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Review Article

Pharmacosomes as an Advanced Vesicular Drug Delivery System: A Comprehensive Review

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ABSTRACT

Vesicular drug delivery systems have gained considerable attention in modern pharmaceutics due to their ability to enhance bioavailability, enable site-specific targeting, and reduce systemic toxicity. Among these systems, pharmacosomes represent an advanced vesicular approach in which drugs containing active hydrogen groups (–COOH, –OH, –NH_2) are covalently conjugated with phospholipids to form amphiphilic drug–lipid complexes. Unlike conventional carriers such as liposomes and niosomes, pharmacosomes integrate the drug into the carrier structure, thereby minimizing drug leakage and improving physicochemical stability. Pharmacosomes exhibit improved solubility, permeability, and bioavailability for both hydrophilic and lipophilic drugs, and can self-assemble into vesicular, micellar, or hexagonal structures depending on their physicochemical characteristics. Various preparation methods, including ether injection, solvent evaporation, and lyophilization, are employed to formulate pharmacosomes, which are further evaluated using techniques such as FTIR, SEM/TEM, DSC, XRPD, and dissolution studies. Despite their advantages, pharmacosomes face certain limitations, including susceptibility to hydrolysis, formulation complexity, and challenges in large-scale production. Recent advancements highlight their potential in targeted drug delivery, nanotechnology integration, and delivery of biopharmaceuticals. This review provides a comprehensive and critical overview of pharmacosomes, including their components, preparation methods, evaluation parameters, applications, and future prospects. Overall, pharmacosomes hold significant promise as an efficient and versatile drug delivery system, although further research is required for clinical translation and commercialization.

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INTRODUCTION

Vesicular drug delivery systems have emerged as an important strategy in modern pharmaceutics for improving the therapeutic performance of drugs. These systems enhance drug bioavailability, enable site-specific targeting, reduce systemic toxicity, and provide controlled drug release.[1,11] The concept of vesicular carriers was first introduced by Alec D. Bangham in 1965 with the discovery of liposomes, initially referred to as "Bingham bodies."[8] This innovation led to the development of various vesicular systems such as liposomes, niosomes, transferosomes, and pharmacosomes.[9,10].Despite significant advancements, conventional vesicular systems often suffer from drawbacks including drug leakage, instability, oxidative degradation, and limited targeting efficiency.[13,14] These challenges restrict their clinical applicability and necessitate the development of more stable and efficient drug delivery systems. Pharmacosomes represent a novel and advanced vesicular drug delivery approach in which drugs containing active hydrogen groups (–COOH, –OH, $–NH_2$) are covalently conjugated to lipids, forming amphiphilic drug–lipid complexes.[2,3] Unlike conventional carriers, the drug becomes an integral part of the delivery system, thereby minimizing leakage and enhancing stability.[17,19] These complexes can self-assemble into various structures such as vesicles, micelles, or hexagonal phases depending on their physicochemical properties.[13,16] Recent studies have demonstrated that pharmacosomes improve solubility, permeability, and bioavailability of both hydrophilic and lipophilic drugs, making them suitable for a wide range of therapeutic applications.[4,21] Additionally, their ability to modulate drug release and enhance biodistribution makes them promising candidates for targeted drug delivery.[18]However, despite these advantages, challenges such as hydrolysis, formulation complexity, and limitations in large-scale production remain.[26,33] Therefore, a comprehensive and critical evaluation of pharmacosomes is essential to understand their potential and limitations. This review aims to provide a detailed and critical overview of pharmacosomes, including their components, preparation methods, evaluation techniques, advantages, limitations, applications, and future prospects in drug delivery.

Vesicular drug delivery system

Vesicular drug delivery systems enhance drug bioavailability and minimize toxicity through targeted delivery to specific sites. Bingham first described the biological origins of these systems in 1965, calling them "Bingham bodies".[8] This discovery paved the way for various vesicular carriers, including liposomes, niosomes, and pharmacosomes. [9,10] By delivering drugs directly to the action site, these systems reduce systemic toxicity and prevent off-target adverse effects.[11]

Advantages of vesicular drug delivery

- Targeted Delivery: Efficiently directs drugs to action sites, reducing toxicity and side effects.[12]
- Versatile Drug Loading: Accommodates both hydrophilic and lipophilic compounds effectively.[14]
- Cost Reduction: Lowers treatment expenses through optimized dosing and efficacy.
- Bioavailability Boost: Enhances absorption of poorly soluble drugs.[13]
- Sustained Action: Slows rapid metabolism and elimination for prolonged exposure.[14]

- Stability Enhancement: Protects against degradation, improving solubility and shelf life.[16]
- Biocompatibility: Natural biomolecule-mimicking carriers that are biodegradable.[15]
- Drug Reservoir Effect: Encapsulates drugs to overcome limitations of traditional forms

Table 1: Type of vesicular drug delivery system.[13]

Lipoidal Biocarriers	Non-lipoidal Biocarriers
A. Pharmacosomes	A. Niosomes
B. Liposomes	B. Bilosomes
C. Ethosomes	C. Aquasomes

Pharmacosomes, introduced by Vaizoglu and Speiser in 1968, represent advanced vesicular drug delivery systems.[2] They form colloidal dispersions by covalently bonding drugs with active hydrogen groups (-COOH, -OH, -NH_2) to lipids, [17,15] creating ultrafine vesicles, micelles, or hexagonal aggregates based on the drug-lipid complex structure [13,16]. Named from "pharmakon" (drug) and "soma" (carrier), they surpass liposomes and niosomes by eliminating leakage,[15] ensuring high entrapment efficiency, and enhancing stability, solubility, permeability, and targeted release.[19] Drugs esterified to lipids (with/without spacers) become amphiphilic prodrugs [22]that improve tissue penetration and biodistribution while reducing toxicity.[18] Post-absorption breakdown into active forms depends on drug size, functional groups, lipid chain length,[20] and spacers, considering both surface and bulk interactions for optimal membrane transfer.[21]

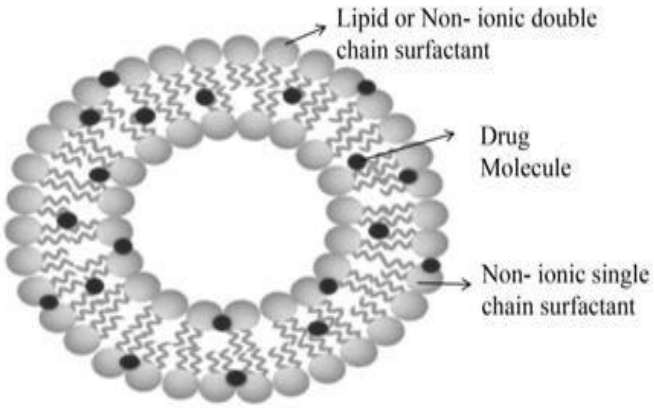

Figure1: Structure of pharmacosomes [3]

Advantages for drug delivery:

- Simplifies precise drug administration protocols.[13]
- Enables direct delivery to infection sites.[24]
- Prolongs circulation of rapidly metabolized drugs.[25]
- Minimizes toxicity through site-specific targeting.[24]

- Supports sustained-release functionality.[26]
- Achieves consistently high entrapment efficiency via covalent drug-carrier bonding.[17]
- Maintains stability determined by drug-lipid complex's physicochemical properties.[27]
- Effectively incorporates both lipophilic and hydrophilic drugs.[13]
- Exhibits phase transition temperatures that influence micellar-to-vesicular structural transformations.[28]

Limitations for drug delivery:

- Targeted drug accumulation may heighten local toxicity.[13]
- Requires specialized expertise for formulation, storage, and administration.[24]
- Susceptible to emulsion instability, aggregation, and hydrolysis during storage.[15]
- Demands advanced technological processes for preparation.[26]
- Synthesis limited to compounds exhibiting sufficient amphiphilicity.[17]
- Hydrophilic portions of water-insoluble drugs face challenges against large bilayer surface areas.[28]
- Covalent bonding is essential to prevent drug leakage.[13]

Aqueous aspects of pharmacosomes

- Drug-lipid integration is straightforward, enabling direct administration to infection sites.[29]
- Hydrolysis, often enzyme-mediated, governs release in most cases, thereby lowering treatment costs.[26]
- Drug size, functional groups, spacer length, and lipid chain characteristics precisely control breakdown into active forms post-absorption, optimizing in vivo pharmacokinetics.[4]
- Dual hydrophilic-lipophilic nature facilitates easy transport via endocytosis or exocytosis across tissues, cell membranes, and barriers.[30]
- Lipid pairing yields self-formed vesicles with inherently high, predictable entrapment efficiency.[18]
- Fatty acid chain length, size, and functional groups dictate the conversion rate to active drug during transit.[30]
- Complex's physical-chemical bonding properties dictate overall formulation stability.[4]

Components of Pharmacosomes

Pharmacosomes rely on three essential elements: active drugs, lipid carriers, and suitable solvents.

1.Drugs

Drugs containing active hydrogen atoms (-COOH, -OH, $-NH_2$) can be chemically linked to lipids, with or without spacer chains. This forms amphiphilic complexes that enhance transfer across biological membranes, tissues, and cell walls.[31]

2.Lipids

Phospholipids serve as the primary structural components, mimicking cell membranes. Common types include phosphoglycerides and

sphingolipids, with phosphatidylcholine being the most frequently used.[32]

3.Solvents

Analytical-grade organic solvents of intermediate polarity and high volatility are selected. These must fully dissolve both phospholipids and drugs, with choices based on matching the polarity of the drug-lipid pair.[33]

Table:2 Comparison on conventional vesicular system and pharmacosomes

Vesicular System	Key Limitations	Pharmacosomes Advantages
Niosomes	Drug leakage, time-intensive preparation, poor stability	Superior stability and efficiency [35]
Liposomes	High cost, oxidation degradation, sedimentation, drug leaching [33]	Lower cost, entrapment independent of volume/bilayer interactions, covalent bonds prevent leakage, oxidation-resistant, no need for pure/natural phospholipids [36]
Transferosomes	Expensive production, oxidative breakdown, phospholipid purity issues [34]	More economical, oxidation-proof, eliminates need for pure/natural phospholipids [37]

Preparation Methods for Pharmacosomes

Pharmacosomes can be prepared using three primary techniques that leverage solvent manipulation and lipid-drug interactions.

1.Ether Injection Method

The drug-lipid complex is dissolved in ether and slowly injected through a fine needle into heated aqueous medium. This process triggers spontaneous formation of vesicles.

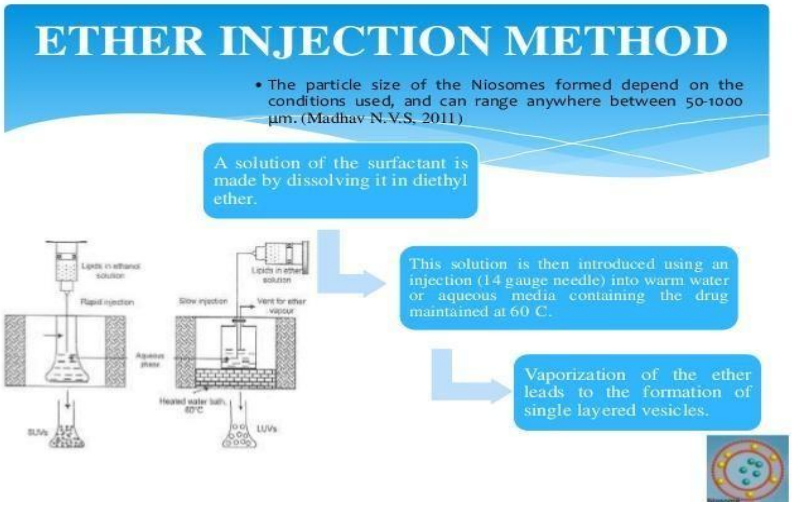

Figure 2: Schematic representation of ether injection method

2. Solvent Evaporation (Hand-Shaking Method)

The drug and lipid are dissolved in a volatile organic solvent, which is then evaporated under vacuum in a round-bottom flask using a rotary evaporator. A thin film forms on the flask wall and is hydrated with aqueous buffer, causing vesicles to detach easily.[39]

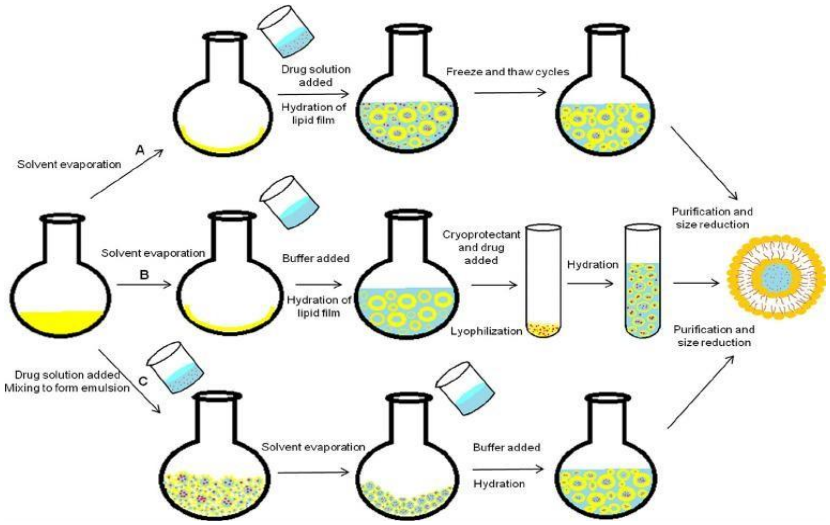

Figure 3: Schematic representation of handshaking method.

3. Anhydrous Co-Solvent Lyophilization

Drugs and phospholipids dissolve in a dimethyl sulfoxide-glacial acetic acid mixture, stirred to clarity, then freeze-dried overnight at low condenser temperature. The resulting complex is nitrogen-flushed, stored at 4°C, and may undergo nozzle mixing for final dispersion.[32]

Evaluation Methods for Pharmacosomes

Pharmacosomes undergo comprehensive characterization to verify formation, structure, and performance.

1. Complex Formation (FTIR)

Fourier Transform Infrared Spectroscopy compares spectra of the drug-lipid complex against individual components and physical mixtures. Peak shifts, disappearance, or new peaks confirm covalent bonding.[40]

2. Surface Morphology

Scanning Electron Microscopy (SEM) or Transmission Electron Microscopy (TEM) reveals particle shape, size, and surface features. Results vary with phospholipid purity, rotation speed, vacuum levels, and preparation method.[42]

3. Drug Content

Known pharmacosomes quantities dissolve in suitable solvents, stir for 24 hours, dilute, and analyze via UV spectrophotometry to quantify entrapped drug.[41]

4. Solubility Studies

Phospholipid complexes test in pH 6.8 buffer and n-octanol using shake-flask method. Drug (50 mg) or equivalent complex shakes with buffer, separates into aqueous/organic phases, and analyzes spectrophotometrically at 276 nm.[21]

5. Differential Scanning Calorimetry (DSC)

Detects drug-excipient interactions through changes in endothermic peaks, onset/melting temperatures, peak shapes, or enthalpy values.[42]

6. X-ray Powder Diffraction (XRPD)

Measures crystallinity via reflection peak intensities. Peak areas under XRPD curves indicate amorphous/crystalline nature.[42]

7. Dissolution Studies

In vitro dissolution studies are essential to evaluate the drug release behavior of pharmacosomal formulations. These studies are typically conducted using a USP dissolution apparatus (Type I or II) in phosphate buffer (pH 6.8 or 7.4) at 37 ± 0.5°C with a rotation speed of 50–100 rpm. A known quantity of formulation is introduced, and samples are withdrawn at predetermined intervals, replaced with fresh medium to maintain sink conditions, and analyzed using UV–visible spectrophotometry. The cumulative drug release is calculated and fitted to kinetic models such as zero-order, first-order, Higuchi, and Korsmeyer–Peppas. Pharmacosomes generally show enhanced and controlled drug release.[22]

Applications of Pharmacosomes

Pharmacosomes offer practical advantages in drug delivery and research:

- Pharmacosomes demonstrate greater stability and extended shelf life compared to other vesicular systems.[24]
- Pharmacosomes effectively transport biological molecules including amino acids and proteins.[26]
- Pharmacosomes enable site-specific drug delivery through temperature modification, especially with cell-specific carriers.[28]
- Pharmacosomes serve as tools to investigate non-bilayer lipid phases and drug mechanisms of action.[18]
- Isoniazid pharmacosomes exhibited improved permeability and macrophage targeting.[7]
- Phytoconstituents such as xanthones, glycosides, and flavonoids showed enhanced pharmacokinetic and pharmacodynamic profiles.[7]

Future scope

Pharmacosomes represent a promising advancement in vesicular drug delivery; however, significant opportunities remain for further research and development. Future studies should focus on enhancing formulation design, expanding therapeutic applications, and addressing current limitations associated with stability and large-scale production. One of the key future directions involves the development of targeted pharmacosomes through the conjugation of ligands such as antibodies, peptides, or small molecules. Such surface-modified systems can enable precise site-specific drug delivery, particularly in cancer therapy and infectious diseases, thereby improving therapeutic outcomes while minimizing systemic toxicity. [43,46] The integration of pharmacosomes with nanotechnology-based drug delivery systems is another promising area. Hybrid systems combining pharmacosomes with nanoparticles or polymeric carriers may offer improved stability, enhanced drug loading, and controlled release characteristics, ultimately leading to better pharmacokinetic and pharmacodynamic profiles. [44,49] In addition, pharmacosomes hold significant potential for the delivery of biopharmaceuticals, including proteins, peptides, and nucleic acids.[50] Their amphiphilic nature facilitates improved membrane permeability, which may help overcome the challenges associated with the oral and intracellular delivery of macromolecules (Emerging biopharmaceutical delivery studies.[45] Despite these advantages, the translation of pharmacosomes from laboratory to clinical application remains limited. Therefore, extensive in vivo studies and well-designed clinical trials are essential to evaluate their safety, efficacy, and long-term stability in humans.[47] Scale-up and industrial production also remain challenging. Future work should focus on developing cost-

effective and reproducible manufacturing techniques that ensure batch-to-batch consistency and long-term stability of pharmacosomal formulations. [33,38] Moreover, regulatory considerations and standardization of evaluation parameters must be addressed to facilitate the approval of pharmacosome-based formulations. Establishing clear guidelines will be essential for their successful commercialization and widespread use in the pharmaceutical industry.[21]

CONCLUSION

Pharmacosomes have emerged as a promising advancement in vesicular drug delivery systems due to their unique approach of covalent drug–lipid conjugation, which integrates the drug into the carrier structure and thereby minimizes leakage while improving physicochemical stability. Compared to conventional vesicular systems such as liposomes and niosomes, pharmacosomes offer enhanced solubility, permeability, and bioavailability for both hydrophilic and lipophilic drugs, making them a versatile platform for drug delivery applications. The ability of pharmacosomes to self-assemble into various structures, along with their improved interaction with biological membranes, contributes to better drug absorption and targeted delivery. In addition, diverse preparation methods and comprehensive evaluation techniques enable optimization of formulation characteristics for improved therapeutic outcomes. Despite these advantages, pharmacosomes are associated with certain limitations, including susceptibility to hydrolysis, formulation complexity, and challenges in large-scale production and industrial application. These issues highlight the need for further optimization and standardization of formulation and manufacturing processes. Future research should focus on the development of targeted pharmacosomal systems, integration with nanotechnology-based carriers, and expansion into biopharmaceutical delivery. Furthermore, extensive in vivo studies and well-designed clinical trials are essential to establish their safety, efficacy, and long-term stability. Addressing regulatory challenges and ensuring reproducibility will also be crucial for successful commercialization. Overall, pharmacosomes represent a significant and evolving drug delivery platform with considerable potential to improve therapeutic efficacy and patient outcomes. Continued research and technological advancements are expected to facilitate their transition from laboratory research to clinical application.

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