



PHARMACOSOMES – A REVIEW

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ABSTRACT

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 are the 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. Because the system is formed by linking a drug (pharmakon) to a carrier (soma), they are called pharmacosomes hence the expression "vesicular constructs" in common for pharmacosomes, liposomes, niosomes, and biosomes. They are amphiphilic phospholipid complexes of drugs bearing active hydrogen that bind to phospholipids. 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 antineoplastic drugs. Developing the pharmacosomes of the drugs has been found to improve the absorption and minimize the gastrointestinal toxicity. Pharmacosomes are like a panacea for most of the problems associated with liposomes, transferosomes, niosomes, and so forth. They are an efficient tool to achieve desired therapeutic goals such as drug targeting and controlled release.

Keywords: Pharmacosomes, Amphiphilic, Targeted drug delivery system, Biosomes.

INTRODUCTION

From time immemorial it has been the endeavour of the physician and the Apothecary to provide patients with the best possible forms of medicines so that recovery from disease is faster and complete. The drugs are delivered in a suitable formulation keeping in view the safety, efficacy and acceptability among other factors, and the formulation is usually known as dosage form or drug delivery system. With the progress in all spheres of science and technology, the dosage forms have evolved from simple mixtures and pills to the highly sophisticated technology intensive drug delivery systems, which are known as Novel Drug Delivery Systems (NDDS).

Quest for New Drug Delivery System (NDDS) has got new impetus since early eighties to have improved therapeutic outcome from the same drug, because the NDDS have several advantages over the conventional dosage form¹⁻¹⁵. Since then several NDDS have been developed and it constitute a sizable portion of the global market. Indian researchers have shifted their interest towards NDDS since early eighties¹⁶⁻²⁰. The driving force behind the development of NDDS has been two-fold. First, the obvious clinical advantages of these systems, and Second, their economic aspects. The NDDS have been and are being developed in order to attain greater control over a drug's pharmacokinetics and pharmacodynamics after administration so that the dosage forms thus produced would be highly effective, safe and better than the conventional products. Often, reformulation of an old drug in a NDDS rejuvenates clinical interest in the drug, thus adding to its effective market life²¹⁻²². This brings us to the economic aspects of NDDS.

The rate of release of a drug is a function of its intrinsic solubility and influenced by particle size, crystallinity, drug derivatization and formation of more-soluble complexes. Various approaches have been investigated to improve the absorption and permeation of biologically active constituents of synthetic and natural origin. These include, development of more soluble prodrug, solid dispersions, preparing complexes with complexing agents like metals, cyclodextrin and phospholipids. Apart from other methods used for modifying the solubility, the complexation with phospholipids have been found to show improvement in both absorption as well as permeation of the active constituent. Phospholipids (phosphatidyl choline) play a major role in drug delivery due to its amphiphilic nature, which can modify the rate of drug release for the enhancement of drug absorption across biological barriers. Developing of amphiphilic drug-lipid complexes or pharmacosomes may prove to be a potential approach for improving therapeutic efficacy of the drugs by improving the bioavailability (through improvement in solubility in GI fluid and permeation across the biomembranes).

An ideal controlled drug-delivery system should possess two characteristics: the ability to reach its therapeutic target and the ability to release the active pharmaceutical ingredient in a controlled manner². One way to modify the original biodistribution of substances is to entrap them in submicroscopic drug carriers such as liposomes, transferosomes, niosomes, polymeric nanoparticles, serum proteins, immunoglobulins, microspheres, erythrocytes, reverse micelles, monoclonal antibodies, and pharmacosomes^{3,4}. However, these vesicular systems are associated with many problems like externally



triggered carriers load drug passively which leads to low drug-loading efficiency and drug leakage in preparation, preservation, and transport *in vivo*. So these 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. The prodrug conjoins hydrophilic and lipophilic properties, thus acquires amphiphilic characters, and therefore found to reduce interfacial tension, and at higher concentrations exhibits mesomorphic behaviour^{1,5}.

MERITS

- Suitable for both hydrophilic and lipophilic drugs.
- The aqueous solution of these amphiphiles 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 liposomes.
- 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 therapy⁶⁻⁸.

PREPARATION

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.

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 conjunct⁹. Muller-Goymann and Hamann produced fenoprofen pharmacosomes using a modified technique that involved diluting lyotropic liquid crystals of amphiphilic drugs¹⁰.

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 transport¹¹.

FORMULATION OF PHARMACOSOMES

Drug salt was converted into acid form to provide an active hydrogen site for complexation. Drug acid was prepared by acidification of aqueous solution of a drug salt, extraction with chloroform and subsequent recrystallization. Drug-PC complex was prepared by associating drug acid with an equimolar concentration of PC. Equimolar concentration of pc and drug acid were placed in round bottomed flask and dissolved in dichloromethane. The solvent was evaporated under vacuum at 40°C in a rotary vacuum evaporator. The pharmacosomes were collected as the dried residue and placed in a vacuum desiccator overnight and then subjected to characterization.

ENHANCED THERAPEUTIC ACTIVITY

The approach has successfully improved the therapeutic performance of various drugs i.e. pindolol maleate, bupranolol hydrochloride, taxol, acyclovir, etc^{12,13}. Zhang and Wang proved that the pharmacosomes can improve the ability of a drug to cross the blood-brain barrier and act as a promising drug-targeting system for the treatment of central nervous system disorders¹⁴. In another study, *in vivo* behaviour of didanosine pharmacosomes was evaluated in rats. The study revealed liver targeting and sustained-release effect in rats after *i.v.* administration. It was also found that there was targeting in the lung and spleen and that drug elimination from the target tissues was slow¹⁵.

Moreover, the incorporation of NSAIDs with phospholipids has been also suggested to improve GI safety of these drugs. It has been reported that the diffusion of NSAIDs across lipid membranes and into



target cells is accelerated when it is present as a complex with phosphatidylcholine (PC) (Lichtenberger et al., 1995). Therefore, developing the drugs as lipid complexes (pharmacosomes) may prove to be a potential approaches to improve solubility and to minimize the GI toxicity of NSAIDs.

EVALUATION OF PHARMACOSOMES

These are evaluated for the following parameters:

Solubility

To determine the change in solubility due to complexation, solubility of drug acid and drug-PC complex was determined in pH 6.8 phosphate buffer and n-octanol by the shake-flask method.

Drug acid (50 mg) (and 50 mg equivalent in case of complex) was placed in a 100-mL conical flask Phosphate buffer pH 6.8 (50 mL) was added and then stirred for 15 minutes. The suspension was then transferred to a 250 mL separating funnel with 50 mL n-octanol and was shaken well for 30 minutes. Then the separating funnel was kept still for about 30 minutes. Concentration of the drug was determined from the aqueous layer spectrophotometrically at 276 nm.²³

Drug content

To determine the drug content in pharmacosomes of drug (e.g: diclofenac-PC complex), a complex equivalent to 50 mg diclofenac was weighed and added into a volumetric flask with 100 mL of pH 6.8 phosphate buffer. Then the volumetric flask was stirred continuously for 24 h on a magnetic stirrer. At the end of 24 h, suitable dilutions were made and measured for the drug content at 276 nm UV spectrophotometrically

Scanning electron microscopy (SEM)

To detect the surface morphology of the pharmacosomes, SEM of the complex was recorded on a scanning electron microscope.

Differential scanning calorimetry (DSC)

Thermograms of drug acid, phosphatidylcholine (80 %) and the drug -PC complex were recorded using a 2910 Modulated Differential Scanning Calorimeter V4.4E (TA Instruments, USA). 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 investigations were carried out over the temperature range 25-50°C at a heating rate of 10°C/ min.

X-ray powder diffraction (XRPD)

The crystalline state of drug in the different samples was evaluated using X-ray powder diffraction. Diffraction patterns were obtained on a Bruker Axs-D8 Discover Powder X-ray diffractometer, Germany. The X-ray generator was operated at 40 kV tube voltages and 40 mA tube current, using lines of copper as the radiation source. The scanning angle ranged from 1 to 60° of 2q in the step scan mode (step width 0.4°C/ min). Drug acid,

phosphatidylcholine 80% (Lipoid S-80) and the prepared complex were analyzed.

Dissolution study

In vitro dissolution studies of drug PC complex as well as plain diclofenac acid were performed in triplicate in a USP (8) six station dissolution test apparatus, type II (Veego Model No.6 DR, India) at 100 rpm and at 37°C. An accurately weighed amount of the complex equivalent to 100 mg of drug acid was put into 900 mL of pH 6.8 phosphate buffer.

Samples (3 mL each) of dissolution fluid were withdrawn at different intervals and replaced with an equal volume of fresh medium to maintain sink conditions. Withdrawn samples were filtered (through a 0.45-mm membrane filter), diluted suitably and then analysed spectrophotometrically at 276 nm.²⁴

CONCLUSION

Vesicular systems have been realized as extremely useful carrier systems in various scientific domains. Over the years, vesicular systems have been investigated as a major drug delivery system, due to their flexibility to be tailored for varied desirable purposes. In spite of certain drawbacks, the vesicular delivery systems still play an important role in the selective targeting, and the controlled delivery of various drugs. Researchers all over the world continue to put in their efforts in improving the vesicular system by making them steady in nature, in order to prevent leaching of contents, oxidation, and their uptake by natural defence mechanisms.

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