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Pharmacosomes: A Novel Drug Delivery System

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Abstract
Pharmacosomes are amphiphilic complex of drug bearing active hydrogen atom and phospholipid bonded by the covalent linkage. Pharmacosomes bearing unique advantage over other conventional vesicle and come up as a alternative potential. Their encapsulations of drug in vesicle, small size, amphiphilic nature prolong existence of drug in systemic circulation, reduces the toxicity, improves cell wall transfer and solubility of poorly water soluble molecule. This review describes all aspects of pharmacosomes including composition, method of preparation, method of characterization and their therapeutic application. Pharmacosomes have been prepared for various non steroidal anti-inflammatory drugs, proteins, cardiovascular and antineoplastic drugs.

Keywords: *Pharmacosomes, Vesicular, Amphiphilic, Phospholipid.*

Introduction
In the past few decades, considerable attention has been focused on the development of new drug delivery system. which in turn controls the rate of drug delivery, sustain the duration of therapeutic action & targeting the drug at required site. These novel drug delivery systems fulfill the following purpose. [2]

- ✓ Controlled administration of therapeutic dose.
- ✓ Maintenances of drug concentration within an optimal range for prolonged action.
- ✓ Maximum efficacy –dose relationship.
- ✓ Reduction of toxic effect or adverse effect.
- ✓ Reduction of frequent dose intake.
- ✓ Enhancement of patient compliance.

One way to modify the original biodistrubution of substance is to entrap them in submicroscopic drug carries such as liposome's, transferosome, niosome, polymeric nanoparticle, serum protein, immunoglobulin, microspheres, erythrocytes, reverse micelles, monoclonal antibodies and pharmacosomes .[4,14] Encapsulation of the drug in vesicular structure is one such system, which can be predicted to prolong the existence of the drug in systemic circulation, and reduce the toxicity, if selective uptake can be achieved. [12, 15]

Vesicles are colloidal particles having a water filled core surrounded by a wall of lipids and surfactants (amphiphiles) arranges in bilayer. If the proportion of water is increased, these amphiphiles can form one or more concentric bilayers. Hydrophilic drugs find a place in the internal aqueous environment while, liphophilic drugs get entrapped in the bilayered wall with electrostatic and /or hydrophobic forces. [13]

Advantages of vesicular drug delivery system
- ✓ Lack of toxicity. [13,16,17]
- ✓ Lack of biodegradation. [13,16,18]
- ✓ Capacity of encapsuling both hydrophilic and liphophilic drug. [13]
- ✓ Capacity of targeting the drug to the site of infection. [12,16]
- ✓ Capacity of prolonging existence of the drug in the systemic circulation. [13]
- ✓ Capacity of reducing the drug toxicity & increasing bioavability. [13,17,18]
- ✓ Increasing the solubility of poorly water soluble drug. [13,17,18]
- ✓ Delay drug elimination of rapidly metabolizable drugs. [12]

Biologic origin of these vesicles was first reported in 1965 by Bingham, and

was given the name Bingham bodies. [5, 19] Conventional chemotherapy for the treatment of intracellular infections is not effective, due to limited permeation of drugs into cells. This can be overcome by use of vesicular drug delivery systems. In recent years, vesicles have become the vehicle of choice in drug delivery. Lipid vesicles were found to be of value in immunology, membrane biology, diagnostic techniques, and most recently, genetic engineering. [12 20, 21] Vesicles can play a major role in modeling biological membranes, and in the transport and targeting of active agents. [12] The phagocytic uptake of the systemic delivery of the drug-loaded vesicular delivery system provides an efficient method for delivery of drug directly to the site of infection, leading to reduction of drug toxicity with no adverse effects. [12]

Table 1: Comparison of few aspects of lipoidal particulate carriers and their applications [10]

Sr No.	Carrier	Composition	Entrapped agent	Unique features
1	Liposome's	Phospholipids: cholesterol: alcohol	Antibiotics, antineoplastic agents, antitubercular drugs	Amphiphilic nature provides solubilization of both hydrophilic and lipophilic drugs, Internalization and amplification of bioactives
2	Transfersomes	Phospholipids: edge activators: alcohols: buffering agent: dye	NSAIDs, anesthetics, steroidal hormones	Ultradeformable vesicles can deform and pass through narrow constriction (from 5 to 10 times less than their own diameter) without measurable loss
3	Ethosomes	Phospholipids: Ethanol	Antifungal agent,antiviral agent,antikera-tinizing agent, NSAIDs	Combinational approach of high concentration of ethanol along with phospholipids synergizes effect of deeper distribution and penetration of drugs in the skin
4	Pharmacosomes	Phospholipids: Dichloromethane	NSAIDs	Colloidal dispersions of drugs covalently bound to lipids, which increased entrapment efficiency; no loss of drug due to leakage, no problem of drug incorporation

Pharmacosomes

Some of the limitation which have been encountered in transferosomes are because of their predisposition to oxidative degradation & purity of natural phospholipids, which overcome by pharmacosomes. [11, 12] The prodrug conjoins hydrophilic and liphophilic properties, and therefore acquires amphiphilic characters. Similar to other vesicle forming components, it was found to reduce interfacial tension and at higher concentrations exhibits mesomorphic behavior. [1, 2, 8]

The term pharmacosomes is explicitly used to describe the zwitterionic, amphiphilic, stoichiometric complexes of polyphenolic compounds with phospholipids. [1,2,11] These are the lipid based drug delivery systems that are appropriately elaborated as the colloidal dispersions of drugs having a covalent, being amphiphilic compounds facilitate membrane, tissue, or cell wall transfer in the organism.[1] 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 pharmacosomes 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. [8, 11]

Table 2: Features and problem associated with conventional vesicular system and over that advantage of pharmacosomes

Vesicular system	Features	Problems	Phamacosomes
Liposome	Microscopic vesicle (25nm to 100µm) of one or more lipid bilayers, separated by water or aqueous buffer compartment	Expensive to prepare, degradation by oxidation, sedimentation, leaching of drug, lack of purity of natural phospholipids	Cheaper to prepare, entrapment efficiency is independent of inclusion volume and drug-bilayer interactions ,covalent linkage prevent drug leakage, oxidation resistant and pure &natural phospholipids not needed.
Niosome	Non- ionic surfactant vesicle	Leaching of drug, time consuming , insufficient stability	More stable, more efficient
Transferosomes	Suitable for both low & high molecular weight &also for liphophilic as well hydrophilic drug.	Expensive, oxidative degradation, lack of purity of natural phospholipids.	Cheaper ,oxidation resistant , pure &natural phospholipids not needed

Advantages

1) Pharmacosomes are suitable for incorporating both hydrophilic and lipophilic drug. [2]

2) In the vesicular & miceller state the phase transition temperature of pharmacosomes have significant effect on their interactions with members. [2]

3) High and predetermined drug loading. [1]

4) Deliver drug directly to the site of infection. [5]

5) Reduction in adverse effects and toxicity. [1]

6) Pharmacosomes can intact with biomembranes enabling a better transfer of active ingredient. [2]

7) Amphiphilicity leads to improved bioavailability of poorly lipid and water soluble drugs. [1]

8) Stable and efficiency due to covalent linkage. [1]

9) Size, functional groups (drug molecule), chain length (lipids) and spacer decides the degradation velocity into active drug molecule. [2]

10) Physiochemical properties of pharmacosomes depend on drug – lipid complex. [4]

11) It can be given orally, topically, extra or intravascularly. [4]

Disadvantages *[1, 28]*

1) Synthesis of compound depends on its amphiphilic nature.

2) Required surface and bulk interaction of lipids with drugs.

3) Required covalent bonding to protect the leakage of drugs.

4) On storage, undergo fusion and aggregation, as well as chemical hydrolysis.

Method of preparation

In general five methods employed to prepare the pharmacosomes.

1) Solvent evaporation method / Hand shaking method :

Firstly a mixture of drug and lipid are dissolved in a volatile organic solvent such as dichloromethane .Thereafter solvent is evaporate using rotatory evaporator in round bottom flask which leaves a thin film of solid mixture deposited on the walls of flask. Then dried film hydrated with aqueous medium & readily gives a vesicular suspension. [1, 2, 3, 11]

2) Ether injection method:

In this method solution containing drug-lipid complex is slowly injected into a hot aqueous medium through gauze needle and vesicle is formed readily. [1, 2, 11]

3) Supercritical fluid process (Solution enhanced dispersion by complex supercritical fluid) - Drug and lipid complex

are dissolved in a supercritical fluid of co_2, then mix into nozzle mixing chamber. [1]

4) Anhydrous co-solvent lyophilization method:

Drug powder and phospholipids dissolved in 1 ml of Dimethyl sulfoxide (DMSO) containing 5% glacial acetic acid, after that agitates the mixture to get clear liquid .Freeze –dried overnight at condenser temperature .Then resultant complex flushed with nitrogen & stored at 4^{o} C. [1]

5) Other approach:

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

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. [11, 30, 31]

Formulation aspects of pharmacosomes preparation

There are three essential components for pharmacosomes preparation.

1) Drug :

Prerequisite for pharmacosomes is an active hydrogen atom (-COOH, -OH, -NH 2 etc.) of the drug. Drug salt was converted into the acid form to provide an active hydrogen site for complexion. Drug phospholipids complex gives amphiphilic nature which improved therapeutic efficacy e.g. Pindolol maleate, Bupranolol hydrochloride, Taxol, acyclovir, etc. [1, 2, 11]

2) Lipid:

Lipid is building block of cell membrane. There are three types of phospholipids generally used in pharmacosomes i.e phosphoglycerides and spingolipids & phosphatidylcholine. The most common phospholipid is phosphatidylcholine molecule. Phosphatidylcholine is bifuctional compound, the phosphatidyl moiety being liphophilic and choline moiety being hydrophilic in nature, therefore upon complexation with drug yield amphiphilic product. [1, 2, 11]

3) Solvents :

For the Pharmacosomes preparation highly pure, volatile and intermediate polar solvent is required. [1, 2, 11]

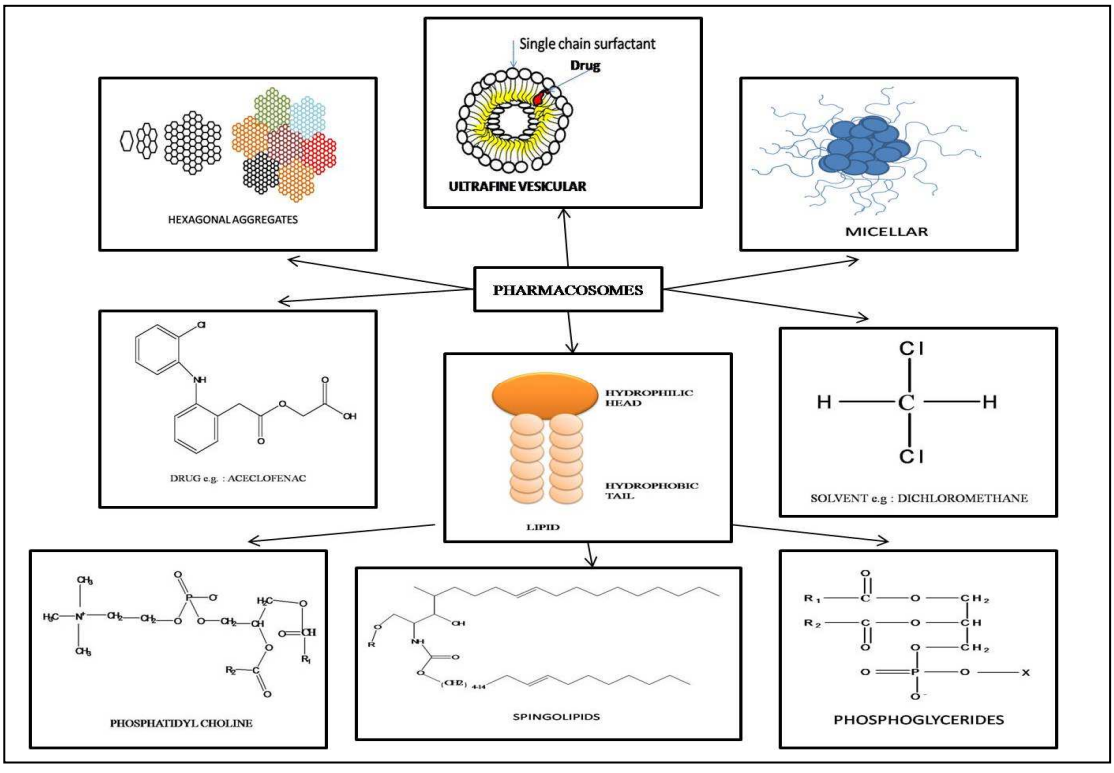

Fig:1 Forms and component of pharmacosomes

Characteration of pharmacosomes

1) FTIR spectroscopy. [2, 11]

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 pharmacosomes can be 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.

2) Surface morphology [1, 2, 3, 6, 11]

Scanning electron microscopy (SEM) or transmission electron microscopy (TEM) can be used to study the Surface morphology of the pharmacosomes. Purity grades of phospholipids ,process variable such as speed of rotation ,vacuum applied or method used affected the shape and size of the pharmacosomes. Phospholipids are of 80% purity required for appropriate pharmacosomes product, low purity grades yield greasy product and high grades lipid prone to oxidative degradation.

3) Solubility studies [2, 11]

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.19 Equal volumes of buffer solutions with a different pH (from 2.0 to 7.4) and 1- octanol containing phospholipids complex are mixed properly in the screw capped penicillin bottles and equilibrated under constant shaking at 37 0 C for 24h. After separating the aqueous phase, the concentration of drug in this aqueous phase is determined by HPLC or UV spectrophotometry.

4) Differential Scanning calorimetry [2, 3, 6, 11]

Differential scanning calorimetry is performed to determine drug excipient compatibility and to demonstrate the possible interactions Here, an interactions in concluded by elimination of endothermic peak ,appearance of new peak, change in peak shape & its onset ,peak temperature/ melting point & relative peak area or enthalpy.

5) X-ray powder diffraction [2, 11]

To determine the degree of crystallinity X-ray powder diffraction is performed. Depending upon the relative integrated intensity of reflection peak degree of crystallinity is measured.

6) In vivo and in vitro evaluations. [2, 11 17, 18, 19, 20, 21]

Depending upon the expected therapeutic activity of biologically active constituents, models of in vivo and in vitro evaluations have been carried out. In vitro dissolution studies of drug-phosphatidylcholine complex as well as plain drug performed with media of different pH in standard dissolution apparatus to determine the pH dependent dissolution profile.

Application

1) Peng-Fei Yue et al prepared the phamacosome of geniposide and characteristics them. They found that pharmacosomes can improve absorption and permeation of biologically active constituent. [2, 11]

2) Pharmacosomes prepared for various poorly soluble non steroidal anti- inflammatory drugs like Aceclofenac, Diclofenac, Aspirin, Fenoprofen. These studies shows that pharmacosomes are able to enhance the dissolution ability and permeation of drug. Permeation of drug across the skin also enhanced when assayed by in vitro percutaneous absorption by using flow through diffusion cell for fenoprofen. [1, 2,4 7]

3) Meihua HAN et al., developed 20(S)-Protopanaxadiol (Ppd) phamacosome by simple thin film-dispersion method which stability is good. [1]

4) Zhang ZR et al.,found mean particle size of 3',5'-dioctanoyl-5-fluoro-2'-deoxyuridine pharmacosomes to be 76 nm with drug loading of 29.02% and entrapment efficiency of 96.62%. [1]

5) Shi et al. prepared a new insulin–phospholipids complex by an anhydrous co-solvent lyophilization method and Compared with native insulin. They found that physicochemical properties of insulin changed significantly especially lipophilicity, that would be contribute to the improved oral absorption of insulin. [1]

6) Jin Yi Guang et al, formulated the negatively charged nanometer Acyclovir succinyl glyceryl monostearate pharmacosomes by Tetra hydro furan injection method. They found that very week effect of centrifugation and heating on pharmacosomes stability, whereas freezing and lyophilization disturpted the pharmacosomes structure. [1, 2]

7) 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. [2]

8) AI PING et al prepared Didanosine pharmacosomes by Tetra hydro furan injection method and concluded that pharmacosomes elicit liver targeting and sustained release effect in target tissue.

9) Few researches have reported that Isoniazide pharmacosomes have improved permeability and macrophage targeting. [1]

10) Pharmacosomes also improve the biopharmaceutical properties of biologically active phytoconstituents such as flavones, glycosides, xanthones. [1]

Table 3: Drug effect after incorporation in pharmacosomes [11, 24, 25, 26, 27, 28, 29]

Drugs	Effect after incorporation in Phamacosome
Pindolol diglyceride	Three to five fold increase in plasma concentration Lower renal clearance
Amoxicillin	Improved cytoprotection and treatment of H.pylori infections in male rats
Taxol	Improved biological activity
Cytarbin	Improved biological activity
Dermatan sulfate	Improved biological activity
Bupranolol hydrochloride	Enhanced effect on intraocular pressure Enhance lymph transport

Conclusions

Pharmacosomes overcome some of the limitation of liposome, niosomes, transferosomes like oxidation, instability ,lack of purity resp.Pharmacosomes have ability to include entrap liphophilic or hydrophilic drugs and release the drug at site of action.They could be used to improve aqueous solubility and permeability of liphophilic and hydrophilic drug resp.It can be give orally,topically,extra or intra vascular.

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