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ADVANCES IN PHARMACOSOMES: A COMPREHENSIVE REVIEW OF FORMULATION STRATEGIES, CHARACTERIZATION TECHNIQUES, AND THERAPEUTIC APPLICATIONS IN DRUG DELIVERY SYSTEMS

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ABSTRACT

Pharmacosomes represent an innovative approach in drug delivery systems, wherein drug molecules are conjugated with lipid vesicles to enhance their solubility, stability, and bioavailability. This review encompasses the recent advancements and emerging trends in the field of pharmacosomes, a dynamic and evolving drug delivery platform. Pharmacosomes, characterized by the conjugation of drug molecules with lipid vesicles, have garnered substantial attention for their potential to address challenges associated with drug solubility and bioavailability.This novel drug delivery system offers several advantages, including improved therapeutic efficacy, reduced toxicity, and targeted delivery to particular tissues or cells. This comprehensive review synthesizes the latest research findings, focusing on the formulation strategies, characterization techniques, and applications of pharmacosomes. The review also explores the impact of pharmacosomes on drug delivery, emphasizing their role in improving therapeutic outcomes, minimizing toxicity, and facilitating targeted delivery. Pharmacosomes have received a lot of interest in the pharmaceutical sector because of their ability to overcome problems connected with poorly water-soluble medicines. This abstract gives an outline of the concept, formulation, and uses of pharmacosomes in drug delivery, highlighting their role in enhancing drug performance and optimizing therapeutic outcomes. By summarizing the current state of knowledge, this review provides valuable insights into the future directions and potential innovations in pharmacosome-based drug delivery systems.

KEYWORDS: Pharmacosomes, drug delivery, lipid vesicles, solubility, stability, bioavailability, therapeutic efficacy, toxicity, targeted delivery, poorly water-soluble drugs.

INTRODUCTION

The formulations, methods, and systems for safely delivering a pharmaceutical ingredient in the body to accomplish its desired therapeutic effects are the primary focus of the novel drug delivery system (NDDS). Securely original medication conveyance is better than the ordinary dose structure. An original medication conveyance framework ought to satisfy the accompanying prerequisites:

• To begin, it administers a specific amount of medication throughout treatment at a rate determined by the body's requirements.

• Besides, it conveys the dynamic medication moiety to the designated site of activity. [1-2]

The natural beginning of these vesicles was first announced in 1965 by Bingham and was given the name Bingham bodies [13,14]. Regular chemotherapy for the treatment of intracellular diseases isn't powerful, because of restricted saturation of medications into cells. This can be overwhelmed by the utilization of vesicular medication conveyance frameworks. Vesicles have emerged as the preferred mode of drug delivery in recent years. Lipid vesicles were viewed as worthwhile in immunology, film science, analytic methods, and most of late, hereditary designing. [13,16,17] Vesicles can assume a significant part in demonstrating organic layers, and in the vehicle and focusing of dynamic specialists. [13] The drug-loaded vesicular delivery system's phagocytic uptake of the systemic delivery makes it possible to efficiently transport the medicine to the location of infection, without causing any side effects or reducing drug toxicity. [13,15]

The Correlation of a couple of parts of lipoidal particulate transporters and their applications are discussed in table 1.

Table 1: Correlation of a couple of parts of lipoidal particulate transporters and their applications:

Sr no.	Carrier	Composition	Entrapped agent	Uniquefeature	Reference
1	Liposomes	Phospholipids, cholesterol, and alcohol.	Antibiotic, antineoplastic, and antitubercular medications	Amphiphilic nature provides solubilisation for both hydrophilic and lipophilic medications, Assimilation and intensification of bioactive.	[15,18]
2	Transferosomes	Phospholipids, edge activators, alcohol buffers and dyes	NSAIDs, anaesthesia, and steroidal hormones	Ultra-deformable vesicles may pass through a thin constriction (5 to 10 times smaller than their diameter) with no visible loss.	[15,18]
3	Ethosomes	Phospholipids and Ethanol.	Antifungal, antiviral, anti-keratinizing, and nonsteroidal anti-	The combined approach of high ethanol and phospholipid concentrations enhances the effect of deeper distribution and	[15,18]

			inflammatory drugs	penetration of medications in the skin.	
4	Pharmacosomes	Phospholipids and Dichloromethane	NSAIDs	Colloidal dispersions of medications covalently linked to lipids, increasing trapping efficiency; minimal drug loss due to leakage; and no issue with drug integration.	[15,18]

Pharmacosomes are one component of a novel medicine administration technology. Vaizoglu and Speriser first introduced them in 1968 [2]. Pharmacosomes are innovative vesicular medication conveyancemechanisms. Vesicular frameworks are concentric lipid bilayer structures that emerge when specific amphiphilic building pieces are uniquely exposed to water. Pharmacosomes are colloidal dispersions containing covalently bound pharmaceuticals in lipids. They give an effective way of drug delivery to the target location, resulting in reduced drug toxicity with minimal side effects, as well as lowering therapy costs by enhancing medicine bioavailability, particularly for inadequately dissolvable medications. Pharmacosomes are appropriate for joining both hydrophilic and lipophilic drugs due to their amphiphilic nature to build their dissolvability, and bioavailability, and diminish gastrointestinal harmfulness of different medications, the framework comprises of interfacing a drug (pharmakon) to a carrier (soma), consequently they are referred to as “Pharmacosomes” Fig .1. [3]

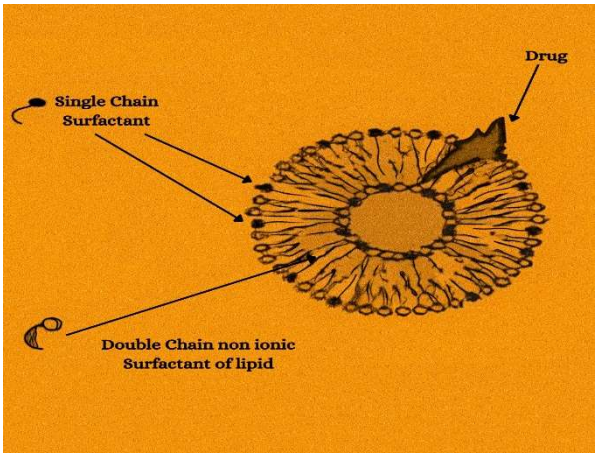

Fig 1: Pharmacosomes

Pharmacosomes' physicochemical characteristics are determined by both the drug and the lipid. Pharmacosomes might be hexagonal, ultrafine vesicles, or micellar. A drug with a free hydroxyl group or an active hydrogen atom (-NH2, -OH, -COOH) can be esterified with or without a spacer

chain to a lipid molecule's hydroxyl group, producing an amphiphilic prodrug. This prodrug combines hydrophilic and lipophilic characteristics, resulting in amphiphilic features. Amphiphilic prodrugs produce pharmacosomes when diluted with water. Both synthetic and natural medications that face challenges such as limited Solubility and permeability can be successfully combined. Pharmacosomes have created for a variety of NSAIDs, proteins, and cardiovascular and anti-cancer medications. The development of pharmacosomes enhanced absorption while reducing gastrointestinal toxicity. Pharmacosomes are amphiphilic drug-lipid complexes. The amphiphilic feature reduces interfacial tension, which enhances contact area and drug bioavailability [4].

Table 2 discusses the features and concerns of the normal vesicular system, as well as the benefits of pharmacosomes.

Table 2: Features and issues with the typical vesicular system, as well as the advantages of pharmacosomes:

Vesicular System	Features	Problems	Pharmacosomes	Reference
Liposomes	Microscopic vesicles (25nm to 100µm) include one or more lipid bilayers separated by water or aqueous buffers.	Drawbacks include high preparation costs, oxidative deterioration, sedimentation, drug leaching, and low purity of natural phospholipids.	Preparation costs are lower, entrapment efficiency is not affected by inclusion volume or drug bilayer interactions, covalent bonding prevents drug leakage, oxidation resistance, and no requirement for pure phospholipids.	[15]
Niosome	Non-ionic surfactant vesicle	Leaching the drug is time-consuming, insufficient stability	More stable and efficient.	[15]

Transferosomes	Suitable for both low and high molecular weight drugs, including lipophilic and hydrophilic.	Expensive, oxidative deterioration, and the purity of natural phospholipids is poor.	Less expensive, oxidation-safe, unadulterated and regular phospholipids are not needed.	[15]

Characteristics of Pharmacosomes:

- The conjugate's physicochemical characteristics regulate the system's overall stability.
- Drug molecules are easily transported through cell membranes and tissues via endocytosis or exocytosis due to their affinity for both fat and water.
- The rate of degradation is contingent upon several factors, including fatty acid chain length in lipids, drug molecule size, and the presence or absence of a spacer. It is possible to adjust each of these variables to maximize in vivo pharmacokinetic behaviour.
- They can be used topically, orally, extravascularly, or intravenously. [5]

Pharmacosomes have the following advantages:

- Pharmacosomes outperform conventional lipid-based delivery technologies in several aspects.
- The drug-lipid combination is covalently bonded to the lipid and depends on the phase transition temperature, not the release rate.
- The medication is covalently bonded to the lipid, preventing any leakage.
- Provides tailored medicine delivery.
- Enzymatic procedures, such as hydrolysis, release the medication from the lipid polymers.
- The drug's metabolism is influenced by its spacer, lipid chain length, functional groups, and size during absorption.
- They lower therapeutic costs.
- They are appropriate for both lipophilic and hydrophilic medicines.
- Amphiphiles in aqueous solution display concentration-dependent behaviour. aggregation.
- The drug and carrier are covalently bonded, resulting in high and consistent entrapment efficiency.
- Pharmacosomes use hydrolysis to release drugs.
- They significantly increase bioavailability for poorly soluble medicines.
- They minimize undesirable effects and toxicity.
- Pharmacosomes eliminate the need to remove unentrapped drugs, unlike liposomes which require this.

- Pharmacosomes enhance the therapeutic effectiveness of medications such bupranolol hydrochloride, pindolol maleate, acyclovir, and taxol.[6, 7, 8, 19, 20].

Pharmacosomes have the following disadvantages:

- Pharmacosomes undergo fusion, aggregation, and chemical degradation when in storage.
- Amphiphilicity of compound governs its synthesis.
- Lipids must interact with medications on both the surface and in bulk.
- Covalent bonding is necessary to avoid medicine leaking.[8,9,19]

Pharmacosomes have the following limitations:

- Amphiphilicity of a molecule can be used for synthesis.
- Drugs interact with lipids both superficially and deeply.
- Restricting medication leakage requires a covalent bond.
- Chemicals can cause pharmacosomes to fuse, agglomerate, or hydrolyze during storage. [10,1]

The formulation characteristics of pharmacosome preparation:

Pharmacosome production requires three important components.[fig.2]

- Drugs: Drugs include active hydrogen atoms (-COOH, OH, and NH2), which can be esterified with lipids to form an amphiphilic molecule with or without a spacer. The formation of such complexes promotes membrane, tissue, and cell wall transfer throughout the body, therefore boosting the therapeutic efficiency of drugs.
- Solvents: The solvents should be very pure and volatile. The preparation involves using a moderately polar solvent.
- Lipid: Phospholipids are the main components of biological membranes. There are two types of phospholipids: phosphoglycerides and sphingolipids. The most common variety is phosphatidylcholine. It is an amphiphilic compound with a glycerol bridge that connects two hydrophobic acyl hydrocarbon chains to the hydrophilic polar head group. Lipids' wetting and dispersion properties can aid increase medication solubility. Amphiphilicity is a key feature in increasing the bioavailability of pharmaceutical molecules.[3,11,12,21]

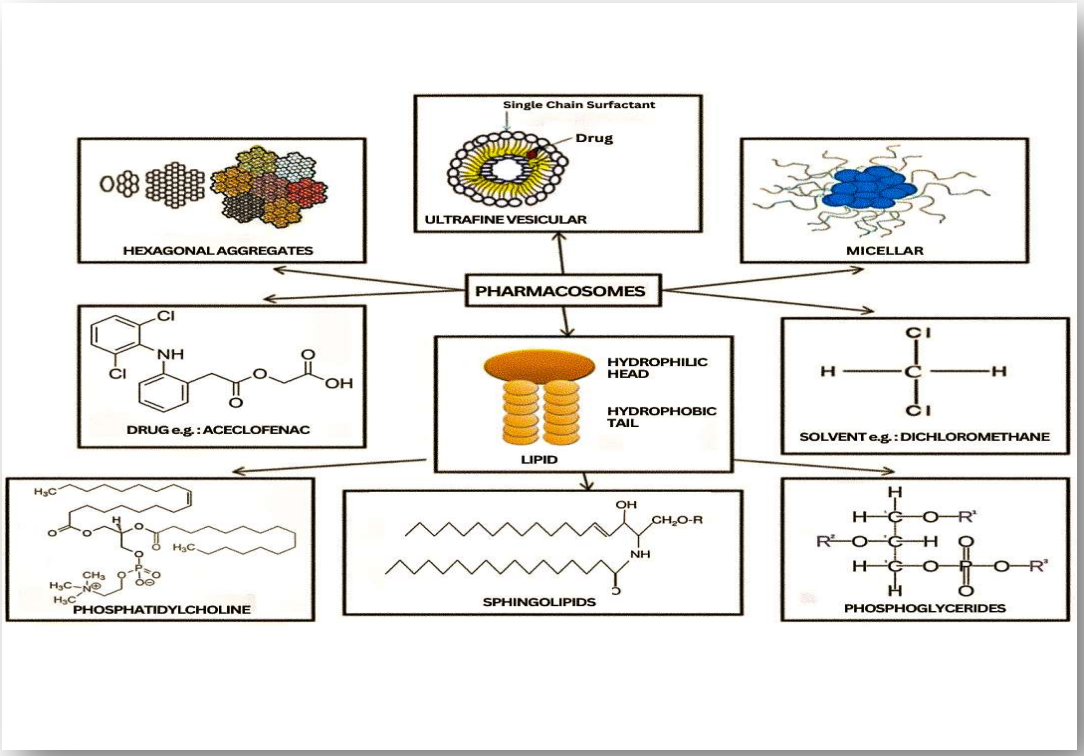

Fig 2: Forms and components of pharmacosome

The method of preparation is:

1. Ether injection method:
   In this approach, a solution containing a drug-lipid combination is appropriately mixed and slowly injected into a heated aqueous medium using a gauze needle, where vesicles form quickly. [22]
2. Handshaking or Method for evaporating solvents:
   Drugs and lipids are solubilized in a volatile organic solvent. The solvent is then evaporated in a round bottom flask using a rotatory evaporator, leaving a thin layer of solid mixture on the flask walls. In watery environments, the dry film hydrates quickly and forms a vesicular suspension. [23]
3. Lyophilization using anhydrous co-solvents:
   First, combine the drug and phospholipids in a dimethyl sulfoxide solution containing glacial acetic acid. The mixture is then mixed to form a clear liquid, which is freeze-dried overnight at condenser temperature. The resultant complex is flushed with nitrogen and stored at 4°C.[24]
4. Supercritical fluid process:

The drug and lipid complexes are solubilised in a supercritical CO_2 solution before being blended in the nozzle mixing chamber. [25]

5. Recent approach:
   A biodegradable micelle-forming drug combination was created by combining a polymer made of polyxyethylene glycol and polyaspartic acid with a hydrophobic Adriamycin. Diluting the micelle without the active ingredient being precipitated in the monomeric drug conjugate [26].
   Muller-Goymann and Hamann [27] dilute the lyotropic liquid crystals of amphiphilic drugs.

   Phosphatidylethanolamine with varied molar ratios of phosphorylcholine and cholesterol, greatly increased cytoprotection by encapsulating amoxicillin and also developed "vesicular constructs" utilizing the aqueous domain [28].

Improved Therapeutic Activity:

The method has successfully increased the therapeutic performance of a variety of drugs, including pindolol maleate, bupranolol hydrochloride, taxol, and acyclovir [44, 45]. Zhang and Wang demonstrated that pharmacosomes can boost a drug's capacity to pass the blood-brain barrier, serving as a promising drug-targeting system for the treatment of central nervous system illnesses [46]. In another work, the in vivo behaviour of didanosine pharmacosomes was investigated in rats. The study discovered liver targeting and sustained-release effects in rats following intravenous treatment. It was also discovered that drugs were targeted in the lungs and spleen and that drug clearance from these organs was delayed [47]. Furthermore, incorporating NSAIDs with phospholipids has been proposed as a way to increase these drugs' gastrointestinal safety. It has been shown that the diffusion of NSAIDs over lipid membranes and into target cells is enhanced when they form a compound with phosphatidylcholine. Developing the drugs into lipid complexes (pharmacosomes) may show to be a feasible technique for improving solubility and minimizing the GI toxicity of NSAIDs. [48]

The characterization of pharmacosomes is:

1. Complex Determination:
   The development of complex and conjugate may be identified by the correlation spectrum found in complex samples with that of discrete constituents, as well as their combination with the help of the FTIR spectrum.[29]
2. Surface Morphology:
   Surface morphology can be seen using scanning electron microscopy (SEM) or transmission electron microscopy (TEM). Purity grades of phospholipids impact the

form and size of pharmacosomes, as well as process factors such as speed of rotation, vacuum applied, or the technique utilized. [25]

3. Drug content:
   To evaluate the drug content in the drug-pc combination, a drug-equivalent complex was weighed and put into a volumetric flask containing the appropriate solvent. The solution is blended using a magnetic stirrer. After 24 hours of appropriate dilution, drug concentration is evaluated UV spectrophotometrically.[30]
4. Differential scanning calorimetry (DSC):
   Differential scanning calorimetry is used to test drug-excipient compatibility and to demonstrate potential interactions. An interaction is completed by the disappearance of the endothermic peak, formation of a new peak, change in peak shape and start, peak temperature/melting point, and relative peak area or enthalpy.[19,20,21,31]
5. X-ray powder diffraction (XRPD):
   The degree of crystallinity is determined using the relative integrated intensity of reflection peaks. The integrated intensity is supplied by the area under curves of the XRPD patterns and indicates the specimen's features.[32]
6. Fourier transforms infrared spectroscopy (FTIR):
   IR spectroscopy can validate the complex's creation by comparing its spectra to that of individual components and their mechanical mixed. The stability of pharmacosomes can be assessed by comparing the spectra of the complex in solid form to the spectrum of its micro dispersion in water following lyophilisation at various time intervals. [20,21]
7. Dissolution studies:
   Dissolution studies in vitro are done using several models available utilizing different buffers, and then the findings obtained are calculated depending on the drug's activity.[33]
8. In vitro drug release rate:
   The in vitro drug release rate is evaluated using the reverse dialysis bag method. In this procedure, pharmacosomes are injected into the dialysis bag while the receiver phase is kept outside. Dialysis bags containing the continuous phase are suspended in a vessel containing the donor phase and agitated at regular intervals. Each dialysis bag is withdrawn and the contents are tested for drug release. This approach has the benefit of increasing the amount of membrane surface area accessible for transfer from the donor to the receptor compartment. Another benefit of this strategy is the enhanced efficiency of personnel as a result of the decrease in the number of stages.[34]

The effect of drug after incorporation in pharmacosomes is discussed in table 3.

Table 3: Drug's impact after integration into pharmacosomes:

Drugs	The following result after incorporation in Phamacosome	Reference

Pindolol diglyceride	Plasma concentration increases three to fivefold. Lower renal clearance.	[7,41]
Amoxicillin	Improved cytoprotection and therapy for H. pylori infections in male rats.	[21,40]
Taxol	Enhanced biological activity.	[21, 41, 42]
Cytarabine	Improved biological activity	[21,41,42]
Dermatan sulfate	Enhanced biological activity.	[21, 41, 42].
Bupranolol hydrochloride	Improved effects on intraocular pressure and Improve lymph transport	[21,43]

The recent approaches of pharmacosomes are discussed in Table 4.

Table 4: Recent Approaches of Pharmacosomes

Drugs	Description	Patent Number	Reference
Tamibarotene-cytarabine	The tamibarotene-cytarabine conjugate has a proper amphipathy, can form a nanoscale dispersive self-assembly transfer system in water and has good anti-tumour activity in vitro and vivo.	CN103242401A	[49]

RGDV-containing cytosine arabinoside	The Ara-C is targeted to a tumour position better by the dual functions that the pharmacosome has a good targeting function and the RGDV serves as a bonding locus for integrating an acceptor. The invention evaluates the antitumor activity of conjugate pharmacosome preparations of the Ara-C series by taking a sarcoma S180 mouse as a model, and the result shows that the conjugate pharmacosome preparations of the Ara-C series have more excellent anti-tumour activity than	CN101690823A	[50]

	each control group.		
Caffeine	The current creation concerns clinical items, Explicitly, the technique for viable heterocyclic anti-microbial conveyance to growth cells using little particles containing caffeine, varying that said strategy incorporates beginning blending of concentrated alcoholic arrangements of anti-infection, single chain oligonucleotide, and purine in the proportions near equimolar ones, and following quick infusion of the pre-arranged arrangement	RU237073C1	[51]

	through a dainty needle in a quickly blended more prominent volume of a watery arrangement utilizing sodium chloride to produce single noncoherent nano-edifices - pharmacosomes - of very small size (1 to 100 nanometres), offering anti-microbial security against sorption on blood capillary walls and in this manner upgrading its entrance into cancer cells and their atomic DNA.		

The following application of pharmacosomes:

Pharmacosomes having a longer shelf life and a more stable profile. They can improve medication absorption and distribution. Pharmacosomes can increase permeability by increasing membrane fluidity. The transition temperature of vesicles in the form of micelles may have a significant influence on vesicular contact with the biomembrane, hence enhancing drug transport across the membrane. Many studies have effectively employed these tactics to increase the therapeutic efficacy of a variety of medications, including pindolol diglyceride, amoxicillin, taxol, cytarabine, dermatan sulfate, and bupranolol hydrochloride. Optimized and investigated the properties of the geniposide pharmacosomes. Pharmacosomes have increased selectivity for effect on certain target cells [35].

Pharmacosomes are building particles that can carry biologically active compounds including nucleic acids and proteins [36].

Diclofenac pharmacosomes were developed and analyzed, and it was determined that their solubility was higher (22.1 g/mL) than that of diclofenac (10.5 g/mL). Following a 10-hour dissolving trial, drug release increased from 60.4% to 87.8% of diclofenac pharmacosomes [37].

Developed and evaluated pharmacosomes of 3',5'-dioctanoyl-5-fluoro-2'-deoxyuridine using central composite design; discovered high targeting efficacy of pharmacosomes in vivo and boosted drug potential to pass through the blood-brain barrier.[38]

Prepared acyclovir pharmacosomes and discovered that plasma proteins in blood absorbed pharmacosomes and interfered with erythrocyte connections, lowering the haemolytic process. [39]

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