical extracts. Phytomedicines are complex chemical mixtures prepared from plants, have been used for health maintenance since ancient times. But many phytomedicines are limited in their effectiveness because they are poorly absorbed when taken orally. The term "phyto" means plant while "some" means cell-like. Phytosomes are little cell like structure. This is advanced forms of herbal formulations which contains the bioactive phytoconstituents of herb extract surrounds and bound by a lipid. So, much work has been directed towards the development of new concept in herbal delivery system i.e., "Phytosomes" which are better absorbed, utilized and as a result produce better results than conventional herbal extracts owing to the presence of phosphatidylcholine which likely pushes the phytoconstituents through the intestinal epithelial cell outer membrane, subsequently accessing the bloodstream 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.

KEYWORDS: Phytosomes, Herbal medicine, Novel Drug Delivery System, Phytomedicine.

INTRODUCTION

Novel drug delivery system is a novel approach to drug delivery that addresses the limitations of the traditional drug delivery systems. Our country has a vast knowledge base of Ayurveda whose potential is only being realized in the recent years. However, the drug delivery system used for administering the herbal medicine to the patient is traditional and out-of-date, resulting in reduced efficacy of the drug. If the novel drug delivery technology is applied in herbal medicine, it may help in increasing the efficacy and reducing the side effects of various herbal compounds and herbs. This is the basic idea behind incorporating novel method of drug delivery in herbal medicines. Thus, it is important to integrate novel drug delivery system and Indian Ayurvedic medicines to combat more serious diseases. For a long time herbal medicines were not considered for development as novel formulations owing to lack of scientific justification and processing difficulties, such as standardization, extraction and identification of individual drug components in complex poly herbal systems. However, modern phyto pharmaceutical research can solve the scientific needs (such as determination of pharmacokinetics, mechanism of action, site of action, accurate dose required etc.) of herbal medicines to be incorporated in novel drug delivery system, such as nanoparticles, microemulsions, phytosomes, matrix systems, solid dispersions, liposomes, solid lipid nanoparticles and so on. In the past, almost all the medicines were from the plants; the plant being man's only chemist for ages. Herbs are staging a comeback, herbal 'renaissance' is happening all over the globe and more and more people are taking note of herbal therapies to treat various kinds of ailments in place of mainstream medicine.[1] There are three main reasons for the popularity of herbal medicines:

1. There is a growing concern over the reliance and safety of drugs and surgery.
2. Modern medicine is failing to effectively treat many of the most common health conditions.
3. Many natural measures are being shown to produce better results than drugs or surgery without the side effects.

Also there is increasing evidence that many current drug therapies simply suppress symptoms and ignore the underlying disease processes. In contrast, many natural products appear to address the cause of many diseases and yield superior clinical results.

On the other hand, the very slow progress in the efficacy of the treatment of severe diseases has suggested a growing need for a multidisciplinary approach to the delivery of therapeutics

to targets in tissues. From this, new ideas on controlling the pharmacokinetics, pharmacodynamics, non-specific toxicity, immunogenicity, bio-recognition and efficacy of drugs were generated. These new strategies, often called drug delivery systems (DDS), are based on interdisciplinary approaches that combine polymer science, pharmaceutics, bioconjugate chemistry.[2]

- **Advantages of Herbal Medicines[3,4]**

1. Herbal medicines are very cheap in comparison to the conventional form of medication. It's something which every pocket can afford, unlike other forms of medication which can create a big hole in your wallet.
2. Herbal medicines are known to be more productive in comparison to other forms of medication in curing certain conditions. Unless mixed with other chemical components, they are known to be all natural.
3. One of the greatest benefits associated with herbal medicine is the less existence of side effects. Also, they tend to offer long lasting benefits in terms of overall wellness.
4. Obesity is a growing problem which is known to have hazardous issues on an individual's health. Herbal medicine can help one deal with the problem of obesity very effectively without consuming much time and efforts.

- **Disadvantages of Herbal Medicines[5,6]**

1. In some instances, individuals switch to herbal medication without realizing that the symptoms can be linked to a different ailment. Unlike, conventional medication which involves constant monitoring of your health, herbal medicines are taken without prescription which means that in some cases, individual might be undergoing a trial and error process with their medication.
2. Although herbal medicines has the potential to cure many ailments, the curing period is usually longer in comparison to conventional medication. One needs to have immense patience while undergoing herbal treatment.
3. Herbal medicines can cause allergic reactions in some cases. Before resorting to herbal medication you need to ensure that you are not allergic to the particular herb that you will be consuming. Conventional medication can also cause allergic reactions, but they are usually taken upon prescriptions which is why the chances of allergic reactions are less.

4. The government does not approve of any kind of herbal medication. It's usually consumed upon the person's own risk, and when it comes to branded herbal supplements one can't expect any kind of quality assurance.

- **Introduction of phytosomes**[6,7]

Phytosomes is a complex of a phospolipid and natural active ingredients. It is claimed that phytosome increases absorption of "conventional herbal extracts" or isolated active principles both topically as well as orally. Hydrophilic phytoconstituents can be complexed with clinically useful nutrients such as phospholipids to convert them into lipid soluble complexes. Such complexes can be used to prepare liposome-like vesicles called as phytosomes.

In phytosomes, the complexation of phospholipids and water soluble active plant components involve chemical bond formation and therefore more stable. The phytosomes substantially improve the bioavailability of these hydrophilic active components. Some of the phospholipids that are reported for phytosome preparation include soy phospholipids, phosphatidylcholine etc. Phytosomes can easily cross the lipid membranes and are reported to increase the bioavailability of poorly lipid soluble plant based drugs by increasing the absorption in gastrointestinal tract. Phytosome is also called as Phytolipids delivery system which forms a bridge between the conventional delivery system and novel delivery system. The term "phyto" means plant while "some" means cell-like. Phytosomes express their behaviour in physical or biological system because of their physical size, membrane permeability, percentage entrapment, chemical composition, quantity and quality of the materials used. In phytosome the lipophilic envelop shields the polar head of polyphenolic molecule and phospholipid molecule and allows the complex to dissolve in low polarity solvents resulting in increased absorption and better bioavailability of the phytoconstituent.

- **Properties of phytosomes**[8,9,10]

1. Physicochemical properties

Phytosomes is a complex between a natural product and natural phospholipids, like soy phospholipids. Such a complex is obtained by reaction of stoichiometric amounts of phospholipids and the substrate in an appropriate solvent. On the basis of spectroscopic data it has been shown that the main phospholipids-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. When treated with water, phytosomes

assumes a micellar shape forming liposomal-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 catechin distearoyl phosphatidylcholine complex, there is the formation of H-bonds between the phenolic hydroxyl ends of the flavones moiety and the phosphate ion on the phosphatidylcholine moiety. Phosphatidyl choline can be deduced from the comparison of 1H-NMR and 13C-NMR spectra of the complex with those of the pure precursors. The signals of fatty chain remain almost unchanged. Such evidence inferred that the too long aliphatic chains are wrapped around the active principle, producing a lipophilic envelope, which shields the polar head of the phospholipid and flavanoid molecule and enables the complex to dissolve in low polarity solvents.

2. Biological properties

Phytosomes are advanced forms of herbal products that are better absorbed, utilized and as a result produce better results than conventional herbal extracts. The increased bioavailability of the phytosome over the non complexed botanical derivatives has been demonstrated by pharmacokinetic studies or by pharmacodynamic tests in experimental animals and in human subjects.

- **Advantages of phytosomes**[11]

Phytosomes have the following advantages

1. It enhances the absorption of lipid insoluble polar phytoconstituents through oral as well as topical route showing better bioavailability, hence significantly greater therapeutic benefit.
2. Appreciable drug entrapment.
3. As the absorption of active constituent (s) is improved, its dose requirement is also reduced.
4. 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.
5. Chemical bonds are formed between phosphatidylcholine molecule and phytoconstituent, so the phytosomes show better stability profile.

6. Application of phytoconstituents in form of phytosome improves their percutaneous absorption and act as functional cosmetics. Recent research shows improved absorption and bioavailability with phytosomes as compared to the conventional means.

7. They can be also used for enhanced permeation of drug through skin for transdermal and dermal delivery.

8. These are platform for the delivery of large and diverse group of drugs (peptides, protein molecules).

9. The vesicular system is passive, non-invasive and is available for immediate commercialization.

10. Phosphatidylcholine, an essential part of the cell membrane used in phytosome technology, acts as a carrier and also nourishes the skin.

11. There is no problem with drug entrapment during formulation preparation. Also, the entrapment efficiency is high and moreover predetermined; because the drug itself forms vesicles after conjugation with lipid.

12. They offer a better stability profile because chemical bonds are formed between the phosphatidylcholine molecules and Phytoconstituents.

13. The dose requirement is reduced due to improved absorption of the main constituent. They can also be given in smaller quantities to achieve the desired results.

- **Difference between phytosomes and liposomes**

Table 1: Difference between phytosomes and liposomes.

Phytosomes	**Liposomes**
Phytosome is a unit of a molecules bounded together.	Liposome is an aggregate of many phospholipid molecules that can enclose other phytoactive molecules but without specifically bonding to them.
Phytosome process the phosphatidylcholine and the plant components actually form a 1:1 or a 2:1 molecular complex depending on the substances complexed. Involving chemical bonds. So they better absorbed and shown better bioavability.	In liposome no chemical bond is formed. The phosphtidylcholine molecules surround the water soluble substance. There may be hundereds or even thousands of phosphtidylcholine molecules surrounding the water soluble compound.
Phytosome complex can somewhat be compared to an integral part of the lipid membrane. Where the polar functionalities of the lipophilic guest interact via hydrogen bonds with the polar head of a phospholipids (i.e. phosphate and ammonium groups). Forming a unique pattern which can be characterized by spectroscopy.	In liposomes. The active principles are dissolved in the central part of the cavity. With no possibility of molecular interaction between the surrounding lipid and hydrophilic substance.
Phytosomes act with the solvent having a reduced dielectric constant such as Acetone, Dioxane, Metyhlenechloride, Hexane and Ethyl acetate etc.	Liposomal drug complex is formed in the presence of the water or buffer solution.

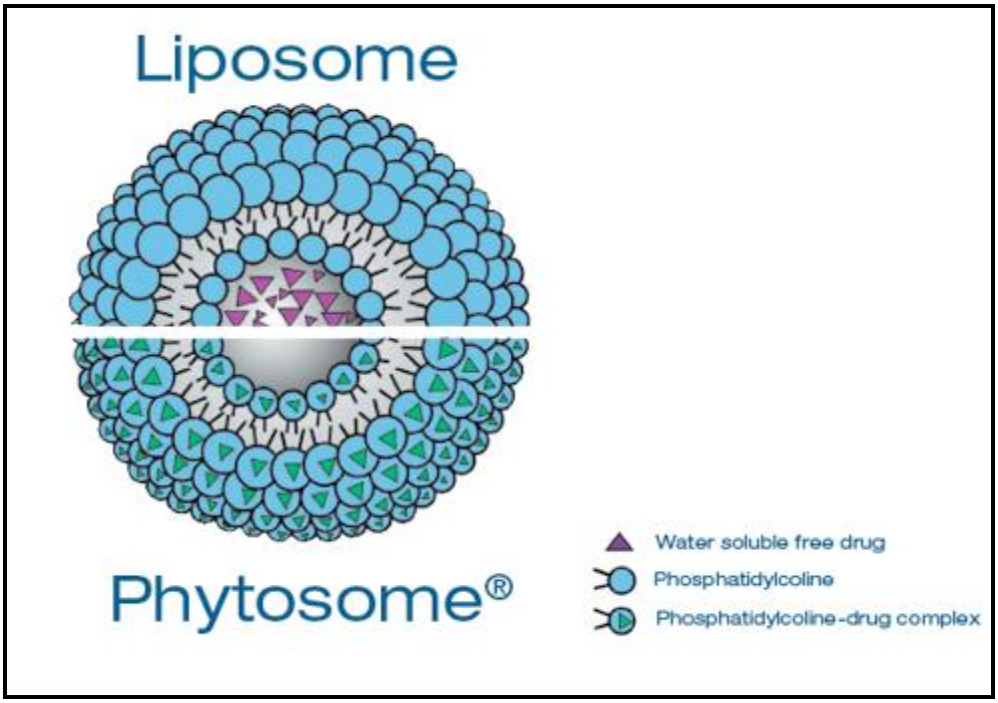

Fig no. 1: Difference between phytosomes and liposomes. The molecular organization of phytosomes (lower segment) liposome (upper segment).

- **Method of preparation of Phytosomes[12,13,14]**

1. Anti-solvent precipitation technique

The specific amount of plant material and soya lecithin were taken into a 100 ml round bottom flask and refluxed with 20 ml of dichloromethane at a temperature not exceeding 60^{o}C for 2 h. The mixture is concentrated to 5-10 ml. Hexane (20 ml) was added carefully with continuous stirring to get the precipitate which was filtered and collected and stored in vacuum desiccators overnight. The dried precipitate is crushed in mortar and sieved through #100 meshes. Powdered complex was placed in amber colored glass bottle and stored at room temperature.

2. Rotary evaporation technique

The specific amount of plant material and soya lecithin were dissolved in 30 ml of tetrahydrofuran in a rotary round bottom flask followed by stirring for 3 hours at a temperature not exceeding 40^{o}C. Thin film of the sample was obtained to which n-hexane was added and continuously stirred using a magnetic stirrer. The precipitate obtained was collected, placed in amber colored glass bottle and stored at room temperature.

3. Solvent evaporation method

The specific amount of plant material and soya lecithin were taken into a 100 ml round bottom flask and refluxed with 20 ml of acetone at a temperature 50 - 60^{o}C for 2 h. The mixture is concentrated to 5-10 ml to obtain the precipitate which was filtered and collected. The dried precipitate phytosome complex was placed in amber colored glass bottle and stored at room temperature.

- **CHARACTERIZATION TECHNIQUES OF PHYTOSOME**[15,16,17]

1. Visualization: Visualization of phytosomes can be done using transmission electron microscopy (TEM) and by scanning electron microscopy (SEM). SEM was used to determine the size of the particle and its appearance. Dry sample was placed on electron microscope brass stub coated with gold in an ion sputter. Random scanning of the complex at 100.

2. Particle 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). Size analysis and zeta potential Malvern Zeta sizer is used to check the particle size and zeta size of phytosomal complex. Argon laser is used for this particle size and zeta sizer characterization.

3. Drug entrapment efficiency: The entrapment efficiency of a drug by phytosomes can be measured by the ultracentrifugation technique. Drug entrapment and loading capacity of drug phytosomal complex was centrifuged at 10000 rpm for 90 minutes at 4°C to separate phytosome from the untrapped drug. The concentration of free drug can be measured by doing ultraviolet spectroscopy. The percentage drug entrapment can be calculated as given formula:

$$\text{Entrapment efficiency \%} = \frac{\text{Weight of total drug – weight of free drug}}{\text{Weight of total drug}\times 100}$$

4. Transition temperature: The transition temperature of the phytosomes can be determined by differential scanning calorimetry.

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.

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.

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

CONCLUSIONS

Phytosomes forms a bridge between the convectional delivery system and novel delivery system. Phytosomes are advanced form of herbal extract that are better absorbed which results better than conventional herbal extract. Phytosomes have improved pharmacokinetic and pharmacological parameter, which in result can advantageously be used in various diseases. The nutraceutical products based on phytosomes technology become present at the site of action of liver, kidney, brain, heart) at similar or less dose as compared to conventional plant extract. Phytosomes have wide scope in cosmetology and many areas of them are to be revealed in future in the prospect of pharmaceutical application.

REFERENCES

1. Bhattacharya S, Ghosh A. Phytosomes: the Emerging Technology for Enhancement of Bioavailability of Botanicals and Nutraceuticals. The Internet Journal of Aesthetic and Antiaging Medicine, 2008; 2(1).
2. Pallav KD, Anupam KP, Ragini GP. A Noval Drug Delivery System for Phytocon-stituents. Journal on New Biological Reports, 2014; 3(3): 212-20.
3. Cottart CH, Nivet-Antoine V, Laguillier-Morizot C, Beaudeux JL. "Resveratrol bioavailability and toxicity in humans," Molecular Nutrition and Food Research, 2010; 54(1): 7-16. http://dx.doi.org/10.1002/mnfr.200900437.
4. Gao L, Liu G, Wang X, Liu F, Xu Y, Ma J. Preparation of a chemically stable quercetin formulation using nanosuspension technology, International Journal of Pharmaceutics, 2011; 1(2): 231-27. http://dx.doi.org/10.1016/j.ijpharm. 2010.
5. Kumar, A., B., Kumar, S.K., Singh, B., Kaur, and S., Singh, A Review On Phytosomes: Novel Approach For Herbal Phytochemicals. Journal of Aisan Journal of Pharmaceutical And Clinical Research, 2017; 10: 41-47.
6. Sharma, A., and P. Kaur, Preparation and Characterization of Phytosomal – Phospholipid complex of P.Amarus and its Tablet formulation. Journal of Pharmaceutical Technology, Research and Management, 2003; 1: 1-18.

7. Jain N. Phytosome: A Novel Drug Delivery System for Herbal Medicine. International Journal of Pharmaceutical Sciences and Drug Research, 2010; 2: 224-228.
8. Choubey A. Phytosome: A Novel approach for Herbal Drug Delivery. International Journal of Pharmaceutical Sciences and Research, 2011; 2: 807-815.
9. Bombardelli E, Mustich G. Bilobalidephospholipid complex, their uses and formulation containing them, U.S. Patent US EPO-275005; 1991.
10. Franco PG, Bombardelli E. Complex compounds of bioflavonoids with phospholipids, their preparation and uses and pharmaceutical and cosmetic compositions containing them. U.S. Patent No-EPO 275005; 1998.
11. Pawar, H.A. Bhangale, B.D., Phytosome as a Novel Biomedicine: A Microencapsulated Drug Delivery System. J Bioanal Biomed, 2015; 7(1): 06-12.
12. Priyanka Rathore, 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.
13. Singh RP, Parpani S, Narke R, Chavan R. Phytosome: Recent advance research for novel drug delivery system. Asian Journal of Pharmaceutical Research and Development, 2014; 2(3): 15-29.
14. Rani B, Vandana, Nagpal M, Arora S. phytosomes: potential carriers for herbal drugs. Ijrrpas, 2013; 2(3): 566-577.
15. Maryana W, Rahma A, Mudhakir D, Rachmawati H. Phytosome containing silymarin for oral administration: Formulation and physical evaluation. J Biomed Sci Eng., 2015; 25: 56.
16. Singh RP, Gangadharappa VH, Mruthunjaya K. Phytosome loaded novel herbal drug delivery system: A review. Int Res J Pharm, 2016; 7(6): 15-21.
17. Nagpal N, Arora M, Swami G, Rageeb, Kapoor R. Designing of a phytosome dosage form with Tecomella undulata as a novel drug delivery for better utilization. Pak J Pharm Sci., 2016; 29(4): 1231-5.