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PHARMACOSOMES: AN OVERVIEW

Thakur Sonam*, Tibrewal Richa,

Jayoti Vidyapeeth Women's University, Jaipur, Rajasthan, India.

ABSTRACT

Pharmacosomes are the colloidal dispersions of drugs covalently bound to lipids and may exist as ultrafine vesicular, micellar or hexagonal aggregates, depending on the chemical structure. They are rightly termed as "pharmacosomes" due to the linking of a drug (pharmakon) to a carrier (soma). Pharmacosome may be defined as a 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. Pharmacosomes are amphiphilic lipid vesicular systems that have shown their potential in improving the bio- availability of poorly water soluble as well as poorly lipophilic drugs. drugs pharmacosomes provide an efficient method for delivery of drug directly to the site of infection, leading to reduction of drug toxicity with no adverse effects also reduces the cost of therapy by improved bioavailability of medication, especially in case of poorly soluble drugs. Pharmacosomes are suitable for incorporating both hydrophilic and lipophilic drugs.Pharmacosomes have been prepared for various non steroidal antiinflammatorydrugs, proteins, cardiovascular and antineoplastic.

INTRODUCTION

Pharmacosomes are amphiphilic complexes of drugs (containing an active hydrogen atom) with lipids. The drugs bound either covalently, electrostatically or by hydrogen bonds to lipids. Pharmacosomes are the colloidal dispersions of drugs covalently bound to lipids,and may exist as ultrafine vesicular, micellar, or hexagonal aggregates, dependingon the chemical structure of drug-lipid complex. Pharmacosomes are amphiphilic phospholipid complexes of drugs bearing active hydrogen that bind to phospholipids. Pharmacosomes impart better biopharmaceutical properties to the drug, resultingin improved bioavailability. Pharmacosomes have been prepared for various non-steroidal anti-inflammatory drugs, proteins, cardiovascular and antineoplastic drugs.Developing the pharmacosomes of the drugs has been found to improve the absorption and minimize the gastrointestinal toxicity. A drug possessing a free carboxyl group or an active hydrogen atom (-NH2, -OH, -COOH) can be esterified with or without a spacer chain to the hydroxyl group of a lipid molecule, thereby producing an amphiphilic prodrug. Such a prodrug conjoins hydrophilic and lipophilic properties and thus manifests amphiphilic characteristics. Upon dilution with water, pharmacosomes are generated from these amphiphilic prodrugs. The thought for the development of the vesicular pharmacosome is based on surface and bulk interactions of lipids with drug. Pharmacosomes being amphiphilic compounds facilitate membrane, tissue, or cell wall transfer in the organism. The amphiphilic characters help pharmacosomes to reduce interfacial tension and at higher concentrations exhibit mesomorphic behavior. This decrease in the interfacial tension leads to an increase in the contact area thereby increasing bioavailability of drugs.

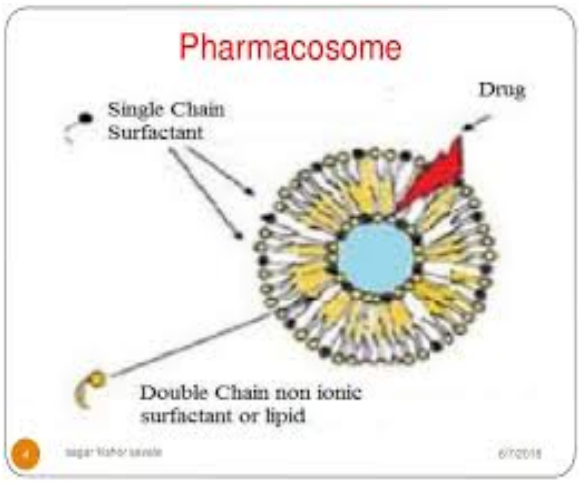

Fig:-1

**Corresponding author: Thakur Sonam |*

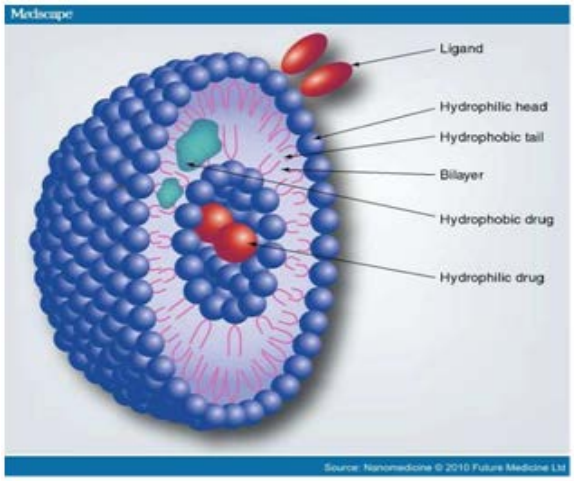

Fig:-2

IMPORTANCE OF PHARMACOSOMES:-

1. Pharmacosomes have some importance in escaping the tedious steps of removing the free unentrapped drug from the formulation.
2. Pharmacosomes provide an efficient method for delivery of drug directly to the site of infection,leading to reduction of drug toxicity with no adverse effects and also reduces the cost of therapy by improved bioavailability of medication, especially in case of poorly soluble drugs.
3. Pharmacosomes are suitable for incorporating both hydrophilic and lipophilic drug.
4. Entrapment efficiency is not only high but predetermined, because drug itself in conjugation with lipids forms vesicles.
5. There is no need of following the tedious,time-consuming step for removing the free, unentrapped drug from the formulation.
6. Since the drug is covalently linked, loss due to leakage of drug,does not take place.
7. No problem of drug incorporation.
8. Encaptured volume and drug–bilayer interaction do not influence entrapment efficiency, in case of pharmacosomes.

MERITS OF PHARMACOSOMES:-

1. Pharmacosomes provide an efficient method for delivery of drug directly to the site of infection, leadingto reduction of drug toxicity with no adverse effects and also reduces the cost of therapy by improved bioavailability of medication, especially in case of poorly soluble drugs. Pharmacosomes are suitable for incorporating both hydrophilic and lipophilic drugs. The aqueous solution of these amphiphiles exhibits concentration dependent aggregation.
2. Entrapment efficiency is not only high but also predetermined, because drug itself in conjugation with lipids forms vesicles and covalently linked together.
3. Unlike liposomes, there is no need of following the tedious, time-consuming step for removing the free, unentrapped drug from the formulation.
4. Since the drug is covalently linked, loss due to leakage of drug, does not take place. However, loss may occur by hydrolysis.
5. No problem of drug incorporation.
6. 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.
7. 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).
8. Pharmacosomes are zwitter ionic, amphiphilic, stoichiometric complexes of polyphenolic compounds with PLs. Unlike other lipid based delivery system, pharmacosomes shows better result in many ways.
9. High and predetermined drug loading
10. Deliver drug directly to the site of infection.
11. Reduction in adverse effects and toxicity.
12. Stable and efficiency due to covalent linkage
13. Size, functional groups (drug molecule), chain length (lipids) and spacer decides the degradation velocity into active drug molecule.

DEMERITS OF PHARMACOSOMES:

1. Synthesis of a compound depends upon 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

LIMITATIONS OF PHARMACOSOMES:-

1. A compound can be synthesised depending on the amphiphilic nature.
2. They require superficial as well as mass drug-lipid interaction.

3. Covalent type of bond is required to restrict drug leakage.
4. Pharmacosomes are susceptible to get fused, aggregate, or hydrolyse by chemicals on storage.

SALIENT FEATURE OF PHARMACOSOMES:-

- The physical and chemical traits of the conjugate control the stability of the whole system.
- As they consist of both water-loving and fat-loving properties, they have an ease of passing through the cell membrane, walls, or tissues either by the action of endocytosis or exocytosis.
- The rate of degradation relies on size, nature of functional group present in the drug molecule, fatty acid chain length in lipids, presence, or absence of spacer. All these factors can be varied to optimize in vivo pharmacokinetic behaviour.
- They can be administered via topical, oral, extra- or intravascular route.

COMPONENTS OF PHARMACOSOMES:-

TABLE: 1

Component	Requirement
Drugs	Functional hydrogen atom from amino, carboxyl, or hydroxyl group that can be esterified
Solvents	High purity, volatile, and intermediate polarity
Lipid	Phospholipids-phosphoglyceride or sphingolipids

CHARETERIZATION OF PHARMACOSOMES:-

1. Complex Determination
2. Stability of Pharmacosomes
3. Scanning Electron Microscopy/Transmission Electron Microscopy
4. Solubility
5. Drug-Lipid Compatibility
6. Crystalline State Measurement
7. Dissolution Studies

1.Complex deremination: With the help of FTIR spectrum, the formation of the complex or the conjugate can be determined by correlating spectrum observed in complex sample with that of discrete constituents and also with their mixture.

2. Stability of pharmacosomes:- 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.

3. Scanning electronmicroscopy/transmission electron microscopy:- To detect the surface morphology of the pharmacosomes,SEM of the complex was recorded on a scanning electronmicroscope. Scanning electron microscopy detect the surface morphology of pharmacosome.

4. Solubility:- The modification in solubility caused by complexation can be evaluated using shake-flask technique. In this technique, the organic phase, that is, 1-octanol and aqueous phase, that is, buffer solution at appropriate Ph consisting of drug-phospholipid conjugate are consorted,
and after constant shaking, equilibrium is maintained at a temperature of 37◦ C for 1 day.The aqueous phase is separated and then concentration is determined using UV or HPLC technique.

5. Drug- liquid compatibility:- Differential scanning calorimetry is a thermoanalytical technique utilised to determine drug-lipid compatibility and their interactions, if any. The thermal response is studied using separate samples and heating them in a sample pan which is closed. The nitrogen gas is purged, and the temperature is maintained in a definite range with a specific heating rate.

6. Crystalline structure management:- The crystalline nature of drug can be determined using X-ray diffraction technique. The tube voltages and tube current can be regulated in the X-ray generator. Copper lines may be used as the source of radiation. The scan angle can be regulated. The overall combined intensity of all reflection peaks is projected by area under curve of X-ray powder diffraction pattern that specifies the specimen attributes.

7. Dissolution studies:- Dissolution studies, in vitro are done using various models available for the purpose. The results are assessed on the basis of apprehended activity of the active constituents therapeutically.

Method of Preparation of PHARMACOSOMES:- Pharmacosomes are usually self vesiculating. The two well established procedures for preparation of pharmacosomes are:

1. Hand-shaking method:-In hand-shaking method, the dried film of drug lipid complex deposited in a round bottom flask upon hydration with aqueous medium readily gives vesicular suspension. In the

drug lipid complex usually, lecithin is added many a times to reduce surface tension of the complex, so when reconstituted in an aqueous medium gives good surface wetting properties. Water is usually used as an aqueous phase

2. Ether injection method:- In ether injection method, organic solution of drug lipid complex was injected slowly into the aqueous medium, wherein the vesicles were readily formed. Here the drug lipid complex is mixed with ether which acts as a solvent and then it is slowly injected in the aqueous medium and spontaneous formation of vesicles takes place.

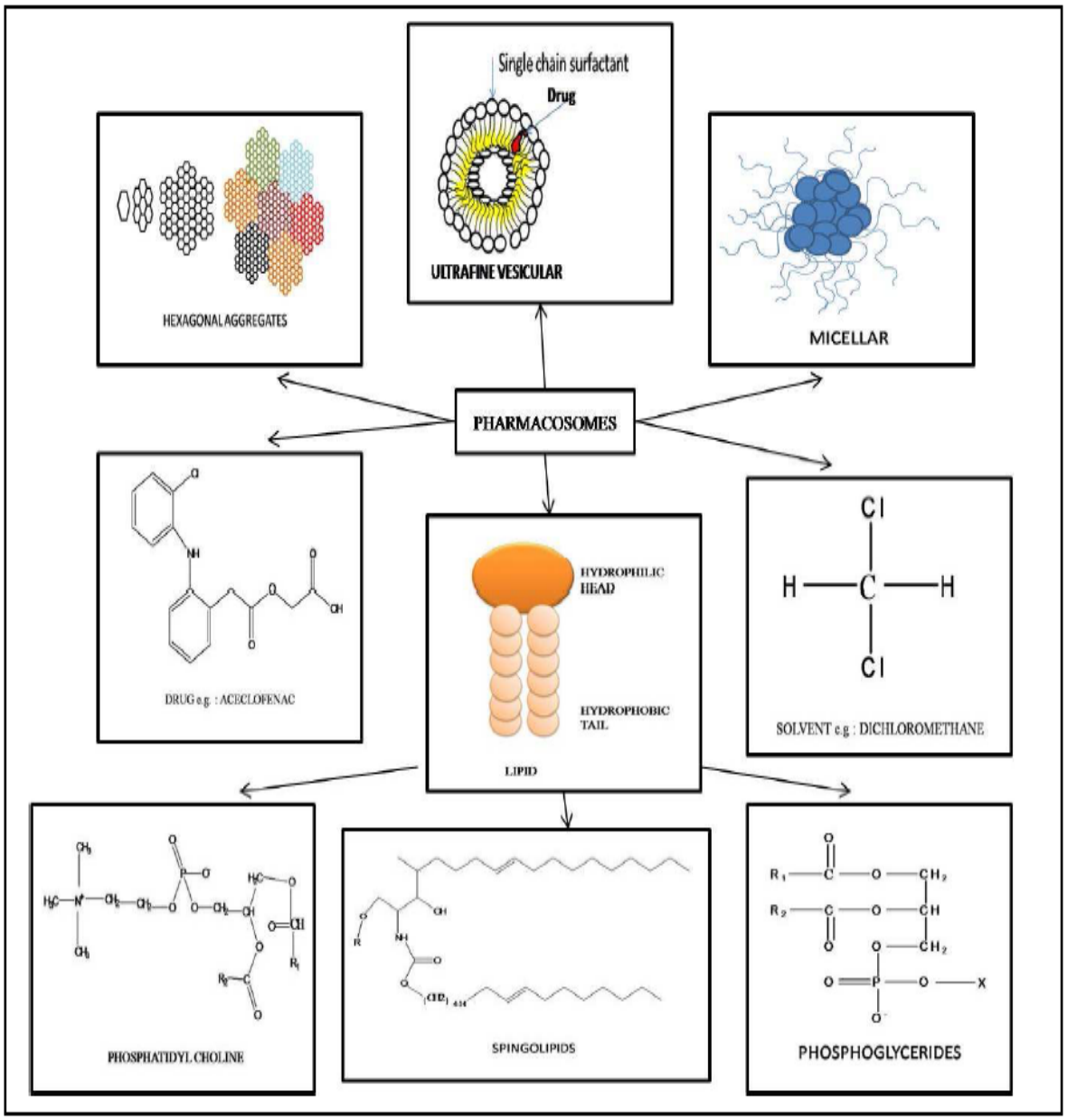

Fig:-3

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 round bottomed flask and dissolved in dichloromethane. The solvent was evaporated under vacuum at 40°C in a rotary vacuum evaporator.

Different evaluation techniques used for Pharmacosomes:-

TABLE:-2

Parameters	Techniques and instrument
Size and size distribution	For measurement of the drug lipid complex
Shape & surface morphology	Scanning electron microscopy(SEM) Transmission electron microscopy (TEM)
Conformation of complex formation	Atomic Force Microscopy (AFM)
State of phospholipid complex.	DSC differential scanning calorimetery X-ray powder diffraction studies
In vitro dissolution studies	Dissolution test apparatus Shake-flask method
Solubility study	Infrared Spectroscopic Analysis
Formation of the complex	Nuclear magnetic resonance (NMR) spectroscopy *13 C-NMR*
Drug content	UV-Visible spectrophotometer

APPLICATION OF PHARMACOSOMES:-

1. Pharmacosomes demonstrate a wider stability profile and greater shelf life.
2. Pharmacosomes have the capacity to augment drug absorption and its transport. Using response surface design, and colleagues optimised the formulated geniposide pharmacosomes and examined their attributes. The ratio of phospholipid to drug, temperature of reaction mixture and concentration of drug were found to be 3, 50 C and 5.5mg/mL, respectively.
3. 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.
4. Pharmacosomes can improve the rate of permeation by improving the membrane fluidity. The transition temperature of vesicles in the form of vesicles and micelles might pose an evident effect on vesicular interaction with biomembrane, hence improving the transfer of drug across membrane.
5. 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 biomemebranes thereby improve the membranes fluidity leading to enhance permeations.
6. The approaches has successfully improved the therapeutic, performance and various drug i.e. pindolol diglyceride , amoxicillin, taxol , cytarbin ,dermatansulfate , bupranolol hydrochloride etc.
7. 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.
8. Tetra hydro furan injection method and concluded that pharmacosomes elicit liver targeting and sustained release effect in target tissue.
9. Isoniazide pharmacosomes have improved permeability and macrophage targeting.
10. Pharmacosomes also improve the biopharmaceutical properties of biologically active phytoconstituents such as flavones, glycosides, xanthones.

CONCLUSION:

Pharmacosomes is not only having high entrapment efficiency but it can be predetermined, because drug itself in conjugation with lipids forms vesicles. The approach of pharmacosomal drug delivery possesses many advantages over conventional vesicular systems. Pharmacosomes have immense potential, and further advantages of the vesicular system can be exploited by extending 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.

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