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Pharmaceutical Sciences **Review Article……!!!**

A REVIEW ON PHARMACOSOMES: A POTENTIAL DRUG DELIVERY SYSTEM

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KEYWORDS:

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ABSTRACT

Pharmacosomes are the drug delivery system which are amphiphilic in nature in which covalent bond links the active hydrogen atom with the phospholipid. Pharmacosomes have an unique characteristics compared to conventional vesicular systems so it can be a better alternative. The drug is encapsulated in very small vesicles which prolongs its existence in systemic circulation. This kind of vesicular drug delivery system finds its applications in immunology, membrane biology, and genetic engineering. The pharmacosomes may exists as hexagonal aggregates, micells, or ultrafine vesicles. They are efficient tools to achieve therapeutic goals like drug targeting and controlled release. This review describes all the aspects related to the pharmacosomes including the composition, method of preparation, characterization and their therapeutic applications.

INTRODUCTION:

Pharmacosomes are novel vesicular drug delivery systems these are the colloidal dispersion of drugs covalently bound to the lipids. These can be an efficient tool for the delivery of the drugs to the target site. The pharmacosomes may exist as ultrafine vesicles, micelles or hexagonal aggregates. They are termed as "pharmacosomes" due to the linking of a drug (pharmakon) to a carrier (soma). Pharmacosome may be defined as a complex of neutral molecule possessing both positive and negative charge, water-loving and fat-loving properties, and an optimum ratio of polyphenol with phospholipids in a complex form. The drugs which face difficulty in solubility and permeability can be effectively formulated into pharmacosomes. The amphiphilic character of pharmacosomes reduces the interfacial tension thus increasing the contact area thus increasing the bioavailability of drugs. [2] The phospholipids like phosphatidylcholine will have a major role in drug delivery due to its amphiphilic nature which helps to modify the rate of drug release for the enhancement of drug absorption across the biological barriers. Producing an amphiphilic drug lipid complexes prove to be the potential approach for improving the therapeutic efficacy of drugs by improving its bioavailability through improvement in the solubility in the GI fluids and better permeation through biological membranes.[3] pharmacosomes are made up of natural lipids which are desirable candidates for the brain targeting due to the rapid uptake by the brain it has better bio acceptability, biodegradability and less toxicity compared to the polymeric nanoparticles. Any drug possessing an active hydrogen atom (-COOH, -OH, $-NH^2$) can be esterified into the lipid with or without a spacer chain which will strongly result in the amphiphilic compound [8]. It is important to evaluate different terms used under novel drug delivery system 1) Sustained or controlled drug delivery systems it provides drug action at a predetermined rate by providing a delayed or constant (zero –order) release. 2) Localized drug delivery devices provide drug action through spatial or temporal control drug release. In recent times different carrier systems are being used for controlling the drug release and enhancing the safety and efficacy of the formulation. Vesicles in the pharmaceutical formulation have become the most preferred carrier for the drugs in the formulation these are now being used extensively in the field of genetic engineering, immunology, membrane biology and also in the diagnostic procedures [10].

Salient Features of Pharmacosomes:

1. As the pharmacosomes possess both water loving and fat loving properties they can easily pass through the biological membranes like cell membranes, and tissues either by process of endocytosis and exocytosis.
2. They can be administered through topical, oral, extravascular or intravascular routes.

3. The physical and chemical properties of the conjugates take care of the stability of whole system.
4. The rate of degradation depends on the size of vesicles, properties of functional groups present in the molecules, fatty acid chain length in lipids and the presence or the absence of spacer [11].

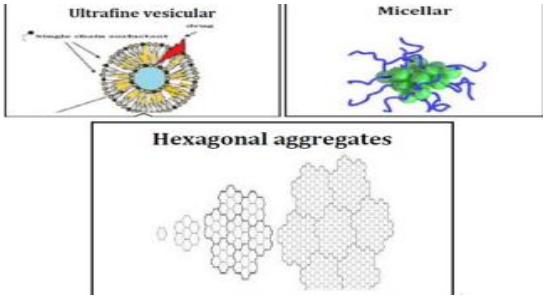

Figure 1 Structure of pharmacosomes

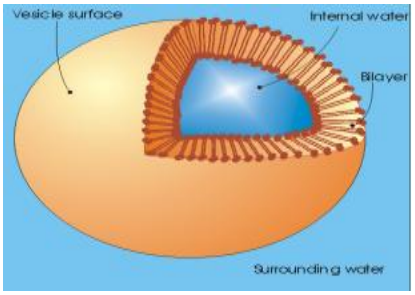

Figure 2 Structure of vesicles

Advantages of Pharmacosomes:

1. Both hydrophilic and hydrophobic drugs can be incorporated [13].
2. Precised drug loading [13].
3. Deliver the drug directly to the site of action [13].
4. Reduction in the adverse effects and toxicity [13].
5. High and predetermined entrapment efficiency as the drug is covalently linked to phospholipid [11].
6. Amphiphilicity leads to the better bioavailability of poor water soluble and lipid soluble drugs [13].
7. Drug leakage does not occur because of the covalent linkage [14].
8. Reduces side effects and toxicity [10].

Limitations of Pharmacosomes:

1. Synthesis of pharmacosomes depends on both hydrophilic and lipophilic nature of the drugs [14].
2. The pharmacosomes require covalent bonding to prevent the leakage or loss of the drug [11].
3. Surface interaction of the drug and the phospholipid is mandatory for the preparation of pharmacosomes [19].
4. Pharmacosomes undergo fusion, aggregation and hydrolysis on storage [13].

Materials for Pharmacosomes:

The essential components for the preparation of pharmacosomes are:

Drugs: Any drug having an active hydrogen atom (-COOH, - OH, -NH_2) is suitable for pharmacosome formulation that can be esterified to the lipid, with or without spacer chain, leading to formation of amphiphilic complexes. Synthesis of such a compound may be guided in such a way that strongly result in an amphiphilic compound, which will facilitate membrane, tissue or cell wall transfer. This kind of approach has successfully improved the therapeutic activity of a number of drugs including i.e. pindolol maleate, bupranolol hydrochloride, Taxol, acyclovir [11].

Lipid: Phospholipids are the major component of biological membranes. There are two types of phospholipids generally phosphoglycerides and spingolipids. The most common is phosphotidylcholine. It is amphiphilic molecule in which a glycerol bridges links a pair of hydrophobic acyl hydrocarbon chains with hydrophilic polar head group. Drug solubility can be increased by the use of lipids by their wetting and dispersion properties. Amphiphilicity is one of the major reasons in increasing bioavailability of the drug molecule. [18]

Solvent: For the preparation of pharmacosomes the solvent must be of high purity and it should be volatile in nature. The solvent with the intermediate polarity that is the polarity between the drug and the phospholipid is selected [19].

Methods of Preparation:

Generally, for the formation of pharmacosomes there is a requirement of drug lipid conjugate. For this purpose, salt form of the drug is converted into acidic form to expose the functional hydrogen atom.

In general, there are four methods of preparation of pharmacosomes they are:

- Solvent evaporation method
- Ether injection method
- Super critical fluid process
- Anhydrous solvent lyophilization method

In general, during the preparation of pharmacosomes solvent evaporation method and Ether injection method are commonly followed. [10]

Solvent evaporation method:

Solvent evaporation method includes the removal of the solvent by the utilization of rotatory evaporator. In this method, firstly a mixture of drug and lipid are dissolved in a volatile organic solvent such as dichloromethane. Thereafter the solvent is evaporated using rotatory evaporator in

round bottom flask which leaves a thin film of solid mixture deposited on the walls of flask. Then dried film is then hydrated with aqueous medium which readily gives a vesicular suspension. [10]

Ether injection method:

Ether injection method is a frequently used method in the preparation of pharmacosomes. In the ether solution an organic solution of the drug & lipid complex is injected slowly into the hot aqueous medium and thus vesicles are readily formed. [10]

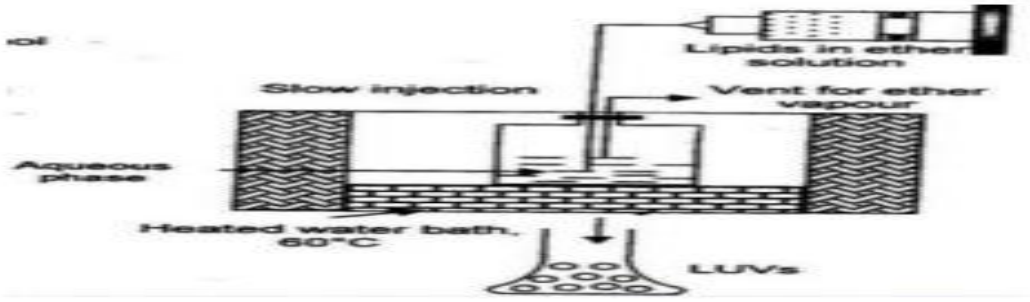

Figure 3 Ether injection method

Super critical fluid process:

This method is known as solution enhanced dispersion by complex supercritical fluid. Drug and lipid complex are premixed in a supercritical fluid of carbon dioxide, then high supersaturation is obtained by passing through the nozzle mixture chamber. The turbulent flow of solvent and carbon dioxide results in fast mixing of dispersion leading to the formation of pharmacosomes. [1]

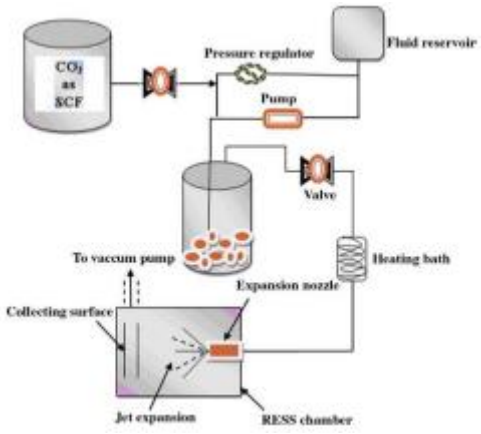

Figure 4 Super critical fluid process

Anhydrous co-solvent lyophilisation method:

This approach involves the dissolving the drug powder and phospholipids in Dimethyl sulfoxide (DMSO) containing 5% glacial acetic acid, after that the mixture is agitated to get clear liquid and freeze dried overnight at condenser temperature. Then resultant complex is flushed with nitrogen & stored at 4 ◦C and so the pharmacosomes are formed. [1]

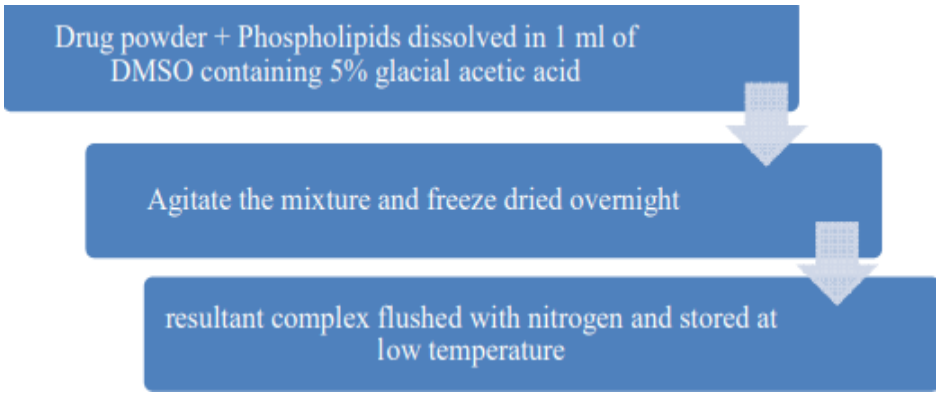

Figure 5 Anhydrous co-solvent lyophilizaion method

Characterization of Pharmacosomes:

Complex determination:

By the means of Fourier transform infrared spectroscopy **[FTIR]** the formation of complex or the conjugate can be determined by correlating the spectrum observed in the complex sample with that of discrete constituents and also with their mixture. [2]

Surface morphology by - SEM / TEM:

These techniques can be used to study the surface morphology of pharmacosomes. the grades and the quality of the materials used during the preparation of pharmacosomes and other variables like method of preparation, vacuum assigned, rotation speed have an impact on the shape and size of the pharmacosomes. The pharmacosomes show greasy nature if they are formulated using low quality lipids can result in large aggregate formation. Those formulated using more than 90% purity grades undergo degradation because of the oxidation this affects the stability of the complex. So, 80% purity phospholipids are commonly used in the pharmacosome preparation. [11]

Drug - lipid compatibility:

Differential scanning calorimetry **[DSC]** is a thermo analytical technique used to determine the drug lipid compatibility and other interactions if any exist. The thermal response is studied using separate samples and heating them in the sample pan which is closed. The temperature is maintained at a specific range at a definite heating rate [10].

Crystal state determination / X-ray powder diffraction studies:

To determine the degree of crystallinity the x-ray powder diffraction studies is performed depending on the relative integrated intensity of the reflection peaks degree of crystallinity is measured [13].

Evaluation of Pharmacosomes:

Drug content:

In order to determine drug content in the drug-lipid complex, the complex with the equivalent to 50mg weight of the drug is weighed and added to the volumetric flask and after that a suitable

solvent is added to the volumetric flask. the solution is stirred for 24 hours. At the end of 2 hours suitable dilutions were made and measured for the drug content by using UV visible spectrophotometer [10,12].

Entrapment efficiency:

To find out the entrapment efficiency of the prepared pharmacosomes 10ml of the prepared pharmacosomes were taken and diluted with 10ml of Phosphate buffer solution of pH 6.8. The resulting solution was sonicated for 10min in bath sonicator. The sonicated mixture was centrifuged at 10,000 rpm for 30 min in a cooling centrifuge at a temperature of 40°C. The entire supernatant liquid was separated and 10ml of phosphate buffer was added to it. The resulting dilution was assayed using UV spectrophotometer. The drug concentration was calculated using calibration curve of the drug and entrapment efficiency was calculated using the formula.

$$EP\ (\%) = [(Ct - Cr)/Ct] \times 100$$

Where EP is the encapsulation percentage,
Ct is the concentration of total drug.
Cr is the concentration of free drug [5].

***In-vitro* dissolution study:**

In vitro dissolution studies for drug complex as well as plain drug should be performed in USP Type II dissolution test apparatus at 75 rpm and at 37ºC. An accurately weighed amount of the complex equivalent to 100 mg of drug should be placed in to 900 ml media (pH 6.8 phosphate buffer). Samples (3 ml each) of dissolution fluid must be withdrawn at different intervals and replaced with the equal volume of fresh media, to maintain sink conditions. Withdrawn samples are diluted suitably and then analysed spectrophotometrically [23].

Table 1: **Different vesicular systems, problems associated with it and advantages of Pharmacosomes over it** [12].

Vesicular system	Structure	Problem associated	Applications	Advantages of Pharmacosomes over other vesicular systems
Liposomes	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	Used in ergosterol membrane, protein synthesis inhibitor, decrease Intra-ocular pressure, inhibition of Prostaglandin, phosphor diesterase, cyclo-oxygenase enzyme inhibitor.	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.
Niosomes	Microscopic lamellar structures of size range between 10 to 1000 nm and mainly composed of biodegradable, and biocompatible surfactants.	Leaching of drug, Time consuming, insufficient stability	Used as anti-cancer, anti-infective agent, anti-inflammatory agent and used in ophthalmic drug delivery, oral drug delivery, transdermal drug delivery, brain targeted delivery system for the vasoactive peptide.	More stable, more efficient
Transferosomes	Ultra deformable vesicles consisting of a lipid bilayer with phospholipids and an edge activator and an ethanol/aqueous core and their size is 300nm	Expensive, Oxidative degradation, lack of purity of natural Phospholipids.	Have the potential for providing controlled release of the administered drug and increasing the stability of labile drugs.	Cheaper, oxidation resistant, pure &natural phospholipids not needed
Ethosomes	Soft, malleable vesicles composed mainly of Phospholipids, ethanol and water having a size range from tens of nanometers to microns.	Poor yield, Loss of product during transfer form organic to water media.	Vesicles of choice for transdermal drug delivery of hydrophilic and impermeable drugs. Used in treatment of AIDS, Diabetes. Parkinson Syndrome.	High yield will be there and loss of drug is not seen.

Table 2: Research works done on Pharmacosomes [12]

S. No	Drug	Solvent	Technique	Result
1	Aceclofenac	Dichloromethane	Solvent evaporation	Improved solubility & dissolution profile
2	Naproxen	Diethyl ether, ethanol, acetone	Ether injection method	Enhancement of solubility and controlled drug release
3	Ketoprofen	Dichloromethane	Conventional solvent evaporation method	Improved solubility and bioavailability
4	Diclofenac	Dichloromethane	Solvent evaporation	Improved solubility and dissolution profile
5	Rosuvastatin	Chloroform, dichloromethane	Solvent evaporation	Sustained drug release and improved bioavailability
6	Etodolac	Acetone, dichloromethane, methanol	Thin film hydration	Increased solubility, entrapment efficiency and sustained drug release
7	Furosemide	Methyl alcohol	Vacuum evaporation	Improved solubility and bioavailability
8	Ornidazole	Dichloromethane, di ethyl ether	Solvent evaporation method, ether injection method	Sustained drug release and improved bioavailability
9	Nimesulide	Dichloromethane	Solvent evaporation method	Improved solubility and dissolution profile
10	Geniposide	Tetrahydrofuran	Vacuum evaporation method	Increase in absorption and permeability
11	Aspirin	Dichloromethane	Solvent evaporation method	Improved solubility and bioavailability
12	Capsaicin	Ethanol	solvent evaporation technique	Showed greater cytotoxicity and potential barrier for cancer therapy
13	Amlodipine	Dichloromethane	Solvent evaporation technique	Sustained drug release
14	Pindolol diglyceride	Acetone, dichloromethane	Thin film hydration method	Three to five times increase in plasma concentration and lower renal clearance
15	Naringenin	Dichloromethane	Solvent evaporation technique	Improved bioavailability
16	Piroxicam	Chloroform	Solvent evaporation technique	Improved bioavailability
17	*Kaempferia galangal* rhizome extract	Ethanol	Conventional solvent evaporation method	Improved bioavailability and analgesic activity
18	Quercetin	Dichloromethane	Solvent evaporation technique	Improved solubility by 12 folds

19	Baicalein	Tetrahydrofuran	discontinuous solvent evaporation method	Improved bioavailability
20	Ibuprofen	Ethanol	Solvent evaporation method	Improved solubility and dissolution profile
21	Acyclovir	Water	tetrahydrofuran injection	Stability from heat, absorbed by plasma protein in blood and reduced haemolytic reaction
22	cholesteryl–adipoyldidanosine (CAD)	Water	tetrahydrofuran injection method	Improved stability
23	Didanosine	Water	tetrahydrofuran injection method	liver targeting and sustained-release effect in the target tissues
24	Bupranolol hydrochloride	Water	covalently linked to 1, 3-dipalmioyl-2- succinyl-glycerol	Enhanced effect on intra ocular pressure in rabbit
25	20(S)-Protopanaxadiol	_	Thin film dispersion method	Showed bioavailability
26	3,5-Dioctanoyl-5-fluoro-2- deoxy uridine	_	Thin layer ultrasonication technique	Improved drug targeting to brain

Application of Pharmacosomes [10]:

1. Enhancement of absorption and permeation of drug.

2. Better stability and shelf life when compared to other vesicular drug delivery systems.

3. The ability of transportation of biological components like proteins and amino acids can be studied.

4. Phytoconstituents such as flavonoids, glycosides, xanthanes etc, shows increase in pharmacokinetic and pharmacodynamic actions.

5. It will improve the therapeutic performance of various drugs.

6. Pharmacosomes have greater degree of selectivity for action on specific target cell.

Conclusion:

Pharmacosomes overcome some of the limitation of liposome, niosomes, transferosomes like oxidation, instability, lack of purity respectively. 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 respectively. It can be given orally, topically, extra or intra vascular.

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