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PHARMACOSOMES: A NOVEL DRUG DELIVERY SYSTEM

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ABSTRACT

Pharmacosomes are colloidal dispersion of drugs covalently bound to lipids and may exist as ultrafine vascular, micellar or hexagonal aggregates, depending on the chemical structure of drug-lipid complex. Pharmacosomes are the amphiphilic phospholipid complexes of drug bearing active hydrogen that bind to phospholipid. It is based on the principle that the drug binds covalently to a lipid where the resulting compound is the carrier and the active compound at the same time. The physicochemical properties depend on drug as well as the lipid. They are mainly prepared by hand-shaking and ether injection method. The Pharmacosomes were evaluated for different parameters such as size, NMR, surface morphology and invitro release rate. This review describes all aspect 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 anti-neoplastic drugs.

KEYWORDS: Pharmacosomes, Vesicular, Amphiphilic, Phospholipid.

INTRODUCTION

Pharmacosomes are amphiphilic complexes of drugs (containing an active hydrogen atom) with lipids. The drug 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, miceller, or hexagonal aggregates, depending on the chemical structure of drug-lipid complex. Pharmacosomes are amphiphilic phospholipid complexes of drugs bearing active hydrogen that bind to phospholipids$_1$. Pharmacosomes impart better biopharmaceutical properties to the drug, resulting in improved bioavailability. Pharmacosomes have been prepared for various non-steroidal anti-inflammatory drugs, proteins, cardiovascular and anti-neoplastic drugs. Developing the Pharmacosomes of the drugs has been found to improve the absorption and minimize the gastrointestinal toxicity. 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.[2]

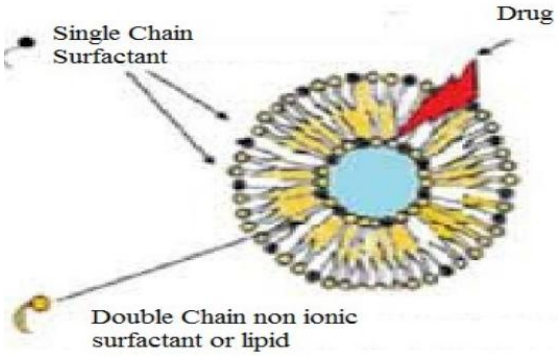

Figure 1: Ethosomes.

Pharmacosomes:-Pharmacosomes are defined as "the colloidal dispersion of drug covalently bound to lipids, and many exist as an ultrafine vesicular micellae or hexagonal aggregates depending upon the chemical structure of drug-lipid complex." The term "Pharmacosomes" is derived from pharmacon, the active principle and soma, the carrier. The idea for the development of vesicular pharmacosomes is based on serface and bulk interaction of lipids with water. Any drug possessing an active hydrogen atom (-COOH, -OH, -NH2, etc.) can be esterified to the lipid with or without spacer chain. Synthesis of such compound many be guided in such a way that strongly amphiphilic compound results, which will facilitate membrane, tissue or cell well transfer in the organism.[3]

Principle:-It is based on the principle that the drug binds covalently to a lipid where the resulting compound is the

carrier and the active compound at the same time. The physicochemical properties depend on drug as well as the lipid.[4]

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 dugs.
3. Pharmacosomes are suitable for incorporating both hydrophilic and lipophillic drugs.
4. Entrapment efficiency is not only high but predetermined, because drug itself in conjugation with lipids forms vesicals.
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 interactions do not influence entrapment efficiency, in case of Pharmacosomes.
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10. Encaptured volume and drug-bilayer interactions do not influence entrapment efficiency, in case of Pharmacosomes.
11. The drug is released from pharmacosome by hydrolysis (including enzymatic).
12. The physicochemical stability of the pharmacosome depends upon the physicochemical properties of the drug-lipid complex.[5,6]

Merits of Pharmacosomes

1. 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. Pharmacosomes are suitable for incorporating both hydrophilic and lipophilic drugs. The aqueous solution of these amphiphilic exhibits concentration dependent aggregation.
2. Reduction in adverse effects and toxicity.
3. Deliver drug directly to the site of infection.
4. Stable and efficiency due to covalent linkage.
5. Size, functional groups (drug molecule), chain length (lipids) and spacer decides the degradation velocity into active drug molecule.[7]

Demerits of Pharmacosomes

1. Synthesis of a compound depends upon its amphiphilic nature.
2. Required covalent bonding to protact the leakage of drugs.
3. Required surface and bulk interaction of lipids with drugs.
4. On storage, undergo fusion and aggregation, as well as chemical hydrolysis.[8]

Limitations of Pharmacosomes

1. A compound can be synthesized depending on the amphiphilic nature.
2. Covalent type of bond is required to restrict drug leakage.
3. They require superficial as well as mass drug-lipid interaction.
4. Pharmacosomes are susceptible to get fused, aggregate, or hydrolyse by chemicals on storage.[9]

Salient feature of Pharmacosomes

- The physical and chemical traits of the conjugate control the stability of the whole system.
- The drug is released from pharmacosome by hydrolysis (including enzyme).
- There is no problem of drug incorporation in the body of the patient.
- 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 beaviour.
- 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.
- 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.
- They can be administered via topical, oral, extra or intra-vascular route.[10]

Table 1: Components of Pharmacosomes.

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

Characterization of Pharmacosomes

1- Complex determination
2- Solubility
3- Scanning Electron Microscopy/Transmission Electron Microscopy
4- Stability of Pharmacosomes
5- Crystalline state measurement
6- Drug-Lipid compatibility
7- Dissolution studies

1- **Complex determination:-** 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.[11]
2- **Solubility:-**The modification in solubility caused by complexation can be evaluated using shake-flask technique.
3- **Scanning electron microscopy/transmission electron microscopy:-**To detect the surface morphology of the Pharmacosomes, SEM of the complex was recorded on the scanning electron-microscope. Scanning electron microscopy detect the surface morphology of pharmacosome.
4- **Stability of Pharmacosomes:-**Solubility of the drug, Phospholipids, their physical mixture and the pharmacosomes can be determined. The apparent coefficient can be determined by the shake-flask method.
5- **Crystalline structure measurement:-**The crystalline nature of drug can be determined using X-ray diffraction technique.
6- **Drug-Lipid compatibility:-**Differential scanning calorimetry is a thermo-analytical technique utilized to determine drug-lipid compatibility and their interaction, if any.
7- **Dissolution studies:-**Dissolution studies, in-vitro are done using various models available for the purpose. The result are assessed on the basis of apprehended activity of the active constituents therapeutically.[12]

Method of preparation of pharmacosomes

Pharmacosomes are usually self vesiculating. The two wall established procedures for preparation of pharmacosomes.

- Hand-shaking method
- Ether injection method

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.[13]

Ether injection method:-In ether injection method, organic solution of drug-lipid complex was injected slowly into the aqueous medium, wherein the vesicals 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 vesicals takes place.[14]

Evalution of pharmacosomes

- **Size:-**The size of vasicals is in the nanorange. The size of the vasicals is usually measured using an instrument known as Zetasizer XS. The principle of this instrument is based on scattering of light. The light ray is passed through the solution containing the vecicals. The size of the vasicals is then measured on the basis of scattered of light.
- **In vitro release rate:-**In the bulk equilibrium reverse dialysis bag technique described here, emulsion is introduced inside the dialysis bag and the continuous (receiver) phase is placed outside. Dialysis bags containing the continuous phase (receiver phase) alone are suspended in a vessel containing the doner phase (diluted emulsion) and the system is stirred. At predetermined time intervals, each dialysis bag is removed and the contents are analyzed for released drug. An advantages of the technique is the increase in the membrane surface area available for transport from the donor to the receiver phases. Another advantage of this method is the increased efficiency in terms of staffing as a consequence of the reduction in the number of steps.[15]
- **Nuclear magnetic resonance:-**Nuclear magnetic resonance (NMR) is the name given to a physical resonance phenomenon involving the observation of specific quantum mechanical magnetic properties of an atimic nucleus in the presence of an applied, external magnetic field.

The principle of NMR usually involves two sequential steps:

- The alignment (polarization) of the magnetic nuclear spins in an applied, constant magnetic field.
- The perturbation of this alignment of the nuclear spines by employing an electro-magnetic, usually radio frequency is dependent upon the static magnetic field and the nuclei of of servation.

NMR spectroscopy is one of the principle techniques used to obtain physical, chemical, electronic and structural information about molecules due to either the chemical shift Zeeman Effects, or the Knight Shift effect, or a combination of both, on the resonant frequencies of the nuclei present in the sample. It is a powerful technique that can provide detailed information on the topology, dynamics and three-dimensional structure of molecules in solution and the solid state.[16]

Surface morphology:- The scanning electron microscope (SEM) is a type of electron microscope that

images the sample surface by scanning it with a high-energy beam of electrons in a raster scan pattern. The electrons interact with the atoms that make up the sample producing signals that contain information about the samples surface topography, composition and other properties such as electrical conductivity.

Table 2: Comparison between Liposomes and Pharmacosomes.

Liposomes		**Pharmacosomes**
Principle	In corporation of drug in the aqueous or lipid phase of a mixture of lipid where the physicochemical properties of the carrier and release of drug will be functions of different lipids used.	Covalent binding of a drug to a lipid where the resulting compound is the carrier and the active compound at the same time. The physicochemical properties depend on drug as well as the lipid.[6]
Loss of drug	Through leakage	No leakage, since drug is covalently bound but loss of drug by hydrolysis is possible.
Manufacturing	Cast fill method Extrusion/sonication Injectable method Reverse phase evaporation etc.	Self dispersion through moderate mixing and sonication.[7]
Separation of free drug	By gel filtration, dialysis, ultrafilteration, ultracentrifugation.	Not necessary since the drug covalently linked.
Volume of inclusion	Decisive in incorporation of drug molecules.	Irrelevant, since the drug is covalently bound.
Surface charge	Achieved through lipid combination.	Depends on the physicochemical structure of the drug lipid complex.[11]
Membrane fluidity	Depends on lipid combination and presence of cholesterol fluidity influences the rate of drug release and physical stability of system.	Depends on phase transition temperature of drug lipid complex. No effect on release rate since the drug is covalently bound.[17]
Release of drug	Diffusion through the bilayer, desorption from the surface or release through degradation of liposomes.	Hydrolysis (including enzymatic).
Physical stability	Relatively good Aggregation through double valenced cation.	Depends on physicochemical properties of drug-lipid complex.[18]

Application of pharmacosomes[19,20]

1- Pharmacosomes demonstrate a wider stability profile and greater shelf life.
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.
3- Pharmacosomes have the capacity to augment drug absorption and its transport.
4- Pharmacosomes can improve the rate of permeation by improving the membrane fluidity.
5- 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 vesicals. The drug shows excellent entrapment efficiency and there is minimal loss of drug due to leakage. Pharmacosomes have immense potential, and further advantages of the vesicular system can be exploited by extending this approach to additional drugs.

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