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A UPDATED REVIEW ON PHARMACOSOMES: A NOVEL STRATEGY FOR CONTROLLED DRUG DELIVERY

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RUNNING TITLE: A REVIEW ON PHARMACOSOMES

Abstract

In the arena of solubility enhancement, several problems are encountered. A novel approach based on lipid drug delivery system has evolved, pharmacosomes. Pharmacosomes are novel vesicular drug delivery systems. They are potential alternative to conventional vesicles. Pharmacosomes are the amphiphilic phospholipids complexes of drugs bearing active hydrogen that bind to phospholipids. Similar to other vesicular systems pharmacosomes provide an efficient method for delivery of drug directly in a controlled manner to the site of infection, leading to reduction of drug toxicity with no adverse effects. They also reduces the cost of therapy by improving bioavailability of medication, especially in the case of poorly soluble drugs. This approach as a drug delivery system certainly promises a reliable, safe, selective and precise method of drug delivery. They may exist as ultrafine vesicular, micellar or hexagonal aggregates, depending on the chemical structure. 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. This narrative review describes the fundamental 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.

Key words : Pharmacosomes, Phospholipid, Amphiphilic, Bioavalaibility.

Introduction

Many researchers and scientists have been working on novel drug delivery system from past few decades, with an aim to develop the system. The main purpose for developing this system is to explain the basis of clinical use of these systems, and their economic aspects [1]. An ideal novel drug delivery system should fulfil two factors:

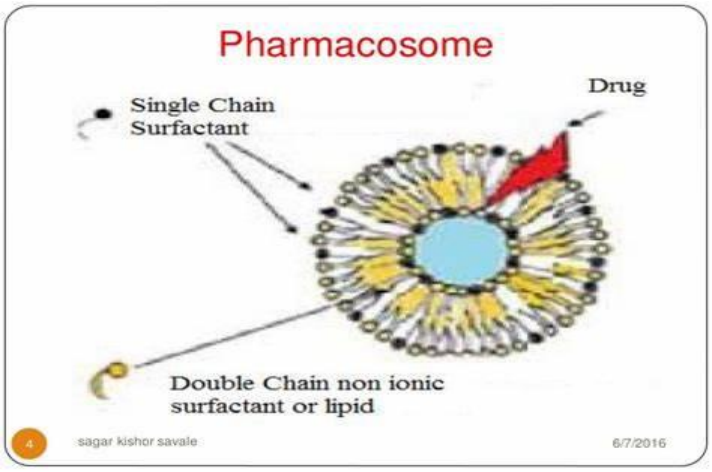
• It should deliver the drug by depending on the body requirements,

• It should deliver the active entity to the target site of action [2] .

The use of this system is to modify the original bio distribution of drugs and to entrap them in sub microscopic drug carriers such as transferosomes, Niosomes, ethosomes, liposomes, Serum proteins, erythrocytes, reverse micelles, monoclonal antibodies, and pharmacosomes [3]. In the recent years, these lipid vesicles were found to have more importance in the field of immunological studies, membrane biology, diagnostic purpose and its techniques and mostly in genetic engineering [4]. Vesicular structures are the systems that prolong the duration of action of the drug in systemic circulation, and reduce toxicity by selective uptake [5] .These vesicles which are developed were first reported in 1965 by Bingham, and these vesicles are named as “Bingham bodies” which play an important role in modelling biological membranes, and in transporting of drug and targeting of drug at site of action [6] .

Pharmacosomes

Pharmacosomes belong to the part of novel drug delivery system. They were first introduced by vaizoglu and Speriser in 1968 [7]. These bear unique advantages over liposome and niosome vesicles and serve as an alternative to conventional vesicles. 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 behaviour.[8] . 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[9]. These systems are formed by linking a drug (pharmakon) to a carrier (soma), so they are called pharmacosomes. After absorption, their velocity of degradation 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 [10], [11] .



Advantages of Pharmacosomes[12]

1.Membrane fluidity has no effect on release rate due to covalent linkage.

2. Leaching of drug does not takes place.

3. Drugs can be delivered directly at the targeted site.

4. Drug releases by hydrolysis.

5. Stable and efficiency due to covalent linkage.

6. Low cost of therapy

7. Hydrophilic and lipophilic drugs are suitable.

8. High and predetermined drug loading.

9. High entrapment efficiency.

10. No need of removing the free un entrapped drug.

11. Improves bioavailability.

12. Reduction in adverse effect and toxicity.

Disadvantages [13]

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.

Salient Features of Pharmacosomes [14]

(a) The physical and chemical traits of the conjugate control the stability of the whole system.

(b) 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.

(c) 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.

(d) They can be administered via topical, oral, extra- or intravascular route.

Components of Pharmacosomes[15]

Drugs

Drugs containing active hydrogen atom (-COOH, OH, NH2) can be esterified to the lipid, with or without spacer chain and they form amphiphilic complex which in turn facilitate membrane, tissue, cell wall transfer in the organisms[16].

Solvents

Organic solvent of analytical grade and intermediate polarity is used in development of pharmacosomes. It must be of high purity and volatile in nature. The phospholipids and the drug must be dissolved in the selected solvent. The selection of solvent depends on

polarity of the drug and the lipid [17] .

Lipids

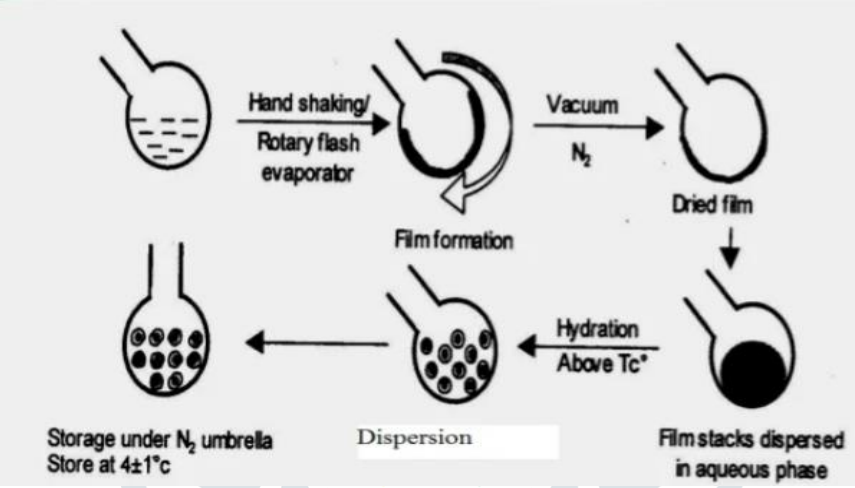
Phospholipids are the major structure component of biological membranes, where two types of phospholipids such as phosphoglycerides and sphingolipids are generally used. The most common phospholipid is phosphotidyl choline moiety. Phosphotidyl choline is an amphiphilic molecule in which a glycerol bridges links a pair of hydrophobic acyl hydrocarbon chains, with a hydrophilic polar head group phosphocholine. Most commercial lecithin products contain 20% phosphatidylcholine. Lecithins containing

phosphatidylcholine can be obtained from vegetables (mainly), animals and microbial sources. Lecithin is also available as a dietary supplement in two forms: as granular lecithin (oil-free refined lecithin with calcium phosphate as a flow agent); and as capsules containing a dispersion in oil[18].

Method of Preparation of Pharmacosomes [19]

1. Hand –Shaking Method :

In the hand-shaking method, a mixture of drug and lipids are dissolved in volatile organic solvent such as dichloromethane in a round bottom flask. The organic solvent is removed at room temperature using a rotary vaccum evaporator, which leaves a thin film of solid mixture deposited on walls of flask. The dried film can then be hydrated with aqueous media and gives a vesicular suspension.



2. Solvent Evaporation Method:

In the solvent evaporation method of preparing the pharmacosomes, the drug is first acidified so that the active hydrogen might be available for complexation. The drug acid is then extracted into chloroform and subsequently recrystallized. The drug-PC complex is prepared by associating drug acid with PC in various molar ratios. The accurately weighed PC and drug acid are placed in a 100 ml round bottom flask and dissolved in sufficient amount of dichloromethane. The mixture is refluxed for one hour. Then the solvent is evaporated off under vacuum at 40°C in a rotary vacuum evaporator. The dried residues are then collected and placed in vacuum dessicator for complete drying.

3. Ether Injection Method:[20]

In this technique, the drug lipid complex is dissolved in an organic solvent. This mixture is then slowly injected into a heated aqueous agent, resulting in the formation of vesicles. The state of amphiphiles depends on the concentration. When the concentration is less, amphiphiles introduce a monomer state but as the concentration is increased, variety of structures may be formed, that is, round, cylindrical, disc, cubic, or hexagon type.

4. Anhydrous Co-solvent Lyophilization Method[21]:

First of all drug and phospholipids are dissolved in solution of dimethyl sulfoxide containing glacial acetic acid. Then mixture is agitated to get clear liquid and then freeze-dried overnight at condenser temperature. The resultant complex is flushed with nitrogen and stored at 4° C.

5. Supercritical Fluid Process[21]:

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 super saturation 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.

Characterisation of pharmacosomes

- **Fourier Transform Infrared Spectroscopy (FTIR)**

With the help of IR spectroscopy the formation of complex can be confirmed by comparing the spectrum of complex with the spectrum of individual components and their mechanical mixture.

- **Surface Morphology [23] :**

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.

- **Stability of Pharmacosomes**:

Correlating the spectrum of complex at various points of time in the solid state with spectrum of dispersion in water consisting of small particles, once the product has been lyophilized, is used to evaluate the stability of the system.

- **Complex Determination :**

The formation of complex and conjugate can be determined by the correlation spectrum observed in complex sample with that of discrete constituents and also with their mixture with the help of FTIR spectrum[24].

- **X-ray Powder Diffraction [25] :**

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.

- **Entrapment efficiency**:

Entrapment efficiency was studied by Ultracentrifugation method. 1ml of invasomal formulation was transferred to Eppendorf tubes, centrifuged at 15000rpm at 4°c for 15 minutes in two cycles to separate the unentrapped drug. The clear fraction was used to determination of free drug. Percentage entrapped is calculated indirectly from the amount of free drug from the formula.[31]

$$\textbf{\textit{Entrapment efficiency}}(\%) = \frac{\textbf{\textit{total drug} - \textit{free drug}}}{\textbf{\textit{total drug}}} \times \mathbf{100}$$

- **Drug Content :**

To determine the drug content in drug – pc complex, complex equivalent to drug weighed and added into volumetric flask with suitable solvent. The solution is mixed by means of magnetic stirrer. After 24 hrs suitable dilutions were done and the drug content is determined UV spectrophotometrically[26].

- **Differential Scanning Calorimetry (DSC) :**

This thermal analytical technique is used to determine the drug-excipients compatibility or interactions. The interaction can be concluded by the elimination endothermic peaks, appearance of peaks and change in peak shape and its onset, peak temperature /melting point and relative peaks area or enthalpy.

- ***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 donor phase (diluted emulsion) and the system is stirred. At predetermined time intervals, each dialysis bag is removed and the contents are analysed for released drug. An advantage of this 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[26].

Applications of Pharmacosomes

- Pharmacosomes possess better stability and shelf life compared to other vesicular drug delivery systems.
- Pharmacosomes used in Targeted drug delivery.
- The mechanism of action of drugs and non-bilayer phases can be studied by using pharmacosomes.
- The mechanism of action of drugs and non-bilayer phases can be studied by using pharmacosomes.
- Phytoconstituents such as flavonoids, glycosides etc., shows both increase in pharmacokinetic and pharmacodynamics actions.
- The ability of transportation of biological components like proteins and amino acids done by using pharmacosomes.
- The approach has successfully improved the therapeutic performance of various drugs i.e. pindolol maleate, bupranolol hydrochloride, taxol, acyclovir etc[27].
- The phase transition temperature of pharmacosomes in the vesicular and micellar state could have significant influence on their interaction with membranes.

- Pharmacosomes can also prepared by incorporating various drugs related to NSAIDs, Anti-fungal, Anti-hypertensive, Anti-cancer, Anti-viral, Diuretics and nucleic acids etc.

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 give orally, topically, extra or intra vascular. In summary, Pharmacosomes represent a highly effective tool for drug delivery in the therapeutic regime of numerous diseases and have the potential to provide more efficacious treatment than conventional drug-delivery platforms. They have a huge potential, thus additional research on this system is necessary to provide more beneficial outcomes.

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