Review Article

PHARMACOSOMES: AN EMERGING VESICULAR SYSTEM

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ABSTRACT

Various types of lipid based vesicular systems have been developed in controlled and targeted drug delivery. Pharmacosomes bearing unique advantages over liposomes and niosomes have come up as potential alternative to conventional vesicles. These are the amphiphilic phospholipid complexes of drugs bearing active hydrogen that bind to phospholipids. They provide an efficient method for delivery of drug directly to the site of infection, leading to reduction of drug toxicity with no adverse effects also reduces the cost of therapy by imparting better biopharmaceutical properties to the drug, resulting in improved bioavailability, especially in case of poorly soluble drugs. Pharmacosomes have been prepared for various non-steroidal anti-inflammatory drugs, proteins, cardiovascular and antineoplastic drugs. This article reflects the potential of pharmacosomes as a controlled and targeted drug delivery system and focuses the methods of preparation and characterization.

Keywords: Pharmacosomes, amphiphilic, controlled and targeted drug delivery system.

INTRODUCTION

Many drugs particularly chemotherapeutic agents have narrow therapeutic window, and their clinical use is limited and compromised by dose limiting toxic effect. So lot of attempts has been made to achieve all lofty goals through novel approaches in drug delivery. A number of novel drug delivery systems have emerged encompassing various routes of administration, to achieve controlled and targeted drug delivery. Novel drug delivery attempts to either controlled release, or by maintaining a relatively constant, effective drug level in the body with concomitant minimization of undesirable side effects. It can also localize drug action by spatial placement of controlled release systems adjacent to, or in the diseased tissue or organ; or target drug action by using carriers or chemical derivatization to deliver drug to particular target cell type. An ideal controlled drug-delivery system should possess two characteristics: the ability to reach its therapeutic target and the ability to release the active pharmaceutical ingredient in a controlled manner [1]. To obtain this goal, approaches are being implemented by paying considerable attention either to control the distribution of drug by incorporating it in a carrier system or by modifying the structure of the drug at the molecular level, or to control the input of drug into the bioenvironment to ensure an appropriate profile of distribution. Different types of pharmaceutical carriers are polymeric, particulate, macromolecular and cellular carrier. Particulate type carrier also known as a colloidal carrier system, includes lipid particles (low and high density lipoprotein-LDL and HDL, respectively), nanoparticles, microspheres, polymeric micelles and vesicular like liposomes, niosomes, pharmacosomes, virosomes, etc [2-5].

VESICULAR SYSTEMS

In the recent years, lipid vesicles were found to be of value in immunology, membrane biology, diagnostic techniques and most recently genetic engineering. These vesicles were first reported in 1965 by Bingham, and were given the name "Bingham bodies" which play a major role in modeling biological membranes, and in the transport and targeting of active agents [6]. Lipid vesicles are one type of many experimental models of biomembranes which evolved successfully, as vehicles for controlled delivery. For the treatment of intracellular infections, conventional chemotherapy is not effective, due to limited permeation of drugs into cells. This can overcome by the use of vesicular drug delivery systems.

Vesicular drug delivery system has some of the advantages like:

- Prolong the existence of the drug in systemic circulation, and perhaps, reduces the toxicity if selective uptake can be achieved due to the delivery of drug directly to the site of infection.
- Improves the bioavailability especially in the case of poorly soluble drugs.
- Both hydrophilic and lipophilic drugs can be incorporated.
- Delays elimination of rapidly metabolizable drugs and thus function as sustained release systems [7].

But these vesicular systems are accompanied with some problems like drug carriers such as particulates (eg., liposomes, nanoparticles, microemulsions) and externally triggered (eg., temperature, pH, or magnetic sensitive) carriers load drugs passively, which may lead to low drug

loading efficiency and drug leakage in preparation, preservation and transport invivo [8].

Some vesicular system associated problems are mentioned in table I

Table I: Problems associated with conventional vesicular systems.

Vesicular system	Problems
Liposomes	Expensive, degradation by oxidation, lack of purity of natural phospholipids.
Niosomes	Time consuming, inefficient, instability.
Transferosomes	Expensive, chemical instability, etc.

As a remedy for these problems, Pharmacosomes have been evolved [9].

PHARMACOSOMES

Pharmacosomes bearing unique advantages over liposome and noisome vesicles, have come up as potential alternative to conventional vesicles. They are the colloidal dispersions of drugs covalently bound to lipids. Depending upon the chemical structure of the drug–lipid complex they may exist as ultrafine vesicular, micellar, or hexagonal aggregates. As the system is formed by linking a drug (pharmakon) to a carrier (soma), they are termed as "pharmacosomes". They are an effective tool to achieve desired therapeutic goals such as drug targeting and controlled release. The criterion for the development of the vesicular pharmacosome is dependent on surface and bulk interactions of lipids with drug. Any drug possessing an active hydrogen atom (-COOH, -OH, -NH2, etc.) can be esterified to the lipid, with or without spacer chain that strongly result in an amphiphilic compound, which will facilitate membrane, tissue, or cell wall transfer, in the organism. The prodrug conjoins hydrophilic and lipophilic properties, thus acquires amphiphilc characters, and therefore found to reduce interfacial tension, and at higher concentrations exhibits mesomorphic behavior [10-11].

MERITS

- Suitable for both hydrophilic and lipophilic drugs. The aqueous solution of these amphiphiles exhibits concentration dependent aggregation.
- High and predetermined entrapment efficiency as drug and carrier form a stoichiometrically defined unit covalently linked together.
- Volume of inclusion doesn't influence entrapment efficiency.
- No need of removing the free, unentrapped drug from the formulation which is required in the case of liposomes.
- As drug is covalently bound, membrane fluidity has no effect on release rate, but in turn depends upon the phase-transition temperature of the drug-lipid complex. No leakage of drug take place as the drug is covalently linked to the carrier.
- Drug can be delivered directly to the site of infection.
- Drug release from pharmacosomes is by hydrolysis (including enzymatic).
- Their degradation velocity into active drug molecule, after absorption depends very much on the size and functional groups of the drug molecule, the chain length of the lipids, and the spacer.
- Improves bioavailability especially in the case of poorly soluble drugs.
- Reduction in adverse effects and toxicity.
- Reduced cost of therapy [12-14].

PREPARATION

In general two methods have been employed to prepare pharmacosomes. They are:

- Hand-shaking method.
- Ether-injection method.

In the hand-shaking method, the dried film of the drug–lipid complex (with or without egg lecithin) is deposited in a round-bottom flask and upon hydration with aqueous medium, readily gives a vesicular suspension. 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. At low concentration the amphiphiles exists in the monomer state. Further increase in monomers may lead to variety of structures i.e., micelles of spherical or rod like or disc shaped type or cubic or hexagonal shape. Mantelli et al., compared the effect of diglyceride prodrug on interfacial tension, with the effect produced by a standard detergent dodecylamine hydrochloride, and found similar effect on lowering of surface tension. Above the critical micelle concentration (CMC), the prodrug exhibits mesomorphic lyotropic behavior, and assembles in supramolecular structures [15,16].

Other Approaches

Another approach for producing pharmacosomes was recently developed in which a biodegradable micelle-forming drug conjunct was synthesized from the

hydrophobic drug adriamycin and a polymer composed of polyoxyethylene glycol and polyaspartic acid. This method has the benefit that although it may be possible to dilute out the micelle, the drug will probably not precipitate because of the water solubility of the monomeric drug conjunct[17]. Muller-Goymann and Hamann produced fenoprofen pharmacosomes using a modified technique that involved diluting lyotropic liquid crystals of amphiphilic drugs [18]. Approaches have been done to attach drugs to various glyceride-like groups, and the resulting amphiphilic molecules have been spontaneously dispersed. They were labeled pharmacosomes because of their tendencies to form unilamellar vesicles. It was suggested that these molecules should enhance lymph transport [19]. Zhang et al. optimized the preparation of 3', 5'-dioctanoyl-5-fluoro-2'-deoxyuridine pharmacosomes and found that the drug phosphatidylcholine ratio, glycerol tristearate concentration and pluronic F-68 concentration, have an influence on the mean particle size, entrapment ratio, and drug loading [20]. Singh et al. formulated "vesicular constructs" by encapsulating antibiotic amoxicillin in aqueous domain by using phosphatidylethanolamine with various molar ratios of phosphatidylcholine and cholesterol which significantly enhanced cytoprotection [21].

CHARACTERISATION

Similar to other vesicular systems, pharmacosomes are characterized for different attributes such as size and size distribution, nuclear magnetic resonance (NMR) spectroscopy, entrapment efficiency, in vitro release rate, stability studies, etc. Mantelli et al. compared the effect of diglyceride prodrug on interfacial tension, with the effect produced by a standard detergent dodecylamine hydrochloride and observed same effect on lowering of surface tension. Above the critical micelle concentration (CMC), the prodrug exhibits mesotropic lyotropic behaviour, and assembles in supramolecular structures [22,23]. The prepared prodrugs are characterized for their structural conformation (by IR, NMR spectrophotometry, thin layer chromatography (TLC), melting point determination), surface tension [24], partition coefficient [25] and prodrug hydrolysis.

ENHANCED THERAPEUTIC ACTIVITY

The approach has successfully improved the therapeutic performance of various drugs i.e. pindolol maleate, bupranolol hydrochloride, taxol, acyclovir, etc [22,26]. Zhang and Wang proved that the pharmacosomes can improve the ability of a drug to cross the blood–brain barrier and act as a promising drug-targeting system for the treatment of central nervous system disorders [27]. In another study, *in vivo* behavior of didanosine pharmacosomes was evaluated in rats. The study revealed liver targeting and sustained-release effect in rats after i.v. administration. It was also found that there was targeting in the lung and spleen and that drug elimination from the target tissues was slow [28].

CONCLUSION

Vesicular systems have been realized as extensively useful carrier systems in various scientific domains. Inspite of certain drawbacks (fusion, aggregation), pharmacosomes still play an important role in the selective targeting, and the controlled delivery of various drugs. Pharmacosomes have immense potential, and further advantages of the vesicular system can be exploited by expanding this approach to additional drugs. The influence of spacer groups and linkage also should be observed more rigorously for further improvement in drug-fate and biological activity of the drug to achieve the therapeutic goal. The system yet requires greater efforts towards investigating the non-bilayer phases and exploring the mechanism of action. Current research trends are generally based on using different approaches like pegylation, biotinyzation etc. for cellular targeting.

REFERENCES

1. Jin.Y et al., "Self-Assembled Drug Delivery Systems-Properties and *In Vitro –In Vivo* Behaviour of Acyclovir Self-Assembled Nanoparticles (san)," Int. J. Pharm, 2006, 309(1–2), 199–207.
2. Vaizoglu,O and Speiser.P.P., Acta Pharm Suec, 1986, 23, 163.
3. Goldberg. EP.Eds., In; Targeted Drugs, 2nd edition, Wiley, Newyork, 1983, 312.
4. Gregoriadis.G., Nature, 1977, 265, 407.
5. Poste.G, Krisch.R and Koestler.T., Liposome Technology, Vol 3, CRC Press Inc, Banco Raton, F1, 1983, 29.
6. Pozansky.M.J and Juliano.R.L., Pharmacol.Rev, 1983, 36, 277.
7. Bangham.A.D, Standish.M.M and Watkins.J.G., J.Mol.Biol, 1965,13, 238.
8. Ogihara Umedai, Sasaki.T, Toyama.H, Odak, Sneha.M, Nishigori.H., Cancer Detect Prev, 1997, 21(6), 490.
9. Vaizoglu.O and Speiser.P.P., Acta Pharm Suec, 1986, 23, 163.
10. Kaur and Kanwar.M., "Ocular Preparations: The Formulation Approach," Drug Dev. Ind. Pharm, 2002, 28(5), 473–493.
11. Biju.S.S et al., "Vesicular Systems: An Overview," Ind. Jour. Pharm. Sci, 2006, 68 (2), 141–153.

12. Vaizoglu.M.O and Speiser.P.P., "Pharmacosomes—A Novel Drug Delivery system," Acta Pharm. Suec, 1986, 23, 163–172.

13. Jain.N.K., Advances In Controlled and Novel Drug Delivery, 2003, CBS Publishers, New Delhi, India, 276.

14. Volkering.F et al., "Influence of Nonionic Surfactants on Bioavailability and Biodegradation of Polycyclic Aromatic Hydrocarbons," App. Environ. Micro, 1995, 61(5), 1699–1705.

15. Steve.A., "Lipophilic Drug Derivatives For Use In Liposomes," US Patent 5534499 (1996).

16. Taskintuna.I et al., "Evaluation of a Novel Lipid Prodrug for Intraocular Drug Delivery: Effect of Acyclovir Diphosphate Dimyristoylglycerol in a Rabbit Model With Herpes Simplex Virus- Retinitis," Retin, 1997, 17(1), 57–64.

17. Lawrence.M.J., "Surfactant Systems: Their Use in Drug Delivery," Chem. Soc. Rev, 1994, 23, 417–424.

18. Muller-Goymann.C.C and Hamann.H.J., "Pharmacosomes: Multilamellar Vesicles Consisting of Pure Drug," Eur. J. Pharm. Biopharm, 1991, 37, 113–117.

19. Valentino.J.Sand William.N.C., Lymphatic Transport of Drugs,1992, CRC Press, Boca Raton, FL, 205.

20. Zhang.Z.R, Wang.J.X and Lu.J., "Optimization of the Preparation of 3',5'-dioctanoyl-5- fluoro- 2'-deoxyuridine Pharmacosomes Using Central Composite Design," Yao Xue Xue Bao, 2001, 36 (6), 456–461.

21. Singh.A and Jain.R., "Targeted Vesicular Constructs For Cytoprotection and Treatment of *H. Pylori* Infections," US Patent 6576,625 (2003).

22. Steve. A., U. S. patent US S, 534, 499 (C1 S14-25, A61K31/70), 1996, 9july, 11.

23. Mantelli. S, Speiser. P and Hauser. H., Chem. Phys. Lipids, 1985, 37, 329.

24. Yadav.J.B., Advanced Practical Physical Chemistry, 1990, Goel Publishing House, Meeruth, India, 74.

25. Leo.A and Hansche.F.D., Chem.Rev, 1971, 17, 525.

26. Taskintuna.I, Banker.A.S, Flores-Aguilar, Lynn.M, Alden.B.G, Hostetler.K.A, Freeman.W.R.,Retina 1997, 17, 57.

27. Zhang. Z. R and Wang. J.X., "Study on Brain Targeting 3',5'-dioctanoyl-5-fluoro-2'-Deoxyuridine Pharmacosomes," Yao Xue Xue Bao, 2001, 36(10), 771–76.

28. Ping.A, Jin.Y and Da-wei.C., "Preparation and *In Vivo* Behavior of Didanosine Pharmacosomes in Rats," Chin. J. Pharm, 2005, 3, 227–235.

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