



PHARMACOSOMES: A POTENTIAL VESICULAR DRUG DELIVERY SYSTEM

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ABSTRACT

Pharmacosome is a potential approach in the vesicular drug delivery system which exhibit several advantages over conventional vesicular drug delivery systems. Pharmacosomes are amphiphilic lipid vesicular system possessing phospholipid complexes of drugs. Drugs bearing active hydrogen atom can be esterified to the lipid. This type of vesicular system improves permeation of drugs across the biomembranes and thus results in an improvement in the bioavailability and can also improve the pharmacokinetic and pharmacodynamic properties of various types of drug molecules. This vesicular system can be characterized by surface morphology, solubility study, differential scanning calorimetry, x-ray powder diffraction, in vitro dissolution study. Pharmacosomes are suitable for incorporating both hydrophilic and lipophilic drugs. Preparations of pharmacosomes are basically performed for various non-steroidal anti-inflammatory drugs, proteins, cardiovascular and antineoplastic drugs.

KEYWORDS: Pharmacosomes, vesicular, phospholipid complexes, bioavailability

INTRODUCTION

A dramatic improvements have been made in the development of drug delivery systems which in turn control the rate of drug delivery, sustain the duration of therapeutic action and targeting the drugs at the specific sites.¹ These improvements result in the development of novel drug delivery system for the following purposes -

- i) Controlled administration of therapeutic dose.
- ii) Maintenance of drug concentration within an optimal range for prolonged action.
- iii) Maximum efficacy-dose relationship.
- iv) Reduction of adverse effects or toxic effects.
- v) Reduction of frequent dose intake.
- vi) Enhancement of patient compliance.

The different types of pharmaceutical carriers are as follows – particulate, polymeric, macromolecular and cellular carrier. Particulate carriers are also called as colloidal carrier system, includes lipid particles, microspheres, nanoparticles, polymeric micelles and vesicular systems.^{2,3,4,5,6} The vesicular systems are concentric lipid bilayer assemblies and these are formed when certain amphiphilic building blocks are confronted with water. Biologic origin of these vesicles was first reported in 1965 by Bingham, and thus called as Bingham bodies.⁷ Vesicular systems extend the therapeutic index by encapsulating the drug molecules inside the vesicular structure. It prolongs the presence of drug molecules in systemic circulation and reduce the toxicity which in turn results in the modification of pharmacokinetics and biodistribution of drugs. Now a days these vesicular systems are widely used in tumour targeting to brain, gene delivery etc.⁸

Advantages of vesicular drug delivery system

- i) Due to small size, chemistry, and distribution these particulate carriers correlate the structure and function of biomolecules.
- ii) Due to size, chemistry and nature, these systems facilitate better drug permeability from biological membrane and enhance the solubilization of practically insoluble drugs.
- iii) Delayed elimination of rapidly metabolized drugs facilitate sustained release.⁹
- iv) These system reduces the adverse effects and provide better targeting to body tissues and specific sites.

v) Site specific targeting can be achieved by modifying the surface properties of carriers.

Features and problems associated with conventional vesicular system^{10,11}

Various types of vesicular systems such as liposomes, niosomes, transferosomes have been developed in the transport and targeting of therapeutic agents. The features and problems of conventional vesicular system are described in table 1.

The problems associated with the conventional vesicular systems can be avoided by the development of pharmacosomes.

Pharmacosomes are amphiphilic lipid vesicular systems possessing phospholipid complexes to improve bioavailability of poorly water soluble as well as poorly lipophilic drugs. These particulate carriers are colloidal dispersion of drugs bound covalently, electrostatically or by hydrogen bonds to phospholipid. Drugs containing active hydrogen atom (-COOH, -OH, -NH₂) can be esterified to the lipid, with or without spacer chain. Depending upon the chemical structure, pharmacosomes exist as ultrafine, micelle or hexagonal aggregates. Like other vesicular system pharmacosomes reduce the interfacial tension at higher concentration due to mesomorphic behaviour. The development of pharmacosome is dependent on surface and bulk interactions of lipids with drugs. Pharmacosome can pass through the biomembranes efficiently and exhibit several advantages over conventional vesicular drug delivery systems. Pharmacosomes have been prepared for various non-steroidal anti-inflammatory drugs, proteins, cardiovascular and anti-neoplastic drugs. Pharmacosomes improved the pharmacokinetic and pharmacodynamic properties of various types of drug molecules.¹²

ADVANTAGES OF PHARMACOSOMES¹⁰

- i) No problem of drug incorporation.
- ii) No risk of leakage of drug as it is covalently conjugated with lipid. However loss may occur due to hydrolysis.
- iii) Predetermined, maximum entrapment efficiency can be achieved as the drug is covalently conjugated with lipid.
- iv) Pharmacosomes are suitable for incorporating both hydrophilic and lipophilic drugs.

- v) In the vesicular and micelle state the phase transition temperature of pharmacosomes have significant effect on their interaction with membranes.
- vi) Pharmacosomes can interact with biomembranes enabling a better transfer of active ingredient. This interaction leads to change in phase transition temperature of biomembranes thereby improving the membrane fluidity leading to enhance permeations.
- vii) Membrane fluidity of pharmacosome depends upon the phase transition temperature of drug-lipid complex but release rate is not affected.
- viii) Pharmacosomes have some importance in escaping the tedious steps of removing the free unentrapped drug from the formulation.
- ix) Physicochemical stability of pharmacosome depends upon the physicochemical properties of drug-lipid complex.
- x) Degradation of drug molecule depends to a great extent on the size and functional groups of drug molecule, chain length of lipid and spacer.
- xi) It can be given orally, topically, extra or intravascularly.
- xii) Reduced cost of therapy.

LIMITATIONS OF PHARMACOSOMES

- i) Covalent bonding is required to protect the leakage of drugs.
- ii) Amphiphilic nature is responsible for synthesis of a compound.
- iii) Surface and bulk interaction of lipid with drug is the basic principle of pharmacosomes.
- iv) On storage, pharmacosome undergoes fusion, aggregation, as well as chemical hydrolysis.¹³

COMPONENTS OF PHARMACOSOMES

The essential three components for the delivery system are as follows

i) Drugs

Drugs containing active hydrogen atom (-COOH, -OH, -NH₂) can be esterified to the lipid, with or without spacer chain and forms amphiphilic complex which in turn facilitate membrane, tissue, cell wall transfer in the organism.¹⁰

ii) Solvent

For the preparation of pharmacosomes, the solvent should have high purity and volatile in nature. A solvent with intermediate polarity (between the polarity of phospholipid and drug) is selected for pharmacosome preparation.¹⁴

iii) Lipid

Phospholipids are the major structural components of biological membranes, where two types of phospholipids exist – phosphodiglycerides and sphingolipids, together with their corresponding hydrolysis products. 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 headgroup, phosphocholine. Most commercial lecithin products contain 20% phosphatidylcholine. Lecithins containing phosphatidylcholine can be obtained from vegetable (mainly), animal, and microbial sources. Lecithin is also available as a dietary supplement in two forms: as granular lecithin (oil-free refined lecithin with calcium phosphate as a flow agent); and as capsules containing a dispersion in oil. Phosphatidylcholine has following advantages

- i) Clinical studies have shown that choline is essential for normal liver function and acts as an effective hepatoprotective. In vitro studies have shown that these phosphatidylcholine increase hepatic collagenase activity and

prevent fibrosis and cirrhosis by encouraging collagen breakdown.^{15,16}

- ii) It maintains cell membrane integrity.

PREPARATION METHODS

Generally pharmacosomes can be prepared by two methods which are as follows¹⁷

i) Hand shaking method- In this method a mixture of drug and lipid are dissolved in a volatile organic solvent such as dichloromethane in a round bottom flask. The organic solvent is removed at room temperature using a rotary evaporator, which leaves a thin film of solid mixture deposited on the walls of flask. The dried film can then be hydrated with aqueous medium and readily gives a vesicular suspension.

ii) Ether injection method- In this method organic solution of drug-lipid complex is injected slowly into the hot aqueous medium wherein the vesicles are formed readily.

CHARACTERIZATION OF PHARMACOSOMES

i) Fourier transform infrared spectroscopy

The formation of the complex can be confirmed by infrared spectroscopy comparing the spectrum of the complex with the spectrum of individual components and their mechanical mixture. Fourier transform infrared spectroscopy is an important analytical tool for the evaluation of stability of the pharmacosome. Stability can be evaluated by comparing the spectrum of the complex in solid form with the spectrum of its microdispersion in water after lyophilization, at different time intervals.¹⁸

ii) Surface morphology

Surface morphology of the pharmacosomes can be observed with scanning electron microscopy (SEM) or transmission electron microscopy (TEM). The shape and size of the pharmacosomes may be affected by the purity grade of phospholipid and the process variables such as speed of rotation, vacuum applied or the method used. Pharmacosomes prepared by low purity grades of lipids yields a greasy product, which in turn results in the formation of sticky large aggregates. Pharmacosomes prepared by very high purity grades (> 90%) lipids are prone to oxidative degradation, which in turn adversely affect the stability of complexes. Most commonly phospholipids of ~ 80% purity have been used.

iii) Solubility studies

Solubility of the drug, phospholipid, their physical mixture and the pharmacosome can be evaluated. The apparent partition coefficient can be determined by the shake-flask method where two phases are mutually saturated before use.¹⁹ Equal volumes of buffer solutions with a different pH (from 2.0 to 7.4) and 1-octanol containing phospholipid complex are mixed properly in the screw-capped penicillin bottles and equilibrated under constant shaking at 37°C for 24 h. After separating the aqueous phase, the concentration of drug in this aqueous phase is determined by HPLC or UV spectrophotometry.

iv) Differential scanning calorimetry

This thermoanalytical technique is performed to determine drug-excipient compatibility and to demonstrate the possible interactions. Here, an interaction is concluded by elimination of endothermic peak(s), appearance of new peak(s), and change in peak shape and its onset, peak temperature/melting point and relative peak area or enthalpy.

v) X-ray powder diffraction

X-ray powder diffraction is performed to determine the degree of crystallinity by using the relative integrated intensity of reflection peaks. The integrated intensity is

given by the area under curves of the XRPD patterns and it represents the specimen characteristics.

vi) In vitro and in vivo evaluations

Depending upon the expected therapeutic activity of biologically active phytoconstituents, models of in vivo and in vitro evaluations have been carried out. For example, in vitro antihepatotoxic activity can be evaluated by antioxidant and free radical scavenging activity of phytosomes. In vitro dissolution studies can be done with media of different pH in a standard dissolution apparatus to determine the pH dependent dissolution profile. The hepatoprotective activity in vivo can be observed by investigating the effect of prepared pharmacosomes on animal against thioacetamide, paracetamol or alcohol induced hepatotoxicity.¹⁴

APPLICATIONS OF PHARMACOSOMES AS NOVEL DRUG DELIVERY SYSTEM

In the development of novel ophthalmic dosage forms pharmacosomes are the amphiphilic lipid vesicular system. Any drug bearing a free carboxyl group or active hydrogen atom can be esterified to the hydroxyl group of a lipid molecule thus forming an amphiphilic prodrug. These are converted to pharmacosome on dilution with tear²⁰ and enhance transport across cornea and facilitates control release profile.²¹ Pharmacosome elicit greater shelf stability.¹²

L.M.Raikhman et al.²² discussed the pharmacosomes as building particles characterized by high degree of selectivity (acting on target cells). These are capable of delivering various biologically active substances including biopolymers (nucleic acid and proteins).

A. Semalty et al.²³ optimized development and evaluation of pharmacosomes of aceclofenac and found the drug content was 91.88% (w/w) for aceclofenac phospholipid complex (1:1) and 89.03% (w/w) for aceclofenac phospholipid complex (2:1). Solubility of aceclofenac pharmacosome was found to be higher than the aceclofenac. In this study the free aceclofenac showed a total of only 68.69% drug release at the end of 4hr dissolution study while aceclofenac pharmacosome (1:1) showed 79.78% and aceclofenac pharmacosome (2:1) showed 76.17% at the end of 4hr dissolution study.

A. Semalty et al.²⁴ studied development of diclofenac pharmacosome and physicochemical evaluation for drug solubility, in vitro dissolution study, drug content, surface morphology, crystallinity and phase transition behaviour. Water solubility of diclofenac pharmacosome was found to be 22.1 μ g/ml as compared to 10.5 μ g/ml of diclofenac. Drug release of diclofenac pharmacosome was 87.8% as compared to 60.4% of diclofenac at the end of 10hr dissolution study and the drug content of diclofenac pharmacosome was found to be 96.2+/-1.1 %. In SEM, pharmacosomes of diclofenac were found to be disc shaped. XRPD analysis and DSC thermograms proved the formation of phospholipid complex. M. Han et al.²⁵ optimized preparation and evaluation of 20(S)-protopanaxadiol pharmacosome and showed that the encapsulation efficiency of protopanaxadiol pharmacosome was (80.84+/-0.53) with the diameter of 100.1 nm and (72.76+/-0.63) with the diameter of 117.3 nm. Thus the selected formulation and technology are simple and preparation properties are more stable.

AI PING et al.²⁶ prepared didanosine pharmacosomes by using tetra hydro furan injection method and investigate the in vivo behaviour of pharmacosomes in rats by determining the drug in plasma and tissues with HPLC. From the result it can be concluded that pharmacosomes elicit liver targeting and sustained release effect in target tissues.

Z R Zhang, J X Wang successfully optimized the preparation of 3',5'-dioctanoyl-5-fluoro-2'-deoxyuridine pharmacosomes²⁷ by using central composite design and concluded that 3',5'-dioctanoyl-5-fluoro-2'-deoxyuridine pharmacosomes showed a good targeting efficiency in vivo and can improve the ability of drug to cross the blood brain barrier.

JIN Yi-Guang et al.²⁸ prepared acyclovir pharmacosomes by tetrahydro furan injection and investigate the following properties-

i) The negatively charged pharmacosome were nanometer vesicles based on analysis of trans-mission electron scanning calorimetry.

ii) The effects of centrifugation and heating on stability of pharmacosomes were weak.

iii) Freezing and lyophilisation disrupted pharmacosomal structure.

iv) The amphiphilic pharmacosomes would insert into rabbit erythrocyte membranes and led to hemolysis. Plasma proteins in blood absorbed pharmacosomes or interfered the interaction with erythrocytes to reduce hemolytic reaction.

A. Semalty et al.²⁹ investigate development and characterization of aspirin -phospholipid complex (in 1:1 molar ratio) for improved drug delivery and found that the drug content was 95.6% for aspirin-phospholipid complex. The free aspirin showed a total of only 69.42% drug release at the end of 10 hr dissolution study while aspirin pharmacosome showed a total of only 90.93% drug release at the end of 10 hr dissolution study in pH 1.2 acid buffer. Thus it can be concluded that aspirin pharmacosomes enhance the bioavailability of aspirin. The GI toxicity is also reduced in case of aspirin-phospholipid complex.

Peng-Fei Yue et al.³⁰ prepared and investigate the characteristics of geniposide pharmacosome and optimize the process by response surface design. The phospholipid to drug ratio, reaction temperature and drug concentration were determined as 3, 50°C, 5.5mg/ml respectively. Thus pharmacosomes can improve absorption and permeation of biologically active constituents.

V.E.Ivan et al.³¹ studied the effect of temperature on cascade system of pharmacosome fusion and demonstrated that a combination of cell-specific drug vehicles (pharmacosomes) containing cascade fusion system, at appropriate temp will have a prominent effect on drug delivery to appropriate sites within an organism by using both heating and cooling of tissues.

The other therapeutic applications are described in table 2.³²⁻³⁷

CONCLUSION

The development of pharmacosome represents a significant advance over the conventional vesicular systems. It offers protective and controlled delivery of various drugs. Influence of spacer groups and linkage should be observed for getting the therapeutic goal. Further different approaches like pegylation, biotinylation have been developed to achieve the realistic practical application.

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Table: 1 FEATURES AND PROBLEMS ASSOCIATED WITH CONVENTIONAL VESICULAR SYSTEM

VESICULAR SYSTEM	FEATURES	PROBLEMS
Liposomes	Microscopic vesicles (25nm to 100μm) of one or more lipid bilayers separated by water or aqueous buffer compartments	Expensive to prepare, degradation by oxidation, sedimentation, leaching of drug; lack of purity of natural phospholipids
Niosomes	Non ionic surfactant vesicles	Aqueous suspension may exhibit aggregation, fusion, leaching or hydrolysis of entrapped drug (limiting the shelf life); Time consuming, inefficient, instability
Transferosomes	Suitable for both low and high molecular weight and also for lipophilic as well as hydrophilic drugs	Expensive, chemical instability due to oxidative degradation, lack of purity of natural phospholipids

Table: 2 THERAPEUTIC APPLICATION OF DRUGS AFTER INCORPORATION IN PHARMACOSOMES

DRUG	EFFECT AFTER INCORPORATION IN PHARMACOSOMES
Amoxicillin	Improved cytoprotection and treatment of <i>H.pylori</i> infections in male rats
Bupranolol hydrochloride	Enhanced effect on intraocular pressure Enhance lymph transport
Cytarbin	Improved biological activity
Dermatan sulphate	Improved biological activity
Pindolol diglyceride	Three to five fold increase in plasma concentration
Taxol	Improved biological activity