WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
Coden USA: WJPRAP Impact Factor 8.63
Volume 15, Issue 13, 16-37. Review Article ISSN 2277–7105

A REVIEW ARTICLE ON LIPID-BASED DRUG DELIVERY SYSTEMS

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Article Received on 03 June 2026,
Article Revised on 23 June 2026,
Article Published on 01 July 2026,
https://doi.org/10.5281/zenodo.21022086

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How to cite this Article: *Khan Kaif, Dr. Nidhi Chauhan, Dr. Megha Shah, Ms Nandini Modi, Diwan Samiya, Bhavya Modi. (2026). A Review Article On Lipid-Based Drug Delivery Systems. World Journal of Pharmaceutical Research, 15(13), 16–37.

ABSTRACT

Poor water solubility of drugs is a major problem in oral drug delivery and often leads to low and unpredictable bioavailability. A large number of newly developed drugs show poor solubility, which limits their absorption in the gastrointestinal tract and reduces therapeutic effectiveness. Lipid-based drug delivery systems (LBDDS) have gained significant attention as an effective approach to overcome these limitations. These systems improve drug solubilization, protect drugs from degradation, and enhance absorption after oral administration. This review discusses the key aspects of lipid-based oral drug delivery systems, including formulation considerations, classification, mechanisms of drug absorption, and characterization methods. Various lipid-based carriers such as nano emulsions, solid lipid nanoparticles, nanostructured lipid carriers, self-emulsifying drug delivery systems, liposomes, and other advanced lipid formulations are described. The role of lipids, surfactants, and digestion processes in improving oral bioavailability is also highlighted. Due to their biocompatibility, biodegradability, and ability to enhance drug absorption, lipid-based drug delivery systems represent a promising strategy for improving the oral delivery of poorly water-soluble drugs.

KEYWORDS: Solid lipid nanoparticle, Nanostructured lipid carrier (NLC), Self-emulsifying drug delivery system (SEDDS), Bioavailability enhancement, Lipid excipients, Nano

emulsion formulation.

1. INTRODUCTION[1,2,3,12,14,15]

The oral route is one of the most preferred methods for drug delivery due to its convenience, cost-effectiveness, and high patient compliance. It is particularly valuable for treating chronic conditions such as diabetes, hypertension, and cancer. However, for a drug to be effectively absorbed through this route, it must remain stable in the gastrointestinal (GI) tract, have suitable membrane permeability, and exhibit optimal solubility. A major challenge in drug development is that more than 40% of newly discovered active pharmaceutical ingredients (APIs) are poorly soluble in water, leading to low oral bioavailability. This limitation has driven the need for innovative delivery systems, with lipid-based drug delivery systems (LBDDS) emerging as a promising solution.

The Biopharmaceutics Classification System (BCS) categorizes drugs based on their solubility and permeability. Many modern drugs fall into Class 2 (low solubility, high permeability) or Class 4 (low solubility, low permeability), where poor dissolution in the GI tract becomes a major barrier to absorption. To address this, researchers have explored various formulation strategies, with Lipid based systems showing significant potential due to their ability to enhance drug solubility and absorption. Lipid-based formulations offer several advantages, including bio compatibility, low toxicity, and versatility in administration routes. A key factor in their effectiveness is lipophilicity, the ability of a drug to dissolve in fats and oils—which directly impacts solubility, membrane penetration, and overall drug performance. By improving solubilization in the gut and modulating drug transport mechanisms (such as inhibiting P-glycoprotein efflux), LBDDS can significantly enhance bioavailability.

2. KEY CONSIDERATIONS FOR FORMULATION DEVELOPMENT[1,3,4]

The primary factors influencing excipient selection in lipid-based formulations include:

a. Solubility
b. Dispersion
c. Digestion
d. Absorption

Additional factors to consider are:

a. Regulatory concerns—irritation potential, toxicity, existing knowledge, and prior experience

b. Solvent capacity
c. Miscibility with other components
d. Physical state at room temperature (e.g., melting point)
e. Self-dispersing capability and role in enhancing formulation dispersion
f. Digestibility and the fate of digestion byproducts
g. Compatibility with capsule materials
h. Purity and chemical stability
i. Production costs

1.1 Solubility

Although lipids (fatty acid derivatives) serve as the primary component of the formulation, surfactants—and sometimes a hydrophilic cosolvent—may be necessary to enhance solubilization and improve dispersion characteristics. Surfactants are classified by their hydrophilic-lipophilic balance (HLB) number, where lower values (≤10) indicate greater lipophilicity and higher values (≥10) suggest increased hydrophilicity. As a general rule for initial formulation design, many lipids used in oral formulations have a specified 'required HLB' value (often provided by suppliers), representing the ideal HLB for the surfactant mixture needed to emulsify the oil in water. Different emulsifiers, as listed in Table 2, can be selected based on their HLB values.

1.2 Dispersion

Formulations that demonstrate adequate drug solubility should also be evaluated for their emulsification and dispersion properties in aqueous environments. Initial screening can involve microscopic examination of the formulation when combined with water. Effective emulsification is indicated by vigorous mixing, diffusion, and interfacial interactions at the water-formulation boundary. Additionally, the absence of drug precipitation upon full mixing with the aqueous medium is essential. Techniques such as laser light scattering can measure emulsion droplet size to identify viable formulations. Ternary phase diagrams are commonly used to analyze emulsification structures and assess formulation behaviour during dilution. A dilution path for a formulation containing 35% surfactant and 65% oil, transitioning through water-in-oil microemulsions and lamellar liquid crystals before forming a stable oil-in-water microemulsion upon dilution. While constructing the full phase diagram may not always be necessary, understanding structural changes during dilution is crucial to ensure stable dispersion. Combining low and high HLB surfactants often yields smaller emulsion droplets compared to single surfactants. These combinations can be studied using pseudo ternary phase diagrams.

1.3 Digestion

Intestinal lipases significantly influence the performance of lipid-based formulations in the gastrointestinal (GI) tract, making their role a critical consideration in formulation design. It is well-established that digestible, yet non-dispersible lipids (e.g., triglycerides) are broken down by lipases into mono-/diglycerides and fatty acids, which subsequently emulsify any remaining oil. Consequently, excessive surfactants may not be required to achieve the necessary small particle sizes and large surface areas for drug release. In 2000, Pouton introduced a classification system (Table 3) for lipid-based formulations, categorizing them based on composition and their reliance on digestion for dispersion.

1.4 Absorption

The ultimate objective of any oral lipid-based formulation is to ensure efficient drug absorption by intestinal mucosal cells. Figure 2 outlines the processes involved in the intestinal environment for such formulations. Initially, components disperse to form lipid droplets (Type I formulations) or emulsion droplets (Types II-III), followed by lipolysis and solubilization of digestible products by bile acids into mixed micelles. The drug is then believed to partition from emulsion droplets and bile salt micelles, facilitating absorption by intestinal mucosal cells

2. GENERAL ROUTES FOR ADMINISTERING LIPID-BASED DRUG DELIVERY SYSTEMS (LBDDS)[1,4]

Lipid-based drug delivery systems (LBDDS) can be administered through various routes, including oral, parenteral (such as intravenous or intramuscular), ocular (through the eyes), intranasal (through the nose), dermal or transdermal (via the skin), and vaginal pathways. Among these options, the oral route remains the most widely favoured and commonly employed method. This preference is primarily due to several significant advantages: it is non- invasive, generally more cost-effective, and associated with fewer complications, such as the local adverse effects that can occur at injection sites with parenteral delivery. Moreover, oral administration is typically regarded as the simplest and most user-friendly approach, making it especially suitable for long term or chronic treatments.

However, when developing LBDDS, especially in the early stages of formulation design, it is crucial to implement a well-structured and logical strategy. Such a systematic approach helps in minimizing issues like unpredictable and inconsistent in vitro (laboratory) and in vivo (in the body) performance, which can otherwise hinder the success of the formulation. To support researchers and developers in this process, various scientific publications have provided comprehensive guidelines that outline suitable administration routes and effective formulation strategies for optimizing the performance and reliability of LBDDS.

3. MECHANISM OF DRUG DELIVERY[2,3]

Drug delivery to specific sites within the body can be achieved through three principal mechanism

a. Passive Targeting
b. Active Targeting
c. Physical Targeting

3.1 Passive targeting

This approach relies on the natural physiology of certain diseased tissues, particularly those with abnormal or "leaky" blood vessels. In passive targeting, the drug or therapeutic agent accumulates in these regions either through systemic circulation or by direct administration or implantation into the site of interest. This technique takes advantage of the enhanced permeability and retention (EPR) effect, which is commonly seen in pathological conditions such as tumours, sites of inflammation, areas affected by infection, or regions undergoing angiogenesis (the formation of new blood vessels). Due to these characteristics, passive targeting has become a well-established strategy in targeting and delivering drugs specifically to such affected areas.

3.2 Active targeting

Unlike passive targeting, active targeting involves a more deliberate and precise delivery system. In this mechanism, the drug or a carrier system—such as nanoparticles or liposomes— is functionalized or conjugated with ligands that have a high affinity for receptors present on the surface of specific cells or tissues. These ligands can include a wide range of biological molecules such as full-length antibodies, antibody fragments, proteins, peptides, aptamers (short, single-stranded DNA or RNA molecules), or small synthetic molecules. This method of targeting is often used to bypass biological barriers—such as the blood-brain barrier (BBB) or cellular membranes—that typically prevent effective drug delivery. Active targeting, by binding to specific receptors or antigens, facilitates receptor-mediated uptake and ensures the drug reaches the intended site with greater efficiency.

3.3 Physical targeting

This strategy involves the application of external physical forces or fields to guide and control the delivery of drug-loaded nanoparticles (NPs) to a specific location within the body. These forces may include magnetic fields, light (especially near-infrared light), or various forms of radiation. A common application of physical targeting is in photothermal therapy, a technique used to treat cancers by using photothermal agents to generate localized heat and destroy cancerous cells or disrupt their growth cycle. In this context, materials such as gold nanoparticles (AuNPs), carbon nanotubes, and graphene-based structures have been employed as effective photothermal agents due to their ability to absorb light and convert it into heat, thus enhancing the efficacy and precision of the treatment.

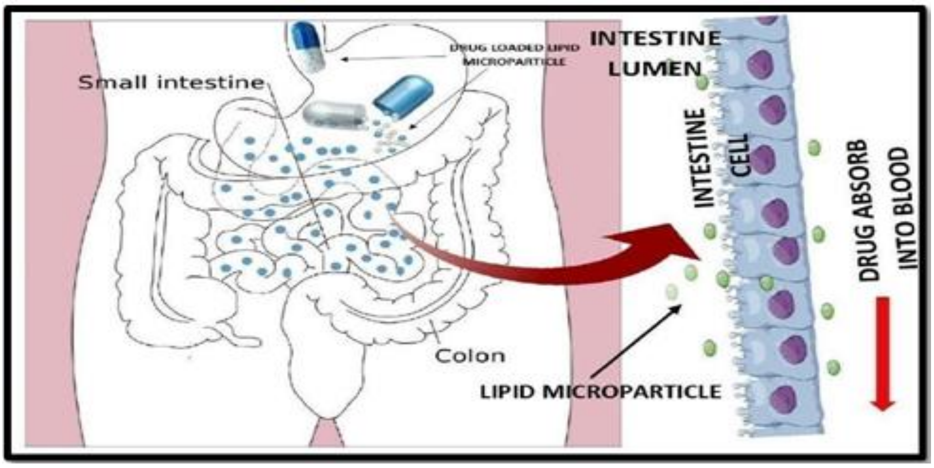
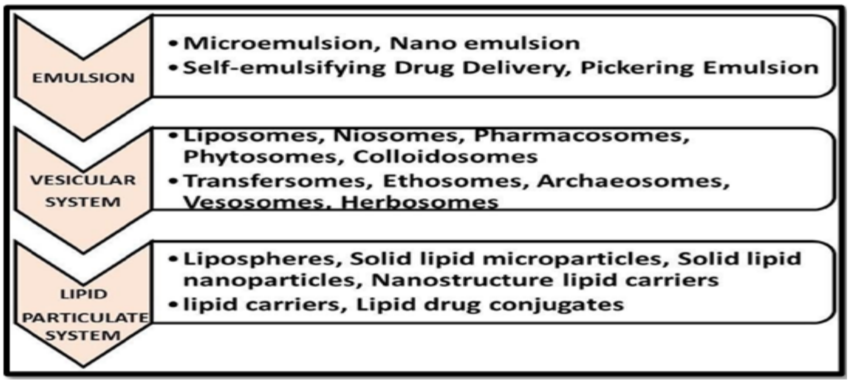


Fig. 1: lipid digestion and drug solubilization process in the small intestine.[3]

4. CLASSIFICATION OF LIPID-BASED DRUG DELIVERY SYSTEM[3]



EMULSION
- Microemulsion, Nano emulsion
- Self-emulsifying Drug Delivery, Pickering Emulsion

VESICULAR SYSTEM
- Liposomes, Niosomes, Pharmacosomes, Phytosomes, Colloidosomes
- Transfersomes, Ethosomes, Archaeosomes, Vesosomes, Herbosomes

LIPID PARTICULATE SYSTEM
- Lipospheres, Solid lipid microparticles, Solid lipid nanoparticles, Nanostructure lipid carriers
- lipid carriers, Lipid drug conjugates

Fig.2: Classification of LBDDS.[3]

4.1 Microemulsions[3,7,8]

Microemulsions are a distinct type of dispersion that may appear transparent or translucent. In experimental studies, when long-chain fatty acids (milky, soap-like emulsions) are titrated with medium- or short-chain alcohols, the resulting emulsions turn translucent or transparent. A microemulsion is defined as "a single, optically isotropic and thermodynamically stable liquid solution composed of water, oil, and an amphiphile." These systems are considered pseudo homogeneous mixtures of water, hydrophobic organic substances, and a combination of surfactant and co-surfactant. Depending on whether it's an oil-in-water or water-in-oil microemulsion, different mixing ratios of water, oil, and surfactants are employed to create the final system. Amphiphiles lower the oil–water interfacial tension through interfacial adsorption, thereby decreasing the free energy required for dispersion, making the system more thermodynamically favourable. There are three primary categories of microemulsions:

a. Water-in-Oil (W/O) Microemulsion

In this type, water or an aqueous solution is dispersed in a water-insoluble liquid, with oil acting as the continuous (external) phase and water as the discontinuous (internal) phase.

b. Oil-in-Water (O/W) Microemulsion

Here, oil is dispersed in an aqueous medium, making water the continuous phase and oil the discontinuous phase.

c. Biocontinous Microemulsion

This structure is isotropic on a macroscopic scale and separates space into two continuous solvent domains. It forms an infinite bilayer with saddle-like curvatures and interconnected channels resembling a sponge. This structure appears when oil and water are present in nearly equal amounts, maintained by a dynamic surfactant-stabilized interface with a net curvature close to zero.

Advantages

- Enhanced physical stability
- Efficient encapsulation of both lipophilic and hydrophilic drugs
- Prolonged drug release
- Small lipid particle size promotes close interaction with the stratum corneum, improving drug absorption through the skin or mucosa

4.2 Nano emulsions[2,3,7,11]

Nano emulsions are an emerging formulation approach for oral drug delivery, particularly suitable for improving the solubility and bioavailability of lipophilic drugs, especially those classified under BCS Class 2 and 4. These systems often use food-grade oils and GRAS (Generally Recognized as Safe) excipients, making them appropriate and safe for oral use. Composed of oil, surfactant, and often a co-surfactant, Nano emulsions range from 20 to 500 nm in size, exhibit isotropic behaviour, and are thermodynamically unstable. Depending on their composition, they can form oil-in-water or water-in-oil types, with either oil or water at the core of each particle. Due to their extremely small droplet size, they can effectively encapsulate active ingredients and remain kinetically stable. Nano emulsions are considered promising lipid-based systems with droplet sizes under 1 μm.

4.3 Self-Emulsifying Drug Delivery Systems (SEDDS)[2,3,7,8]

SEDDS are binary systems composed of oils and surfactants that can spontaneously emulsify when exposed to an aqueous phase, forming fine oil-in-water emulsions with gentle agitation. These systems efficiently dissolve hydrophobic drugs in the oil phase and are often classified into micro (SMEDDS) and nano (SNEDDS) variants based on their droplet size. They offer numerous benefits, including improved oral bioavailability, reduced dosing frequency, consistent plasma drug levels, and protection of drugs from harsh gastrointestinal environments. The system allows pre-dissolution of active ingredients, which can then be encapsulated in soft or hard gelatine capsules. SEDDS are particularly advantageous for BCS Class 2 drugs by overcoming solubility limitations in the gastrointestinal tract. One notable example includes Pueraria-loaded SMEDDS pellets, developed using a combination of chromophores EL and 1,2propanediol as the oil phase, which demonstrated enhanced bioavailability and sustained release.

4.4 Liposomes[2,3,4,5,11]

Liposomes are species of vesicular structures composed of phospholipids, featuring hydrophilic heads and hydrophobic tails. They form spherical, concentric bilayers that enclose an aqueous phase, making them ideal for carrying both hydrophilic and hydrophobic drugs—water-soluble agents are contained within the aqueous core, while lipophilic compounds are held within the lipid bilayers. They range in size from 10 nm to several micrometres and are categorized based on size and number of bilayers. The three main types are: Multilamellar Vesicles (MLVs): Multiple lipid bilayers separated by aqueous layers. Liposome preparation techniques include lipid film hydration, reverse-phase evaporation, and solvent injection methods, all involving the removal of organic solvents during rehydration.

4.5 Lipid Nanoparticles[2,4,5,6,7,9,10,11]

Lipid-based nanoparticles are a novel class of drug carriers designed for therapeutic applications. They utilize physiological lipids to facilitate controlled drug release and improve absorption consistency in the gastrointestinal tract. These nanoparticles enhance oral bioavailability, particularly by promoting the solubilization of drugs with food-derived lipids. Their lipid core allows for better delivery of poorly water-soluble drugs (BCS Class 2 and 4). Lipid nanoparticles are categorized into lipospheres, Solid Lipid Microspheres (SLM), Solid Lipid Nanoparticles (SLN), and Nanostructured Lipid Carriers (NLCs). NLCs were developed to overcome SLN limitations such as drug expulsion during storage and limited drug loading capacity. These particles are commonly produced using techniques like high-pressure homogenization and double emulsion methods.

4.6 Liposphere[3,4,11]

Nanoparticles, microparticles, microemulsions, and liposomes are examples of multi-unit drug delivery systems, which are generally preferred over single-unit systems because they ensure uniform drug distribution and absorption in the gastrointestinal tract. However, these systems may present toxicity concerns due to residual organic solvents used in their preparation. Lipid microspheres, or lipospheres, have emerged as a new fat-based encapsulation technique for delivering bioactive substances while mitigating such issues. A liposphere consists of a solid, hydrophobic lipid core where the active pharmaceutical ingredient is either dissolved or dispersed, surrounded by a phospholipid monolayer that acts as a stabilizing outer coat. These solid lipid particles typically range from 0.01 to 100 micrometres in diameter.

Advantages

- Enhanced drug stability, higher drug loading capacity, and controlled drug release.
- Effective controlled delivery of various drugs such as anti-inflammatory agents, local anaesthetics, antibiotics, and anti-cancer drugs.
- Prolonged plasma drug concentration, improved bioavailability, extended shelf life,

and protection against drug hydrolysis.

4.7 Solid Lipid Microparticles (SLMs)[3,4]

Solid lipid microparticles are stabilized by a surfactant layer that surrounds a hydrophobic core, solid at both room and body temperatures. In these systems, the active drug is either dissolved or uniformly dispersed within the stable lipid matrix. They are synthesized by replacing the liquid oil component in traditional oil-in-water emulsions with solid lipids at room temperature. Due to the use of biocompatible and biodegradable components, these particles exhibit excellent vivo tolerance. Their larger size compared to nanoparticles prevents them from penetrating biological membranes, thereby avoiding nanoparticle-associated toxicities. Additionally, the smaller specific surface area of SLMs reduces the need for surfactants, further minimizing potential toxicity.

Advantages

- Improved bioavailability of poorly water-soluble drugs.
- Modified or sustained drug release profiles.
- The solid lipid matrix shields sensitive drugs from degradation.

4.8 Nanostructured Lipid Carriers (NLCs)[3,6]

NLCs are composed of both solid and liquid lipids, offering multiple advantages over traditional drug delivery systems. These include enhanced permeability, greater bioavailability, reduced side effects, prolonged circulation time, and targeted tissue delivery. Solid Lipid Nanoparticles (SLNs), A precursor to NLCs, have been widely studied for various routes of administration such as topical, oral, parenteral, and cutaneous. The crystalline structure of the lipid matrix significantly affects drug release, with the presence of defects in the high-energy crystal lattice facilitating release. If a transition to a more stable, low-energy state occurs during storage, the drug may be prematurely released. Unlike emulsions, NLCs prevent particle aggregation and maintain drug immobilization due to their solid matrix structure. They also retain the benefits of SLNs, such as minimal toxicity, biodegradability, and controlled drug release, while avoiding organic solvents during formulation.

Advantages

- Enhanced physical stability and sustained drug release.
- Easy to scale up and prepare.
- Better dispersion in aqueous media.

- High capacity for both hydrophilic and lipophilic drug entrapment.
- Suitable for topical applications due to the GRAS status of lipid components.
- Small particle size allows closer contact with the skin or mucosa, improving absorption.

4.9 Niosomes[2,3,8,11]

Niosomes are vesicular systems made from non-ionic surfactants and cholesterol. Structurally similar to liposomes due to their bilayer arrangement, Niosomes differ in that their components provide enhanced stability. They are capable of encapsulating both hydrophilic drugs (in the aqueous core) and lipophilic drugs (within the bilayer membrane).

Advantages

- More osmotically active, chemically stable, and longer lasting than liposomes.
- Functional groups on their surface allow for easy modification.
- Biocompatible and low toxicity due to their non-ionic nature.
- Biodegradable and non-immunogenic.
- Dual encapsulation capabilities (hydrophilic and lipophilic drugs).
- Improved therapeutic efficacy via targeted and sustained drug delivery.
- Easily sourced raw materials.

5.10 Pharmacosomes[3,11]

Pharmacosomes, first introduced by Vaizoglu and Speiser in 1986, are lipid-based complexes that can enhance drug solubility and penetration while reducing gastrointestinal toxicity. Any drug containing an active hydrogen atom (e.g., $-COOH$, $-OH$, $-NH_2$) can be chemically linked to lipids with or without a spacer.

Advantages

- High drug loading achieved via equimolar complexation with phospholipids (PLs).
- No need for separating unentrapped drug, unlike liposomes.
- Covalent attachment eliminates drug leakage, although hydrolysis may still occur.
- Drug entrapment is independent of bilayer interactions and entrapment volume.
- Stability is governed by properties of the drug-lipid complex rather than bilayer fluidity.
- Suitable for poorly soluble drugs, improving their bioavailability.

5.11 Phytosomes[2,3]

Phytosomes are formed by complexing phosphatidylcholine with standardized plant extracts or polyphenolic compounds in non-polar solvents. Various solvents—both protic and aprotic—have been used, with ethanol being preferred for its efficiency and minimal residue. These complexes enhance the pharmacological activity of plant constituents by increasing their solubility and bioavailability. Studies have documented their effects across various body systems, including cardiovascular, neurological, gastrointestinal, immunological, respiratory, and musculoskeletal systems.

Advantages

- Enhanced oral and topical delivery of lipid-insoluble phytochemicals.
- Improved bioavailability via phospholipid complexation.
- Greater lipid solubility makes them ideal for cosmetic applications.
- Useful in delivering liver-protective flavonoids.
- Commercially viable, non-invasive system with lower dosage requirements.
- Enhanced stability due to chemical bonds between phospholipids and phytoconstituents.
- Superior drug trapping and targeted tissue delivery.
- Preferred over liposomes in skin-care products due to better emulsion/cream formation.

5.12 Transfersomes[2,3,11]

A proprietary technology developed by IDEA AG, Transfersomes are deformable vesicles designed to mimic biological cell vesicles. These carriers exhibit exceptional elasticity and can navigate through pores significantly smaller than their own size, making them ideal for controlled and targeted delivery.

Advantages

- Suitable for both hydrophilic and lipophilic drugs due to their dual-affinity structure.
- Can squeeze through tight biological pores without structural damage.
- Biocompatible and biodegradable, composed of natural phospholipids.
- High drug entrapment efficiency (~90% for lipophilic drugs).
- Protects drugs from enzymatic degradation.
- Acts as a slow-release depot for both systemic and topical administration.
- More flexible and efficient than conventional liposomes.

Ethosomes[2,3]

Ethosomes are phospholipid-based nanocarriers enriched with high concentrations of ethanol, enhancing drug penetration through the skin. These soft vesicles are composed primarily of phospholipids, ethanol, and water, and can range from tens of nanometres to micrometres in size.

Advantages

- Effective in acne treatment by improving drug permeation and forming depots.
- Used topically to manage arthritis symptoms.
- Improved transdermal delivery of respiratory drugs like salbutamol sulphate.

5.14 Herbosomes[3,11]

Herbosomes integrate herbal constituents with lipids to form complexes that significantly enhance the bioavailability ofplant extracts. This system bridges traditional herbal medicine with advanced drug delivery platforms. Due to the poor solubility and molecular size of many plant compounds, Herbosomes enable better systemic absorption and stability.

Advantages

- Improve both oral and topical delivery of polar phytoconstituents.
- Significantly increase bioavailability due to the phospholipid complex.
- Better suited than liposomes for cosmetic applications due to higher lipophilicity.
- Effective for delivering liver-protective flavonoids.
- Readily commercialize, passive, and non-invasive.
- Lower dosing requirements due to improved absorption.
- Strong chemical bonds between phospholipids and herbal components enhances stability.
- Provide better drug trapping and targeted delivery.
- Ideal for skincare due to improved emulsion and cream stability.

5. FORMULATION APPROACHES FOR LBDDS[1,4,6,11,12]

5.1 Spray Congealing

Also known as spray cooling, this method involves spraying molten lipid into a cooling chamber, where it solidifies into spherical particles upon contact with cool air. The solid particles are collected from the chamber’s base and can be filled into hard gelatin capsules or compressed into tablets. Ultrasonic atomizers are often employed to generate solid particles in this process. Key parameters include the excipient’s melting point, formulation viscosity, and cooling air temperature to ensure rapid droplet solidification.

5.2 Spray Drying

This technique resembles spray congealing but differs in the atomizing chamber’s air temperature. Here, a drug solution (in organic solvent or water) is sprayed into a hot air chamber, where the solvent evaporates, yielding solid drug microparticles. Alongside lipid excipients, solid carriers like silicon dioxide can be incorporated. Gelucire (a lipid excipient) improves drug release by forming hydrogen bonds with the active substance, stabilizing amorphous drug microparticles.

5.3 Adsorption onto Solid Carrier

A simple and cost-effective method (in terms of equipment), this process involves adsorbing a liquid-lipid formulation onto solid carriers such as silicon dioxide, calcium silicate, or magnesium aluminometasilicate. The liquid formulation is blended with the carrier, which must exhibit strong adsorption capacity and maintain good flow properties post-adsorption. Gentamicin and erythropoietin formulations with capryl caproyl polyoxylglycerides (Labrasols) were successfully converted into solid intermediates without losing bioavailability. Benefits include excellent content uniformity and high lipid exposure. Ito et al. developed a solid gentamicin formulation using emulsifiers and adsorbents (e.g., calcium silicate, magnesium aluminometasilicate, and silicon dioxide) via a kneading process.

5.4 Melt Granulation

Also called palletization, this method converts a powdered drug mixture into granules or pellets. A meltable binder (in molten form) is sprayed onto the powder under high-shear mixing (a "pump-on" technique). Alternatively, the binder is blended with the powder, melting due to particle friction during mixing. The molten binder forms liquid bridges, creating granules that become spheronized pellets under controlled conditions. Depending on powder fineness, 15%– 25% lipid-based binder may be used. Critical parameters include binder particle size, mixing time, impeller speed, and melt viscosity. For instance, diazepam’s dissolution rate improved when formulated as melt agglomerates with solid dispersions. Lactose monohydrate was meltagglomerated using PEG 3000 or Gelucire 50/13 in a high-shear mixer. Lipid excipients like polyoxylglycerides, partial glycerides, polysorbates, and lecithin are used to create selfmicroemulsifying systems.

5.5 Supercritical Fluid-Based Method

This approach coats drug particles with lipids to form solid dispersions. The drug and lipid excipients are dissolved in an organic solvent and supercritical fluid (e.g., carbon dioxide) under elevated temperature and pressure. Coating occurs by gradually reducing pressure and temperature, decreasing the coating material’s solubility and causing it to precipitate onto drug particles. Key considerations include the formulation’s solubility in the supercritical fluid and the drug’s stability during processing.

5.6 Other Formulation Tools

Assessing drug solubilization in bile salt-lecithin mixed micelles is a straightforward and effective diagnostic test. Solubility can be analysed via spectrophotometry or HPLC, providing rapid insight into a drug’s potential solubilization in the gut. Steroid solubility enhancement ratios demonstrate that solubilization cannot be predicted solely by octanol-water partition coefficients. With advancing computing power, molecular dynamics modelling may become a valuable tool for studying lipid formulation structures and partitioning behaviour.

6. EXCIPIENTS USED FOR LIPID-BASED ORAL DRUG DELIVERY[1,3]

A broad selection of excipients is available for formulating lipid-based preparations, but choosing compatible ones can seem overwhelming. Despite this variety, regulatory approval constraints limit the number of suitable excipients for oral drug delivery that fall under approved categories (Fig. 3).

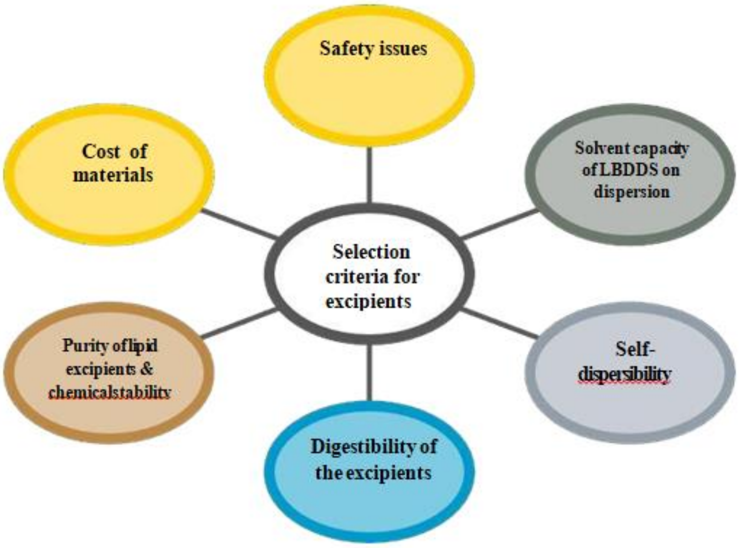


Fig. 3: Selection criteria for excipients used in LBDDS.[3]

6.1 Lipid

The carboxylic acid group in fatty acids provides a favourable site for ester linkage formation with alcohols. Lipids are fatty or waxy organic compounds that dissolve readily in non-polar solvents like ether but not in polar solvents such as water. Examples include oils, sterols, waxes, cholesterol, fat-soluble vitamins, mono-, di-, and triglycerides, and phospholipids. While unsaturated fats are a subset of lipids, the terms are not interchangeable. A physicochemical classification system has been developed to categorize lipids based on their polarity, considering their interaction with bulk water and behaviour at air-water interfaces.

Several factors influence the bioavailability, texture, and acceptability of lipid-based drug delivery systems (LBDDS), including solvent capacity, miscibility, self-dispersibility, digestibility, and regulatory concerns like toxicity, irritancy, purity, and chemical stability. Dietary oils and permeation enhancers are commonly used in lipid-based formulations. Many lipids are amphiphilic, containing both lipophilic and hydrophilic regions. Lipids can be classified into:

a. Homolipids

These are fatty acid esters with alcohols, composed solely of carbon, hydrogen, and oxygen, making them simple lipids. Key materials for oral delivery include long- and medium-chain fatty acids linked to triacylglycerols (glycerol-based molecules). Fatty acids like stearic, oleic, linoleic, and linolenic acid share an 18-carbon chain but differ in double-bond numbers. Examples include beeswax, carnauba wax, and glycerides (fats & oils).

b. Heterolipids

These contain nitrogen and phosphorus in addition to carbon, hydrogen, and oxygen, as seen in phospholipids and glycolipids, also termed compound lipids. Examples are phosphoglycerates (e.g., phosphatidic acid) and phosphosphingolipids (e.g., dioleoyl phosphatidylcholine).

c. Complex lipids

This category includes lipoproteins and chylomicrons, which transport cholesterol and other lipids in the body. Their structure consists of an apolar core (cholesterol esters or triacylglycerols) surrounded by a phospholipid monolayer embedded with apoproteins. Phospholipids, such as phosphatidylcholine, are commonly used in formulations. Phosphatidylcholine contains four hydrolyzable ester bonds: two fatty acid-glycerol esters, a glycerophosphate ester, and a phosphocholine ester.

6.2 Emulsifiers

Selecting the right emulsifier is crucial for designing effective lipid-based drug delivery systems. Emulsifiers must maintain dispersion stability under environmental stresses like pH, ionic strength, and temperature fluctuations while preventing particle agglomeration. Table 1 lists common emulsifiers used in lipid-based preparations. The choice depends on the administration route—topical and ocular routes may cause skin-related issues, whereas oral formulations must avoid physiological effects. Combining emulsifiers can create synergistic effects and improve stability.

6.3 Surfactants

Surfactants enhance formulation bioavailability. For instance, ethoxylated glycerides (e.g., Cremophor® EL) derived from ricinoleic acid (with a hydroxyl group at the 12th carbon) increase hydrophilicity and bioavailability. Surfactants improve drug dissolution, intestinal permeability, and tight junction permeability. They are particularly effective in boosting absorption of lipophilic drugs. Ethoxylated surfactants like Gelucire®, Labrasol®, and Cremophor® also inhibit Pglycoprotein (P-GP)-mediated drug efflux.

However, surfactant selection is limited due to safety concerns for oral use. Non-ionic surfactants (e.g., polyethoxylated lipids) are preferred. Their use in hard and soft gelatin capsules is restricted because they may cause brittleness due to dehydration. Capryl caproyl macrogol glycerides, derived from medium-chain triglycerides and low-molecular-weight macrogols, are a notable exception.

7. CHARACTERIZATION OF LIPID-BASED DRUG DELIVERY SYSTEMS[1,3,4]

7.1 Appearance

The uniformity and colour of the formulation can be assessed at equilibrium using a graduated glass cylinder or a transparent glass container.

7.2 Colour, Odor, and Taste

These attributes are particularly crucial for orally administered formulations. Variations in taste, especially of active ingredients, may result from changes in particle size, crystal structure, and subsequent dissolution. Alterations in colour, odour, or taste may also signal chemical instability.

7.3 Density

The specific gravity or density of the formulation is a critical parameter. A reduction in density often suggests the presence of entrapped air within the formulation's structure. High-precision hydrometers can be used to measure density at a specific temperature.

7.4 PH Value

The pH of aqueous formulations should be measured at a set temperature using a pH meter, ensuring equilibrium is reached to avoid "pH drift" and electrode coating by suspended particles. Adding electrolytes to stabilize pH should be avoided, as they may disrupt the suspension's physical stability.

7.5 Self-Dispersion and Sizing of Dispersions

Evaluating the dispersion rate and resulting particle size of lipid-based systems is important. Dispersion rate can be measured, and particle size analysis can be conducted using an optical microscope (for micron-sized particles) or a particle size analyser.

7.6 Droplet Size and Surface Charge (Zeta Potential)

Microemulsion vesicle size distribution can be determined via electron microscopy or light scattering techniques. Dynamic light-scattering measurements are taken at a 90° angle using a spectrophotometer with a 632 nm neon laser, with data processed by the instrument's built-in computer. Recent advancements in particle characterization have led to increased interest in photon correlation spectroscopy (PCS) for assessing particle size distribution. The surface charge is measured using a zeta potential analyser, which determines the zeta potential (ZP). ZP indicates particle surface charge, reflecting repulsive forces between droplets. For stable nano emulsions (preventing flocculation and coalescence), ZP should typically exceed 30 mV.

7.7 Viscosity Measurement

A Brookfield-type rotary viscometer can measure the viscosity of lipid-based formulations under varying shear rates and temperatures. Samples should be pre-immersed and maintained at 37 ± 0.2°C in a thermostatic bath. Calibration ensures accurate apparent viscosity readings at equilibrium. Since apparent viscosity is exponential, results are best reported as log-apparent viscosity.

7.8 In Vitro Studies

Lipid digestion models can evaluate lipid-based drug delivery systems in vitro. Simulated lipolysis release testing helps assess excipient performance and predict vivo behavior. This system maintains constant pH during reactions involving hydrogen ion release/consumption, adjusting with reagent additions as needed. The model consists of a temperature-controlled vessel (37 ± 1°C) containing intestinal fluid (digestion buffer, bile salt, and phospholipid). A lipid-based formulation is introduced, followed by pancreatic lipase and colipase to initiate digestion. Fatty acid release lowers pH, which is monitored via a pH electrode connected to a pH-stat controller and auto-burette. Sodium hydroxide is added to neutralize fatty acids, maintaining preset pH. The digestion extent is quantified by NaOH consumption. Samples taken during digestion can be centrifuged into poorly dispersed oil, highly dispersed aqueous, and pellet phases. Drug quantification in the aqueous phase suggests no precipitation, aiding in vivo performance predictions.

7.9 In Vivo Studies

In Vivo studies help determine how excipients affect drug bioavailability and pharmacokinetics. Since lipid-based formulations enhance intestinal drug uptake, lymphatic absorption studies are essential. However, limited clinical data and variability in animal models complicate lymphatic drug transport research.

7.10 In Vitro-In Vivo Correlation (IVIVC)

IVIVC enhances the development and commercialization of lipid-based formulations. Correlating in vitro and in vivo data can shorten development time and improve product quality. Techniques like solubility testing, dissolution studies, lipolysis assessment, and intestinal membrane models (isolated tissue or cell cultures) provide formulation insights. Caco-2 cells, which produce chylomicrons upon lipid exposure, mimic in vivo enterocytes. Further research is needed to identify optimal in vivo models for evaluating lipid-based formulations.

8. APPLICATION[1,2,3,5,7]

- Thus far, the advancement of efficient lipid-based delivery systems has primarily relied on empirical findings. Conducting methodical physicochemical evaluations of structure and stability not only accelerates the development of improved formulations but could also enhance comprehension of the complex mechanisms governing lipid carrier interactions with living systems. Consequently, these systems aim to serve as accurate, efficient, and secure vehicles for transporting genes and therapeutic drugs.

- LBDDS can be employed to deliver a diverse array of pharmaceutical agents, encompassing new chemical compounds, proteins and peptides, nucleic acids (DNA, siRNA), and targeted cellular delivery.
- For an extended period, lipid-based formulations have been utilized to enhance the uptake of hydrophobic drugs with limited water solubility. Lipids rank among the most versatile excipients currently available, offering formulators numerous possibilities for optimizing and controlling drug absorption for poorly soluble compounds. Available formulation options include lipid suspensions, solutions, emulsions, microemulsions, mixed micelles, SEDDS, SMEDDS, thixotropic vehicles, thermosetting matrices, and liposomes.
- Although lipid-based formulations are not a novel technological innovation, they have proven instrumental in mitigating the inconsistent and inadequate gastrointestinal absorption of lipophilic, poorly soluble drugs. In numerous cases, they have also shown the ability to reduce or eliminate food-induced variations in drug absorption. Despite these advantages, only around 25 to 100 commercially available oral drug products currently utilize lipid-based formulations.

9. CONCLUSION & FUTURE PERSPECTIVE[1,2,3,4,5,10]

- The persistent challenge of poor water solubility in drugs, stemming from drug discovery efforts, continues to trouble pharmaceutical researchers despite their dedicated work. Multiple physiological obstacles within the gastrointestinal tract—such as degradation by acids and proteases, along with low intestinal permeability—result in diminished systemic absorption and restricted oral bioavailability of macromolecular drugs, thereby hindering the formulation of clinically viable products.
- A crucial factor in the effectiveness of lipid-based formulations for boosting drug bioavailability is the inherent lipophilicity of the drug candidate itself. The realization that lipid-based formulations can achieve adequate oral bioavailability even for highly insoluble drugs is promising. However, certain limitations—such as formulation stability, manufacturing techniques, and the absence of comprehensive data on drug solubility in lipids—highlight the need for deeper investigation into establishing appropriate regulatory standards for lipid-based systems to drive progress in this field.
- Additional research is required to develop suitable in vivo models that can accurately translate in vitro findings to real-world physiological conditions. A more holistic

strategy must be adopted to overcome existing challenges. A thorough evaluation of the advantages and drawbacks of lipid-based oral drug delivery systems (DDS) is essential. Such an approach would facilitate the refinement of formulations by optimizing key parameters (e.g., lipid excipient selection, physicochemical characteristics, functionalization, toxicity, drug-loading efficiency, release kinetics, and intestinal stability) and enable the rational design of lipid-based systems to enhance in vivo performance, ultimately paving the way for clinical success.

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