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Pharmacosomes: A Novel Strategy for Controlled Drug Delivery

K R Veena *, S K Savitha
Department of Pharmaceutics, Ezhuthachan College of Pharmaceutical Sciences, Neyyattinkara-695124, TVM, Kerala, India

Abstract

There are several different lipid based vesicular systems have been developed as controlled and targeted drug delivery systems. Pharmacosomes are one of the novel vesicular drug delivery systems. They are potential alternative to conventional vesicular system. Pharmacosomes are the amphiphilic phospholipids complexes of drugs with phospholipids and that 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, and an optimum ratio of polyphenol with phospholipids in a complex form. Pharmacosomes are amphiphilic lipid vesicular systems that having the ability in improving the bio- availability of poorly water soluble as well as poorly lipophilic drugs.

Key words: Amphiphilic, vescicular , micellar, controlled delivery.

INTRODUCTION

The most suitable system is the Novel drug delivery system compared to conventional systems and approachable in developing the drug delivery system which improves the therapeutic efficacy of new as well as pre-existing drugs thus provides controlled and sustained drug delivery to the specific site.

Many systems including liposome, noisome, microspheres, virosomes, microemulsion, monoclonal antibodies, and erythrocytes have demonstrated their potential for application in effective drug delivery. Vesicular system like niosome and liposome has more convenient in controlled drug delivery system.

Vesicular drug delivery system has some of the advantages like,

1. The drug is in systemic circulation reduces the toxicity and can be achieved because of the indirectly delivery of drug to the site of infection.
2. Improves the bioavailability especially in case of poorly soluble drugs.
3. Both hydrophilic and lipophilic drugs can be incorporated.
4. Delays elimination of rapidly metabolizable drugs and thus function as sustained release systems.

The vesicular systems are highly ordered assemblies of one or several concentric lipid bilayers formed, when certain amphiphilic building blocks are confronted with water. The limitations of conventional vesicle system can be overcome by the "Pharmacosome" approach. The prodrug (complex) conjoins hydrophilic and lipophilic 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].

Pharmacosomes are amphiphilic, colloidal dispersions of drugs covalently bound to lipids, and may exists as ultra fine vesicular, micellar, or hexagonal aggregates, depending on the chemical structure of the drug lipid complex. These are the lipid based drug delivery systems that are appropriately elaborated as the colloidal dispersions of drugs having a covalent, electrostatic or hydrogen bonding with lipid. They are rightly termed as "pharmacosomes"due to the linking of a drug (pharmakon) to a carrier (soma)., Pharmacosomes are amphiphilic lipid vesicular systems that have shown their potential in improving the bioavailability of poorly water soluble as well as poorly lipophilic drugs. These amphiphilic drug-lipid complexes are stable and more bioavailable with low interfacial tension between the system and the GI fluid, thereby facilitating membrane, tissue, or cell wall transfer, in the organism. The salient features of pharmacosomes increases entrapment efficiency, easy removal of unentraped drug from the formulation, no loss of drug due to leakage, no problem of drug incorporation and no influence of uncaptured volume and drug-bilayer interaction on entrapment efficiency.

Similar to other vesicular systems 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 reduce 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 due to their amphiphilic property to improve their solubility, bioavailability and minimize the gastrointestinal toxicity of various drugs. So, developing the drugs as pharmacosomes may prove to be a potential approach to improve the bioavailability of drugs and also to minimize the GI toxicity. The amphiphilic characters help pharmacosomes to reduce interfacial tension and at higher concentrations exhibit mesomorphic behaviour. This decrease in the interfacial tension leads to an increase in the contact area thereby increasing bioavailability of drugs[2]. Different structures of pharmacosomes are shown in fig.1.

SALIENT FEATURES OF PHARMACOSOMES

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 depends 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 through topical, oral, extra or intravascular route.

ADVANTAGES OF PHARMACOSOMES

- Pharmacosomes are zwitter ionic, amphiphilic, stoichiometric complexes of polyphenolic compounds with Phospholipids. Unlike other lipid based delivery system, pharmacosomes shows better result in many ways.
- As drug is covalently bound, membrane fluidity has no effect on release rate, but in turn.
- Depends upon the phase-transition temperature of the drug-lipid complex.
- No leakage of drug take place as the drug is covalently linked to the carrier.
- Drug can be delivered directly to the site of infection.
- Drug release from pharmacosomes is by hydrolysis (including enzymatic).
- Their degradation velocity into active drug molecule, after absorption depends very much on the size and functional groups of the drug molecule, the chain length of the lipids, and the spacer.
- Reduced cost of therapy. Suitable for both hydrophilic and lipophilic drugs. The aqueous solution of these amphiphiles exhibits concentration dependent aggregation[3].
- High and predetermined entrapment efficiency as drug and carrier are covalently linked together.
- Drug can be delivered directly to the site of infection.
- Improves bioavailability especially in case of poorly soluble drugs.
- Reduction in adverse effects and toxicity.
- Reduction of cost of the therapy.
- Their degradation velocity into active drug molecule, after absorption depends very much on the size and functional groups of the drug molecule, the chain length of lipids and the spacer.

LIMITATIONS OF PHARMACOSOMES

- Synthesis of a compound depends upon its ampiphilic nature.
- Required covalent bonding to protect the leakage of drugs.
- Pharmacosomes, on storage, undergo fusion and aggregation, as well chemical hydrolysis.
- It requires surface and bulk interaction of lipids with drugs[4].

FORMULATION ASPECTS OF PHARMACOSOMES PREPARATION

Drugs:

Any drug possessing an active hydrogen atom (-COOH, -OH, $-NH_2$) suitable for pharmacosome formulation that can be esterified to the lipid, with or without spacer chain, leading to 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, in the organism . The approach has successfully improved the therapeutic efficacy of a number of drugs i.e. pindolol maleate, bupranolol hydrochloride, taxol, acyclovir.

Lipids:

Lipid is building block of cell membrane. There are three types of phospholipids generally used in pharmacosomes i.e phosphoglycerides and spingolipid and 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.

Solvents :

Pharmacosomes preparation includes the use of highly pure, volatile and intermediate polar solvent.

METHOD OF PREPARATION [3]

In general five methods are employed to prepare the pharmacosomes.

1) Solvent evaporation method / Handshaking 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.

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.

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.

4) Anhydrous co-solvent lyophilization method:

Drug powder and phospholipids dissolved in 1ml 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 and stored at 4^0C.

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[5].

CHARACTERIZATION OF PHARMACOSOMES

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.

2. 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.

3. Scanning Electron Microscopy/Transmission Electron Microscopy:

These techniques can be utilized for studying the surface order of pharmacosomes. The purity grades of the lipid being used and few variables observed during operation (method of preparation, vacuum assigned and rotational speed) alter the shape and size of pharmacosomes. Pharmacosomes are formed of greasy nature if prepared using lower purity grades of lipids resulting in large aggregate formation and those fabricated using lipids of more than 90% purity grade show susceptibility to degradation due to oxidation, which affects complex stability. So, 80% purity grade is the commonly used phospholipid grade.

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 0C for 1 day. The aqueous phase is separated and then concentration is determined using UV or HPLC technique[6].

5) Drug-Lipid Compatibility:

Differential scanning calorimetry is a thermo analytical technique utilized 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[7].

6) Crystalline State Measurement:

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[8].

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 constituent's therapeutically.

8) **Drug-Release Kinetics:**

The kinetics of furosemide release from the Pharmacosomes were determined by fitting the curves to distinct models (summarized in Table no. 1). The criterion for selecting the most appropriate model was based on a goodness-of-fit test[9].

9) *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 analyzed 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[10].

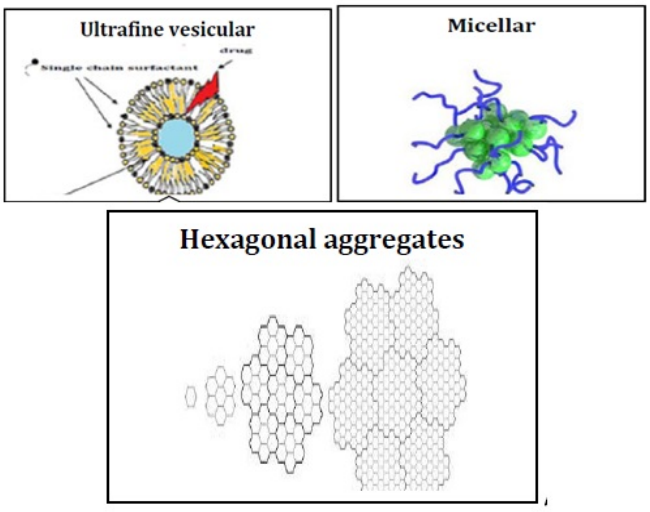

Figure I: Structure of pharmacosome

Table I: Drug Kinetics Models

S.No	Models
1	Zero order kinetics
2	First order kinetics
3	Higuchi Kinetics
4	Ritgar peppas model

Table II: Therapeutic Application of Drugs with Pharmacosomes

Drug	Effect after incorporation in Pharmacosomes
Pindolol diglycerides	Three to five fold increase in plasma concentration lower renal clearance
Amoxycillin	Improved cytoprotection and treatment of H.pylori infections in male rats
Taxol	Improved biological activity
Cytarabin	Improved biological activity

APPLICATIONS OF PHARMACOSOMES[11]

1. Pharmacosomes provides a wider stability profile and greater shelf life.
2. Pharmacosomes have the capacity to augment drug absorption and its transport. Using response surface design, Yue et al. and colleagues optimized 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 0C and 5.5mg/mL, respectively.
3. Pharmacosomes can enhances 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.
4. Khare demonstrated the prominent effect of cascade fusion system of pharmacosomes at appropriate temperature on drug targeting in an organism by applying heating and cooling phenomenon on tissues.
5. Pharmacosomes have achieved a new level by enhancing therapeutic effects of several drugs like pindolol derivative, taxol, bupranolol acid derivative, cytarabin, amoxicillin, dermatan sulphate.
6. Pharmacosomes are the amphiphilic lipid vesicular system, can be used for the development of novel ophthalmic dosage forms. Amphiphilic prodrug forms pharmacosomes, when diluted with tear and modify corneal drug transport and release profile.
7. Pharmacosomes have greater degree of selectivity for action on specific target cells. Raikhman et al. described pharmacosomes as building particles capable in the transport of biologically active substances including nucleic acids and proteins.

CONCLUSION

The pharmacosomes seem to be potential candidate as an oral controlled drug delivery system in this era of novel and controlled drug delivery systems. The developed formulations are expected to improve the patient compliance, form better dosage regimen and provide optimum maintenance therapy to several diseases. Pharmacosomes bearing a unique advantage over liposomes and niosomes vesicles have come up as potential alternative to conventional vesicles. The drug shows excellent entrapment efficiency and there is minimal loss of drug due to leakage. Similar to other vesicular system Pharmacosomes still play an important role in the selective targeting, and the controlled delivery of the controlled delivery of various drugs.

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