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# VESICULAR DRUG DELIVERY SYSTEM (PHARMACOSOMES): A REVIEW

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## ABSTRACT

Numerous issues arise in the field of solubility augmentation. Pharmacosomes, a revolutionary lipid-based medication delivery method, have emerged. Pharmacosomes can be hexagon-shaped assemblies of colloidal drug dispersions covalently bonded to the phospholipid, or they can be colloidal, nanometric size micelles or vesicles. Because of their special qualities, which include tiny size, amphiphilicity, active drug loading, high entrapment efficiency, and stability, they function as suitable carriers for the precise delivery of pharmaceuticals. They aid in reduced therapy costs, drug leakage and toxicity, enhanced bioavailability of poorly soluble medications, and restorative benefits in addition to helping with regulated release of the drug at the site of action. The range of applications for this delivery technology has expanded to include many herbal medications as well as medications for cancer, heart conditions, inflammation, and protein delivery. Thus, pharmacosomes present fresh difficulties as well as chances for developing an enhanced innovative vesicular drug delivery system.

**KEYWORDS:** Vesicular Drug Delivery System, Pharmacosomes, Methods of Preparation, Uses etc.

## INTRODUCTION

The creation of novel medication delivery systems has received a lot of attention during the last few decades. It in turn regulates the rate of medication delivery, keeps the therapeutic effect going for a longer time, and directs the medicine to the necessary location. The following goals are achieved by these cutting-edge medication delivery systems.[1]

- Therapeutic dose administered under strict control.
- Keeping the medication's concentration within the ideal range for extended action.
- Maximum effectiveness –dosage correlation.
- Decrease in harmful or harmful effects.
- Decreased use of frequent doses.
- Improvement in patient adherence.

Placing the material in submicroscopic drug carriers such as pharmacosomes, polymeric nanoparticles, reverse micelles, erythrocytes, immunoglobulin, liposomes, transferosomes, and niosomes can alter the original biodistrubution of the substance.[2,3] If selective absorption is successful, encapsulating the drug in a vesicular structure is one such system that should extend the drug's half-life in the bloodstream and lessen its toxicity.[4,5]

Vesicles are colloidal particles with a bilayer arrangement of lipids and surfactants (amphiphiles) encircling a water-filled center. These amphiphiles can create one or more concentric bilayers if the water content is increased. medications that are hydrophilic find a home in the interior aqueous environment, whereas medications that are lipophilic become trapped in the bilayered wall by hydrophobic or electrostatic forces.[6]

### Benefits of the Vesicular Drug Delivery System[4,6,7,8,9]

- Less chance of toxicity.
- Biodegradation is absent.
- The ability to package drugs that are both lipophilic and hydrophilic.
- The medication's ability to target the infection location.
- The ability to extend the drug's duration within the bloodstream systems.
- Potential to raise medication bioavailability while lowering toxicity.
- Improving a drug's water solubility that isn't very soluble.

- With medications that metabolize quickly, postpone drug elimination.

The term "Bingham bodies" refers to the biologic origin of these vesicles, which Bingham originally reported in 1965. Due to the restricted medication penetration into cells, conventional chemotherapy is ineffective in treating intracellular infections. Vesicular drug delivery techniques can be used to get around this. Vesicles have taken over as the preferred medication delivery vehicle in recent years. Immunology, membrane biology, diagnostic methods, and, most recently, genetic engineering have all found applications for lipid vesicles.[4,10,11]

Vesicles can be very useful in transporting and directing active substances, as well as simulating biological membranes.[4] Drug toxicity can be reduced without causing side effects thanks to the phagocytic absorption of the drug-loaded vesicular delivery system, which offers an effective way to deliver the medicine directly to the site of infection.[4]

**PHARMACOSOMES**

The name "pharmacosomes" refers to the amphiphilic ratio complexes of polyphenolic chemicals with phospholipids that have a zwitterion. It's a sort of drug delivery mechanism that works with vesicles.[12] By directing the medication to the exact location, the vesicle-based drug delivery method lowers toxicity and increases the medicine's bioavailability. Pharmacosomes are a unique drug delivery method in which drugs are covalently bound to lipids and exist as vesicle-based, micellar, or polygonal-shaped aggregates, depending on the complex chemical structure of the drug macromolecule.

By joining a medication (Pharmakon) to a carrier (soma), the pharmacosomes are formed.[13] Compared to other vesicle-based systems like liposomes, niosomes, and transferosomes, pharmacosomes may be able to traverse the biomembrane quickly and offer a number of advantages. Improved bioavailability is a result of pharmacosomes' increased biopharmaceutical qualities.[14]

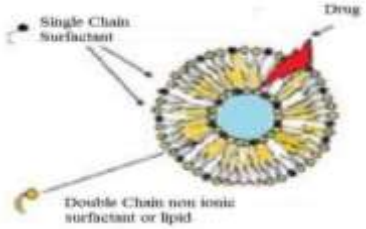


**Fig. 1: Pharmacosomes.**

Prodrugs, or Pharmacosommes, combine with water to generate pharmacosomes, which then come together to form multilayers. By considering the bulk features of the drug-lipid conjugate in mind, this approach is created while maintaining the surface qualities. There are currently many pharmacosomes available that contain protein, anti-tumor, non-steroidal anti-inflammatory, and vascular formulations.[15]

The occurrence of pharmacosomes will enhance the absorption of medication and reduce gastrointestinal toxicity. Pharmacosomes carry out a larger degree of medication transmission via moving with biomembranes. Through this interaction, the biomembrane's natural process temperature will change, improving the membrane's thinness and increasing permeability. Pharmacosomes will reduce problems with low drug incorporation, low solubility, and low outflow that are associated with the defense of polar compounds.

For the treatment of numerous illnesses, the carrier mediated drug delivery (CMDD) method may prove beneficial. By using drug targeting to a specific cell or inner compartment, controlling the release profile, using a chemical agent, or a combination of these, the therapeutic index (TI) of both conventional and innovative medications can be improved.[16]

**Pharmacosomes have the following therapeutic advantages[14,16]**

- The medication is more effective.
- Drug delivery to the designated location.
- Reducing toxicity may result in fewer side effects.
- Healthcare expenses are decreased.
- There will be greater patient compliance.

Pharmacosomes may enhance the water solubility of analgesic medications, according to numerous researchers. These phospholipid complexes, or pharmacosomes, can be synthesized and assessed for physicochemical testing. Pharmacosomes' increased water solubility will enhance dissolution and reduce gastrointestinal toxicity. Pharmacosomes, or the ketoprofen-phospholipid complex, were also made using an easy-to-replicate technique. This indicates that ketoprofen transforms into a complex with phospholipids that has a higher solubility and dissolution profile.[17]

A unique medication delivery device called a pharmacosome has colloidal dispersions that include drugs covalently bound to lipids. This is frequently an effective technique for

achieving targeted medication and controlled release formulation therapeutic aims. Colloidal drug delivery techniques include vesicles, micellar solutions, and liquid dispersions.[18]

## PHARMACOSOME SALIENT FEATURES[19]

- The efficiency of entrapment is predetermined in addition to being high. Unlike liposomes, the medication itself conjugates with lipids to create vesicles, therefore eliminating the free, unentrapped drug from the formulation doesn't require the same laborious, time-consuming steps.
- Since the medication is covalently bonded, loss from drug leakage does not occur. But hydrolysis could result in a loss.
- The patient's body is incorporating the medication without any issues.
- In the case of a pharmacosome, captured volume and drug-bilayer interactions have no bearing on entrapment efficiency. In contrast, these parameters significantly impact the efficiency of entrapment when it comes to liposomes.
- The lipid component of liposomes determines the film's smoothness, which affects the medication's release rate and the structure's physical strength. However, because the drug is covalently bound, the stage progress temperature of the medication lipid complex in pharmacosomes determines the film smoothness, but it has no effect on the discharge rate.
- Hydrolysis, including enzymatic, liberates the medication from the pharmacosome.
- There is less phospholipid transfer and exchange, and less solubilization by HDL. The physical and chemical characteristics of the drug-lipid combination determine the physicochemical stability of the pharmacosome.
- These methods enable numerous transfers over the lipophilic membrane system or tissue, via cellular walls piggybacking endocytosis and exocytosis, following medicine, because of their amphiphilic behavior.
- Following retention, the rate at which the drug's atoms break down into a functional form is determined by the spacer, the length of the lipid chain, and the size and beneficial groups of the pharmaceutical particle. For advanced in vivo pharmacokinetics, these can be modified in a moderately significant way.
- They may be given orally, intravenously, or topically.

## COMPONENT OF PHARMACOSOMES[20]

The following three elements are necessary for the creation of pharmacosomes:

**1. Drugs**

Medications with active hydrogen atoms (-COOH, OH, NH2) can be esterified to lipids with or without a spacer chain, forming an amphiphilic compound that helps organisms move their membranes, tissues, and cell walls.

**1. Solvents**

For the preparation of Pharmacosmes, the solvents should have high purity and volatile in nature. A solvent with intermediate polarity is selected for pharmacosome preparations.

**2. Lipid**

Phospholipids are the major structure component of biological membranes, wheretwo type of phospholipids generally used- phosphoglycerides and spingolipids. The most common phospholipid is phosphotidyl choline 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.

**PHARMACOSOMES' BENEFITS[21]**

1. Pharmacosomes provide an effective way to transport medication straight to the infection site, resulting in a decrease in drug toxicity with no side effects and a reduction in therapy costs due to increased medication bioavailability, particularly for poorly soluble medications.
2. It is possible to incorporate both lipophilic and hydrophilic medicines into pharmacosomes. These amphiphiles' aqueous solution demonstrates concentration-dependent aggregation.
3. Because the drug creates vesicles and makes covalent links with lipids during conjugation, the entrapment efficiency is both high and predefined.
4. The free, unentrapped medication can be removed from the formulation without the need to go through the laborious, time-consuming phase that is required for liposomes.
5. Despite the drug's covalent bond, there is no loss from drug leakage. However, hydrolysis may result in loss.
6. There are no drug inclusion issues.
7. In the case of a pharmacosome, captured volume and drug-bilayer interactions do not alter entrapment efficiency. However, in the case of liposomes, these variables have a significant influence over entrapment efficiency.

8. The liposome's lipid composition determines the fluidity of its membrane, which in turn affects the system's physical stability and the rate at which the medication releases.

## PHARMACOSOME LIMITATIONS[22]

1. The compound's amphiphilic character is necessary for its production.
2. Surface and bulk lipid-drug interaction is the basic idea of pharmacosomes.
3. When the pharmacosomes are placed in storage, they go through fusion, aggregation, and hydrolysis.
4. Covalent bonds are necessary to stop medication leaks.

## PHARMACOSOME PREPARATION

Techniques have been used to create pharmacosomes:

### 1) Hand-shaking method

- The medication and lipid shell should be combined in the flask with a circular bottom when using the hand-shaking method.
- A thin layer of deposition forms on the walls after the organic solvent is evaporated at room temperature using a rotating vacuum evaporator.
- To create vesicular suspension, the dry film is hydrated with buffer and manually rotated in a single direction.[23]

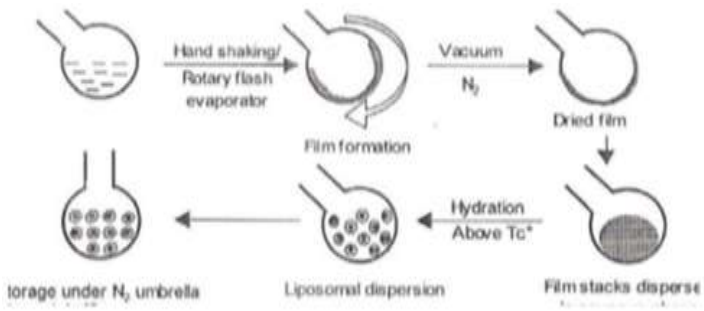


**Fig. 2: Hand Shaking Method.**

### 2) The ether injection technique

- The drug-lipid complex is dissolved in a predetermined amount of ether, and the resulting mixture is then gradually injected into a heated buffer solution to create the vesicles.
- The concentration affects the vesicle's characteristics, particularly its form.
- Depending on the amphiphilic condition, a range of shapes, including spherical, cylindrical, disc, cubic, and hexagonal types, may form.[18,24,25]

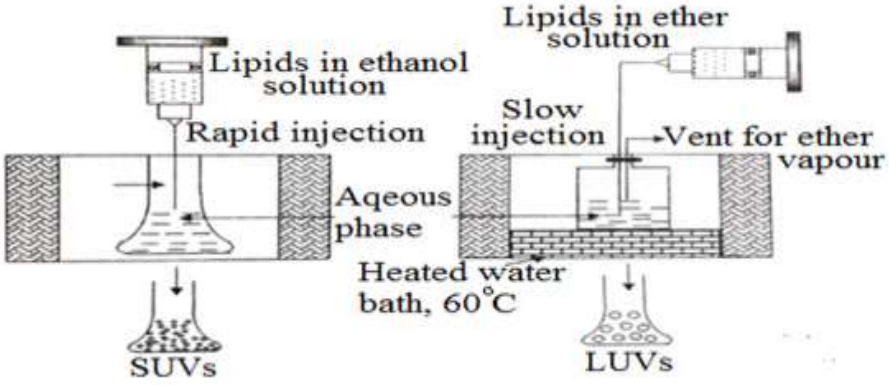


**Fig.3: Ether Injection Method.**

**3) Anhydrous co-solvent lyophilization technique**

- The drug and phospholipids are dissolved in a dimethyle sulfoxide solution including glacial acetic acid. The combination is then shaken to obtain a transparent liquid, and it is freeze-dried for a whole night at condenser temperature.
- After obtaining the complex, it is nitrogen flushed and kept at 4˚c.[26]

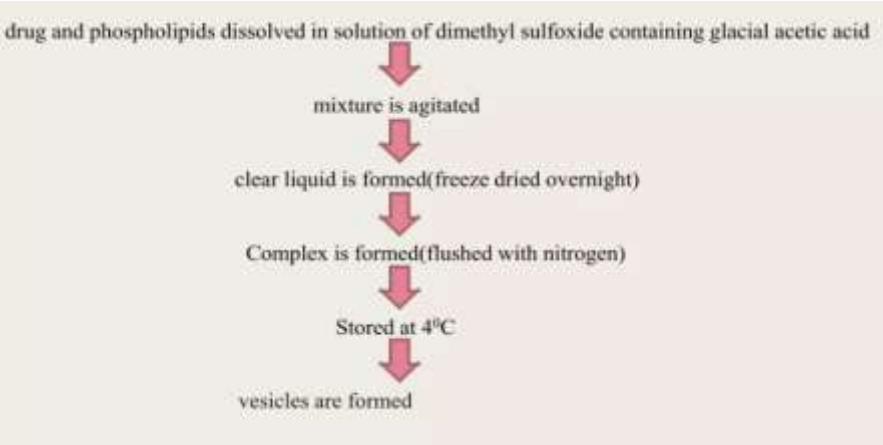


**Fig. 4: Anhydrous Co-Solvent Lyophilyzation Method.**

**4) Supercritical fluid method**

- The process is called complicated supercritical fluid solution enhanced dispersion. The turbulent flow of solvent and carbon dioxide results in fast mixing of dispersion leading to the formation of pharmacosomes.
- The drug and lipid complex are mixed together in a supercritical carbon dioxide fluid, and high super saturation is achieved by passing through a nozzle mixture chamber.
- The turbulent flow of carbon dioxide and solvent causes the dispersion to mix quickly, which promotes the formation of pharmacosomes.[27]

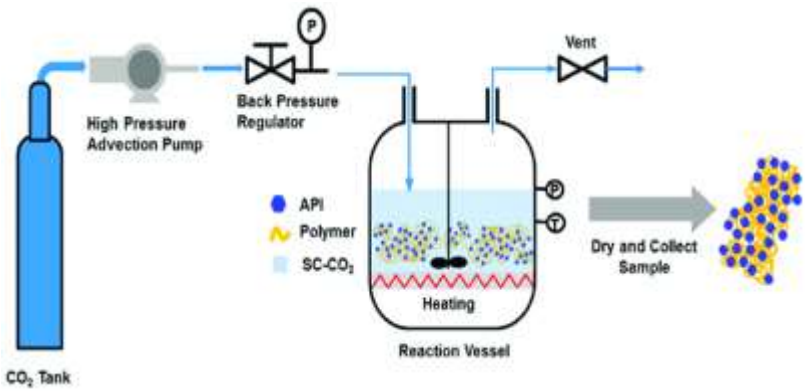


**Fig. 5: Supercritical Fluid Process.**

**5) Solvent evaporation technique**

- The drug is first acidified in the solvent evaporation process of pharmacosome preparation in order to potentially release the active hydrogen for complexation.
- After being extracted into chloroform, the drug acid is then recrystallized. The drug-PC complex is made by combining PC with drug acid in different molar ratios. A appropriate volume of dichloromethane is added to a 100 ml round-bottom flask along with the precisely weighed PC and drug acid.
- The combination undergoes an hour-long reflux. The solvent is then removed using a rotary vacuum evaporator operating under vacuum at 40 °C.[28]
- After that, the dried residues are gathered and put in a vacuum desiccator to finish drying.

**6) Other approaches**

A different method of creating pharmacosomes was recently discovered, involving the synthesis of a biodegradable drug combination that forms micelles from the hydrophobic medication adriamycin and a polymer made of polyoxyethylene glycol and polyaspartic acid. The advantage of this technique was that the medication could be diluted without precipitating in the monomeric drug conjunct.[23] Using a modified method, Muller-Goymann and Hamann created fenoprofen pharmacosomes by diluting lyotropic liquid crystals of an amphiphilic drug.[28] Drugs have been attached to a variety of glyceride-like groups using different techniques, and the resulting amphiphilic molecules have spread on their own. Singh et al. created "vesicular constructs" that considerably increased cytoprotection by encasing the antibiotic amoxicillin in an aqueous domain using phosphatidylethanolamine in different molar ratios of phosphatidylcholine and cholesterol.[29]

## CHARACTERIZATION OF PHARMACOSOMES

### 1. Complex Determination

The FTIR spectrum can be used to determine the development of complex and conjugate by comparing the correlation spectrum of the complex sample with that of discrete constituents and also with their mixture.[30]

### 2. Surface morphology

The surface morphology can be examined using transmission electron microscopy (TEM) or scanning electron microscopy (SEM). Purity grades of phospholipid influenced the pharmacosome's size and form as well as process variables like rotation speed, vacuum used, and technique.

### 3. Drug content

The drug-pc complex's content can be ascertained by weighing the drug-equivalent complex and adding it to a volumetric flask along with an appropriate solvent. A magnetic stirrer is used to mix the solution. UV spectrophotometric analysis is used to evaluate the drug content after a 24-hour stable dilution.[31]

### 4. Differential scanning calorimetry (DSC)

The compatibility or interactions between the medicine and the excipient are ascertained using this thermal analytical approach. The removal of endothermic peaks, the emergence of peaks, modifications to peak shape and onset, peak temperature/melting point, and relative peak area/enthalpy can all be used to conclude the interaction.

### 5. X-ray power diffraction (XRPD)

The relative integrated intensity of reflection peaks is used to detremine the degree of crystallinity. The specimen charetrics are represented by the itegrated intensity, which is determined by the area under the curves of the XRPD patterns.[32]

### 6. Fourier transforms infrared spectroscopy (FTIR)

The creation of the complex can be verified using IR spectroscopy by contrasting its spectrum with the spectra of its constituent parts and their mechanical mixed.

### 7. In-vitro Study

A model of in-vivo and in-vitro evaluation is conducted based on the anticipated therapeutic efficacy of biologically active elements.

## USES FOR PHARMACEUTICALS[33]

1. One advantage of pharmacosomes over other vesicular drug delivery methods is their extended shelf life and greater stability.
2. Creating pharmacosomes out of the medicine can increase its penetration and absorption.
3. Viral particles, which can alter the transition temperature from vesicle to micelle, are responsible for the passage of drugs across biological membranes.
4. When it comes to cell-specific drug vehicles in particular, phagosomes have the ability to deliver pharmaceuticals to specific areas by altering their temperature. Pindolol diglyceride, amoxicillin, taxol, cyclobine, dermatansulfate, and bucanolol hydrochloride are a few medications that have shown enhanced pharmacological effect through the formation of pharmacosomes.
5. Pharmacosomes can be utilized to investigate drug modes of action and non-bilayer phases. PEGylation and biotinyzation are used in the current study's pharmacosome manufacturing process. When used in ocular drug administration, phytoconstituents such as flavonoids, glycosides, xanthones, etc., exhibit enhanced pharmacokinetic and pharmacodynamic actions through changed corneal drug transport and release through dilution with tears, where the medication is intended to have an amphiphilic nature.
6. The ability of pharmacosomes to transport biological elements such as amino acids and proteins.
7. The Tetrahydrofuran injection method was developed using pharmacosomes, and didanosine was examined in rats' in vitro behavior. The results showed that pharmacosomes had an extended effect in both the targeted site and the liver.

## CONCLUSION

Drugs are bound to lipids by pharmacosomes via hydrogen, van der Waals, and covalent bonding processes. The medicine has very little leakage and a high trapping efficiency. Similar to other vesicular drug delivery methods, pharmacosomes allow for controlled and specialized medication delivery. Pharmacosomes improve therapeutic action and reduce toxicity from drugs. The pharmacosomes' physicochemical stability is determined by the physicochemical properties of the drug-lipid combination. To avoid dangerous and undesired effects on other places, drugs might be directly targeted to the site of action. They can also be used to lower the dosage of the medication given, increase the pharmacological action of the drug, and increase the bioavailability of medications with limited bioavailability.

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