Pharmacosomes as a novel vesicular drug delivery system

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INTRODUCTION

From the very beginning of the human race; the question is going on for newer and better alternatives, and in case of drugs it will continue; continue till we find a drug with maximum efficacy and no side effects. Many drugs, particularly chemotherapeutic agents, have narrow therapeutic window, and their clinical use is limited and compromised by dose limiting toxic effect. Thus, the therapeutic effectiveness of the existing drugs is improved by formulating them in an advantageous way. In the past few decades, considerable attention has been focused on the development of new drug delivery system (NDDS). The NDDS should ideally fulfill two prerequisites. Firstly, it should deliver the drug at a rate directed by the needs of the body, over the period of treatment. Secondly, it should channel the active entity to the site of action. Conventional dosage forms including prolonged release dosage forms are unable to meet none of these. 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 [1-3]. Approaches are being adapted to achieve this goal, by paying considerable 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 bioenvironment to ensure an appropriate profile of distribution. Novel drug delivery system aims at providing some control, whether this is of temporal or spatial nature, or both, of 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 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. Different types of pharmaceutical carriers are present. They are particulate, polymeric, 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), microspheres, nanoparticles, polymeric...
micelles and vesicular like liposomes, niosomes pharmacosomes, virosomes, etc. The vesicular systems are highly ordered assemblies of one or several 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 [1,4]. 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 site of infection, leading to reduce of drug toxicity with no adverse effects. They can incorporate both by hydrophilic and lipophilic drugs have become the vehicle of choice in drug delivery and lipid vesicles were found to be of value Vesicular drug delivery reduces the cost of therapy by improved bioavailability of medication, especially in case of poorly soluble drugs. Vesicular drug delivery systems delay drug elimination of rapidly metabolizable drugs, and function as sustained release systems. This system solves the problems of drug insolubility, instability, and rapid degradation. Encapsulation of the drug in have specific advantages while avoiding demerits associated with conventional dosage forms because these particles can act as drug reservoirs. These carriers play an increasingly important role in drug delivery because by slowing drug release rate, it is possible to reduce the toxicity of drug. In general vesicles made of natural or synthetic phospholipids are called liposomes. Different types of pharmaceutical carriers are used. They are particulate, polymeric, macromolecular, and cellular carrier. 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 vesicle composition, size, lamellarity, tapped volume, surface charge and concentration can control the vesicle characteristics. The vesicles may act as a depot, releasing the drug in a controlled manner. Vesicular delivery system provide an efficient method for delivery of drug

**Definition**

These are defined as colloidal dispersions of drugs covalently bound to lipids and may exist as ultrafine vesicular, micellar or hexagonal aggregates, depending on the chemical structure of drug-lipid complex [1,2]. The prodrug conjoins hydrophobic and lipophilic properties and therefore acquires amphiphilic charactersand was found to reduce interfacial tension and thus at higher concentrations exhibits mesomorphic behavior. Because the system is formed by linking a drug (pharmakon) to a carrier (soma), they are called pharmacosomes.

**Vesicular Systems**

Vesicular structures is one such system, which can be expected to prolong the duration of the drug in systemic circulation, and reduce the toxicity by selective up taking. Biologic origin of these vesicles was first reported in 1965 by Bingham, and was given the name Bingham bodies. Consequently, a number of vesicular delivery systems such as liposomes, niosomes, pharmacosomes etc, were developed. Now a day’s vesicle as a carrier system in immunology, membranebiology and diagnostic technique and most recently in genetic Engineering. It provides an efficient method for delivery to the site of infection, leading to reduce of drug toxicity with no adverse effects. They can incorporate both by hydrophilic and lipophilic drugs have become the vehicle of choice in drug delivery and lipid vesicles were found to be of value Vesicular drug delivery reduces the cost of therapy by improved bioavailability of medication, especially in case of poorly soluble drugs. Vesicular drug delivery systems delay drug elimination of rapidly metabolizable drugs, and function as sustained release systems. This system solves the problems of drug insolubility, instability, and rapid degradation. Encapsulation of the drug in have specific advantages while avoiding demerits associated with conventional dosage forms because these particles can act as drug reservoirs. These carriers play an increasingly important role in drug delivery because by slowing drug release rate, it is possible to reduce the toxicity of drug. In general vesicles made of natural or synthetic phospholipids are called liposomes. Different types of pharmaceutical carriers are used. They are particulate, polymeric, macromolecular, and cellular carrier. 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 vesicle composition, size, lamellarity, tapped volume, surface charge and concentration can control the vesicle characteristics. The vesicles may act as a depot, releasing the drug in a controlled manner. Vesicular delivery system provide an efficient method for delivery of drug
directly to the site of infection, leading to reduction of toxicity with no adverse effect vesicular drug delivery reduce the cost of therapy by improve bioavailability of medication especially in case of poorly soluble drugs. They can incorporate both hydrophilic & lipophilic drug. Micro emulsions 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. 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 [2,5,7]. 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 [4, 5].
- But these vesicular systems are accompanied with some problems like drug carriers such as particulates (e.g., liposomes, nanoparticles, micro emulsions) 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* [5].

Some vesicular system associated problems are mentioned in table 1.

<table>
<thead>
<tr>
<th>Vesicular system</th>
<th>Problems</th>
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<tr>
<td>Liposomes</td>
<td>Expensive, degradation by oxidation, lack of Purity of natural phospholipids.</td>
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<tr>
<td>Niosomes</td>
<td>Time consuming, inefficient, instability</td>
</tr>
<tr>
<td>Transferosomes</td>
<td>Expensive, chemical instability etc.</td>
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**Advantages of Pharmacosomes Over Other Vesicular Systems**

- Pharmacosomes bearing unique advantages over liposome and niosome vesicles have come up as potential alternative to conventional vesicles.
- The limitations of transfersomes can be overcome by the “pharmacosome” approach [7].
- Different types of lipid based vesicular systems have been developed now a days for several applications inside the controlled and targeted drug delivery.
- Pharmacosomes bearing unique advantages over liposomes along with niosomes have been emerged as potential alternative to conventional vesicles.

- These are the amphiphilic phospholipid complexes of drugs which having active hydrogen that bind to phospholipids. They provide an efficient method for delivery of drug directly to the site of infection as well as reduction of drug toxicity with no adverse effects along with low cost of therapy,
- They help for better biopharmaceutical properties to the drug, resulting in improved bioavailability, especially in case of poorly soluble drugs.
- Pharmacosomes have been produced for several applications like non-steroidal anti-inflammatory drugs, proteins, cardiovascular and antineoplastic drugs [8].
- In case of pharmacosome, volume of inclusion does not influence entrapment efficiency. On the other hand in case of
Liposomes, the volume of inclusion has great influence on entrapment efficiency.

- In pharmacosomes membrane fluidity depends upon the phase transition temperature of the drug lipid complex but it has no effect on release date because the drug is covalently bound. In liposomes, the lipid composition decides its membrane fluidity, which affects the rate of drug release and physical stability of the system.
- 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. Unlike liposomes in pharmacosomes there is no need of following the tedious, time consuming step for removing the free, unentrapped drug from the formulation.
- In liposomes there are chances of sedimentation and leaching of drug but in pharmacosomes the leakage of drug does not take place because the drug is covalently linked to the carrier [1].
- Suitable for both hydrophilic and lipophilic drugs.
- Interaction of pharmacosomes leads to change in the phase transition temperature of biomembranes improves membrane facility and enhanced permeation.
- Volume of inclusion doesn’t influence entrapment efficiency.
- No leakage of drug take place as the drug is covalently linked to 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 [9-11].

**Materials for pharmacosomes**

There are three essential components for pharmacosome preparation.

- **Drugs:** Drugs containing active hydrogen atom (-COOH, OH, NH2) can be esterified to the lipid, with or without spacer chain and they forms 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 pharmacosome preparations.
- **Lipid:** Phospholipids are the major structure component of biological membranes, where two type of phospholipids generally used- phosphoglycerides and spingolipids. The
most common phospholipid is phosphatidylcholine molecule. Phosphatidylcholine is an amphipathic molecule in which a glycerol bridges links a pair of hydrophobic acyl hydrocarbon chains, with a hydrophilic polar head group, phosphocholine [12,13].

Formulation of pharmacosomes

Drug salt was converted into acid form to provide an active hydrogen site for complexation. Drug acid was prepared by acidification of aqueous solution of a drug salt, extraction with chloroform, and subsequent recrystallization. Drug-PC complex was prepared by associating drug acid with an equimolar concentration of PC. Equimolar concentration of PC and drug acid were placed in a round-bottomed 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].

Enhanced therapeutic activity

The approach has successfully improved the therapeutic performance of various drugs i.e. Pindolol maleate, bupranolol hydrochloride, taxol, acyclovir, etc [15, 16]. 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 [17]. In another study, in vivo behaviour 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 [18]. Moreover, the incorporation of NSAIDS with phospholipids has been also suggested to improve GI safety of these drugs. It has been reported that the diffusion of NSAIDS across lipid membranes and into target cells is accelerated when it is present as a complex with phosphatidylcholine (PC). Therefore, developing the drugs as lipid complexes (pharmacosomes) may prove to be a potential approaches to improve solubility and to minimize the GI toxicity of NSAIDS.

METHODS FOR PREPARATION OF PHARMACOSOMES

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

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

**Hand-shaking 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. Mantelliet 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 [11,12].

**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. An alternative approach for producing pharmacosomes was recently reported 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 approach 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.

**Applications of pharmacosomes**

- Pharmacosomes elicit greater shelf stability.
- The phase transition temperature of pharmacosomes in the vesicular and micellar state could have significant influence on their interaction with membranes and interact with bi membranes enabling a better transfer of active ingredient. This interaction leads to change in phase transition temperature of
biomembranes thereby improve the membranes fluidity leading to enhance permeations.

- The approaches has successfully improved the therapeutic, performance and various drug i.e. pindolol diglyceride, amoxicillin, taxol, cytarbin, dermatansulfate, bupranolol hydrochloride etc [1].

CONCLUSION

Pharmacosomes is not only having high entrapment efficiency but it can be predetermined, because drug itself in conjugation with lipids forms vesicles. Unlike liposomes, there is no need of following the tedious, time-consuming step for removing the free, unentrapped drug from the formulation. Since the drug is covalently linked, loss due to leakage of drug, does not take place. However, loss may occur by hydrolysis. There is no problem of drug incorporation. Encaptured volume and drug-bilayer interactions do not influence entrapment efficiency, in case of pharmacosome. These factors on the other hand have great influence on entrapment efficiency in case of liposomes. 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. The drug is released from pharmacosome by hydrolysis (including enzymatic). Phospholipid transfer/exchange is reduced, and solubilization by HDL is low. The physicochemical stability of the pharmacosome depends upon the physicochemical properties of the drug-lipid complex. Due to their amphiphilic behavior, such systems allow, after medication, a multiple transfer through the lipophilic membrane system or tissue, through cellular walls piggyback endocytosis and exocytosis. 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. They can be given orally, topically, extra- or intravascularly. They help in achieving increased bioavailability, reduce the cost of therapy and provide controlled as well as targeted release of drug.

REFERENCES