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Phyto-vesicles: conduit between conventional and novel drug delivery system

Nidhi Mishra, Narayan P Yadav*, Jaya Gopal Meher, Priyam Sinha

Herbal Medicinal Product Department, Central Institute of Medicinal and Aromatic Plants (CSIR-CIMAP), Lucknow 226015 India

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ABSTRACT

Objective: To discuss the preparation, characterization, targeting and formulation aspect of phospholipids based drug delivery system i.e. Phyto-vesicles. **Methods:** The methods of phyto-vesicles preparation on R & D scale and different analytical techniques to characterize them have been discussed. **Result:** Phyto-vesicles are the advanced form of herbal drug delivery systems as its structure includes water soluble head and two fat soluble tails which act as an effective emulsifier. **Conclusion:** It is concluded that phytovesicular delivery system has improved pharmacokinetic and pharmacodynamic parameter as compared to conventional system Therefore, phyto-vesicles are called as conduit between conventional and novel drug delivery system.

1. Introduction

The method by which a drug is delivered can have a significant effect on its efficacy. Some drugs like Ginseng and Rosemary have an optimum concentration range within which maximum benefit is derived and concentrations above or below this range can be toxic or produce no therapeutic benefit at all. On the other hand, 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. Keeping in view the above facts new ideas on controlling the pharmacokinetics, pharmacodynamics, non-specific toxicity, immunogenicity, biorecognition 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 and molecular biology. An ideal drug delivery system possesses two elements (i) ability to target (ii) to control the drug release. Targeting will ensure high efficiency of the drug and reduce the side effects especially when dealing with drugs that are presumed to kill cancer cells but can also kill healthy cells when delivered to them. The prevention of side effects is achieved by controlled release of drug[1]. Therefore, different types of delivery system are used for variety of synthetic drugs, phytomolecules and herbal extracts to ensure better bioavailability and targeted delivery. Some of these delivery system are Cubosomes, Colloidosomes, Ethosomes, Aquasomes, Niosomes, Liposomes and Nanoparticles. Cubosomes are bicontinuous cubic phases consisting of two separate, continuous but nonintersecting hydrophilic regions divided by a lipid layer that is contorted into a periodic minimal surface with zero average curvature. Colloidosomes are solid microcapsules formed by the self assembly of colloidal particles at the interface of emulsion droplets. They are hollow, elastic shells whose permeability and elasticity can be precisely controlled. Ethosomes are noninvasive delivery carriers that enable drugs to reach the deep skin layers and/or the systemic circulation. It contains phospholipids, alcohol in relatively high concentration and water. Aquasomes are spherical particles used for drug and antigen delivery. The particle core is composed of non crystalline calcium phosphate or ceramic diamond and is covered by a polyhydroxyl oligomeric film. Colloidal dispersion of drugs covalently bound to a lipid and may exists as ultrafine

*Corresponding author: Narayan P. Yadav, Herbal Medicinal Product Department, Central Institute of Medicinal and Aromatic Plants (CSIR-CIMAP), Lucknow 226015, India.
Tel: 9451244418; Fax: 0522 2716141
E-mail: npyadav@gmail.com
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vesicular, micellar or hexagonal aggregates, depending on the chemical structure of the drug-lipid. Liposomes (Table 1) are small artificial vesicles of spherical shape that can be produced from natural non toxic phospholipids and cholesterol. Because of their size, hydrophobic and hydrophilic character as well as biocompatibility, liposomes are promising systems for drug delivery. A niosome is non-ionic surfactant formed mostly by cholesterol incorporation as an excipient. They are structurally similar to liposome in having a bilayer, however, the materials used to prepare niosomes make them more stable and thus niosomes offer many more advantages over liposomes[2-3]. Nanoparticles having diameter of 10-1 000 nm are drug loaded particles which can be embedded or dissolved in nanoparticles prepared by taking natural polymer or synthetic chemicals as the carriers. Comparison of these delivery systems is given in Table 2.

Over the past century, phytochemical and phytopharmalogical sciences established the composition, biological activities and health promoting benefits of numerous plant products. But many phytomedicines like epigallocatechin obtained from green tea leaves, grape procynadins, silybin obtained from silymarin are limited in their effectiveness because they are poorly absorbed when taken by mouth either due to their large molecular size, which cannot absorb by passive diffusion or due to their poor lipid solubility limiting their ability to pass across the lipid rich biological membranes resulting to poor bioavailability. To overcome this complexation with certain other clinically useful nutrients substantially improves the bioavailability. The nutrients so helpful for enhancing the absorption are the phospholipids. Phospholipids are complex molecules employed as natural digestive aids and as carrier for both fat miscible and water miscible nutrients[4-8].

Advantages of phospholipids based carrier systems in comparison to other delivery systems are (i) these systems show enhanced permeation of drug through skin for transdermal and dermal delivery, (ii) these are platform for the delivery of large and diverse group of drugs (peptides, protein molecules), (iii) their composition is safe and the components are approved for pharmaceutical and cosmetic use, (iv) Low risk profile- the toxicological profiles of the phospholipids are well documented in the scientific literature, (v) high market attractiveness for products with proprietary technology, (vi) Relatively simple to manufacture with no complicated technical investments required for production of Ethosomes & (vii) the vesicular system is passive, non-invasive and is available for immediate commercialization.

Phyto-vesicles often known as herbosomes developed to incorporate standardized plant extracts or water soluble constituents into phospholipids (such as Phosphotidylcholine (PC) derived from soy bean, Phosphotidylserine) to produce lipid compatible molecular complexes, called as phyto-vesicles and significantly improve their absorption and bioavailability. PC is not merely a passive "carrier" for the bioactive flavonoids of the Phyto-vesicle but is itself a bioactive nutrient with documented clinical efficacy for liver diseases such as alcoholic hepatic steatosis; drug induced liver damage and hepatitis. To appreciate the uniqueness of Phyto-vesicles it is necessary to differentiate them from liposomes. The main difference between Phyto-vesicles and liposomes is that in Liposomes the active principle is dissolved in the medium contained in the cavity or in the layers of the membranes whereas in the Phyto-vesicles it is an integral part of the membrane, being the molecule anchored through chemical bonds to the polar head of the phospholipids. The unit phyto-vesicle is a molecular-level association involving as few as two molecules (one PC plus one polyphenol). The unit liposome is an aggregate of hundreds of phospholipids molecules into a spherule, within which other molecules are compartmentalized but not specifically bonded. Whereas, the liposome concept remains unproven as an oral delivery vehicle, the phyto-vesicle is known to dramatically enhance oral delivery[12,13]. Various Phyto-vesicles herbal formulations are given in Table 3. Phyto-vesicles of selected plant drugs would make the drugs better bioavailable, dramatically enhance bioavailability due to their complex with phospholipids, ensure faster drug delivery and improve absorption in intestinal tract. Phyto-vesicles permeates the non-lipophillic membrane and absorbed better in intestinal lumen. Phyto-vesicles would be given in small quantity and desired result can be achieved. Therefore it has been proved that the Phyto-vesicles technology is a breakthrough model for (i) marked enhancement of bioavailability (ii) significantly greater clinical benefit (iii) assured delivery to the tissues (particularly liver tissues)[9-11]

2. Material and method

2.1. Chemicals

All the chemicals used were of analytical grade and were obtained from Hi-Media Laboratories Pvt. Ltd, Mumbai

2.2. Method of preparation

Most of the bioactive constituents of herbal drugs are water soluble molecules. However, water soluble phytoconstituent like many flavonoids are poorly absorbed e.g. *Ginkgo biloba* (*G. biloba*) and silymarin (i) either due to their multiple-ring large size molecules which can not be absorbed by simple diffusion, or (ii) due to their poor miscibility with oils and other lipids, severely limiting their ability to pass across the lipid-rich outer membranes of the enterocytes of the small intestine. Water-soluble phytoconstituent molecules (mainly polyphenol) can be converted into lipid-compatible molecular complexes, which are called Phyto-vesicles. Mareno and Lampertico (1991), Jiang et al (2001), reported the methods of Phyto-vesicle preparation[14-27] on R & D scale as discussed below: