Academic Sciences International Journal of Pharmacy and Pharmaceutical Sciences

ISSN- 0975-1491 Vol 4, Suppl 3, 2012

Review Article

PHARMACOSOMES: OPENING NEW DOORS FOR DRUG DELIVERY

TANU GOYAL, ASHWANI SINGH RAWAT AND MEENAKSHI CHAUHAN*

Delhi Institute of Pharmaceutical Sciences and Research, New Delhi, India. Email: meenakshikanwar@yahoo.com

Received: 16 Dec 2010, Revised and Accepted: 25 Sep 2011

ABSTRACT

One of the most recent advancements in the domain of solubility enhancement lead to the development of pharmacosomes, a novel lipid based drug delivery system. These are the colloidal dispersions of drugs covalently bound to the phospholipids. They may exist as ultrafine vesicular, micellar or hexagonal aggregates depending upon the chemical structure of the drug-lipid complex. Their very small size and unique properties such as amphiphilicity, active loading of drugs, high and predetermined entrapment efficiency, stability make them an appropriate carrier for delivering drugs with precision and selectivity. They help in achieving increased bioavailability, reduce the cost of therapy and provide controlled as well as targeted release of drug. There is reduction in the drug leakage and toxicity while the therapeutic efficacy increases. It is advancing as a method used for delivery of various drugs like non-steroidal anti-inflammatory drugs, cardiovascular drugs, antineoplastic drugs and proteins. This approach as a drug delivery system certainly promises a reliable, safe, selective and precise method of drug delivery.

Keywords: Pharmacosomes, Solubility, Phosphatidylcholine, Amphiphilic complex, Bioavailability.

INTRODUCTION

Majority of the drugs are poorly soluble or insoluble in water, which results in poor bioavailability for the reason that the solubility of a drug plays an important role in determining the rate and extent of its absorption[1].

The Biopharmaceutical classification system (BCS) was introduc ed by Amidon et al in 1995[22]. According to the biopharmaceutical classification system[2], for class II-drugs dissolution rate is the limiting factor for the drug absorption. Similarly for class IV-drugs the dissolution rate can be the limiting factor. The rate of drug release is a function of its intrinsic solubility and subjective to its particle size, crystallinity, drug derivatization, etc. Numerous approaches have been explored for enhancing the dissolution rate of poorly water-soluble drugs including reducing particle size, solubilization in surfactant systems, drug derivatization, producing liquisolid formulations, manipulation of the solid state of a drug substance, solid dispersion formulations and preparing complexes (with complexing agents like metals and cyclodextrin)[3]. On the other hand, methods used for modifying the solubility, the complexation with phospholipids have been found to show improvement in both, absorption as well as permeation of the complexed active constituents[4,5]. Advances have been made in the area of vesicular drug delivery, leading to the development of systems that allow drug targeting, and the sustained or controlled release of conventional medicines[24]. Pharmacosome is one of the important milestones in this series as the carrier is having a wide range of advantages over the other vesicular carrier system.

In the present review, considerable attention has been given to provide an outlook of what are these complexes, basic ingredient used to formulate these carriers, methods of preparation, evaluating parameters and the potential applications of the pharmacosomes.

Pharmacosomes

The term pharmacosomes is explicitly used to describe the zwitterionic, amphiphilic, stoichiometric complexes of polyphenolic compounds with phospholipids. These are the lipid based drug delivery systems that are appropriately elaborated as the colloidal dispersions of drugs having a covalent, electrostatic or hydrogen bonding with lipids[6]. They are rightly termed as "pharmacosomes" due to the linking of a drug (pharmakon) to a carrier (soma). These amphiphilic complexes of phospholipids bear an active-H atom and may exist as ultrafine vesicular, micellar or hexagonal aggregates depending upon the chemical structure of drug-lipid complex as shown in **Figure 1**. A drug possessing a free carboxyl group or an active hydrogen atom (-NH_2, -OH, -COOH) can be esterified with or without a spacer chain to the hydroxyl group of a lipid molecule, thereby producing an amphiphilic prodrug. Such a prodrug conjoins hydrophilic and lipophilic properties and thus manifests amphiphilic characteristics. Upon dilution with water, pharmacosomes are generated from these amphiphilic prodrugs. The thought for the development of the vesicular pharmacosome is based on surface and bulk interactions of lipids with drug[5].

Pharmacosomes being amphiphilic compounds facilitate membrane, tissue, or cell wall transfer in the organism. The amphiphilic characters help pharmacosomes to reduce interfacial tension and at higher concentrations exhibit mesomorphic behaviour[7]. This decrease in the interfacial tension leads to an increase in the contact area thereby increasing bioavailability of drugs.

Merits and Demerits of Pharmacosomes

Pharmacosomes bear a wide range of merits in general and also over other lipid based vesicular carriers but also put up with certain limitations of their own **(Table 1 and 2).**

METHODS FOR PREPARATION OF PHARMACOSOMES

Different methods have been reported for the preparation of pharmacosomes by various groups of researchers **(Figure 2)**. Drug lipid complex is prepared from drug acid by using techniques such as solvent evaporation, ether-injection, dilution of lyotropic liquid crystals of amphiphilic drugs, anhydrous co-solvent lyophilisation, supercritical fluid process, etc[6, 7].

FORMULATION ASPECTS OF PHARMACOSOMES PREPARATION

Drugs

Any drug possessing an active hydrogen atom (-COOH, -OH, -NH 2 etc.) can be esterified to the lipid, with or without spacer chain, leading to amphiphilic complexes. Synthesis of such a compound may be guided in such a way that strongly result in an amphiphilic compound, which will facilitate membrane, tissue, or cell wall transfer, in the organism [4,8,9]. The approach has successfully improved the therapeutic efficacy of a number of drugs i.e. pindolol maleate, bupranolol hydrochloride, taxol, acyclovir, etc [10,11].

Lipids

Lipid or lecithin or phosphatidylcholine is the chief molecular building block of cell membranes **(Figure 1).** Phospolipids are the hydrophobic or electrostatic zwitterionic molecules which upon complexation with the drug yield amphiphilic products which render phospholipids water soluble and the drug lipid soluble[8].

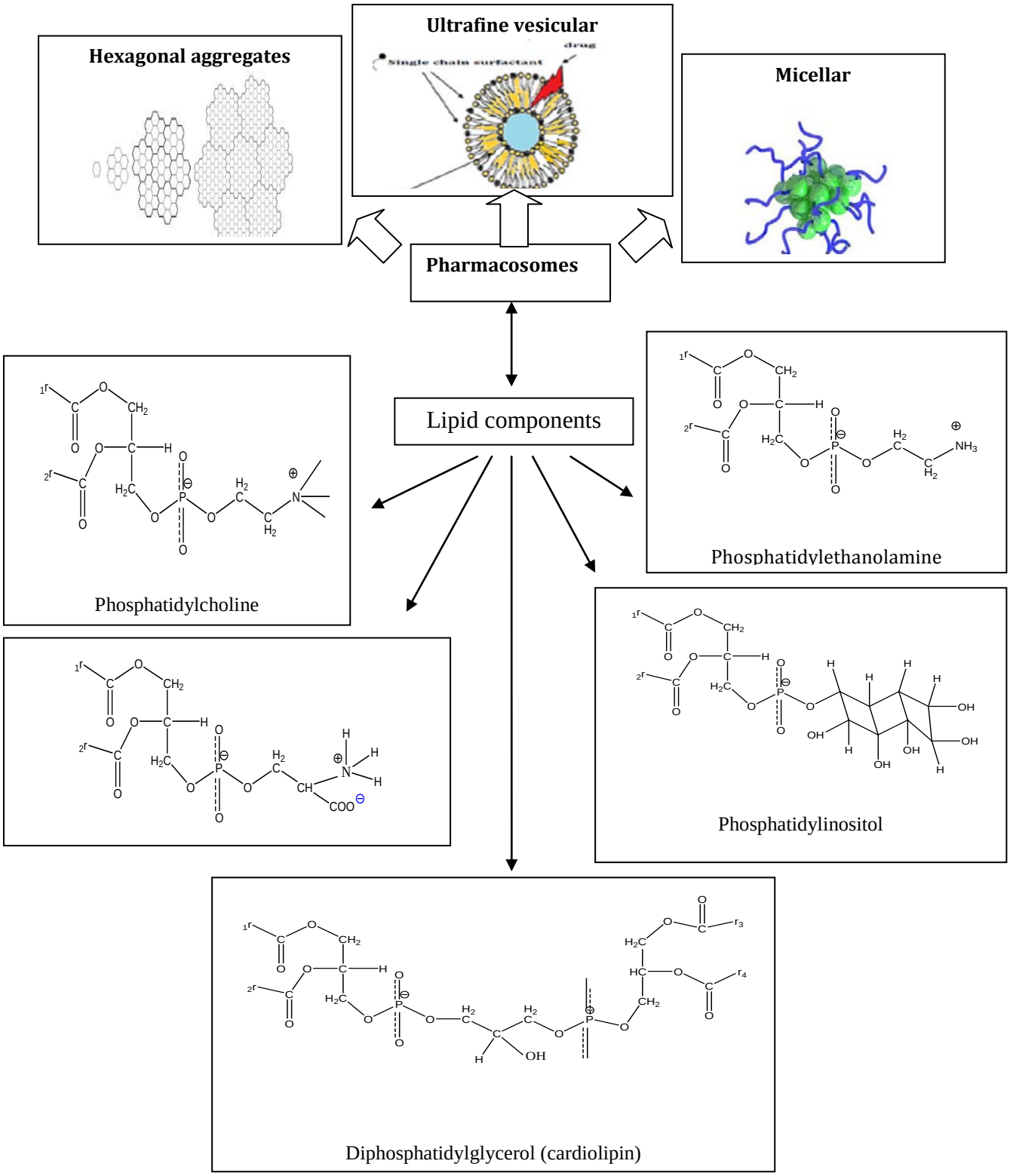

Table 1: Merits of Pharmacosomes

General advantages	
Pharmacosomes' Merits	1. High and predetermined drug loading. 2. Deliver drug directly to the site of infection. 3. Reduction in adverse effects and toxicity. 4. Amphiphilicity leads to improved bioavailability of poorly lipid and water soluble drugs. 5. Economical. 6. Stable and efficiency due to covalent linkage. 7. Size, functional groups (drug molecule), chain length (lipids) and spacer decides the degradation velocity into active drug molecule.

Over liposomes	1. No need to remove free, unentrapped drug. 2. Covalent linkage prevents drug leakage in pharmacosomes. 3. Entrapment efficiency is independent of inclusion volume and drug-bilayer interactions. 4. Cheaper, oxidation resistant and pure natural phospholipids not needed.
Over Niosomes	1. More stable. 2. More Efficient. 3. Less time consuming.
Over Transfersomes	1. Cheap. 2. Chemically stable.

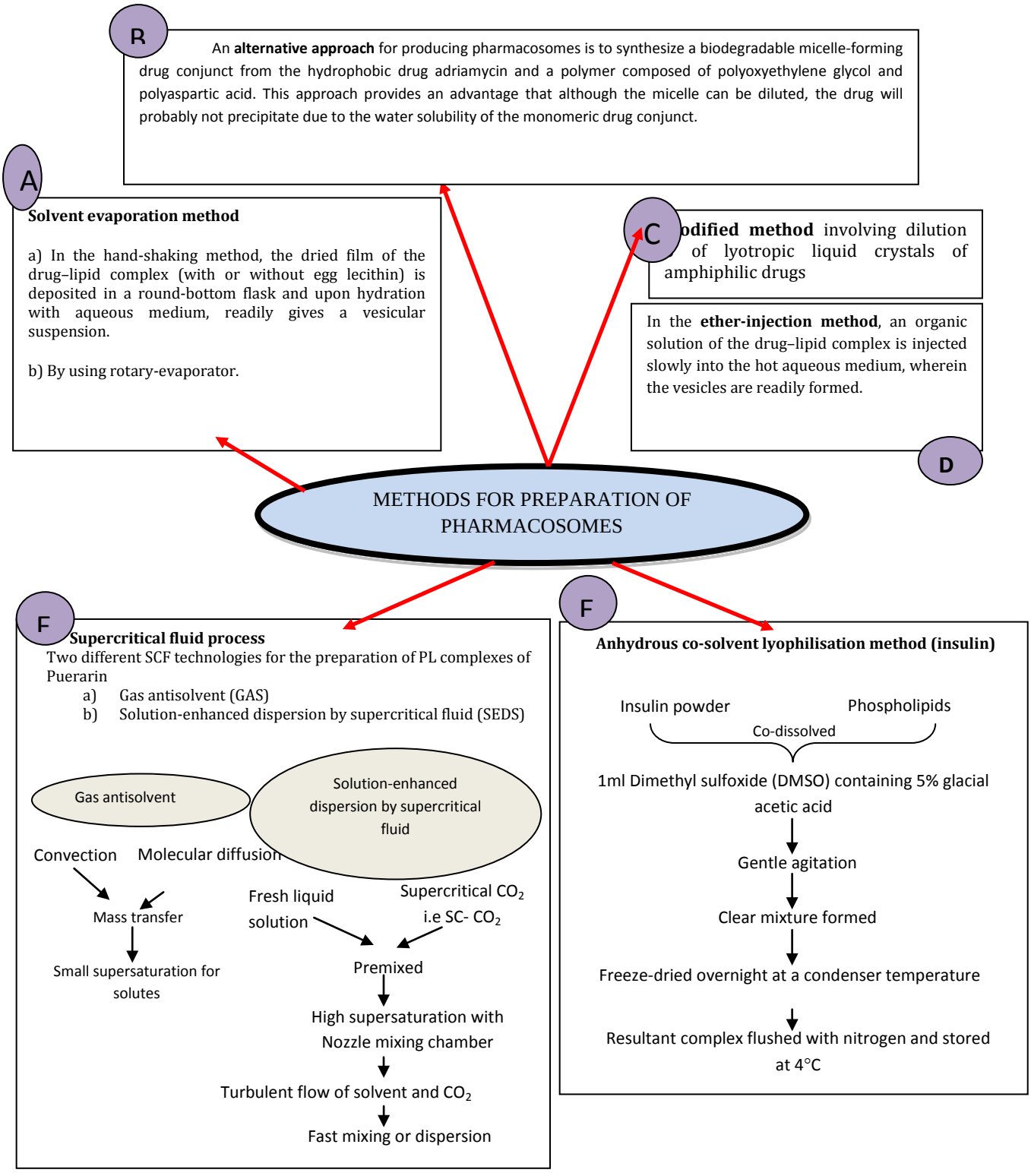

Fig. 2: Methods of Preparation of Pharmacosomes

Table 2: Demerits of Pharmacosomes

Demerits of Pharmacosomes
1. Synthesis of a compound depends upon its amphiphilic nature.
2. Required surface and bulk interaction of lipids with drugs.
3. Required covalent bonding to protect the leakage of drugs.
4. On storage, undergo fusion and aggregation, as well as chemical hydrolysis.

Phospholipids (amphiphilic surfactants) increase the solubility of drug by their wetting and dispersion properties. This amphiphilicity further leads to improved bioavailability of the drug. Surface-active phospholipids get adsorbed and form a protective hydrophobic cover on the surface of mucus that covers the surface epithelium and is suggested to protect the gastrointestinal tissues by providing a hydrophobic layer between the epithelium and luminal contents[2].

Phospholipids are natural components; their different purity grades may have different effects in shape and surface morphology. The surface was found to be sticky in the complexes prepared with low purity grades (40 %) of phospholipids. On the other hand the surface of the complexes prepared with the high purity grades of phospholipids (80%) show rough, non-sticky and free-flowing nature[7].

EVALUATION TECHNIQUES

Various techniques used for the evaluation of the pharmacosomes are summarized in **Table 3:**

Table 3: Different evaluation techniques used for Pharmacosomes

Parameters	Techniques and instrument
Size and size distribution	For measurement of the drug lipid complex
Shape & surface morphology	Scanning electron microscopy(SEM) Transmission electron microscopy (TEM)
Conformation of complex formation	Atomic Force Microscopy **(**AFM)
State of phospholipid complex.	DSC differential scanning calorimetery X-ray powder diffraction studies
In vitro dissolution studies	Dissolution test apparatus Shake-flask method
Solubility study	Infrared Spectroscopic Analysis
Formation of the complex	Nuclear magnetic resonance (NMR) spectroscopy *13 C-NMR*
Drug content	UV-Visible spectrophotometer

RESEARCH UPDATE ON PHARMACOSOMES

Several studies show that pharmacosomes are able to enhance the dissolution ability of the poorly soluble non steroidal anti-inflamatory drugs. The solubility of the diclofenac phosphatidylcholine (80 %) complex was enhanced to 22.1 mg mL^{-1} when compared to that of diclofenac[12] (10.5 mg mL^{-1}). Similarly the Aceclofenac[13] loaded pharmacosomes prepared through solvent evaporation technique showed a release rate of 79.78% at the end of 4hrs. Aspirin[14] and Naringenin[15] loaded pharmacosomes also depicted similar results. Further studies by Garcia *et al*., (1998) on dioleylphosphatidylcholine (DOPC) complex of ketoprofen (KP) showed solubility enhancement ability of the pharmacosomes. The permeation of the drug across the skin was also enhanced in the complex when assayed by *in vitro* percutaneous absorption by using a flow-through diffusion cell. Muller-Goymann and Hamann[16] developed fenoprofen pharmacosomes using a modified technique that involved diluting lyotropic liquid crystals of amphiphilic drugs.

JIN Yi-Guang et al.[17], formulated the negatively charged nanometer Acyclovir succinyl glyceryl monostearate pharmacosomes by the tetrahydrofuran injection method. Transmission electron microscope and laser scattering method were used for the analysis of the complex formed. Very weak effect of centrifugation and heating were found on the stability of the pharmacosomes whereas freezing and lyophilization disrupted the Pharmacosome structure. *In vivo*, pharmacosomes were found absorbed by the plasma proteins in the blood thereby reducing the haemolytic reaction. Meihua HAN et al.[18], developed 20(S)-Protopanaxadiol (Ppd) pharmacosome by simple thin film-dispersion preparation properties were found to be stable. Tube shaped pharmacosomes of 5′-cholesterylsuccinyl-dideoxyinosine (CS-ddI) were devoloped by means of THF injection method by Ping et al[19]. CS-ddI and ddI in plasma and tissues were determined with the help of HPLC. Half life of CS-ddI in plasma of rat was found to be 7.64 min, CS-ddI got concentrated in liver quickly after iv administration, there was also some concentration in lung and spleen; its elimination from target tissues was found slow as the half-life of CS-ddI in liver was 10 d.

Zhang ZR et al.[20],found mean particle size of 3',5'-dioctanoyl-5-fluoro-2'-deoxyuridine pharmacosomes (DO-FudR-PS) to be 76 nm with drug loading of 29.02% and entrapment efficiency of 96.62%. They also reported that the concentration of FUdR in various tested organs was quite high when determined by reversed phase High Performance Liquid Chromatography after i.v. administration of DO-FUdR-PS and FUdR. The brain AUC ratio of DO-FUdR-PS to FUdR was confirmed to be 10.97. Few researchers have also reported that the isoniazid pharmacosomes have improved permeability and macrophage targeting. Shi *et al*.[21] prepared a new insulin–phospholipid complex by an anhydrous co-solvent lyophilization method. Compared with native insulin, the physicochemical properties of insulin changed significantly after it was complexed with phospholipids. It was concluded that the characteristics, especially the improved lipophilicity, would contribute to the improved oral absorption of insulin[23].

It may be concluded that pharmacosomes are promising delivery system for poorly soluble drugs and can also improve the biopharmaceutical properties of biologically active phytoconstituents such as flavones, glycosides, xanthones, and so on. Consequently, the pharmacosomes can play the role of simple, safe, effective and stable drug delivery systems that can be developed by simple and reproducible methods for better therapeutic performance.

REFERENCES

1. Orienti F, Bigucci B, Luppi T, Cerchiara G, Zuccari P, Giunchedi V, Zecchi. Polyvinylalcohol substituted with triethyleneglycolmonoethylether as a new material for preparation of solid dispersion of hydrophobic drugs. European Journal of Pharmaceutics and Biopharmaceutics, 2002;54: 229–233.
2. Löbenberg R, Amidon GL. Modern Bioavailability, Bioequivalence and Biopharmaceutics classification system. New Scientific Approaches to international regulatory standards. European Journal of Pharmaceutics and Biopharmaceutics, 2000;50: 3–12.
3. Varshosaz J, Talari R, Mostafavi SA, Nokhodchi A. Dissolution Enhancement of Gliclazide using *in situ* Micronization by Solvent Change Method. Powder Technology, 2008;187: 222–30.
4. Jain NK. Advances in Controlled and Novel Drug Delivery. CBS Publishers: 2003. p. 276.
5. Kavitha D, Sowjanya N, Panaganti S. Pharmacosomes: An Emerging Vesicular System. International Journal of Pharmaceutical Science Review and Research, 2010;5: Article-030.
6. Semalty A, Semalty M, Rawat BS, Singh D, Rawat MSM. Pharmacosomes: The lipid based novel drug delivery system. Expert Opinion On Drug Delivery, 2009;6**:** 599-612.

7. Semalty A, Semalty M, Rawat BS, Singh D, Rawat MSM. Development and evaluation of pharmacosomes of aceclofenac. Indian Journal of Pharmaceutical Sciences, 2010;72: 576-81.
8. Vaizoglu O, Speiser PP. Pharmacosomes: a novel drug delivery system. Acta Pharmaceutica Suecica, 1986;23: 163 –72.
9. Volkering F, Breure AM, Van Andel JG, Rulkens WH. Influence of Nonionic Surfactants on Bioavailability and Biodegradation of Polycyclic Aromatic Hydrocarbons. Applied and Environmental Microbiology, 1995; 61: 1699–705.
10. Steve A, U. S. Patent US S, 534, 499 (C1 S14-25, A61K31/70), 1996.
11. Taskintuna I, Ibrahim MD, Banker AS, Floresaguilar M, Bergeronlynn, Germaine BS, Aldern, Kathy A., Hostetler, Karl, Y., Freeman, William, R. Evaluation Of A Novel Lipid Prodrug for Intraocular Drug Delivery: Effect of Acyclovir Diphosphate Dimyristoylglycerol in a Rabbit Model With Herpes Simplex Virus-1 Retinitis. Retina, 1997;17: 57–64.
12. Semalty A, Semalty M, Singh D, Rawat MSM. Development and physicochemical evaluation of pharmacosomes of diclofenac. Acta Pharmaceutica, 2009;59: 335–44.
13. Semalty A, Semalty M, Rawat BS, Singh D, Rawat MSM. Development and evaluation of pharmacosomes of aceclofenac. Indian Journal of Pharmaceutical Sciences, 2010;72: 576-81.
14. Semalty A, Semalty M, Rawat BS, Singh D, Rawat MSM. Development and Characterization of Aspirin-Phospholipid Complex for Improved Drug Delivery. International Journal of Pharmaceutical Sciences and Nanotechnology, 2010;3: 940-47.
15. Semalty A, Semalty M, Singh D, Rawat MSM. Preparation and Characterization of Phospholipid Complexes of Naringenin for effective drug delivery. Journal of Inclusion Phenomena and Macrocyclic Chemistry, 2010;67: 253–60.
16. Muller-Goymann CC, Hamann HJ. Pharmacosomes: Multilamellar vesicles consisting of Pure Drug. European Journal of Pharmaceutics and Biopharmaceutics, 1991;37: 113-17.
17. Yiguang J, Tongc L, Ping A, Miao L, Houb X. Self-Assembled Drug Delivery Systems-Properties and *In Vitro –In Vivo* Behaviour of Acyclovir Self-Assembled Nanoparticles (SAN). International Journal of Pharmaceutics, 2006;309: 199–207.
18. Han M, Chen J, Chen S, Wang X. Preparation and study in vitro of 20(S)-protopanaxadiol pharmacosomes. Zhongguo Zhong Yao Za Zhi, 2010; 35: 842-6.
19. Ping A, Jin Y, Da-wei C. Preparation and *In Vivo* Behavior of Didanosine Pharmacosomes in Rats. Chinese Journal of Pharmaceutics, 2005; 3: 227–35.
20. Zhang ZR, Wang JX. Study on Brain Targeting 3',5'-dioctanoyl-5-fluoro-2'-Deoxyuridine Pharmacosomes. Yao Xue Xue Bao, 2001; 36: 771–6.
21. Cui F, Shi K, Zhang L, Tao A, Kawashima Y. Biodegradable Nanoparticles Loaded with Insulin-phospholipid Complex for Oral Delivery: Preparation, *in vitro* characterization and *in vivo* evaluation. Journal of Controlled Release, 2006; 114: 242-248.
22. Wagh MP, Patel JS. Biopharmaceutical Classification System: Scientific basis for biowaver extensions. International Journal of Pharmacy and Pharmaceutical Sciences, 2010;1 :12-19.
23. Lichtenberger LM, Wang ZM, Romero JJ, Ulloa C, Perez JC, Giraud MN, Barreto JC. Non steroidal anti-inflammatory drugs (NSAIDs) associated with zwitterionic phospholipids: Insight into the mechanism and reversal of NSAID-induced gastrointestinal injury. Nature Medicine, 1995; 1: 154-8.
24. Sharma S, Mishra L, Grover I, Gupta A, Kaur K. Liposomes: Vesicular system ann overview. International Journal of Pharmacy and Pharmaceutical Sciences, 2010; 4: 15-21.