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A VITAL ROLE OF PHARMACOSOME'S ON CONTROLLED AND NOVEL DRUG DELIVERY

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ABSTRACT

Various types of lipid based vesicular systems have been developed in controlled and targeted drug delivery system. Pharmacosomes is a novel vesicular drug delivery system, bearing unique advantages over liposome and noisome have come up as potential alternative to conventional vesicles. Pharmacosomes are the amphiphilic phospholipids complexes of drugs bearing active hydrogen that bind to phospholipids. They 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 imparting better biopharmaceutical properties to the drug, resulting in improved bioavailability, especially in case of poorly soluble drugs. This system shows low entrapment efficiency and drug leakage during storage for hydrophilic drugs. They help in controlled release of drug at the site of action as well as in reduction in cost of therapy, drug leakage and toxicity, increased bioavailability of poorly soluble drugs, and restorative effects. Pharmacosomes have advantages over liposomal, transferosomal, and niosomal drug delivery systems. They are mainly prepared by hand-shaking and ether injection method. The Pharmacosomes were evaluated for different parameters such as size, surface morphology and *In vitro* release rate. It is advancing as a method used for delivery of various drugs like non-steroidal anti-inflammatory drugs, cardiovascular drugs, antineoplastic drugs and proteins. This article reviews the potential of pharmacosomes as a controlled and targeted drug delivery system and highlights the methods of preparation and characterization.

KEYWORDS

Pharmacosome's, Advantages, Preparation, Characterization and Applications.

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INTRODUCTION

The novel drug delivery system has been exploited a lot in the past few decades, and attention is also being paid to further develop this system. The two ideal requirements for a system to be novel are: drug delivery at a predetermined rate and for predetermined span of time; conveying the active entity to the target site[1]. The advantages of novel drug delivery system includes: incorporation of therapeutic dose at controlled rate, sustaining drug concentration within an optimal range, optimum

dose at right time and at right location, relationship between maximum efficacy and the dose of drug, minimizes adverse or toxic effects, freedom from frequent dose intake, improved patient compliance[2].

In the recent years, lipid vesicles were found to be of value in immunology, membrane biology, diagnostic techniques and most recently genetic engineering. These vesicles were first reported in 1965 by Bingham, and were given the name "Bingham bodies" which play a major role in modeling biological membranes, and in the transport and targeting of active agents[3]. Lipid vesicles are one type of many experimental models of bio membranes which evolved successfully, as vehicles for controlled delivery for the treatment of intracellular infections, conventional chemotherapy is not effective, due to limited permeation of drugs into cells. This can overcome by the use of vesicular drug delivery systems. Vesicular drug delivery system has some of the advantages like:

Vesicular drug delivery system has some of the advantages like:

- Prolong the existence of the drug in systemic circulation, and perhaps, reduces the toxicity if selective uptake can be achieved due to the delivery of drug directly to the site of infection.
- Improves the bioavailability especially in the case of poorly soluble drugs.
- Both hydrophilic and lipophilic drugs can be incorporated.
- Delays elimination of rapidly metabolizable drugs and thus function as sustained release systems[4,5].

Various approaches have been investigated to improve the absorption and permeation of biologically active constituents of synthetic and natural origin. These include the development of more soluble pro-drug, solid dispersions and complexation with agents such as metals, cyclodextrin and phospholipids (PLs). Apart from other methods used for modifying the solubility, the complexation with PLs has been found to show improvement in both absorption as well as permeation of the active constituents[6-7].

Pharmacosomes as new drug delivery systems were first reviewed by Vaizoglu and Speiser in 1986[8]; Pharmacosomes 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 the drug-lipid complex[5,9].

Pharmacosomes having distinctive compensation over liposome and niosome vesicles have emerged up as potential alternative to conventional vesicles. They are the colloidal dispersions of drugs covalently bound to lipids. Depending upon the chemical structure of the drug–lipid complex they may exist as ultrafine vesicular, micellar, or hexagonal aggregates[9]. Many constraints of various classical vesicular drug delivery systems, such as problems of drug incorporation, leakage from the carrier, or insufficient shelf life, can be avoided by the pharmacosome approach. The idea for the development of the vesicular pharmacosome is based on surface and bulk interactions of lipids with drug. 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 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[9-10].

Salient Features of Pharmacosomes[5]

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.

Advantages of Pharmacosome's[5, 10-13]

- Pharmacosomes are zwitterionic, amphiphilic, stoichiometric complexes of polyphenolic

compounds with PLs. Unlike other lipid based delivery system, pharmacosomes shows better result in many ways[10].

- 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 dependant aggregation.
- High and predetermined entrapment efficiency as drug and carrier are covalently linked together.
- Drug can be delivered directly to the site of infection.
- Drug release from pharmacosomes is by hydrolysis.
- Improves bioavailability especially in case of poorly soluble drugs.
- Reduction in adverse effects and toxicity.
- Reduced cost of 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[5,11-13].

Limitations of Pharmacosome's[14]

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

Materials for Pharmacosomes

There are three essential components for pharmacosomes preparation.

- **Drugs:** Drugs containing active hydrogen atom (-COOH, OH, NH2) can be esterified to the lipid, with or without spacer chain and they forms amphiphilic complex which in turn facilitate membrane, tissue, cell wall transfer in the organisms.
- **Solvents:** For the preparation of Pharmacosmes, the solvents should have high purity and volatile in nature. A solvent with intermediate polarity is selected for pharmacosomes preparations.
- **Lipid:** Phospholipids are the major structure component of biological membranes, where two type of phospholipids generally used phosphoglycerides and spingolipids. The most common phospholipid is phosphotidylcholine molecule. Phosphotidylcholine is an amphipathic molecule in which a glycerol bridges links a pair of hydrophobic acyl hydrocarbon chains, with a hydrophilic polar head group, phosphocholine[15,16].

Preparation of Pharmacosome's

Two methods have been used to prepare vesicles:

❖ The hand-shaking method and

❖ The ether-injection method.

In the hand-shaking method, the dried film of the drug-lipid complex (with or without egg lecithin) is deposited in a round-bottom flask and upon hydration with aqueous medium, readily gives a vesicular suspension. In the ether-injection method, an organic solution of the drug–lipid complex is injected slowly into the hot aqueous medium, wherein the vesicles are readily formed[5,17-18].

An alternative approach for producing pharmacosomes was recently reported in which a biodegradable micelle forming drug conjunct was

synthesized from the hydrophobic drug Adriamycin and a polymer composed of polyoxyethylene glycol and polyaspartic acid. This approach 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[16]. Muller-Goymann and Hamann produced fenoprofen pharmacosomes using a modified technique that involved diluting lyotropic liquid crystals of amphiphilic drugs[19]. Attempts have been made to attach drugs such as β-blockers to various glyceride-like groups, and the resulting amphiphilic molecules have been spontaneously dispersed. They were labelled pharmacosomes because of their tendencies to form unilamellar vesicles and these molecules should enhance lymph transport[20].

Characterization of Pharmacosome's[21]

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[9].

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[17].

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 ^{0}C for 1 day. The aqueous phase is separated and then concentration is determined using UV or HPLC technique[22].

Drug-Lipid Compatibility

Differential scanning calorimetry is a thermoanalytical 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.

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[17].

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[29].

***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[17].

Applications of Pharmacosome's

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, 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 ^{0}C and 5.5mg/mL, respectively[23].
3. 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.
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[24].
5. Pharmacosomes have achieved a new level by enhancing therapeutic effects of several drugs (Table No.1) like pindolol derivative, taxol, bupranolol acid derivative, cytarabin, amoxicillin, dermatan sulphate, and so forth[13, 23, 25].
6. Pharmacosomes, the amphiphilic lipid vesicular system, can be used for the development of novel ophthalmic dosage forms. Amphiphilic prodrug forms pharmacosomes, when diluted with tear[25, 26], and modify corneal drug transport and release profile[27].
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[28].

1. Semalty and colleagues studied the development of pharmacosomes of aceclofenac and evaluated them. A higher drug content was 91.88% (w/w) for 1:1 aceclofenac phospholipid complex and 89.03% (w/w) for 2:1 aceclofenac phospholipid complex. The solubility was higher in case of aceclofenac pharmacosomes than aceclofenac. Moreover, the drug release over 4 hrs of dissolution study was only 68.69% in case of free aceclofenac, while it was 79.78% for 1:1 aceclofenac pharmacosome and 76.17% for 2:1 aceclofenac pharmacosomes for the same span of time[18].
2. Semalty *et al*. studied the development of diclofenac pharmacosome, and it was found that solubility was enhanced in pharmacosomes (22.1 μg/mL) as compared to diclofenac (10.5 μg/mL). Drug release was also improved from 60.4% of diclofenac to 87.8% of diclofenac pharmacosomes after 10 hrs of dissolution study. Observed drug content of diclofenac pharmacosomes was 96.2 ± 1%[29].
3. Han and colleagues optimized the preparation of 20(S)-protopanaxadiol pharmacosomes and observed the encapsulation efficiency of pharmacosome, which was 80.84 ± 0.53 for a diameter of 100.1 nmand 72.76±0.63 for the diameter of 117.3 nm[30].
4. Ping *et al*. prepared didanosine pharmacosomes using tetrahydrofuran injection method and studied the *in vivo* behaviour in rats. It was found that pharmacosomes may be a potential delivery system for prolonged effects in targeted tissues and liver targeting[12].
5. Zhang *et al*. using central composite design, regulated pharmacosomes of 3',5'-dioctanoyl-5-fluoro- 2'-deoxyuridine and observed good targeting efficiency of pharmacosomes *in vivo* and improved drug potential to pass through blood brain barrier [31].
6. Yi-Guang et al. prepared acyclovir pharmacosomes and observed that the plasma proteins in blood absorbed pharmacosomes and interfered with the interactions of erythrocytes and hence reduced haemolytic reaction[32].
7. Semalty *et al*. prepared aspirin-phospholipid complex (1: 1molar ratio) and observed the enhanced bioavailability of aspirin and reduced gastrointestinal toxicity[22].

Table No.1: Therapeutic Application of Drugs after incorporation with Pharmacosomes

S.No	Drug	Effect after Incorporation in Pharmacosomes
1	Pindolol diglyceride	Three to five fold increase in plasma concentration Lower renal clearance[33]
2	Amoxicillin	Improved cytoprotection and treatment of H.pylori infections in male rats[34]
3	Taxol	Improved biological activity[35]
4	Cytarbin	Improved biological activity[36]
5	Dermatan sulfate	Improved biological activity[36]
6	Bupranolol hydrochloride	Enhanced effect on intraocular pressure[37] Enhance lymph transport[38]

CONCLUSION

Pharmacosomes bearing a unique advantage over liposome's 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. Like other vesicular drug delivery systems, Pharmacosomes, on storage, undergo fusion and aggregation, as well chemical hydrolysis. 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. Current research trends are generally based on using different approaches like pegylation, biotinyzation etc. for cellular targeting.

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CONFLICT OF INTEREST

None declared.

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