ADVANCES IN DRUG–PHOSPHOLIPID CONJUGATES FOR ENHANCED ORAL DRUG BIOAVAILIBILITY

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ABSTRACT

Oral drug delivery is widely preferred due to its convenience and patient compliance; however, the oral bioavailability of many drugs is limited by poor aqueous solubility, low permeability, and extensive first-pass metabolism. Drug–phospholipid complexes (DPCs) have emerged as an effective strategy to overcome these limitations and enhance oral drug absorption. In these systems, drug molecules form molecular complexes with phospholipids, resulting in improved lipophilicity, solubility, dissolution rate, membrane permeability, and gastrointestinal absorption. Additionally, phospholipids may facilitate lymphatic transport and reduce first-pass metabolism, leading to improved pharmacokinetic performance.

Various methods, including solvent evaporation, anti-solvent precipitation, freeze-drying, and supercritical fluid technology, have been employed for the preparation of DPCs. Their physicochemical properties are characterized using techniques such as FTIR, DSC, XRD, NMR, and electron microscopy. Recent advances in nanotechnology have further enhanced the potential of DPCs through the development of nano-phospholipid complexes and hybrid lipid-based delivery systems. This review highlights the principles, preparation methods, characterization techniques, mechanisms of bioavailability enhancement, recent advances, and pharmaceutical applications of drug–phospholipid complexes. The available evidence suggests that DPCs represent a promising platform for improving the oral delivery and therapeutic efficacy of poorly bioavailable drugs.

KEYWORDS: Drug–phospholipid complexes, oral bioavailability, phospholipids, lipid-based drug delivery, phytosomes, drug absorption.

1. INTRODUCTION:

Oral administration remains the most widely preferred route for drug delivery because of its convenience, patient compliance, cost-effectiveness, and suitability for long-term therapy. Despite these advantages, the successful oral delivery of many therapeutic agents is often limited by poor bioavailability resulting from low aqueous solubility, inadequate permeability across the gastrointestinal membrane, extensive first-pass metabolism, and chemical or enzymatic degradation within the gastrointestinal tract. It is estimated that a significant proportion of newly discovered drug candidates exhibit poor water solubility, which presents major challenges in achieving adequate therapeutic concentrations following oral administration. Consequently, improving the oral bioavailability of poorly absorbed drugs has become a central focus in pharmaceutical research and formulation development. **[**1,2**]**
Numerous formulation strategies have been investigated to overcome these limitations, including solid dispersions, cyclodextrin inclusion complexes, lipid-based formulations, nanoparticles, self-emulsifying

drug delivery systems, and nanocrystals. Among these approaches, lipid-based drug delivery systems have gained considerable attention because of their ability to enhance both drug solubility and intestinal absorption. Phospholipids, which are natural amphiphilic molecules and major constituents of biological membranes, possess excellent biocompatibility and safety profiles, making them attractive excipients for oral drug delivery applications. [3,4]

Drug–phospholipid complexes (DPCs), also referred to as pharmacosomes or phytosomes in certain contexts, represent a promising lipid-based approach for enhancing the oral bioavailability of poorly soluble drugs and bioactive compounds. In these systems, drug molecules interact with phospholipids through hydrogen bonding, electrostatic interactions, or van der Waals forces to form stable molecular complexes. Unlike simple physical mixtures, drug–phospholipid complexes exhibit altered physicochemical properties, including increased lipophilicity, improved membrane affinity, enhanced dissolution characteristics, and greater stability. These features contribute significantly to improved gastrointestinal absorption and therapeutic performance. [5,6]

The concept of drug–phospholipid complexation has attracted growing interest over the past two decades due to its effectiveness in improving the delivery of a wide range of pharmaceutical compounds. Several natural products, such as curcumin, quercetin, silybin, resveratrol, and berberine, have demonstrated markedly enhanced absorption and bioavailability when formulated as phospholipid complexes. Similarly, numerous synthetic drugs with poor aqueous solubility have shown improved pharmacokinetic profiles following complexation with phospholipids. The versatility of this technology has expanded its applications across various therapeutic areas, including anticancer, anti-inflammatory, antimicrobial, cardiovascular, and central nervous system disorders. [7,8]

The mechanism by which drug–phospholipid complexes enhance oral bioavailability involves multiple pathways. Complexation increases the apparent solubility and wettability of hydrophobic drugs, facilitates their interaction with intestinal membranes, and promotes transcellular transport across the gastrointestinal epithelium. In addition, the lipidic nature of phospholipids may stimulate lymphatic transport, thereby reducing hepatic first-pass metabolism and increasing systemic drug exposure. Furthermore, phospholipid complexes can provide protection against chemical and enzymatic degradation, contributing to enhanced stability during gastrointestinal transit. [9,10]

Advances in formulation science and nanotechnology have further expanded the potential of drug–phospholipid complexes. Recent developments include nano-phospholipid complexes, phospholipid complex-loaded nanoparticles, self-emulsifying phospholipid systems, and targeted lipid-based carriers designed to achieve improved therapeutic efficacy. Modern characterization techniques such as Fourier transform infrared spectroscopy (FTIR), differential scanning calorimetry (DSC), nuclear magnetic resonance (NMR), and X-ray diffraction (XRD) have facilitated a deeper understanding of drug–phospholipid interactions and their influence on formulation performance. [11,12]

Given the increasing number of poorly soluble drug candidates emerging from modern drug discovery programs, drug–phospholipid complex technology offers a valuable platform for enhancing oral absorption and therapeutic outcomes. This review highlights the fundamental principles, preparation methods, characterization techniques, mechanisms of bioavailability enhancement, recent advances, and future prospects of drug–phospholipid complexes in oral drug delivery systems. [13,14]

1.2 SCOPE AND OBJECTIVES OF THE REVIEW

The growing interest in drug–phospholipid complex technology has led to significant advances in formulation design, characterization methods, and therapeutic applications. This review aims to provide a comprehensive overview of drug–phospholipid complexes, focusing on their role in enhancing oral drug bioavailability. The review discusses the fundamental principles of complex formation, mechanisms of bioavailability enhancement, preparation techniques, characterization methods, recent advancements, and pharmaceutical applications. Furthermore, current challenges, future prospects, and opportunities for clinical translation are highlighted to provide insights into the potential of DPCs as an effective strategy for improving oral drug delivery. [15,16]

2. ORAL DRUG BIOAVAILABILITY: AN OVERVIEW

Oral bioavailability is a critical pharmacokinetic parameter that determines the extent and rate at which an orally administered drug reaches the systemic circulation in its unchanged form. It directly influences the therapeutic efficacy, dosage requirements, and clinical performance of pharmaceutical products. Although oral administration is the most preferred route of drug delivery, several physiological and physicochemical barriers can limit drug absorption and reduce systemic availability. Therefore, understanding the factors affecting oral bioavailability is essential for the development of effective drug delivery systems. **[**17,18**]**

2.1 DEFINITION OF BIOAVAILABILITY

Bioavailability is defined as the fraction or percentage of an administered dose of a drug that reaches the systemic circulation in an unchanged form and becomes available at the site of action. For intravenous administration, bioavailability is considered 100% because the drug is directly introduced into the bloodstream. In contrast, orally administered drugs often exhibit lower bioavailability due to incomplete absorption and first-pass metabolism in the gastrointestinal tract and liver. Bioavailability is commonly evaluated using pharmacokinetic parameters such as maximum plasma concentration (Cmax), time to reach maximum concentration (Tmax), and area under the plasma concentration–time curve (AUC). **[19,20]**

2.2 FACTORS AFFECTING ORAL BIOAVAILABILITY

The oral bioavailability of a drug is influenced by several interrelated factors, which can be broadly categorized into drug-related factors, physiological factors, and formulation factors.

2.2.1 DRUG-RELATED FACTORS

Drug-related factors are intrinsic physicochemical properties of the drug molecule that influence its dissolution, absorption, and transport across biological membranes.

2.2.2AQUEOUS SOLUBILITY

Drug dissolution in gastrointestinal fluids is a prerequisite for absorption. Poorly water-soluble drugs exhibit slow dissolution rates, resulting in reduced absorption and low bioavailability. Many newly developed drugs suffer from solubility-related limitations because of their highly lipophilic nature. [21]

2.2.3LIPOPHILICITY

Lipophilicity determines the ability of a drug to permeate biological membranes. While moderate lipophilicity promotes membrane transport, excessively lipophilic drugs may exhibit poor aqueous solubility, thereby reducing overall absorption. **[**22**]**

2.2.4MOLECULAR SIZE AND STRUCTURE

Large molecular weight compounds generally have lower permeability across intestinal membranes than smaller molecules. Structural characteristics such as hydrogen bonding capacity and molecular flexibility also influence absorption. **[**23**]**

2.2.5PKA AND DEGREE OF IONIZATION

The ionization state of a drug depends on its pKa and the pH of the gastrointestinal environment. Non-ionized drug molecules generally cross biological membranes more readily than ionized forms, thereby affecting oral absorption. [24]

2.2.6 PHYSIOLOGICAL FACTORS

Physiological conditions within the gastrointestinal tract significantly influence drug absorption and bioavailability.

2.2.7GASTROINTESTINAL PH

The pH varies throughout the gastrointestinal tract and affects drug solubility, dissolution, and ionization. Drugs may exhibit different absorption profiles depending on the site of absorption and local pH conditions. [25]

2.2.8GASTRIC EMPTYING AND INTESTINAL TRANSIT TIME

The rate at which a drug passes through the gastrointestinal tract determines the time available for dissolution and absorption. Delayed gastric emptying may prolong drug dissolution, whereas rapid transit can reduce absorption. [26]

2.2.9FIRST-PASS METABOLISM

Drugs absorbed from the gastrointestinal tract pass through the liver before reaching systemic circulation. Extensive metabolism in the intestinal wall and liver can substantially decrease the amount of active drug available in the bloodstream. [27]

2.2.10TRANSPORTERS AND EFFLUX PROTEINS

Membrane transporters such as P-glycoprotein (P-gp) can actively transport drugs back into the intestinal lumen, thereby reducing absorption and bioavailability. [28]

2.2.11FORMULATION FACTORS

The design and composition of a dosage form can greatly affect drug dissolution and absorption.

2.2.12PARTICLE SIZE

Reduction in particle size increases surface area, enhancing dissolution rate and drug absorption. Micronization and nanonization are widely used techniques to improve bioavailability. [29]

2.2.13EXCIPIENTS

Excipients can influence drug release, solubility, permeability, and stability. Certain excipients may act as absorption enhancers or inhibit efflux transporters. [30]

2.2.14DOSAGE FORM DESIGN

The type of formulation, such as tablets, capsules, suspensions, lipid-based systems, or nanoparticles, affects drug release and absorption behavior. Advanced formulation approaches are often employed to overcome bioavailability limitations. [31]

2.3 BIOPHARMACEUTICS CLASSIFICATION SYSTEM (BCS)

The Biopharmaceutics Classification System (BCS) is a scientific framework used to classify drug substances based on their aqueous solubility and intestinal permeability. It serves as an important tool for predicting oral absorption and guiding formulation development. According to the BCS, drugs are classified into four categories:

Table 2.1. Biopharmaceutics Classification System (BCS)

BCS Class	Solubility	Permeability	Example Drugs
Class I	High	High	Metoprolol, Propranolol
Class II	Low	High	Curcumin, Celecoxib, Ketoconazole
Class III	High	Low	Cimetidine, Atenolol
Class IV	Low	Low	Hydrochlorothiazide, Furosemide

BCS Class I drugs generally exhibit good oral absorption and do not require extensive formulation interventions. In contrast, Class II and Class IV drugs often face significant bioavailability challenges because of poor solubility and/or permeability limitations. [32,33]

2.4 IMPORTANCE OF IMPROVING BIOAVAILABILITY OF BCS CLASS II AND IV DRUGS

The majority of newly discovered drug candidates belong to BCS Class II and Class IV categories, making bioavailability enhancement a major concern in pharmaceutical development.

2.4.1BCS CLASS II DRUGS

BCS Class II drugs possess high permeability but poor aqueous solubility. Their absorption is primarily limited by dissolution rate. Strategies that enhance solubility and dissolution, such as drug–phospholipid complexes, solid dispersions, lipid-based formulations, and nanocrystals, can significantly improve oral bioavailability. [34]

2.4.2BCS CLASS IV DRUGS

BCS Class IV drugs exhibit both poor solubility and poor permeability, making them the most challenging category for oral delivery. These compounds often require advanced drug delivery systems capable of simultaneously improving dissolution and membrane transport. Drug–phospholipid complexes have shown considerable potential in addressing these limitations through enhanced lipophilicity, membrane interaction, and intestinal absorption. [35]

Improving the bioavailability of BCS Class II and IV drugs can reduce dose requirements, minimize variability in drug absorption, improve therapeutic efficacy, and enhance patient compliance.

Consequently, the development of innovative formulation approaches such as drug–phospholipid complexes has become increasingly important in modern pharmaceutical research. [36]

3. DRUG–PHOSPHOLIPID COMPLEXES: CONCEPT AND FUNDAMENTALS

Drug–phospholipid complexes (DPCs) have emerged as an effective lipid-based formulation strategy for improving the oral bioavailability of poorly soluble and poorly permeable drugs. These complexes are formed through specific molecular interactions between drug molecules and phospholipids, resulting in enhanced physicochemical and biopharmaceutical properties. Owing to their ability to improve solubility, dissolution rate, membrane permeability, and therapeutic efficacy, DPCs have gained significant attention in pharmaceutical research and development. [37,38]

3.1 DEFINITION OF DRUG–PHOSPHOLIPID COMPLEXES

Drug–phospholipid complexes are molecular complexes formed by the interaction of drug molecules with phospholipids in a specific stoichiometric ratio. The interaction generally occurs through hydrogen bonding, electrostatic attraction, or van der Waals forces between the polar functional groups of the drug and the polar head group of the phospholipid. Unlike conventional formulations, where the drug is merely dispersed in a carrier, DPCs involve the formation of a stable molecular association that modifies the physicochemical characteristics of the drug. This association enhances lipophilicity, facilitates membrane transport, and improves oral absorption. **[39,40]**

3.2 HISTORICAL DEVELOPMENT

The concept of phospholipid complexation originated from efforts to improve the absorption of plant-derived bioactive compounds with poor bioavailability. In the late 1980s, researchers developed phospholipid complexes of herbal constituents and introduced the term “phytosome” to describe these systems. The technology was initially applied to flavonoids such as silybin and later expanded to include curcumin, quercetin, ginkgo flavones, and numerous synthetic drugs. Over time, advances in formulation science and analytical techniques have enabled the development of more sophisticated drug–phospholipid complexes with enhanced stability and bioavailability. Today, DPC technology is recognized as a versatile platform for oral, transdermal, and targeted drug delivery applications. **[41,42]**

3.3 DIFFERENCE BETWEEN PHYSICAL MIXTURES, LIPOSOMES, PHYTOSOMES, AND DRUG–PHOSPHOLIPID COMPLEXES

Although these systems involve phospholipids, they differ significantly in structure, preparation, and performance.

3.3.1PHYSICAL MIXTURES

A physical mixture consists of a simple blending of drug and phospholipid without any significant molecular interaction. The drug remains in its original crystalline or amorphous form, and the enhancement in bioavailability is generally limited. No stable complex is formed between the components. **[43]**

3.3.2LIPOSOMES

Liposomes are vesicular systems composed of one or more phospholipid bilayers surrounding an aqueous core. Drugs may be entrapped within the aqueous compartment or incorporated into the lipid bilayer. In liposomes, the drug is encapsulated rather than chemically associated with phospholipids. Liposomes are widely used for targeted and controlled drug delivery. [44]

3.3.3PHYTOSOMES

Phytosomes are specialized phospholipid complexes prepared from plant-derived bioactive compounds, particularly polyphenols and flavonoids. In phytosomes, the phytoconstituent forms a molecular complex with phospholipids, resulting in enhanced absorption and therapeutic efficacy. Phytosomes are essentially a subclass of drug–phospholipid complexes specifically designed for herbal compounds. [45]

3.3.4DRUG–PHOSPHOLIPID COMPLEXES

Drug–phospholipid complexes encompass both phytoconstituents and synthetic drugs. In these systems, the drug is molecularly complexed with phospholipids, leading to increased lipophilicity, improved membrane permeability, enhanced dissolution, and better bioavailability. Unlike liposomes, the drug is not encapsulated but is directly associated with phospholipid molecules. [46]

TABLE 3.1. COMPARISON OF DIFFERENT PHOSPHOLIPID-BASED SYSTEMS

Parameter	Physical Mixture	Liposome	Phytosome	Drug–Phospholipid Complex
Drug–phospholipid interaction	Absent	Encapsulation	Molecular complex	Molecular complex
Structural organization	Simple blend	Vesicular system	Molecular complex	Molecular complex
Bioavailability enhancement	Low	Moderate	High	High
Suitable for herbal compounds	Limited	Yes	Excellent	Yes
Suitable for synthetic drugs	Yes	Yes	Limited	Excellent

3.4 MECHANISM OF COMPLEX FORMATION

The formation of drug–phospholipid complexes involves molecular interactions between functional groups present in the drug molecule and the polar head group of phospholipids. Functional groups such as hydroxyl (-OH), amino (-NH_2), carboxyl (-COOH), and carbonyl (>C=O) commonly participate in complex formation.

The phospholipid molecule contains a hydrophilic polar head and hydrophobic fatty acid tails. During complexation, the polar head group interacts with the drug molecule through hydrogen bonding or electrostatic attraction, while the hydrophobic tails remain free to interact with lipid membranes. This arrangement results in increased lipophilicity and improved affinity for biological membranes, thereby enhancing absorption and bioavailability. [47,48]

The major mechanisms involved in bioavailability enhancement include:

- Improved drug solubility and wettability
- Increased membrane permeability
- Enhanced dissolution rate
- Improved gastrointestinal absorption
- Promotion of lymphatic transport
- Reduced first-pass metabolism
- Enhanced stability against degradation

3.5 TYPES OF PHOSPHOLIPIDS USED

The selection of phospholipids plays a crucial role in determining the properties and performance of drug–phospholipid complexes.

3.5.1 PHOSPHATIDYLCHOLINE (PC)

Phosphatidylcholine is the most widely used phospholipid in DPC formulations. It is a major component of biological membranes and possesses excellent biocompatibility and amphiphilic characteristics. PC forms stable complexes with a wide range of drugs and phytoconstituents and significantly improves solubility, permeability, and oral absorption. Because of its safety and effectiveness, phosphatidylcholine is considered the phospholipid of choice for most DPC formulations. [49]

3.5.2 PHOSPHATIDYLETHANOLAMINE (PE)

Phosphatidylethanolamine is another naturally occurring phospholipid commonly found in cell membranes. It possesses a smaller polar head group than phosphatidylcholine, which influences membrane fluidity and drug interaction characteristics. PE has been investigated for the preparation of lipid-based formulations requiring enhanced membrane fusion and permeability. [50]

3.5.3 PHOSPHATIDYLSERINE (PS)

Phosphatidylserine is an anionic phospholipid that contains a serine residue in its polar head group. It plays an important role in cell signaling and membrane function. Due to its negative charge, PS can interact strongly with positively charged drug molecules and has been explored for specialized drug delivery applications, particularly in neurological and targeted delivery systems. [51]

3.5.4 Soy Phospholipids

Soy phospholipids are natural phospholipid mixtures obtained from soybean lecithin and represent one of the most economical and widely used sources of phospholipids in pharmaceutical formulations. They primarily contain phosphatidylcholine along with phosphatidylethanolamine, phosphatidylinositol, and phosphatidylserine. Soy phospholipids offer excellent safety, biodegradability, and large-scale availability, making them highly suitable for commercial DPC production. [52]

TABLE 3.2. COMMON PHOSPHOLIPIDS USED IN DRUG–PHOSPHOLIPID COMPLEXES

Phospholipid	Characteristics	Applications
Phosphatidylcholine	High biocompatibility, amphiphilic nature	Most commonly used in DPCs
Phosphatidylethanolamine	Enhanced membrane interaction	Lipid-based formulations
Phosphatidylserine	Negatively charged phospholipid	Targeted and neurological delivery
Soy phospholipids	Economical, natural source, biodegradable	Commercial DPC formulation

4. MECHANISM OF BIOAVAILABILITY ENHANCEMENT BY DRUG–PHOSPHOLIPID COMPLEXES

Drug–phospholipid complexes (DPCs) improve oral bioavailability through multiple mechanisms that collectively enhance the solubility, dissolution, permeability, stability, and absorption of poorly bioavailable drugs. The amphiphilic nature of phospholipids enables effective interaction with both aqueous gastrointestinal fluids and lipid-rich biological membranes, thereby facilitating drug transport across physiological barriers. These mechanisms contribute significantly to increased systemic drug exposure and improved therapeutic efficacy. [53,54]

4.1 IMPROVED SOLUBILITY

Poor aqueous solubility is a major factor limiting the oral bioavailability of many drugs. Drug–phospholipid complexation enhances the apparent solubility of poorly water-soluble compounds by modifying their physicochemical properties and improving their interaction with gastrointestinal fluids. The amphiphilic structure of phospholipids allows the complex to exhibit both hydrophilic and lipophilic characteristics, promoting better dispersion and dissolution in the gastrointestinal environment. [55]

4.1.1 INCREASED WETTABILITY

Wettability refers to the ability of a liquid to spread over the surface of a solid material. Poorly soluble drugs often possess hydrophobic surfaces that resist wetting by gastrointestinal fluids. When complexed with phospholipids, the hydrophilic polar head groups of phospholipids increase surface wettability, facilitating rapid contact with dissolution media. Improved wettability enhances the dissolution process and increases the amount of drug available for absorption. [56]

4.1.2 IMPROVED DISPERSION IN GASTROINTESTINAL FLUIDS

Drug–phospholipid complexes exhibit improved dispersibility in gastrointestinal fluids compared with pure drugs. The amphiphilic nature of phospholipids promotes the formation of fine dispersions and prevents drug aggregation. This increased dispersion leads to a larger effective surface area available for dissolution and absorption, thereby enhancing oral bioavailability. [57]

4.2 ENHANCED MEMBRANE PERMEABILITY

Effective oral absorption requires drug molecules to permeate the intestinal epithelium and enter systemic circulation. Drug–phospholipid complexes enhance membrane permeability by increasing the affinity of drugs for biological membranes and facilitating transcellular transport. [58]

4.2.1 INCREASED LIPOPHILICITY

Complex formation with phospholipids increases the apparent lipophilicity of many drug molecules. The hydrophobic fatty acid chains of phospholipids improve the ability of the drug to partition into lipid-rich biological membranes. Enhanced lipophilicity facilitates membrane penetration and promotes efficient absorption through the intestinal epithelium. [59]

4.2.2 IMPROVED INTESTINAL ABSORPTION

The structural similarity between phospholipids and cell membrane components enables DPCs to interact effectively with intestinal epithelial cells. These interactions enhance transcellular transport and improve drug uptake across the gastrointestinal barrier. Several studies have demonstrated significantly higher absorption rates and plasma drug concentrations for phospholipid complexes compared with uncomplexed drugs. [60]

4.3 IMPROVED DISSOLUTION RATE

The dissolution rate of a drug is a critical determinant of oral absorption, particularly for poorly soluble compounds. Drug–phospholipid complexes improve dissolution behavior by altering the physical state of the drug and reducing crystallinity. [61]

4.3.1 REDUCED CRYSTALLINITY

Many poorly soluble drugs exist in highly crystalline forms that dissolve slowly in gastrointestinal fluids. During complex formation, the crystalline structure may become partially disrupted, resulting in reduced crystallinity. Lower crystallinity increases molecular mobility and facilitates faster dissolution, leading to improved drug absorption. [62]

4.3.2 AMORPHIZATION

In some cases, drug–phospholipid complexation converts crystalline drug molecules into an amorphous or partially amorphous state. Amorphous materials possess higher free energy and greater apparent solubility than their crystalline counterparts. Consequently, amorphization contributes to enhanced dissolution rates and improved bioavailability. [63]

4.4 LYMPHATIC TRANSPORT

Lymphatic transport represents an important pathway through which lipid-based formulations can enhance oral bioavailability. Because phospholipids are naturally involved in lipid digestion and absorption, drug–phospholipid complexes may associate with lipid absorption pathways within the gastrointestinal tract. After absorption, a portion of the drug can be transported through the intestinal lymphatic system rather than directly entering the portal circulation. This pathway bypasses hepatic first-pass metabolism and increases the amount of drug reaching systemic circulation. [64]

4.4.1BYPASSING HEPATIC FIRST-PASS METABOLISM

Many drugs undergo extensive metabolism in the liver before reaching systemic circulation, resulting in substantial loss of active drug. Lymphatic transport reduces exposure to hepatic metabolic enzymes and enhances systemic drug availability. This mechanism is particularly beneficial for highly lipophilic drugs that are susceptible to significant first-pass metabolism. [65]

4.5 Protection Against Degradation

Drug degradation within the gastrointestinal tract can significantly reduce oral bioavailability. Drug–phospholipid complexes provide a protective microenvironment that shields drug molecules from adverse gastrointestinal conditions. [66]

4.5.1IMPROVED STABILITY IN THE GASTROINTESTINAL TRACT

The molecular association between drugs and phospholipids can protect sensitive compounds from hydrolysis, oxidation, enzymatic degradation, and acidic conditions encountered in the gastrointestinal tract. Enhanced stability prolongs drug residence time, preserves drug integrity, and increases the amount of intact drug available for absorption. This protective effect is especially important for natural products and chemically unstable drugs. [67,68]

5. METHODS OF PREPARATION OF DRUG–PHOSPHOLIPID COMPLEXES

The preparation method plays a crucial role in determining the physicochemical properties, complexation efficiency, stability, and bioavailability of drug–phospholipid complexes (DPCs). Several techniques have been developed to facilitate the interaction between drug molecules and phospholipids, each offering specific advantages and limitations. The choice of method depends on the physicochemical characteristics of the drug, type of phospholipid, desired product properties, and scale of production. [70,71]

5.1 SOLVENT EVAPORATION METHOD

PRINCIPLE

The solvent evaporation method is the most widely employed technique for preparing drug–phospholipid complexes. It is based on dissolving both the drug and phospholipid in a common organic solvent, allowing molecular interactions to occur. Subsequent removal of the solvent results in the formation of a stable drug–phospholipid complex. [72]

PROCEDURE

1. Drug and phospholipid are weighed in a predetermined molar ratio.
2. Both components are dissolved in a common organic solvent such as ethanol, methanol, dichloromethane, or chloroform.
3. The solution is stirred continuously to facilitate complex formation.
4. The solvent is removed under reduced pressure using a rotary evaporator.
5. The resulting residue is dried under vacuum to remove residual solvent.
6. The dried complex is collected, pulverized, and stored appropriately. [73]

ADVANTAGES

- Simple and widely used technique.
- High complexation efficiency.
- Suitable for both synthetic drugs and phytoconstituents.
- Easy scale-up for industrial production.
- Produces homogeneous complexes. [74]

LIMITATIONS

- Use of organic solvents may pose toxicity concerns.
- Possibility of residual solvent contamination.
- Not suitable for thermolabile compounds requiring prolonged evaporation.
- Environmental concerns associated with solvent disposal. [75]

5.2 ANTI-SOLVENT PRECIPITATION METHOD

PRINCIPLE

This method is based on the precipitation of the drug–phospholipid complex by adding a solution containing the drug and phospholipid into a non-solvent (anti-solvent) in which the complex has low solubility. The sudden decrease in solubility promotes complex formation and precipitation. [76]

PROCEDURE

1. Drug and phospholipid are dissolved in a suitable organic solvent.
2. The resulting solution is slowly added to an anti-solvent such as n-hexane or water under continuous stirring.
3. Complex precipitation occurs due to reduced solubility.
4. The precipitate is separated by filtration or centrifugation.
5. The collected complex is dried and stored. [77]

ADVANTAGES

- Simple and economical process.
- Low energy requirement.
- Produces fine particles with improved surface area.
- Suitable for poorly soluble compounds. [78]

LIMITATIONS

- Particle size distribution may be difficult to control.
- Incomplete precipitation may reduce yield.
- Residual solvent may remain in the product.
- Requires optimization of solvent-to-anti-solvent ratio. [79]

5.3 FREEZE-DRYING METHOD (LYOPHILIZATION)

PRINCIPLE

Freeze-drying involves freezing a solution containing the drug and phospholipid followed by sublimation of the solvent under reduced pressure. This process preserves the molecular structure and produces highly porous complexes. [80]

PROCEDURE

1. Drug and phospholipid are dissolved in a suitable solvent system.
2. The solution is frozen at very low temperatures.
3. Frozen samples are subjected to lyophilization.
4. Ice crystals are removed by sublimation under vacuum.
5. A dry porous drug–phospholipid complex is obtained. [81]

ADVANTAGES

- Suitable for heat-sensitive compounds.
- Produces highly porous products with enhanced dissolution.
- Minimal thermal degradation.
- Improved stability of bioactive compounds. [82]

LIMITATIONS

- Expensive equipment and operating costs.
- Time-consuming process.
- Difficult scale-up for large-scale production.
- Requires specialized handling conditions. **[83]**

5.4 SUPERCRITICAL FLUID TECHNOLOGY

PRINCIPLE

Supercritical fluid technology utilizes supercritical carbon dioxide (SC-CO_2) as a solvent or anti-solvent to facilitate drug–phospholipid complex formation. Above its critical temperature and pressure, CO_2 exhibits properties of both liquids and gases, enabling efficient particle formation with minimal solvent residues. [84]

PROCEDURE

1. Drug and phospholipid are dissolved in an organic solvent.
2. Supercritical CO_2 is introduced into the system.
3. Rapid expansion or precipitation leads to complex formation.
4. Solvent is removed by depressurization.
5. The resulting complex particles are collected and dried. [85]

ADVANTAGES

- Environmentally friendly process.

- Minimal residual solvent content.
- Produces uniform particles.
- Suitable for large-scale pharmaceutical manufacturing.
- Enhanced product purity. [86]

LIMITATIONS

- High equipment cost.
- Requires specialized operational expertise.
- Limited applicability for certain compounds.
- Process optimization can be complex. [87]

5.5 REFLUX METHOD

PRINCIPLE

The reflux method involves heating a solution containing the drug and phospholipid under controlled conditions while preventing solvent loss through condensation. Continuous heating promotes molecular interaction and complex formation. [88]

PROCEDURE

1. Drug and phospholipid are dissolved in an appropriate solvent.
2. The mixture is heated under reflux for a specified period.
3. Continuous stirring facilitates interaction between components.
4. After completion, the solvent is removed by evaporation.
5. The residue is dried and collected as the drug–phospholipid complex. [89]

ADVANTAGES

- Simple laboratory-scale technique.
- Efficient complex formation.
- Suitable for drugs with moderate thermal stability.
- Requires minimal specialized equipment. [90]

LIMITATIONS

- Not suitable for thermolabile drugs.
- Longer processing time.
- Potential degradation due to prolonged heating.
- Solvent recovery may be required. [91]

5.6 SOLVENT INJECTION METHOD

PRINCIPLE

In the solvent injection method, a drug–phospholipid solution prepared in an organic solvent is injected into an aqueous phase. Rapid solvent diffusion promotes spontaneous formation of drug–phospholipid complexes with reduced particle size. [92]

PROCEDURE

1. Drug and phospholipid are dissolved in a volatile organic solvent.
2. The solution is injected slowly into distilled water under stirring.
3. Complex formation occurs due to solvent diffusion and self-assembly.
4. Organic solvent is removed by evaporation.
5. The complex is collected by centrifugation or filtration and dried. [93]

ADVANTAGES

- Produces small and uniform particles.
- Simple and reproducible process.
- Suitable for nano-sized formulations.
- Improved dissolution properties. [94]

LIMITATIONS

- Requires careful control of injection rate.
- Possible residual solvent contamination.
- Lower yield compared with solvent evaporation.
- Scale-up challenges for industrial production. [95]

TABLE 5.1. COMPARISON OF PREPARATION METHODS FOR DRUG–PHOSPHOLIPID COMPLEXES

Method	Principle	Major Advantages	Major Limitations
Solvent Evaporation	Solvent removal after complex formation	Simple, high efficiency	Residual solvent issues
Anti-solvent Precipitation	Precipitation in non-solvent	Economical, fine particles	Variable particle size
Freeze-Drying	Sublimation of frozen solvent	Suitable for thermolabile drugs	Expensive and time-consuming
Supercritical Fluid Technology	SC-CO_2-mediated complex formation	Solvent-free, uniform particles	High equipment cost
Reflux Method	Heating under solvent reflux	Simple and effective	Not suitable for heat-sensitive drugs
Solvent Injection	Injection into aqueous phase	Small particle size	Scale-up difficulties

6. CONCLUSION

Drug–phospholipid complexes (DPCs) have emerged as a promising and effective strategy for overcoming the challenges associated with poor oral bioavailability of many therapeutic agents. By forming molecular complexes with phospholipids, drugs can exhibit improved solubility, enhanced dissolution rate, increased membrane permeability, greater gastrointestinal stability, and reduced first-pass metabolism. These advantages collectively contribute to improved absorption and enhanced therapeutic efficacy.

The versatility of DPC technology has enabled its successful application to a wide range of synthetic drugs and phytoconstituents, particularly those belonging to BCS Class II and Class IV categories. Various

preparation methods, including solvent evaporation, anti-solvent precipitation, freeze-drying, supercritical fluid technology, reflux, and solvent injection techniques, have been developed to produce stable and efficient complexes. Advanced characterization tools such as FTIR, DSC, XRD, NMR, SEM, and TEM have further improved the understanding of drug–phospholipid interactions and formulation behavior.

Recent advancements in nanotechnology and lipid-based drug delivery systems have expanded the potential applications of DPCs through the development of nano-phospholipid complexes, hybrid formulations, and targeted delivery approaches. Despite challenges related to large-scale manufacturing, formulation stability, and regulatory considerations, the growing body of preclinical and clinical evidence highlights the significant potential of DPCs in enhancing oral drug delivery.

Overall, drug–phospholipid complexes represent a versatile, biocompatible, and clinically relevant formulation platform capable of addressing major bioavailability limitations. Continued research focused on process optimization, novel phospholipid materials, and clinical translation is expected to further strengthen their role in modern pharmaceutical development and improve therapeutic outcomes for poorly bioavailalable drugs [96,100]

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