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Advances in Lipid Nanoparticle-Based Oral Drug Delivery: Overcoming Bioavailability and Gastrointestinal Barriers

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Abstract:

Due to patient compliance and ease, oral drug delivery is the most often used therapeutic administration technique. However, low permeability, enzymatic breakdown, and poor water solubility limit the bioavailability of many medications. Lipid solid lipid nanoparticles (SLNs) and nanostructured lipid carriers (NLCs), two types of nanoparticles (LNPs), have become potential delivery systems. for enhancing oral drug absorption. This review highlights the classification, functional mechanisms, and formulation factors affecting LNP-based drug delivery systems. This review discusses recent strategies, such as lymphatic transport enhancement, permeability modulation, and drug encapsulation methods. The applications of LNPs in delivering anticancer, antidiabetic, antiviral, and nutraceutical agents are also addressed. Despite regulatory and technical hurdles, continued research and innovation in lipid-based systems have the potential to revolutionize oral drug delivery.

Keywords: Oral drug delivery, Bioavailability enhancement, Lymphatic transport, Drug encapsulation, Controlled release, poorly water-soluble drugs.

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1. INTRODUCTION

Lipids make up lipid-based nanoparticles, which are incredibly tiny spherical particles. These are new formulations and delivery methods for medicinal drugs [1-2]. To treat incurable diseases and increase life expectancy, drug research is crucial. Lipophilic medicines make up more than 40% of newly approved medications for a variety of illnesses [3]. However, lipophilic drugs are ineffective for direct human administration due to their limited solubility [4]. With notable expansion in the industrial and research sectors in recent years, the potential of LNP-based medications has come to light increasingly [5]. In 2021, the market for LNP-based gene therapy

was valued at about $3.5 billion, with a predicted a compound annual growth rate between 2021 and 2026 of almost 18.5% [6]. The development of formulations with a variety of compositions and physicochemical characteristics, intended to provide optimal therapeutic efficacy for a range of medicinal moieties, has been made easier by the availability of various natural oils, fats, and their synthetically modified equivalents [7].

Due to their low bioavailability, traditional oral formulations like tablets or capsules frequently fail to deliver medications directly to the affected area. The potential of nano drug delivery systems (NDDSs) for the treatment of ulcerative colitis has been made clear by developments in nano biomedical engineering [8-9]. Making use of the distinct characteristics of the intestinal inflammatory microenvironment, NDDS can develop intelligent delivery systems that react to lesions by employing active and passive targeting techniques to guarantee regulated release at the inflammatory location.

Gastrointestinal patches containing safe surfactants and polymers with mucoadhesive qualities have recently drawn interest for oral insulin delivery [10]. Lipid-based nanoparticles and biocompatible and biodegradable polymeric nanocarriers have also become attractive oral delivery vehicles for biopharmaceuticals, providing regulated protein release and protease resistance [11-12]. Three key developments have contributed to the growing significance of proteins and peptides: improvements in human pathophysiology, the development of biotechnology and genetic engineering, which have made large-scale production easier, and improvements in analytical techniques that have led to the discovery of many bioactive peptides and hormones [13]. Table 1

2. Lipid-based oral medication delivery system classification

The Lipid Formulation Classification System (LFCS) classifies lipid formulations according to their constituents, such as digestibility, dispersibility, and hydrophobicity [14]. First put forth as a functioning model in 2000, the LFCS was extended in 2006 to include more varieties of lipid-based formulations [15]. Figure 1

Figure 1. Classification of Lipid-Based Drug Delivery Systems,made by python

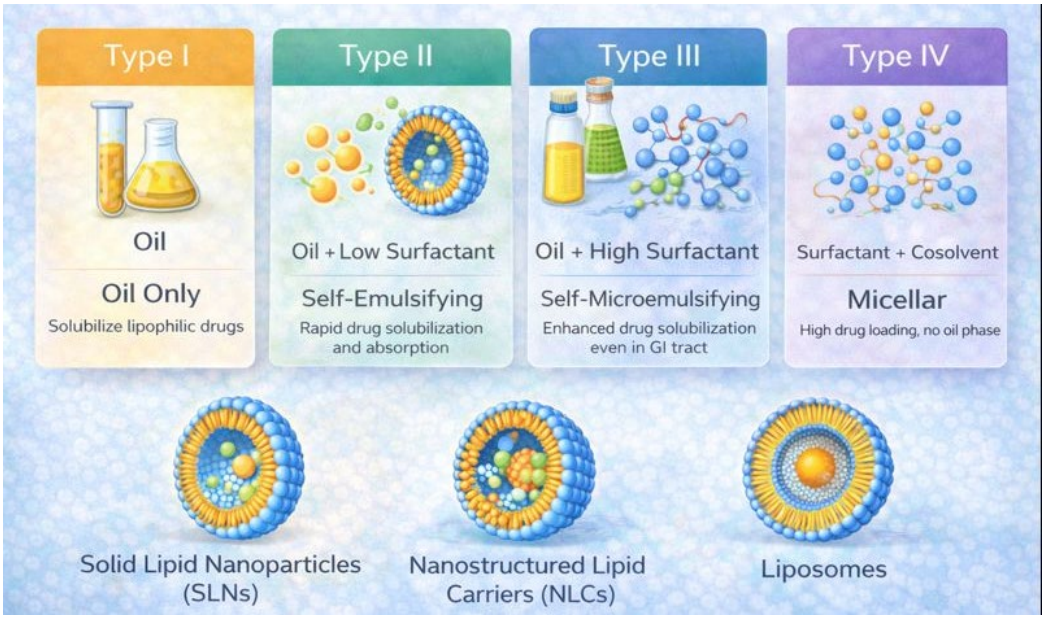

Table:1 LIPID FORMULATION CLASSIFICATION SYSTEM BY POUTON

Type	Characteristics	Advantages	Type
Solid Lipid Nanoparticles (SLNs)	Consisting of solid lipids at ambient and physiological temperatures	Increased stability, regulated pharmacological release	Solid Lipid Nanoparticles (SLNs)
(NLCs) Nanostructured Lipid Carriers	Combination of solid and liquid lipids	Higher drug loading, less drug expulsion	Nanostructured Lipid Carriers (NLCs)
Liposomes	Phospholipid bilayer vesicles	Biocompatible, can carry both hydrophilic and hydrophobic drugs	Liposomes
Self-emulsifying Drug Delivery Systems (SEDDS)	Isotropic mixes that generate emulsions in the gastrointestinal tract	Improved solubility and absorption	Self-emulsifying Drug Delivery Systems (SEDDS)

In order to get to a consensus that may be used as a framework for assessing the efficacy of lipid-based formulations, the pharmaceutical industry has been discussing LFCs more thoroughly in recent years [16]. LFCs' main objective is to make it easier to interpret in vivo studies, which will make it easier to identify the best formulations for drugs based on their physicochemical properties [17]. Figure 2

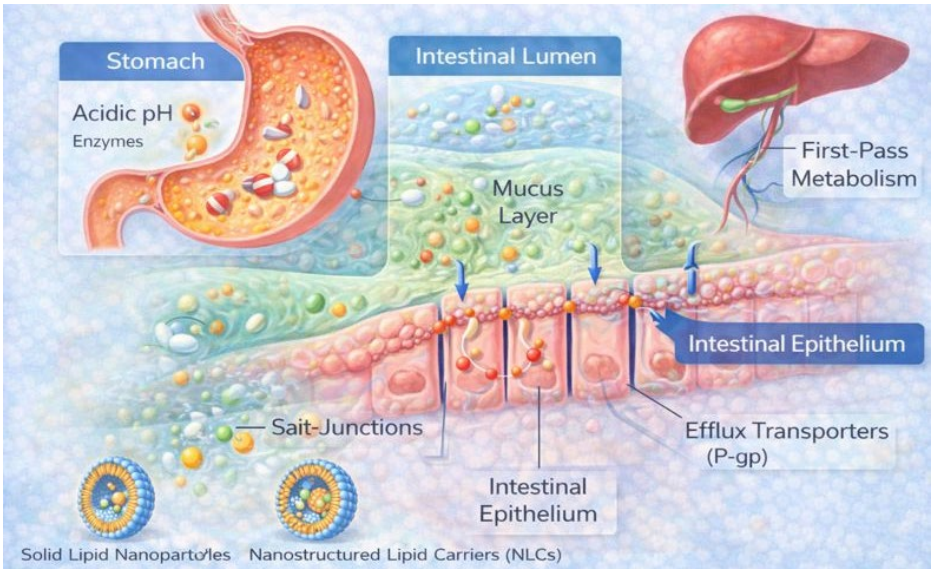

Figure 2. Gastrointestinal Barriers Affecting Oral Bioavailability made by python

3. Factors affecting the permeability-limited oral bioavailability

The following are the primary considerations influencing the selection of excipients for lipid-based formulations: [18]

1. Solubility
2. Dispersion,
3. Breakdown
4. Assimilation.

The other factors are as follows:

- Regulatory concerns: annoyance, toxicity, expertise, and
- Awareness,
- The solvent's effectiveness,
- Miscibility
- The destiny of digested items and their digestibility
- Compatibility with capsules, Purity, chemical stability, and product cost.

3.1 Solubility

The main ingredients in the formulation are lipids, which are derivatives of fatty acids. To improve dispersion qualities and promote solubilization, one or more surfactants and sometimes a hydrophilic co-solvent may be required [19]. The hydrophilic-lipophilic balance (HLB) number is used to categorize surfactants; a low value (≤10) denotes greater lipophilicity, whereas a higher value (≥10) denotes stronger hydrophilicity [20]. For formulation design, as a first step, the majority of lipids used in these oral formulations have a known ‘necessary HLB' value, usually available from suppliers, that corresponds to the ideal HLB for the surfactant mixture required to emulsify the oil in water. Based on their HLB values, different emulsifiers can be used for different formulations [21.]

3.2 Dispersion

It is necessary to evaluate the emulsification and dispersion properties of formulations that exhibit sufficient solubility of the drug candidate in aqueous environments. Microscopic analysis of the formulation after it has been mixed with water can be used for a first screening. Effective emulsification is indicated by intense mixing, as well as diffusion and stranding mechanisms at the water/formulation interface [22]. Another crucial need is the lack of drug precipitate after the formulation and aqueous medium have been thoroughly mixed. To find promising formulations, it is useful to measure the particle size of emulsion droplets using laser light scattering or other techniques [23]. One often used method to determine the kinds of structures created by emulsification and to describe how a formulation behaves along the dilution pathway is the creation of ternary phase diagrams [24].

3.3 Digestion

When designing lipid-based formulations, the activity of intestinal lipases should be taken into account because it can have a substantial impact on how the formulations behave in the gastrointestinal tract. Lipases are known to break down non-dispersible but digestible lipids, like triglycerides, into fatty acids and mono-/diglycerides, which emulsify any remaining oil [25.] Therefore, to guarantee the creation of the essential small particle sizes and large surface areas for drug release, substantial surfactant concentrations might not be required. Based on the

formulation's constituents and its dependence on digestion to facilitate dispersion, Poulton (2000) suggested a classification scheme for lipid-based formulations [26].

3.4 Breakdown

Any oral lipid-based formulation's main goal is to guarantee that intestinal mucosal cells effectively absorb the medication. This demonstrates how a lipid-based medication formulation works in the intestinal environment [27]. Table 2, Colloidal mixed micelles are formed by first dispersing the components to form lipid droplets (type I formulations) or emulsion droplets (types II–III). This is followed by lipolysis and bile acids solubilizing the digestion products [28]. It is believed that the medication then separates from the bile salt-mixed micelles and emulsion oil droplets to be taken up by the intestinal wall's mucosal cells . Figure 3

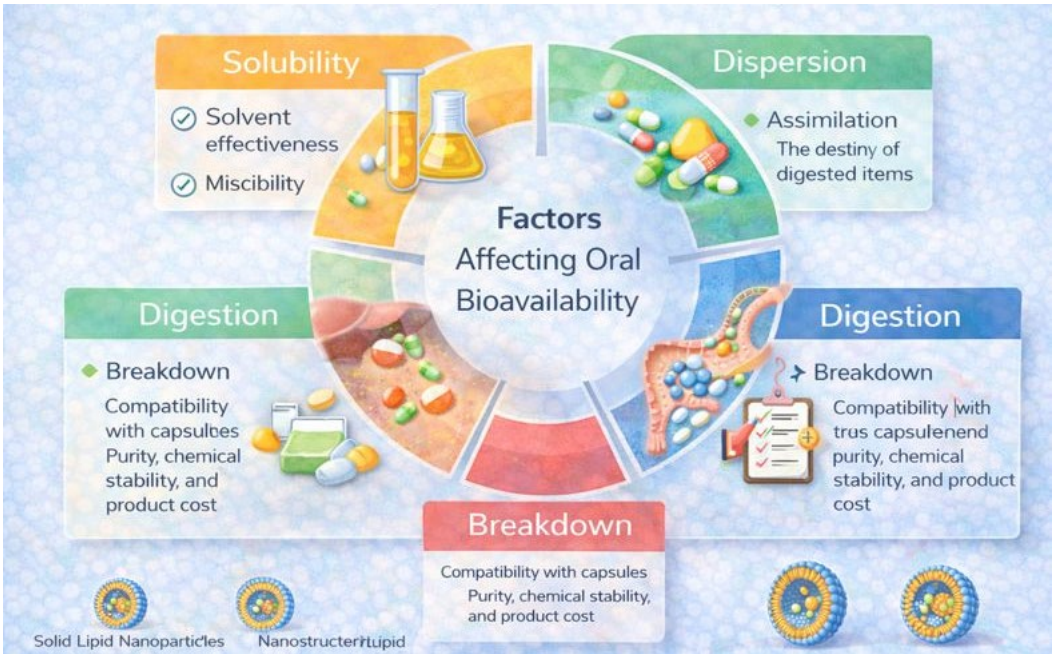

Figure 3. Factors Affecting Oral Bioavailability of Lipid-Based Formulations

4. Strategies for Improving the Oral Bioavailability of Poorly Water-Soluble Drugs Using LBDDS

TABLE 2: Using LBDDS to increase oral bioavailability

Strategy	Brief Description
Stimulation of intestinal lymphatic transport	LBDDS, encompassing LCT, is expected to enhance the lymphatic transport of lipophilic pharmaceutical compounds. This may also affect the extent of first-pass metabolism, as intestinal lymph circulation circumvents the liver.
Enhancing Lymphatic Transport	Lipophilic pharmaceuticals integrated into triglyceride-rich lipid-based drug delivery systems (LBDDS) are absorbed through intestinal lymphatic transport, circumventing first-pass hepatic metabolism. This enhances systemic exposure and bioavailability.
Changes in the biochemical	Specific lipids and surfactants can impair the functionality of intestinal secretion transporters situated in the gut wall, such as P-glycoprotein.

barrier	This phenomenon results in enhanced absorption of pharmaceuticals that act as substrates for these enzymes or transporters.
Extended retention in the stomach	The incorporation of lipids into the gastrointestinal tract (GIT) diminishes peristaltic activity and stomach emptying. This effect facilitates the breakdown process in the upper gut and positively influences medication absorption.
Changes in the physical barrier	Various combinations of lipids and/or surfactants, coupled with their digestive byproducts, may augment intestinal absorption by enhancing membrane permeability. Surfactants can facilitate the fluidization of the intestinal cell membrane and the disruption of tight junctions, resulting in increased membrane permeability.
Increased solubilization	The presence of lipids in the gastrointestinal system stimulates increased secretion of bile salts and endogenous bile lipids, including cholesterol and phospholipids, facilitating the emulsification of lipids and the solubilization of medicines. As a result, this leads to the production of intestinal mixed micelles 31 .

5. Mechanisms of LNP-Mediated Oral Drug Delivery

Lipid nanoparticles (LNPs) facilitate oral drug delivery through several mechanisms that address key physiological barriers in the gastrointestinal (GI) tract.

- Degradation Protection: LNPs safeguard encapsulated pharmaceuticals from the corrosive acidic conditions of the stomach and enzymatic breakdown in the intestine, thereby enhancing medication stability and oral bioavailability [30-3.]
- Enhanced Permeability: LNPs can promote both transcellular and paracellular transport of drugs across the intestinal epithelium by interacting with cellular membranes, fluidizing lipid bilayers, or transiently opening tight junctions [22-32].
- Lymphatic Uptake: Lipid-based carriers can facilitate drug absorption via the intestinal lymphatic system, allowing the drug to bypass hepatic first-pass metabolism and enhance systemic bioavailability, particularly for highly lipophilic drugs [20-28.]
- Controlled Release: LNPs allow sustained and controlled drug release by modulating the lipid composition and structural matrix, thus reducing the dosing frequency and improving the therapeutic efficacy [33-17.] Figure 4

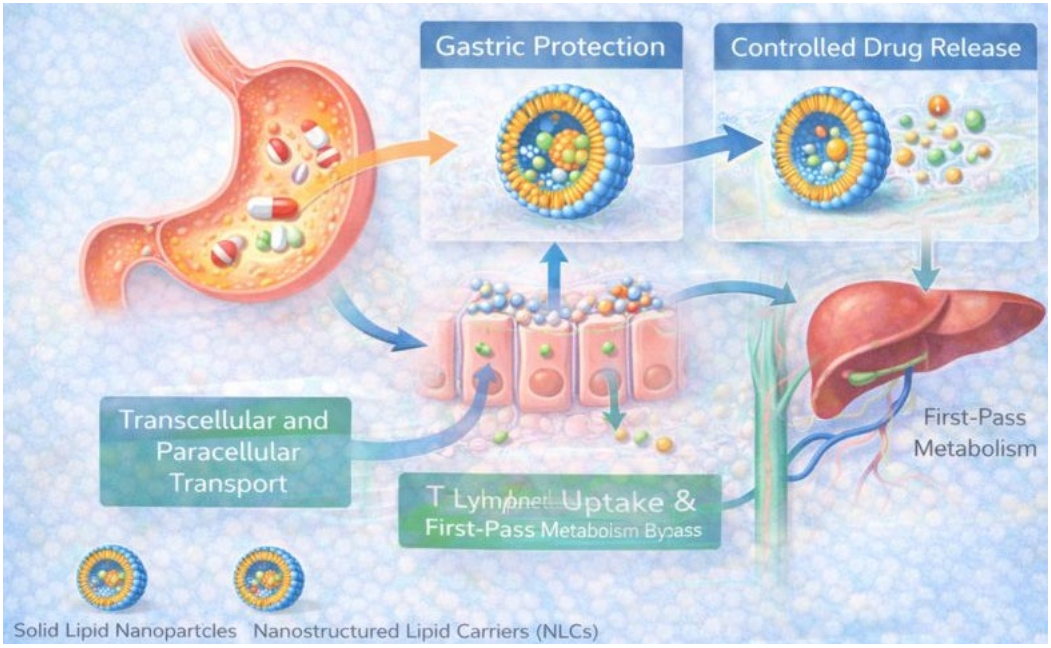

Figure 4. Mechanisms of LNP-Mediated Oral Drug Delivery

6. Applications in Oral Drug Delivery

Drug Type	Examples	Benefits of LNPs	References
Anticancer agents	Paclitaxel, Curcumin	Improved solubility and stability	33-34
Antidiabetics	Insulin, Metformin	Enhanced bioavailability, protection from GI degradation	35-36
Antivirals	Lopinavir, Ritonavir	Improved absorption, reduced toxicity	37-38
Antibiotics	Ciprofloxacin, Erythromycin	Targeted delivery, reduced resistance	39-40
Nutraceuticals	Omega-3 fatty acids, Vitamin D	Increased intestinal uptake	41-42

7. Drug Loading

Drug loading into nanocarriers, such as mesoporous silica nanoparticles (MSNs), is a promising approach to creating amorphous, extremely stable pharmacological formulations with enhanced bioavailability, solubility, and dissolution rates. A large drug payload, minimal exterior surface deposition, maximum pore filling, and controlled release at the intended site of action are all characteristics of an efficient loading technique.

Two main mechanisms facilitate drug encapsulation into MSNs.

- **Drug–carrier interactions**: Drug molecules are adsorbed onto the internal or external surfaces of MSNs by covalent attachment, electrostatic interactions, van der Waals forces, and hydrogen bonds, among other non-covalent interactions [43].

- **Nanoconfinement effect**: When the pore size of MSNs is smaller than the critical radius for nucleation, crystallization is suppressed, leading to the stabilization of the drug in an amorphous state. This phenomenon significantly enhances solubility and dissolution [44-45.]

The efficiency of drug loading depends on the following factors:

- **Carrier properties**: surface area, pore size, pore volume, and surface functional groups
- **Solution properties**: pH, drug solubility, solvent affinity with the drug and carrier
- **Loading method**: influences drug distribution, crystallinity, and release behaviour [46-47.]

7.1 Characterization of Drug-Loading Efficiency

The efficiency of drug loading is often assessed by extracting the drug with appropriate solvents and subsequently conducting quantitative analysis. In vitro release experiments are generally conducted in mimicked bodily fluids, such as phosphate-buffered saline, at 37 °C. The drug concentration in aliquots collected at consistent intervals can be quantified using analytical methods such as

- High-performance liquid chromatography (HPLC),
- Gel permeation chromatography (GPC),
- Calorimetric assays,
- Mass spectrometry (MS) was used

The choice of analytical technique depends on the drug molecular weight, chemical stability, solubility, and required sensitivity and precision [48].

7.2 Drug Loading Methods

Drug loading into porous carriers, such as MSNs, can be achieved via:

a. Solvent-based methods

This involves immersing MSNs in a drug-containing organic solution. Adsorption occurs, followed by solvent removal via filtration, evaporation, or drying. This method is suitable for heat-sensitive drugs and offers high control over loading but is limited by the following:

- Use of large volumes of organic solvents,
- Time-consuming drying steps,
- Low yield and scale-up difficulties [49-50.]

b. Solvent-free methods

These approaches involve mixing the active pharmaceutical ingredient (API) directly with MSNs without the use of solvents. They are:

- Faster and environmentally friendly,
- Allow prediction of loading efficiency based on the drug/MSN ratio,
- Concerns regarding residual solvents were eliminated.

However, solvent-free methods may lead to drug recrystallization, affecting stability over time [51].

7.3 Factors Influencing Encapsulation Efficiency and Drug Loading

Encapsulation efficiency (EE) and drug loading capacity (DL) are essential metrics in the formulation of nanoparticle-based drug delivery systems. They directly affect the therapeutic efficacy, release profile, and overall performance of lipid nanoparticles (LNPs) and mesoporous

carriers, such as mesoporous silica nanoparticles (MSNs) [52]. A multitude of interconnected elements influence the EE and DL:

a. Physicochemical Properties of the Drug

The solubility, hydrophilicity/hydrophobicity, molecular weight, and chemical stability of a drug significantly affect its compatibility with the lipid matrix or porous carrier. Lipophilic drugs tend to exhibit higher loading efficiencies in lipid-based systems because of their enhanced affinity for lipid matrices [53-54] . Conversely, hydrophilic drugs often face challenges in lipid encapsulation and may require surface modification or complexation techniques to enhance their loading [49] .

b. Characteristics of the Carrier:

Key attributes of nanocarriers, such as particle size, surface area, pore size, pore volume, and surface functional groups, determine their capacity to accommodate and retain drug molecules. For mesoporous silica nanoparticles (MSNs), a higher surface area and larger pore volume enable more drugs to be encapsulated or adsorbed [53-46] . Surface functionalization (e.g., amine, thiol, or PEGylation) can also influence drug–carrier interactions and loading efficiency [54] .

c. Drug-to-Carrier Ratio:

An optimal drug-to-carrier ratio ensures adequate drug incorporation without saturation or waste. Excessive drug content can lead to surface deposition or crystallization, thereby reducing the stability and release control of the formulation. Empirical optimization is often required to balance the EE and DL for each specific drug–carrier combination [55] .

d. Method of Drug Loading:

Loading techniques play a vital role in determining the degree and distribution of drug within the carrier. Solvent-based methods typically allow deeper penetration into porous matrices, while solvent-free or melt techniques are faster and eco-friendly but may yield less uniform distribution or higher crystallinity [56-57] .

e. pH and Solvent Environment:

The ionization state of the drug and carrier, determined by pH, affects electrostatic interactions during encapsulation. Additionally, the polarity and viscosity of the solvent influence drug diffusion and distribution within the carrier matrix [29] .

f. Temperature and Processing Conditions:

Higher processing temperatures may increase drug solubility and diffusion, facilitating better drug incorporation. However, the thermal degradation of the drug or lipid matrix may occur if not properly controlled. Therefore, encapsulation processes should be optimized to avoid the loss of drug activity or leakage [48] .

g. Stirring Speed and Emulsification Parameters

In emulsion-based systems (e.g., SLNs or NLCs), the stirring rate, surfactant concentration, and emulsification time affect the particle size and drug entrapment. Fine-tuned parameters can result in smaller particles with a higher surface area and better encapsulation [58] .

7.4 Strategies to Improve Encapsulation Efficiency and Loading Capacity

Enhancing encapsulation efficiency (EE) and loading capacity (LC) is crucial for augmenting the therapeutic potential and cost-effectiveness of lipid-based drug delivery systems. Numerous formulation and process-related techniques have been devised to enhance drug loading and trapping in lipid nanoparticles (LNPs), mesoporous carriers, and hybrid nano systems. [59]

a. Optimizing the Lipid Composition and Drug–Lipid Affinity:

The choice of lipid type substantially affects medication incorporation. The incorporation of both solid and liquid lipids in nanostructured lipid carriers (NLCs) amplifies matrix irregularities, therefore improving drug entrapment relative to solid lipid nanoparticles (SLNs) alone [59] . Aligning the lipophilicity of the drug with that of the lipid phase can optimize solubility and partitioning into the carrier [60] .

b. Surface Functionalization of Carriers

Functionalization of the nanoparticle surface with groups such as amines, PEG, or phospholipids improves drug–carrier interactions. Surface-modified mesoporous silica nanoparticles (MSNs) exhibit a higher EE owing to enhanced hydrogen bonding, electrostatic interactions, and steric stabilization [61-46] .

c. Use of Surfactants and Emulsifiers

In LNP formulations, surfactants not only stabilize the nanoparticles but also reduce the interfacial tension, improving drug solubilization during emulsification. Higher surfactant concentrations can improve EE, although excessive amounts may lead to drug leakage or toxicity [51-62] .

d. Drug Pre-dissolution and Solubilization:

Pre-dissolving the drug in a lipid or co-solvent phase before nanoparticle formation improves drug distribution within the carrier and minimizes the surface deposition. The use of co-solvents, such as ethanol or propylene glycol, enhances the solubility of poorly water-soluble drugs, improving their loading [63] .

e. Adjusting Process Parameters:

Key parameters, including homogenization pressure, stirring velocity, emulsification duration, and cooling rate, can be tuned to regulate particle size and encapsulation characteristics. Higher shear rates typically diminish particle size and enhance entrapment by augmenting the surface area [64] .

f. Use of Ion Pairing or Complexation

The formation of ion pairs between charged drugs and counterions can enhance lipophilicity and drug entrapment in lipid matrices. Similarly, drug–polymer or cyclodextrin inclusion complexes can improve solubility and retention in the carrier system [65-66] .

g. Solid Dispersion and Co-precipitation Techniques

Solid dispersion methods, particularly for hydrophobic drugs, involve co-processing the drug and lipid carrier using melt extrusion, spray drying, or solvent evaporation. These techniques result in molecularly dispersed drugs with a higher amorphous content and improved EE [48] . Figure 6

h. Freeze-Drying and Cryoprotectants

Post-formulation freeze-drying with suitable cryoprotectants (e.g., trehalose and mannitol) stabilizes nanoparticles and preserves drug loading over time, especially for thermolabile compounds [67] .

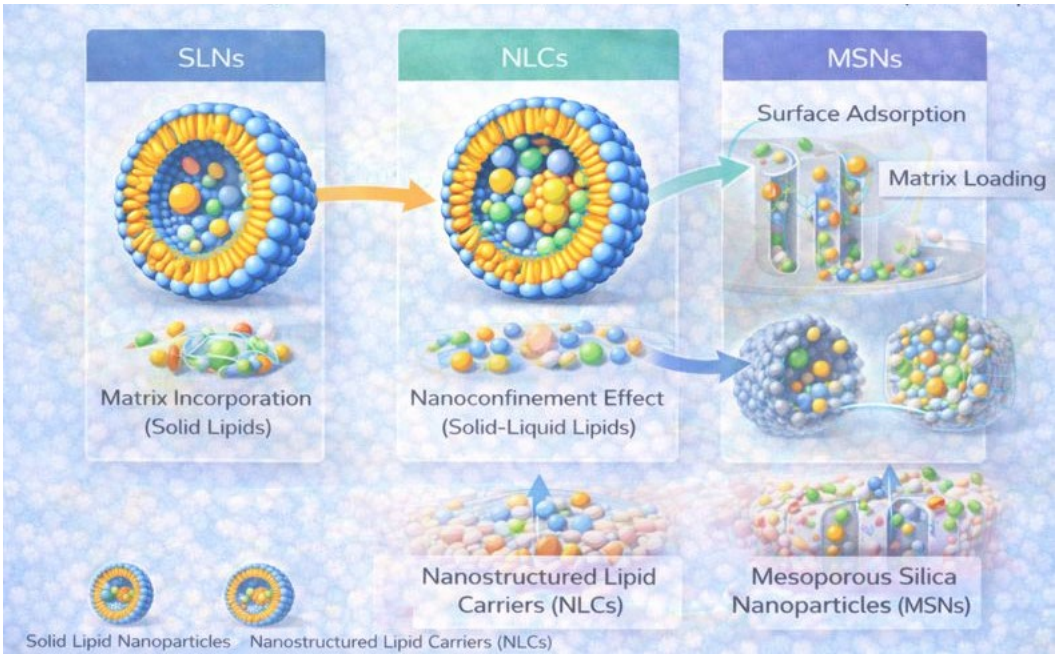

Figure 6. Drug Loading and Encapsulation Mechanisms in Lipid Nanoparticles

8.Conclusion:

Oral drug delivery continues to be the most favoured administration route due to its ease, non-invasiveness, and elevated patient compliance. Nonetheless, a considerable percentage of novel and established pharmaceuticals, particularly those exhibiting inadequate water solubility, diminished permeability, or vulnerability to enzymatic degradation, encounter substantial obstacles when administered orally. Lipid-based nanoparticles (LNPs), such as solid lipid nanoparticles (SLNs), nanostructured lipid carriers (NLCs), liposomes, and mesoporous systems, have emerged as innovative platforms capable of surmounting these restrictions.

This review explores the physicochemical basis, classification, and mechanisms by which LNPs enhance drug delivery through the gastrointestinal tract. By leveraging mechanisms such as drug solubilization, nanoconfinement, lymphatic transport, and epithelial permeability modulation, these systems not only improve bioavailability but also enable sustained and targeted drug release. Drug loading and encapsulation efficiency—two critical parameters in nanocarrier design—have been shown to be influenced by multiple interrelated factors, including carrier material properties, drug characteristics, process conditions, and the method of drug incorporation.

The encapsulation efficiency (EE) and loading capacity (LC) can be significantly enhanced through various strategies, such as optimization of lipid matrices, functionalization of carriers, selection of appropriate surfactants and solvents, and control of emulsification or loading conditions. In particular, advances in mesoporous silica-based systems and hybrid nanostructures offer novel avenues for stabilizing amorphous drug forms, preventing recrystallization, and enabling controlled-release kinetics.

LNPs are utilized throughout several therapeutic categories, encompassing anticancer treatments, antidiabetic medications, antivirals, antibiotics, and nutraceuticals. Each application

uniquely benefits from the capacity of LNPs to improve medication solubility, stability, and targeted drug absorption. For example, curcumin- and paclitaxel-loaded lipid nanoparticles have shown promising anticancer efficacy, whereas insulin-loaded NLCs have opened the door for non-invasive peptide-based treatments for diabetes. Similarly, LNP-based systems have improved the oral delivery of antivirals and nutraceuticals, further supporting the versatility of these carriers.

Despite these promising advances, several limitations remain. Challenges such as scale-up manufacturing, regulatory approval, potential toxicity of surfactants and excipients, and long-term storage stability must be addressed before widespread clinical application can be achieved. Furthermore, the complexity of gastrointestinal physiology, including enzymatic activity, mucus barriers, and variable pH, demands that formulations be tailored carefully to individual drugs and disease states.

Future advancements in this domain encompass the creation of intelligent lipid nanoparticles (LNPs) that enable site-specific targeting, stimuli-responsive release, and the concurrent administration of numerous therapeutic drugs. The incorporation of computer modeling, machine learning, and high-throughput screening in formulation development may expedite the discovery of optimal nanoparticle design. Regulatory science must advance to address the increasing complexity of lipid-based nanomedicines and formulate explicit criteria for quality control, safety assessment, and bioequivalence.

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