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A Review on Pharmacosomes.

Sonam Ranga*, Amit Kumar.

Department of Pharmaceutics, Jaipur College of Pharmacy, Sitapura, Jaipur, Rajasthan, India.

Review Article

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*For Correspondence

Department of Pharmaceutics,
Jaipur College of Pharmacy,
Sitapura, Jaipur. Rajasthan,
India.

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ABSTRACT

Various types of lipid based vesicular system have been developed in controlled and targeted drug delivery system. One of the most recent advancements in the domain of solubility enhancement lead to the development of pharmacosomes, a novel lipid based drug delivery system. 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. 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. Pharmacosomes impart better biopharmaceutical properties to the drug resulting into improved bioavailability. The pharmacosomes show greater shelf stability, facilitated transport across the cornea, and a controlled release profile. Pharmacosomes have been prepared for various non-steroidal anti-inflammatory drugs, proteins, cardiovascular and antineoplastic drugs. They are amphiphilic phospholipids complexes of drugs bearing active hydrogen that bind to phospholipids.

INTRODUCTION

The most suitable system is the Novel drug delivery system 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 and meets the real and appropriate drug demand of the body. This is capable of providing the drug to a specific site of action. It is more important it will be reduces the side effects. 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 noisome and liposome has more convenient in controlled drug delivery system. 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 transfersomes can be overcome by the "Pharmacosome" approach. The prodrug 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. Furthermore, the effect of covalent linkages and addition of spacer group on rate of in vivo hydrolysis and subsequent pharmacokinetics is to be exhaustively studied, in order to exploit more advantages of this system. 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. Depending on the chemical structure of the drug-lipid complex, they are defined as colloidal dispersions of drug covalently bound to lipids existing as ultrafine vesicular, micelle, or hexagonal aggregates. Controlled drug-delivery system should be possessing two characteristics: the ability to reach its therapeutic target and the ability to release the active pharmaceutical ingredient in a controlled manner. Pharmacosomes are efficient tool to achieve desired therapeutic goals such as drug targeting and controlled release. Any drug possessing an active hydrogen atom (-COOH, -OH, -NH₂, etc.) can be esterified to the lipid, with or without spacer chain that strongly result in an amphiphilic compound, which will facilitate membrane, tissue, or cell wall transfer, in the organism. 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. 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 pharmacosomes approach. Pharmacosomes bearing unique advantages over liposome and noisome vesicles have come up as potential alternative to conventional vesicles. The system yet requires greater efforts towards investigating the non-bilayer phases, and exploring the mechanism of action. Pharmacosomes bearing unique advantages over liposome and noisome have come up as potential alternative to conventional vesicles. 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. The system yet requires greater efforts towards investigating the non-bilayer phases, and exploring the mechanism of action. Like other vesicular drug delivery systems, pharmacosomes, on storage, undergo fusion and aggregation, as well chemical hydrolysis [1,2,3,4,5].

The Salient Features of Pharmacosomes [6,8,9,2,3]

- Encaptured volume and drug-bilayer interactions do not influence entrapment efficiency, in case of Pharmacosomes.
- Due to their amphiphilic behavior, such systems allow, after medication, a multiple transfer through the lipophilic membrane system or tissue, through cellular walls piggyback endocytosis and exocytosis.
- Unlike liposome, there is no need of following the tedious, time-consuming step for removing the free, untrapped drug from the formulation.
- In the drug is released from pharmacosomes by hydrolysis (including enzymatic). Phospholipids transfer/exchange is reduced, and solubilization by HDL is low.
- No problem occurs in drug incorporation.
- The physicochemical stability of the pharmacosomes depends upon the physicochemical properties of the drug- lipid complex.
- Entrapment efficiency is not only high but predetermined, because drug itself in conjugation with lipids forms vesicles.
- Following absorption, their degradation velocity 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. These can be varied relatively precisely for optimized in vivo pharmacokinetic.

Limitation of Pharmacosomes

- The leakage of drug can be protected by the formation of covalent bond.
- For the synthesis of compound the amphiphilic nature is required.
- The basic principle for pharmacosomes are surface and bulk interaction of lipid with drug
- The pharmacosomes undergo fusion, aggregation as well as hydrolysis when they set on storage.

Merits

These are suitable for both hydrophilic and lipophilic drugs.

- The aqueous solution of these amphiphilic exhibits concentration dependent aggregation
- High and predetermined entrapment efficiency as drug and carrier form a stoichiometrically defined unit covalently linked together.
- Volume of inclusion doesn't influence entrapment efficiency.
- No need of removing the free, untrapped drug from the formulation which is required in the case of liposome.
- 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.
- Improves bioavailability especially in the case of poorly soluble drugs.
- Reduction in adverse effects and toxicity.
- Reduced cost of therapeutics.

Demerits of Pharmacosomes

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

Method of Preparations ^[10, 11]

In general two methods have been employed to prepare pharmacosomes.

- Ether-injection method.
- Hand-shaking method.

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.

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.

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.

At low concentration the amphiphilic exists in the monomer state. Further increase in monomers may lead to variety of structures i.e., micelles of spherical or rod like or disc shaped type or cubic or hexagonal shape. Mantelli et al. compared the effect of diglyceride prodrug on interfacial tension, with the effect produced by a standard detergent dodecylamine hydrochloride, and found similar effect on lowering of surface tension. Above the critical micelle concentration (CMC), the prodrug exhibits mesomorphic lyotropic beh Attempts have been made to attach drugs such as β - blockers to various glycoside-like groups and the resulting amphiphilic molecules have been spontaneously dispersed. They were labeled pharmacosomes because of their tendencies to form unilamellar vesicles and these molecules should enhance lymph transportavior, and assembles in supramolecular structures.

Components of Pharmacosomes

For a delivery system three components are Drugs, solvent and carries (lipid).

Drugs

Any drug processing an active hydrogen atom (-COOH, -OH,-NH₂ etc) can be esterified to the lipid, with or without spacer chain resulting into amphiphilic complexes. These synthesized amphiphilic complexes (pharmacosome), facilitate membrane, tissue, or cell wall transfer, in the organism.

Solvent

An analytical grade organic solvent is required for the preparation of pharmacosome. It must be of high purity and volatile in nature. The PLs and the drug must be dissolved in the selected solvent either simply by its addition or by refluxing. The selection of solvent depends on polarity of the drug and the lipid. A solvent with intermediate polarity is selected for pharmacosome preparation.

Lipids

Lipid or lecithin is the principal molecular building block of cell membranes. It is miscible both in water and in oil / lipid environment and well absorbed orally. Lecithin is a dietary supplement in two forms: as granular lecithin and a capsule, containing dispersion in oil. Comparison by weight of unrefined and refined soy lecithin is given in Table 1.

Table 1: Composition by weight of unrefined and refined soy lecithin

S. No.	Oil-Free Compound	Unrefined Lecithin	Refined Lecithin
1	Phosphatidyl choline	17.5%	23%
2	Phosphatidyl ethanolamine	15.0%	20%
3	Phosphatidyl inositol	10.0%	14%
4	Other phospholipids	14-18%	-
5	Unrefined soy oil	31-34%	0-3%
6	Glycolipids	13-16%	13-16%
7	Neutral lipids (mostly triglycerides)	2-4%	-

Characertization of Pharmacosomes [12,13,14,15,5,6,8]

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 will be determined in the help of FTIR spectrum.

Solubility

With the help of shake –flask Techniques the determination of change in solubility due to complexation can be evaluated .In this techniques solubility of drug acid and drug PC- complex was determined in phosphate buffer 6.8 and n-octanol was also determined. In this technique, the drug acid and n-octanol i.e phosphate buffer at Ph OF drug-phospholipid conjugated are mixed after constant shaking , equilibrium is maintained with the tempetatute of 37 °C for 24 hrs. The separation of aqueous phase is occurring and concentration is determined using UV or HPLC techniques.

Scanning electron mircoscopy

Scanning electron microscopy detect the surface morphology of pharmacosome.

Drug content

To determine the drug content in drug – pc complex , coplex is equivalent to drug was weighed and added into volumetric flask with Ph 6.8 Phosphate buffer . Then volumetric flask was stired for 24 hrs on magnetic stirrer. After 24 hrs suilatble dilution were made and measured for the drug content at 276nm UV spectrophotometrically.

Differential scanning calorimetry

This thermanalytical techniues is used to determine the drug – excipient compatibility intercatons were recorded using a 2910 Modulated Differential Scanning Calorimeter V4.4E.The thermal behaviour was studied by heating 2.0 ± 0.2 mg of each individual sample in a covered sample pan under nitrogen gas flow. The investigatin were carried out over the temperature range 25-250 °C at a heating rate of $10^{\circ}\text{C min}^{-1}$. The intercaton can be concludes by the elimination endothermic peaks, appearance of peaks and change in peak shape and its onset , peak temperatre /melting point and relative peaks area or enthalpy.

X-ray power diffraction (XRPD)

It is performed to detremine the degree of crystallinity by usibg the relative integrated intensity of reflection peaks . The itegrated intensity is given by the area under curves of the XRPD patterns and it represents the specimen charetristics.

Fourier transform infrared spectroscopy (FTIR)

With the help of IR sprctroscopy the formation of complex can be confirmed by comparing the spetrum of complex with the spectrum of indiviual components and their mechanical mixture.In different time interval the stability can be detrmind by comapring the spectrum of complex in solid form with the spectrum of microdispersion in water after lyophilization techniques.

In – Vitro Study

Depending upon the expected therapeutic activity of biologically active constituents, model of in –vivo and in- vitro evaluation have been carried out.

Surface Morphology

With the help of scanning electron mircoscopy(SEM) or transmision electron microscopy (TEM) , the surface morphology can be observed. Purity grades of Phospholipid affected to shape and size of pharmacosome and the process variables such as speed of rotation , vaccum applied or the method used.

Applications

- Greater shelf stability of pharmacosomes.
- When the interaction of the vesicular and micellar take place in the phase transition temperature of pharmacosomes will be significant influence occurring and interact with biomembranes enabling a better transfer of active – ingredients.
- When interaction in change in phase transition temperature of biomembranes thereby improve the membranes fluidity leading to enhance permeations.
- The approaches has successfully improves the therapeutic, performance and various drug i.e pindolo diglyceride, amoxicillin etc.

Table 2: Drug effect after incorporation in pharmacosomes reference

S. No.	Drugs	Effect after incorporation in pharmacosome
1	Pindolol diglyceride	Three to five fold increase in plasma concentration Lower renal clearance
2	Amoxicillin	Improved cytoprotection and treatment of <i>H.pylori</i> infections in male rats
3	Taxol	Improved biological activity
4	Cytarbin	Improved biological activity
5	Dermatan sulfate	Improved biological activity
6	Bupranolol hydrochloride	Enhanced effect on intraocular pressure
7	Pegylation	Improved biological activity
8	Biotinyzation	Improved biological activity

CONCLUSION

Pharmacosomes is not only having high entrapment efficiency but it can be predetermined, because drug itself in conjugation with lipids forms vesicles. The physicochemical stability of the pharmacosome depends upon the physicochemical properties of the drug-lipid complex. Due to their amphiphilic behavior, such systems allow, after medication, a multiple transfer through the lipophilic membrane system or tissue, through cellular walls piggyback endocytosis and exocytosis. Pharmacosomes still play an important role in the selective targeting, and the controlled delivery of various drugs. Pharmacosomes have immense potential, and further advantages of the vesicular system can be exploited by expanding this approach to additional drugs.

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