



Pharmacosomes: A Potential Vesicular Drug Delivery System

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ABSTRACT

Lipid based drug delivery systems have been examined in various studies and exhibited their potential in controlled and targeted drug delivery. Pharmacosomes, a novel vesicular drug delivery system, offering a unique advantage over liposomes and niosomes, and serve as potential alternative to these conventional vesicles. They constitute an amphiphilic phospholipid complex with drug bearing an active hydrogen atom covalently that bind to phospholipids. They provide an efficient delivery of drug required at the site of action, which ultimately reduces the drug toxicity with reduced adverse effects and also reduces the cost of therapy by imparting better biopharmaceutical properties to the drug, resulting in increases bioavailability, especially in case of poorly soluble drugs. As the system is formed by binding the drug (pharmakon) to carrier (soma), they are termed as pharmacosomes. Depending upon the chemical structure of the drug lipid complex they may exist as ultrafine vesicular, micellar and hexagonal aggregate. Drug having active hydrogen group such as carboxyl, hydroxyl group can be esterified to lipids, resulting in amphiphilic compound. Pharmacosomes are widely used as carriers for various non-steroidal anti-inflammatory drugs, proteins, cardiovascular and antineoplastic drugs. The release of drug from pharmacosomes is generally governed by the process of enzymatic reaction and acid hydrolysis. Here, in the present review paper we have discussed the potential of pharmacosomes as a controlled and targeted drug delivery system and highlighted the method of preparation and characterization.

Keywords: Pharmacosomes, amphiphilic, targeted drug delivery system, biosomes, phospholipids, bioavailability.

INTRODUCTION

Most of the drugs, particularly chemotherapeutic agents, have shown to have narrow therapeutic window, and their clinical use is limited. Thus, their therapeutic effectiveness may be increased by incorporating them in an advantageous manner. In the past few decades, considerable attention had been focused on the development of novel drug delivery system (NDDS). The NDDS should ideally fulfill two requirements. Firstly, it should deliver the drug at a rate directed by the needs of the body, over the period of treatment. Secondly, it should deliver the active moiety to the site of action. Unfortunately, at present no available drug delivery system behaves ideally, but sincere attempts have been made to achieve them through various novel approaches in drug delivery. Various approaches have been adapted to achieve this goal, by paying attention either to control the distribution of drug by incorporating it in a carrier system, or by altering the structure of the drug at the molecular level, or

to control the input of the drug into the bio-environment to ensure its appropriate profile of distribution. Novel drug delivery system aims at providing a temporal or spatial nature, or both, drug release in the body. Novel drug delivery attempts to either sustain drug action at a predetermined rate, or by maintaining a relatively constant, effective drug level in the body with minimization of undesirable side effects. It can also localize drug action by spatial placement of controlled release systems adjacent, or in the infected tissue or organ; or target drug action by using carriers or chemical derivatization to deliver drug to particular site of action. Various types of pharmaceutical carriers are identified and investigated for their therapeutic applications. They are classified as particulate, polymeric, macromolecular and cellular carriers. Particulate type carriers also termed as a colloidal carrier system, includes lipid particles (low and high density lipoprotein-LDL and HDL, respectively), microspheres, nanoparticles, polymeric micelles and vesicular like liposomes, niosomes, pharmacosomes, virosomes, etc.,^[1] The vesicular systems are highly ordered assemblies of one or more concentric lipid bilayers formed, when certain amphiphilic building blocks are confronted with water. Vesicles can be formed from a diverse range of amphiphilic building blocks.^[2] Novel drug delivery attempts to either

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controlled release, or by maintaining relatively constant, effective drug level in the body with minimization of undesirable side effects.^[3]

Vesicular Systems

Vesicular structures are the one, which can be expected to prolong the duration of the drug in systemic circulation, and reduces the toxicity by selective up-take. Biologic origin of these vesicles was first reported in 1965 by Bingham, and termed as Bingham bodies, which played a major role in modeling biological membranes, and helps in the transport and targeting of active agents. Consequently, a number of vesicular delivery systems such as liposomes, niosomes, pharmacosomes etc., were developed. Nowadays vesicles are gaining importance as a potential carrier system in fields of immunology, membrane biology, diagnostics and recently in genetic engineering. They can offer wide range of incorporation of both hydrophilic and lipophilic drugs as a vehicle of choice in drug delivery. Lipid vesicles were found to be of value in vesicular drug delivery that reduces the cost of therapy by improved bioavailability of medication, especially in case of poorly soluble drugs. Delay drug elimination time of rapidly metabolized drugs, and function as sustained release systems.^[4] This system solves the problems of drug insolubility, instability, and rapid degradation. Encapsulation of the drug in the delivery system has specific advantages while avoiding demerits associated with conventional dosage forms. These carriers play an increasingly important role in drug delivery because by slowing drug release rate, it may possible to reduce the toxicity of drug.^[5] In general, vesicles made of natural or synthetic phospholipids are called liposomes.^[6] They possess an infrastructure consisting of hydrophilic, amphiphilic and lipophilic moieties together and as a result can accommodate drug molecules with a wide range of solubility. The characteristics of the vesicle formulation are variable and controllable. Altering the vesicle composition, size, lamellarity, tapped volume, surface charge and concentration can control the vesicular properties drastically. It may act as a depot, releasing the drug in a controlled manner. 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.^[7]

Vesicular drug delivery system has some of the advantages like:

1. Prolong the existence of the drug in systemic circulation and reduces the toxicity if selective uptake can be achieved due to the delivery of drug directly to the site of infection.
2. Improves the bioavailability especially in the case of poorly soluble drugs.
3. Both hydrophilic and lipophilic drugs can be incorporated.
4. Delays elimination of rapidly metabolizable drugs and thus function as sustained release systems.^[8]

But these vesicular systems are accompanied with some problems like drug carriers such as particulates (e.g., liposomes, nanoparticles, microemulsions) and externally triggered (e.g., 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 *in-vivo*.^[9]

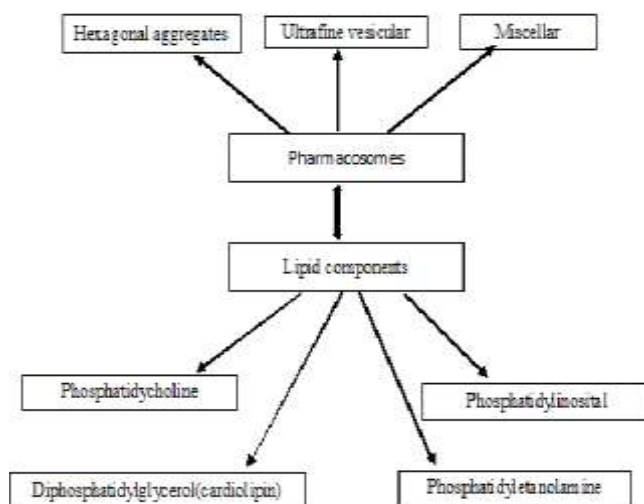


Fig. 1: Components of Pharmacosomes

Pharmacosomes

Pharmacosomes bearing unique advantages over liposome and niosome vesicles and are serve as an 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 serve as an effective tool to achieve desired therapeutic goals in terms of drug targeting and controlled release of drug. The criterion for the development of the vesicular pharmacosome is dependent on surface and bulk interactions of lipids (Figure 1). Any drug possessing an active hydrogen atom (-COOH, -OH, -NH₂, etc.) can be esterified into the lipid, with or without spacer chain that strongly result in the formation of an amphiphilic compound, which facilitates better penetration in to the target site. The prodrug conjoins with hydrophilic and lipophilic properties, thus acquires amphiphilic characters, and therefore found to reduce interfacial tension, and at higher concentrations exhibits mesomorphic behavior.^[10]

Advantage of Pharmacosomes

1. As the drug is covalently bound to lipid, membrane fluidity has no effect on release rate, but depends upon the phase-transition temperature of the drug-lipid complex.
2. No leaching of drug takes place because the drug is covalently bound to the carrier.
3. Drugs can be delivered directly to the site of infection.
4. Drug release from pharmacosomes is generally governed by hydrolysis (including enzymatic).
5. Their degradation velocity into active drug molecule, after absorption depends on their size and functional groups of the drug molecule, the chain length of the lipids, and spacer.^[11]
6. Reduced cost of therapy.
7. Suitable for both hydrophilic and lipophilic drugs. The aqueous solution of these amphiphiles exhibits concentration dependant aggregation.
8. High and predetermined entrapment efficiency of drug and carrier are covalently linked together.
9. Volume of inclusion doesn't influence on entrapment efficiency.

10. No need of removing the free un-entrapped drug from the formulation which is required in case of liposomes.
11. Improves bioavailability especially in case of poorly soluble drugs.
12. Reduction in adverse effects and toxicity.

Advantages of pharmacosomes over other vesicular systems

1. In case of pharmacosomes, volume of inclusion does not influence on entrapment efficiency. On the other hand, in case of liposomes, the volume of inclusion has great influence on entrapment efficiency.
2. In pharmacosomes, the membrane fluidity depends upon the phase transition temperature of drug-lipid complex but it has no effect on release rate because the drug is covalently bound. In liposomes, the lipid composition is one of the crucial factors that decide its membrane fluidity, which affects the rate of drug release and physical stability of the system.
3. Drug release from pharmacosomes is by hydrolysis (including enzymatic) unlike liposomes the release of drug is by diffusion through bilayer, desorption from the surface or degradation of liposomes.
4. Unlike liposomes in pharmacosomes there is no need of following the tedious, time consuming step for removing the free, un-entrapped drug from the formulation.
5. In liposomes there are chances of sedimentation and leaching of drug but in pharmacosomes the incidence of leakage of drug does not take place because the drug is covalently linked to the carrier. ^[12]

Salient features of pharmacosomes

1. Entrapment efficiency is not only high but predetermined, because drug itself in conjugation with lipids forms vesicles.
2. Unlike liposomes, there is no need of following the tedious, time-consuming step for removing the free, unentrapped drug from the formulation.
3. Since the drug is covalently linked, loss due to leakage of drug, does not take place. However, loss may occur by hydrolysis.
4. No problem of drug incorporation into the lipids.
5. In pharmacosome, the encapsulated volume and drug-bilayer interactions do not influence on entrapment efficiency. However, these factors have great influence on entrapment efficiency in case of liposomes.
6. The lipid composition in liposomes decides its membrane fluidity, which in turn influences the rate of drug release, and physical stability of the system. However, 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 to lipids.
7. Phospholipid transfer/exchange is reduced, and solubilization by HDL is low.
8. The physicochemical stability of the pharmacosomes depends upon the physicochemical properties of the drug-lipid complex.
9. Following absorption, their degradation velocity into active drug molecule depends to a great extent on the size and functional groups of drug molecule, the chain length of the lipids, and the spacer. These can be

varied relatively precisely for optimized *in vivo* pharmacokinetics.

10. They can be given orally, topically, extra or intravascularly.

Limitations

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

Components used for the formulation of 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 amphiphilic complex which in turn facilitate membrane, tissue, cell wall transfer in the organisms.

Solvents

For the preparation of pharmacosomes, the solvents should have high purity and volatile in nature. A solvent with intermediate polarity is selected for pharmacosomes preparation.

Lipids

Phospholipids are the major structure component of biological membranes, where two types of phospholipids such as phosphoglycerides and spingolipids are generally used. The most common phospholipid is phosphotidyl choline moiety. Phosphotidyl choline is an amphiphilic molecule in which a glycerol bridges links a pair of hydrophobic acyl hydrocarbon chains, with a hydrophilic polar head group phosphocholine.

Methods of preparation

There are two methods which have been employed to prepare vesicles;

Hand-shaking method

In the hand-shaking 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 vacuum evaporator, which leaves a thin film of solid mixture deposited on the walls of flask. The dried film can then be hydrated with aqueous media and gives a vesicular suspension.

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.

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 offered the benefit of diluting the micelle without the drug getting precipitated in the monomeric drug conjunct. ^[13] Muller-Goymann and Hamann produced fenoprofen pharmacosomes using a modified technique that involved diluting lyotropic liquid crystals of amphiphilic drug. ^[14] Approaches had been done to attach drugs to various glyceride-like groups, and the

resulting amphiphilic molecules had been spontaneously dispersed. 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.^[15]

Characterization of pharmacosomes

FTIR Spectroscopy

The formation of the complex can be confirmed by IR spectroscopy comparing the spectrum of the complex with the spectrum of individual components and their mechanical mixture. Stability of pharmacosome is evaluated by comparing the spectrum of the complex in solid form with the spectrum of its micro dispersion in water after lyophilization at different time intervals.

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 grades of phospholipid and the process variables such as speed of rotation, vacuum applied. It is prepared by low purity grades of lipids yields a greasy product, which in turn results in the formation of sticky large aggregates and it is also prepared by very high purity grades (>90%) lipids are prone to oxidative degradation, which in turn adversely affect the stability of complexes. Most commonly used phospholipids are of 80 % purity.

Solubility studies

Solubility of the drug, phospholipids, their physical mixture and the pharmacosomes can be determined. The apparent partition coefficient can be determined by the shake-flask method where two phases are mutually saturated before use. 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 24h. After separating the aqueous phase, the concentration of drug in this aqueous phase is determined by HPLC or UV spectrophotometry.

Differential scanning calorimetry

This thermo analytical technique had performed to determine drug-excipient compatibility and to demonstrate the possible interactions.

X-ray powder diffraction

It has been 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.

In vivo and in vitro evaluations

Depending upon the expected therapeutic activity of biologically active constituents, models of *in-vivo* and *in-vitro* evaluations had been carried out.^[16]

Applications of pharmacosomes

1. Pharmacosomes elicit greater shelf stability.
2. Pharmacosome can improve absorption and permeation of biologically active constituent.
3. The effect of temperature on cascade system of pharmacosome fusion and demonstrated that a combination of cell-specific drug vehicles (pharmacosome) containing cascade fusion system, at appropriate temp will have a prominent effect on drug

delivery to appropriate sites within an organism by using heating and cooling of tissues.

4. The approaches have successfully improved the therapeutic, performance and various drug i.e. pindolol diglyceride, amoxicillin, taxol, cytarbine, dermatansulfate, bupranolol hydrochloride etc., (Table 1).

Table 1: Therapeutic applications of pharmacosomes

Drugs	Therapeutic applications
Pindolol diglyceride	Three to five fold increase in plasma concentration with lower renal clearance as compared with free drug.
Amoxicillin	Improved cytoprotection and treatment of <i>H. pylori</i> infections in male rats.
Taxol, Cytarbine, Dermatansulfate	Improved anticancer and biological activity of anticancer agents
Bupranolol hydrochloride	Enhanced effect on intraocular pressure and enhance lymph transport

Vesicular systems had realized as extensively useful carrier systems in various scientific domains. In spite of certain drawbacks (fusion, aggregation), it 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, biotinylation etc. for cellular targeting. 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, xanthenes, 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.

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