Review Article

PHARMACOSOMES: A NOVEL CARRIER FOR DRUG DELIVERY

A. KRISHNA SAILAJA

Associate Professor, RBVRR Women's college of Pharmacy, Hyderabad

Email: shailaja1234@rediffmail.com

ABSTRACT

In the area of solubility enhancement, several problems are encountered. A novel approach based on lipid drug delivery system has evolved pharmacosomes. Pharmacosomes are colloidal, nanometric size micelles, vesicles or may be in the form of a hexagonal assembly of colloidal drug dispersions attached covalently to the phospholipid. They act as a carrier for delivery of drugs quite precisely owing to their unique properties like small size, amphiphilicity, active drug loading, high entrapment efficiency, and stability. They help in the controlled release of drug at the site of action as well as in reduction in the cost of therapy, drug leakage and toxicity, increased the bioavailability of poorly soluble drugs, and restorative effects. There has been an advancement in the scope of this delivery system for a number of drugs used for inflammation, heart diseases, cancer, and protein delivery along with a large number of herbal drugs. Hence, pharmacosomes open new challenges and opportunities for improved novel vesicular drug delivery system. In this article, the advantages and limitations of pharmacosomes, Preparation methods and their applications have been discussed in detail.

Keywords: Entrapment efficiency, SEM, Zeta potential, DSC.

INTRODUCTION

Pharmacosomes word derived from "pharmakon": drug "soma": carrier. Pharmacosomes are colloidal dispersions of drug covalently bound to lipids and may exist as ultrafine vesicular, micellar, or hexagonal aggregates, depending on the chemical structure of the drug-lipid complex. Pharmacosomes are amphiphilic phospholipid complexes of drugs bearing active hydrogen that bind to phospholipids. Pharmacosomes impart better biopharmaceutical properties to the drug, resulting in improved bioavailability. Pharmacosomes have been prepared for various non-steroidal anti-inflammatory drugs, proteins, cardiovascular and antineoplastic drugs. Developing the pharmacosomes of the drugs has been found to improve the absorption and minimize the gastrointestinal toxicity [1, 2].

IMPORTANCE

Pharmacosomes have some importance in escaping the tedious steps of removing the free unentrapped drug from the formulation. Pharmacosomes provide an efficient method for delivery of drug directly to the site of infection, leading to a reduction of drug toxicity with no adverse effects and also reduces the cost of therapy by improved bioavailability of medication, especially in the case of poorly soluble drugs. They can be given orally, topically, extra-or intravascularly. Pharmacosomes are suitable for incorporating both hydrophilic and lipophilic drugs[3,4].Entrapment efficiency is not only high but predetermined because of drug itself in conjugation with lipids forms vesicles. There is no need of following the tedious, time-consuming steps for removing the free, unentrapped drug from the formulation. Since the drug is covalently linked, loss due to leakage of the drug does not take place. No problem of drug incorporation.Encaptured volume and drug-bilayer interactions do not influence entrapment efficiency, in the case of pharmacosomes.In pharmacosomes, membrane fluidity depends upon the phase transition temperature of the drug-lipid complex, but it does not affect release rate since the drug is covalently bound. The drug is released from pharmacosomes by hydrolysis (including enzymatic).The physicochemical stability of the pharmacosomes depends upon the physiochemical properties of the drug-lipid complex. Following absorption, their degradation velocity into active drug molecule depends to a great extent on the size and functional groups of the drug molecule, the chain length of lipid, and the spacer [5,6].

MATERIALS FOR PHARMACOSOMES

There are three essential components for pharmacosomes preparation.

Drugs

Drugs containing active hydrogen atom (-COOH, OH, NH2) can be esterified to the lipid, with or without spacer chain and they form an amphiphilic complex which in turn facilitate membrane, tissue, cell wall transfer in the organisms[7,8].

Solvents

For the preparation of Pharmacosomes, the solvents should have high purity and volatile in nature. A solvent with an intermediate polarity is selected for pharmacosomes preparations [9, 10].

Lipid

Phospholipids are the major structure component of biological membranes, where two type of phospholipids generally used phosphoglycerides and sphingolipids. The most common phospholipid is phosphatidylcholine molecule. Phosphatidylcholine is an amphipathic molecule in which a glycerol bridge links a pair of hydrophobic acyl hydrocarbon chains, with a hydrophilic polar head group, phosphocholine [11].

PREPARATION

Two methods have been used to prepare vesicles:

- The hand-shaking method
- The ether injection method

Hand-Shaking Method

In the method, the dried film of the drug-lipid complex (with or without lecithin) is deposited in a round-bottom flask and upon hydration with an aqueous medium, readily gives a vesicular suspension [12].
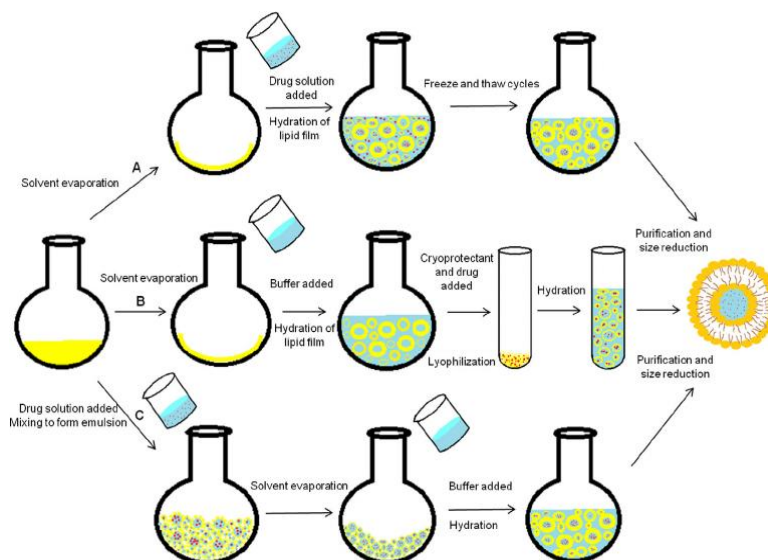
Figure 1: Schematic representation of handshaking method.

ETHER-INJECTION METHOD

In the ether injection method, an organic solution of the drug-lipid complex is injected slowly into the hot aqueous medium, wherein the vesicles are readily formed [13].
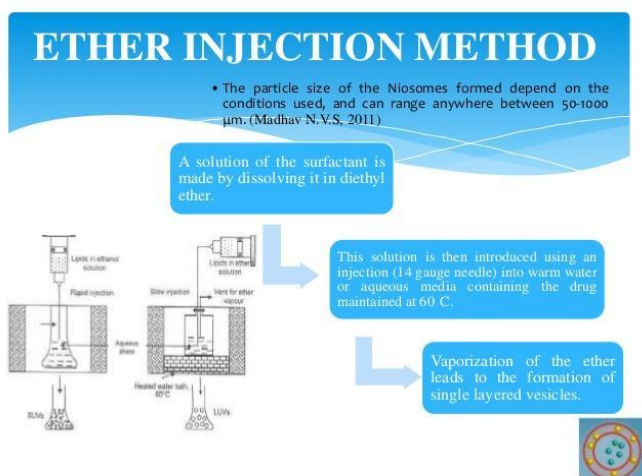

Figure 2: schematic representation of ether injection method.

FORMULATION

- Drug salt was converted into an acid form to provide an active hydrogen site for complexation.
- Drug acid was prepared by acidification of an aqueous solution of drug salt, extraction into chloroform, and subsequent recrystallization.
- Drug –Pc complex was prepared by associating drug with an equimolar concentration of Pc.
- The equimolar concentration of Pc and drug acid were placed in a round-bottom flask and dissolved in dichloromethane.
- The solvent was evaporated under vacuum at 40°**C** in a rotary vacuum evaporator.
- The pharmacosomes were collected as the dried residue and placed in a vacuum desiccator overnight and then subjected to characterization [14, 15].

EVALUATION OF PHARMACOSOMES

Pharmacosomes are evaluated for the following parameters.

Solubility

To determine the change in solubility due to complexation, the solubility of drug acid and the drug-Pc complex was determined in pH 6.8 phosphate buffer and n-octanol by the shake-flask method. Drug acid (50 mg) (and 50 mg equivalent in the case of complex) was placed in a 100ml conical flask. Phosphate buffer pH 6.8 (50 ml) was added and then stirred for 15 minutes. The suspension was then transferred to a 250 ml separating funnel with 50 ml n-octanol and shaken well for 30 minutes.Then the separating funnel was kept still for about 30 minutes. The concentration of the drug was determined from the aqueous layer spectrophotometrically at 276 nm [16].

Drug content

To determine the drug content in pharmacosomes of drug (e g: diclofenac-Pc complex), a complex equivalent to 50 mg diclofenac was weighed and added into a volumetric flask with 100 ml of pH 6.8 phosphate buffer.Then the volumetric flask was stirred continuously for 24 hrs on a magnetic stirrer. At the end of 24hrs, suitable dilutions were made and measured for the drug content at 276 nm UV spectrophotometrically.

Scanning electron microscopy (SEM)

To detect the surface morphology of the pharmacosomes, SEM of the complex was recorded on a scanning electron microscope.

Differential scanning calorimetry (DSC)

Thermograms of drug acid, phosphatidylcholine (80 %) and the drug-Pc complex were recorded using a 2910 modulated differential scanning calorimeter v4.4E. The thermal behavior was studied by heating 2.0 ± 0.2 mg of each individual sample in a covered sample pan under nitrogen gas flow. The investigations were carried out over the temperature range 25-250 °**C** at a heating rate of 10°**C** min.

X-ray powder diffraction (XRPD)

The crystalline state of the drug in the different samples was evaluated using X-ray powder diffraction. Diffraction patterns were obtained on Bruker Axs-D8 Discover powder X-ray diffractometer, Germany.The thermal behavior was studied by heating 2.0 ± 0.2 mg of each individual sample in a covered sample pan under nitrogen gas flow. The investigations were carried out over the temperature range 25-250 °C at a heating rate of 10°C min-1. The x-ray generator was operated at 40 kV tube voltages and 40 mA current, using lines of copper as the radiation source. The scanning angle ranged from 1 to 60°**C** of 2q in the step scan mode (step width 0.4° min-1).Drug acid, phosphatidylcholine 80% (Lipoid s-80) and the prepared complex were analyzed.

Dissolution study

In vitro dissolution studies of drug-Pc complex as well as plain diclofenac acid were performed in triplicate in a USP (8) six station dissolution test apparatus, type 2 at 100 rpm and at 37 °**C**.An accurately weighted amount of the complex equivalent to 100 mg of drug acid was put into 900 ml of pH 6.8 phosphate buffer.Samples (3 ml each) of

dissolution fluid were withdrawn at different intervals and replaced with an equal volume of fresh medium to maintain sink conditions. Withdrawn samples were filtered (through a 0.45-mm membrane filter), diluted suitably and then analyzed spectrophotometrically at 276 nm.

APPLICATIONS

- The approach has successfully improved the therapeutic performed of various drugs i.e. pindolol maleate, bupranolol hydrochloride, taxol, acyclovir, etc [17].
- Pharmacosomes can interact with bimembranes enabling a better transfer of active ingredient. This interaction leads to change in phase transition temperature of bimembranes thereby improving the membrane fluidity leading to enhance permeations.
- Pharmacosomes, the amphiphilic lipid vesicular system, can be used for the development of novel ophthalmic dosage forms. Amphiphilic prodrug forms pharmacosomes, when diluted with tear25, 26 , and modify corneal drug transport and release profile2
- Pharmacosomes have a greater degree of selectivity for action on specific target cells. Raikhman et al. described pharmacosomes as building particles capable of the transport of biologically active substances including nucleic acids and proteins
- Yi-Guang et al. prepared acyclovir pharmacosomes and observed that the plasma proteins in blood absorbed pharmacosomes and interfered with the interactions of erythrocytes and hence reduced haemolytic reaction
- Semalty et al. studied the development of diclofenac pharmacosome, and it was found that solubility was enhanced in pharmacosomes (22.1 g/mL) as compared to diclofenac (10.5 g/mL). Drug release was also improved from 60.4% of diclofenac to 87.8% of diclofenac pharmacosomes after 10 hrs of dissolution study. Observed drug content of diclofenac pharmacosomes was $96.2 \pm 1\%$
- Pharmacosomes have the capacity to augment drug absorption and its transport. Using response surface design, Yue et al. and colleagues optimized the formulated geniposide pharmacosomes and examined their attributes. The ratio of phospholipid to drug, temperature of reaction mixture and concentration of drug were found to be 3, 50 0C and 5.5mg/mL, respectively.

CONCLUSION

Pharmacosomes are considered to be novel carrier for drug delivery. The drug shows excellent entrapment efficiency and there is minimal loss of drug due to leakage. They have special advantages over liposomes as they avoid drug leakage and improve the stability of the drug delivery system. Cellular targeting can be achieved by using pharmacosomes. Still, research should be done to reduce the fusion and aggregation, as well chemical hydrolysis upon storage.

REFERENCES

1. Gupta, R. P. Singh, P. Lokwani, S. Yadav, and S. K. Gupta, "Vesicular system as targeted drug delivery system: an overview," International Journal of Pharmacy and Technology, vol. 3, no. 2, pp. 987–1021, 2011.
2. R. C. Doijad, D. S. Bhambere, M. V. Fakirappa, and N. V. Deshmukh, "Formulation and characterization of vesicular drug delivery system for anti-HIV drug," Journal of Global Pharma Technology, vol. 1, no. 1, pp. 94–100, 2009.
3. M. J. Pozansky and R. L. Juliano, "Biological approaches to the controlled delivery of drugs: a critical review," Pharmacological Reviews, vol. 36, no. 4, pp. 277–336, 1983.
4. A. D. Bangham, M. M. Standish, and G. Weissmann, "The action of steroids and streptolysin S on the permeability of phospholipid structures to cations," Journal of Molecular Biology, vol. 13, no. 1, pp. 253–259, 1965.
5. U. Ogihara, T. Sasaki, H. Toyama, O. M. Sneha, and H. Nishigori, "Rapid diagnostic imaging of cancer using radiolabeled liposomes," Cancer Detection and Prevention Journal, vol. 21, pp. 490–496, 1997.
6. D. Kavitha, J. Naga Sowjanya, and S. Panaganti, "Pharmacosomes: an emerging vesicular system,"International Journal of Pharmaceutical Sciences Review and Research, vol. 5, no. 3, pp. 168–171, 2010.
7. S. Biju, S. Talegaonkar, P. Mishra, and R. Khar, "Vesicular systems: an overview," Indian Journal of Pharmaceutical Sciences, vol. 71, pp. 421–427, 2009.
8. M. P. Wagh and J. S. Patel, "Biopharmaceutical classification system: scientific basis for biowaiver extensions," International Journal of Pharmacy and Pharmaceutical Sciences, vol. 2, no. 1, pp. 12–19, 2010.
9. R. Löbenberg and G. L. Amidon, "Modern bioavailability, bioequivalence and biopharmaceutics classification system. New scientific approaches to international regulatory standards," European Journal of Pharmaceutics and Biopharmaceutics, vol. 50, no. 1, pp. 3–12, 2000.
10. J. Varshosaz, R. Talari, S. A. Mostafavi, and A. Nokhodchi, "Dissolution enhancement of gliclazide usingin situ micronization by solvent change method," Powder Technology, vol. 187, no. 3, pp. 222–230, 2008.
11. V. E. Ivanov, Y. S. Moshkovskii, and L. M. Raikhman, "Effects of temperature on cascade systems of pharmacosome fusion," Pharmaceutical Chemistry Journal, vol. 15, no. 9, pp. 619–621, 1981.
12. M. K. Rawat, A. Jain, and S. Singh, "In vivo and cytotoxicity evaluation of repaglinide-loaded binary solid lipid nanoparticles after oral administration to rats," Journal of Pharmaceutical Sciences, vol. 100, no. 6, pp. 2406–2417, 2011
13. N. K. Jain, Advances in Controlled and Novel Drug Delivery, CBS, 2003.
14. S. Sharma, L. Mishra, I. Grover, A. Gupta, and K. Kaur, "Liposomes: vesicular system an overview,"International Journal of Pharmacy and Pharmaceutical Sciences, vol. 2, no. 4, pp. 15–21, 2010.
15. A. Semalty, M. Semalty, B. S. Rawat, D. Singh, and M. S. M. Rawat, "Pharmacosomes: the lipid-based new drug delivery system," Expert Opinion on Drug Delivery, vol. 6, no. 6, pp. 599–612, 2009.
16. A. Semalty, M. Semalty, B. S. Rawat, D. Singh, and M. S. M. Rawat, "Development and evaluation of pharmacosomes of aceclofenac," Indian Journal of Pharmaceutical Sciences, vol. 72, no. 5, pp. 576–581, 2010.
17. A. Steve, "Lipophilic drug derivatives for use in liposomes," US Patent S, 534, 499, (C1 S14-25, A61K31/70), 1996.